



# Appetite after weight loss by energy restriction and a low-fat diet–exercise follow-up

E Doucet<sup>1</sup>, P Imbeault<sup>1</sup>, S St-Pierre<sup>1</sup>, N Alméras<sup>1</sup>, P Mauriège<sup>1</sup>, D Richard<sup>1</sup> and A Tremblay<sup>1\*</sup>

<sup>1</sup>Division of Kinesiology, Department of Social and Preventive Medicine, Laval University, Ste-Foy, Québec, Canada G1K 7P4

**OBJECTIVE:** The aim of the present study was to determine the impact of weight loss on appetite as measured by visual analog scale (VAS).

**METHODS:** Seventeen subjects (10 men and seven women) took part in a 15 week weight loss program which consisted of drug therapy (fenfluramine 60 mg/day) or placebo coupled to an energy restriction (–2930 kJ/day; phase 1) followed by an 18 week low-fat diet–exercise follow-up (phase 2). Subjects were given a standardized breakfast before and after phase 1 as well as after phase 2. Individuals were asked to fill out VAS before and at 0, 10, 20, 30, 40, 50 and 60 min after this test meal. Blood samples were drawn before the meal and at 0, 30 and 60 min postprandially and analyzed for glucose and insulin. Fasting plasma cortisol and leptin were also determined.

**RESULTS:** An increase in the fasting desire to eat, hunger and prospective food consumption (PFC) was observed after phase 1 and to an even greater extent after phase 2 in both men and women. In the fasting state, positive correlations were observed between changes in the desire to eat ( $r=0.76$ ;  $P<0.05$ ) as well as changes of PFC ( $r=0.82$ ;  $P<0.05$ ) and changes in cortisol at the end of phase 1 for women. In response to phase 1, statistically significant correlations were found between changes of hunger ( $r=0.64$ ;  $P<0.05$ ) and desire to eat ( $r=0.67$ ;  $P<0.05$ ) as measured by AUC in response to the meal and changes of fasting plasma cortisol in men. The most consistent predictor of changes of baseline desire to eat ( $r=0.68$   $P<0.05$ ), fullness ( $r=-0.78$ ,  $P<0.05$ ) and PFC ( $r=0.91$ ,  $P<0.01$ ) during phase 2 was the change in fasting cortisol in men. Changes of fullness were also associated with changes of fasting leptin in men ( $r=0.68$ ;  $P<0.05$ ) during phase 2.

**CONCLUSION:** These results suggest that weight loss is accompanied by an increase of baseline appetite in both men and women and that the most consistent predictor of these changes in appetite seems to be changes in fasting plasma cortisol.

*International Journal of Obesity* (2000) 24, 906–914

**Keywords:** weight loss; appetite; cortisol; visual analog scale

## Introduction

Obesity prevalence has increased considerably throughout the latter half of this century. This increase in obesity was paralleled to important changes in food consumption patterns.<sup>1</sup> In a context where virtually unlimited access to high-fat foods is made possible, the maintenance of energy balance seems to be difficult to achieve for many individuals. This might be due to the fact that this type of dietary regimen has a weak potential to produce potent satiety signals and to inhibit subsequent energy intake.<sup>2,3</sup> This situation often leads to passive overconsumption and thus to positive energy and fat balance, and over time to excess body fat storage. In this context, it can be speculated that the potential of this type of dietary regimen to suppress appetite-related feelings may not be as effective as that which characterized the lifestyle of our ancestors. Thus, subjective feelings of hunger and satiety might play an important role in the

etiology of obesity, and nutritional strategies are now consequently being developed by health professionals to promote satiety with a minimal energy intake.

Another important dimension of this problem that has been scarcely documented up to now is the question as to whether appetite is altered by weight loss. This hypothesis came from the fact that weight loss is characterized by numerous metabolic and/or endocrine adaptations that might in turn affect appetite in the reduced-obese state. Indeed, weight loss has been shown to reduce sympathetic nervous system activity,<sup>4</sup> plasma leptin<sup>5</sup> and insulin,<sup>6</sup> all of which have been shown to inhibit food and energy intake.<sup>7–10</sup> Moreover, weight loss has also been shown to improve glycemic control,<sup>11</sup> which is partly reflected by a decrease in fasting glucose. This might be problematic in a context where a decrease in glycemia has been shown to trigger episodes of feeding.<sup>12,13</sup> It is thus possible that, in order to achieve a comparable level of satiety to what was experienced while still obese, a more substantial amount of energy has to be consumed to compensate for the reduced impact of the above-mentioned factors on appetite-related variables. This phenomenon might in turn partly explain the fact that most reduced-obese individuals regain the weight lost within a relatively short period of time if no

\*Correspondence: A Tremblay, Division of Kinesiology, PEPS, Laval University, Ste-Foy, Québec, Canada G1K 7P4.  
E-mail: angelo.tremblay@kin.msp.ulaval.ca  
Received 23 July 1999; revised 17 December 1999; accepted 23 February 2000

intervention is undertaken to prevent this unfortunate outcome.<sup>14</sup>

Few studies have directly addressed the issue as to whether appetite scores are affected by prolonged energy deficit and consequent weight loss. In this context, Heini *et al*<sup>15</sup> have observed that during controlled weight loss, although no significant changes in hunger–satiety levels were found, some positive correlations were observed between postprandial changes in these variables and fractional changes in glucose and insulin. Results from the same group have also demonstrated that during energy restriction, changes in leptin are accompanied by changes in hunger–satiety ratings<sup>16</sup> which might be partly explained by the fact that leptin levels were shown to predict palatability scores.<sup>17</sup> It has also been reported that, in response to weight loss induced by energy restriction and physical activity, changes in day-long visual analog scale (VAS) measurements were associated with changes in leptin and glucose.<sup>18</sup>

We thus hypothesized that the reduced-obese state would be characterized by an increase of VAS variables measured in the fasting state and that a given amount of calories would exert a lesser influence over the subjective feelings of hunger and satiety due to some hormonal adaptations to weight loss. In this study, we measured the impact of a standardized breakfast test meal on the subjective feelings of appetite as measured by VAS as well as their relation to changes in fasting plasma glucose, insulin, leptin and cortisol in the obese state, after a 15-week drug therapy intervention in the reduced-obese state, and after an additional 18-week low-fat diet–exercise follow-up.

## Methods

Seventeen obese subjects (10 men and seven women) underwent weight loss by drug therapy (60 mg/day of fenfluramine) or placebo treatment coupled to a non-macronutrient specific energy restriction for a 15-week period (phase 1). Since this study was double-blind, subjects were given a number in the order in which they were recruited for the study. Drug or placebo had already been randomly assigned to these numbers while respecting the ratio of 5 to 1 drug- or placebo-treated individual, respectively. Phase 1 was followed by an ~18-week low-fat diet–exercise follow-up (phase 2). A detailed description of this two-phase weight loss program is given below and has been previously described.<sup>19</sup> Subjects gave their written consent to participate in this study, which received approval from the Laval University Medical Ethics Committee.

It is important to note that following the suspension of fenfluramine and dexfenfluramine further to a potential association with disturbances in cardiac

valvular function,<sup>20,21</sup> all subjects (including placebos) were subjected to an echocardiogram. Following this assessment, a detailed analysis of cardiac valvular function was performed by cardiologists, who detected no abnormalities in response to the use of fenfluramine under these conditions.<sup>22</sup>

### Weight loss program

This program was designed as a two-phase program as previously described.<sup>19</sup> Phase 1 consisted of a 15-week non-macronutrient specific energy restriction of 2930 kJ/day (–700 kcal/day) coupled to drug therapy (fenfluramine 60 mg/day) or placebo. Following phase 1, a low fat diet from which 30% of total energy intake (EI;  $8445 \pm 158$  and  $7590 \pm 273$  kJ for men and women, respectively) came from fat, 53% from carbohydrates and 17% from proteins, as well as an aerobic exercise prescription (60–75% of  $\text{VO}_2$  max; 3–5 times a week; 45–60 min/session) were prescribed to subjects for a mean duration of 18 weeks (phase 2). To ensure proper monitoring of exercise intensity and duration and to verify the subjects' compliance to the exercise prescription, they had to wear a heart rate monitor (Polar Vantage XL™ HRM, Stamford, CT) during their exercise sessions to assess mean heart rate and duration of the training sessions.

Noteworthy is the fact that phase 2 was continued until a resistance to further lose fat was achieved in subjects. That is, a threshold beyond which a further reduction and/or manipulation of energy intake and/or an increase in energy expenditure derived from physical activities would have caused subjects to feel unable to comply with the prescription over time. This was done to ensure long term maintenance of the healthier lifestyle which resulted from this intervention program. Since this approach was individualized, some subjects reached this resistance to further lose fat before others and thus the duration of this follow-up period was different amongst individuals (from 8 to 24 weeks).

### Standardized breakfast test meal

Subjects were asked to come to the laboratory after a 12 h overnight fast. They were then asked to eat a standardized breakfast meal test which consisted of whole wheat bread, butter, peanut butter, strawberry jam, mozzarella cheese and orange juice. The meal was designed to have a food quotient of 0.85 and an energy content of 2993 kJ (715 kcal) and 2574 kJ (615 kcal) for men and women, respectively (see Appendix A). To increase the energy content of the test meal in men without changing the food quotient, a glass of 2% milk fat milk was added to this breakfast test meal. Subjects were instructed to eat everything within a 20 min period. This test meal measurement was performed at three different times during the protocol, before phase 1 as well as after phases 1 and 2.

### Visual analog scale measurements (VAS)

Desire to eat, hunger, fullness and prospective food consumption (PFC) were rated immediately before (after a 12 h overnight fast) and at 0, 10, 20, 30, 40, 50 and 60 min after the standardized test meal on a 150 mm VAS which was adapted from Hill and Blundell.<sup>23</sup> Questions were asked as follows: (1) 'How strong is your desire to eat?' (very weak–very strong); (2) 'How hungry do you feel?' (not hungry at all–as hungry as I have ever felt); (3) 'How full do you feel?' (not full at all–very full); and (4) 'How much food do you think you could eat?' (nothing at all–a large amount). The before breakfast measurement was considered as the fasting measurement for all four variables. In order to calculate values of AUC in response to the meal for the above variables, measurements at 0, 10, 20, 30, 40, 50 and 60 min were considered in this calculation by using the trapezoid method, thus not including the fasting score obtained before breakfast. Hence, higher values for AUC in response to the meal are indicative of a lesser suppression of the test meal for the desire to eat, hunger and PFC and at the opposite greater values of AUC in response to the meal for fullness indicate a greater impact of the meal over this variable. Noteworthy is the fact that the measurements of VAS were performed at least 2–4 weeks after the interruption of drug therapy after phase 1 and at least 48 h after the last bout of exercise following phase 2, when they had become resistant to further losses of body fat. At all sampling times subjects had been weight stable. In this sense, we can consider that subjects were in energy balance even if weight stability is a gross index of energy balance. Moreover, before every visit to the laboratory subjects were instructed to eat as they would normally. Women were also tested between days 5 and 12 of their menstrual cycle at all three testing periods. Also of importance is the fact that VAS measurements were always performed in the same environment, ie at the same table with the same lighting in the same room, which was kept free of odors and sounds as well as other factors that might contaminate this measurement (visual stimuli, individuals in the room, etc). Under these conditions, VAS measurements in our laboratory have been shown to be highly reliable both before and in response to a meal.<sup>24</sup>

### Blood sampling and analysis

It is important to note that all blood samples were drawn after an overnight fast of at least 12 h through a venous catheter from an antecubital vein at around 08:00 at all three sampling times. Moreover, subjects were instructed to abstain from physical exercise 48 h before blood sampling. Subjects were also instructed to eat as they would normally before visits to the laboratory and women were tested between days 5 and 12 of their menstrual cycle before and after phase 1 as well as after phase 2.

### Glucose and insulin concentrations

Blood samples were collected in tubes containing EDTA and Trasylol (Miles Pharmaceuticals, Rexdale, Ontario, Canada) in the fasting state at 0, 30 and 60 min after the meal. Plasma glucose was measured enzymatically,<sup>25</sup> whereas plasma insulin concentration was determined by radioimmunoassay with polyethylene glycol separation.<sup>26</sup>

### Plasma leptin and cortisol concentrations

Fasting plasma leptin concentrations were determined with a highly sensitive commercial double-antibody RIA (Human Leptin Specific RIA Kit, LINCO Research, St Louis, MO, USA), which detects relatively low leptin levels of 0.5 ng/ml and which does not crossreact with human insulin, proinsulin, glucagon, pancreatic polypeptide or somatostatin. Our coefficients of variation for the repeated assays ranged from 4.0 to 5.5% for the lower leptin concentrations and from 6.5 to 8.5% for higher plasma leptin concentrations.<sup>27</sup> Plasma cortisol concentrations were determined by radioimmunoassay (ICN Biomedicals Inc., Costa Mesa, CA) from fasting plasma samples.

### Statistical analysis

Jump Software 3.1.6.2. from the SAS Institute Inc. (Cary, NC, USA) was used for all analysis. Multivariate analysis of variance (MANOVA) for repeated measures were first performed on all variables to assess the effects of gender, treatment, time and their interaction. Since gender effects as well as gender×time interactions were observed, genders were analysed separately. Moreover, since no treatment×time interactions were noted, placebos and drug treated individuals were pooled together for further analysis. To verify the effect of treatment on VAS variables, paired *t*-tests were performed with a Bonnferroni correction. For these analyses, since two comparisons were performed, the alpha level was set at 0.025. Pearson correlations were also performed between the changes of VAS variables (fasting and AUC in response to the test meal) as well as hormonal changes. The alpha level for Pearson correlations was set at  $P < 0.05$ . All data are expressed as mean ± s.e.m.

## Results

As shown in Table 1, phase 1 caused a significant decrease in body weight (−11.6 and −7.3 kg), body mass index (−3.8 and −2.9 kg/m<sup>2</sup>) and fat mass (−9.9 and −5.6 kg) in men and women respectively, whereas phase 2 caused a significant decrease in fat mass in men only (−4.1 kg). Fat-free mass was also slightly reduced in response to phase 1 in both men

**Table 1** Subjects' characteristics before and after treatment

Variables	Before phase 1		After phase 1		After phase 2	
	Men	Women	Men	Women	Men	Women
Age (y)	45.0±1.1	40.1±1.8	—	—	—	—
Body weight (kg)	102.2±3.3	86.7±2.3	90.6±2.4 <sup>a</sup>	79.4±3.2 <sup>a</sup>	88.2±1.8 <sup>a</sup>	77.6±3.3 <sup>a</sup>
BMI (kg/m <sup>2</sup> )	33.6±0.7	34.3±0.8	29.8±0.6 <sup>a</sup>	31.4±1.2 <sup>a</sup>	29.1±0.4 <sup>a</sup>	30.1±1.3 <sup>a</sup>
Fat mass (kg)	37.5±2.1	41.6±2.4	27.6±1.5 <sup>a</sup>	36.0±2.4 <sup>a</sup>	23.5±1.1 <sup>b</sup>	33.4±3.1 <sup>a</sup>
Fat-free mass (kg)	64.8±2.0	45.1±1.7	63.1±2.0	43.3±1.3	64.7±1.9	44.3±2.0

Mean±standard error of the mean; *n* = 10 and *n* = 7 for men and women, respectively; BMI = body mass index; means which do not share the same letter are significantly different from one another.

and women and, as expected, a slight non-significant increase of this variable was noted after phase 2.

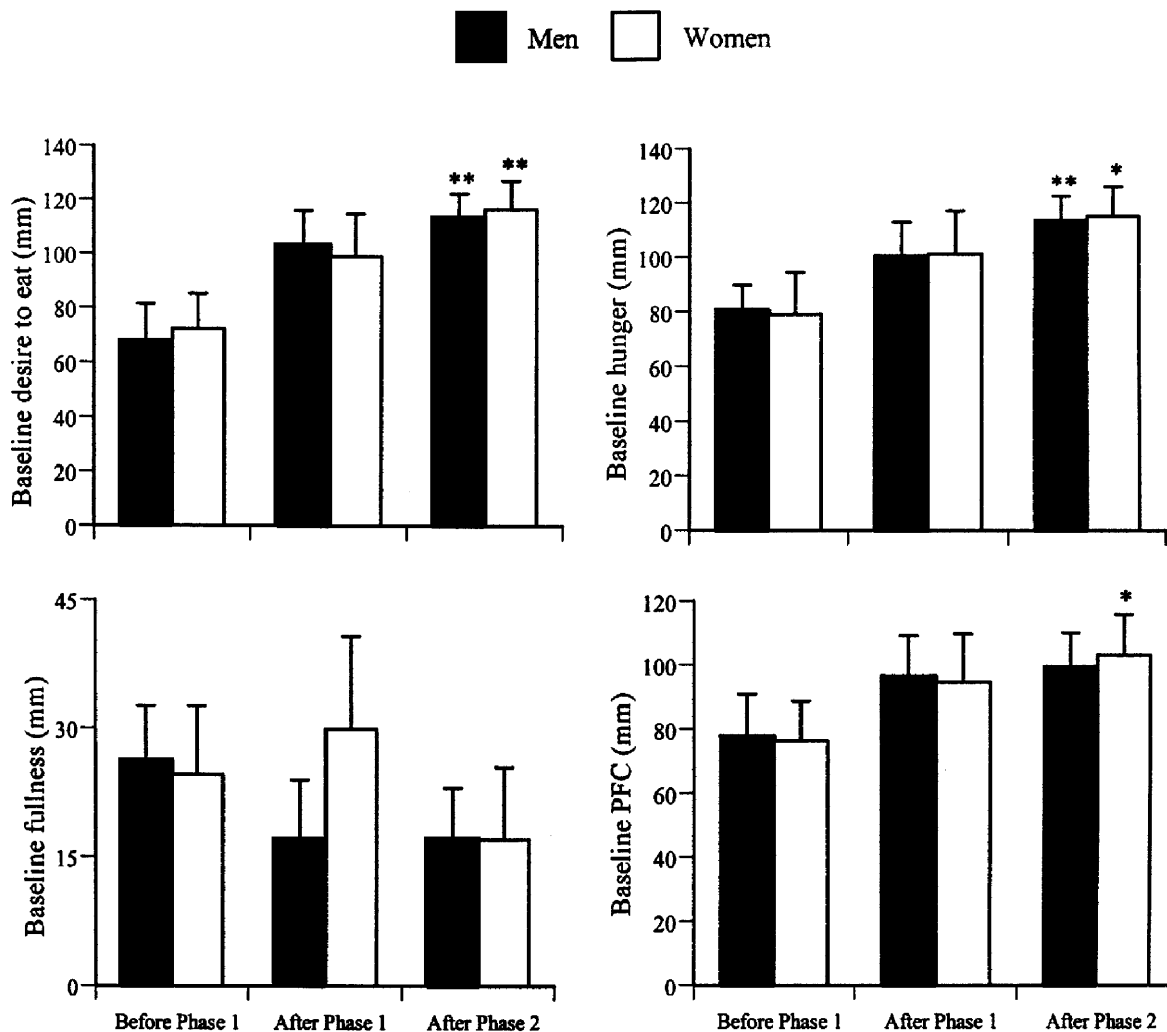
**Changes of fasting VAS scores in response to phases 1 and 2**

Figure 1 presents results from the comparison of the effects of weight loss on VAS variables measured in the fasting state in the 17 subjects who completed both phases 1 and 2. As a result of this program, the fasting desire to eat, hunger and PFC were all increased in response to phase 1, although not significantly. Moreover, at the end of phase 2 fasting desire to eat and

hunger were significantly greater than before phase 1 values, while PFC was only significantly different from before phase 1 values in women. The measurement of fasting fullness remained statistically unchanged in response to this whole program, be it after phase 1 or 2 in both sexes.M

**Changes of post-prandial VAS scores in response to phases 1 and 2**

Values of AUC in response to the test meal for VAS variables are shown in Table 2. No significant difference was observed for both men and women be it after



**Figure 1** Effects of weight loss on VAS variables measured in the fasting state before and after 15 weeks of drug therapy (phase 1) as well as after an 18 week low-fat diet–exercise follow-up (phase 2). \*,\*\*significantly different from before phase 1 measurement at 0.03 and 0.01, respectively. PFC= prospective food consumption and *n* = 10 men and 7 women.

phases 1 or 2, indicating that a meal of a given caloric content seems to influence variables of VAS in a similar fashion before and after weight loss.

**Correlates of changes of VAS scores in the fasting and postprandial states during phase 1**

Simple correlations between changes in VAS variables measured in the fasting state and changes in fasting insulin, glucose, leptin and cortisol which occurred during phase 1 were performed for both men and women. These analyses did not reveal any significant association, except for changes in cortisol which were significantly associated to changes in desire to eat ( $r=0.76, P<0.05$ ) and to changes in PFC ( $r=0.82, P<0.05$ ) in the fasting state for women. As for changes in the variables of VAS calculated as AUC in response to the test meal, significant associations were found between changes in fasting cortisol and changes in AUC desire to eat ( $r=0.66, P<0.05$ ) and hunger ( $r=0.64, P<0.05$ ) in men. On the other hand, negative associations were found between changes in AUC of hunger ( $r=-0.87, P<0.05$ ) and PFC ( $r=-0.84, P<0.05$ ) in response to the test meal and changes in fasting plasma insulin for women in response to phase 1 of this program.

Correlation analyses were also performed between changes in VAS variables in the fasting state and in response to a meal and changes in body weight and fat mass. These analyses revealed a significant association between changes in fat mass and changes in fasting PFC ( $r=0.64, P<0.05$ ) in men in response to phase 1.

**Correlates of changes of VAS scores in the fasting and postprandial states during phase 2**

Presented in Table 3 are results from correlation analyses performed between changes of VAS variables in the fasting state and changes in fasting insulin, glucose, leptin and cortisol which occurred during phase 2. In men, changes in leptin were positively and significantly associated with changes in fullness ( $r=0.68, P<0.05$ ). In addition, it would seem that in men the change of fasting plasma cortisol was the most consistent predictor of changes in desire to eat ( $r=0.68, P<0.05$ ), fullness ( $r=-0.78, P<0.01$ ) and PFC ( $r=0.91, P<0.01$ ). In women, the best predictor of changes in the variables of VAS would seem to be changes in glycemia, even if the

only variable that came close to statistical significance was fullness ( $r=0.71, P=0.07$ ).

Simple correlations were also performed on changes of VAS variables calculated as AUC in response to the test meal which occurred during phase 2 of VAS and changes of fasting insulin, glucose, leptin and cortisol as well as AUC for glucose and insulin measured during the test meal. These analyses failed to reveal any significant association (results not shown).

Figure 2 presents the regression lines for changes in desire to eat and PFC in the fasting state plotted against changes in fasting cortisol, insulin and leptin. As expected, even when pooling men and women together, the association was still statistically significant between fasting values of desire to eat ( $r=0.58, P<0.01$ ) and PFC ( $r=0.67, P<0.01$ ) and fasting cortisol. On the other hand, no significant associations were found between these two markers of appetite and fasting insulin and leptin.

**Discussion**

The main finding of this study is that, in men and women having undergone considerable weight loss through energy restriction followed by a low-fat diet—physical exercise intervention, an increase in appetite scores as measured by VAS is observed in the fasting

**Table 3** Correlation coefficients between fasting changes of leptin, cortisol, insulin and glucose and fasting subjective feelings of hunger and satiety as measured by VAS during phase 2

	Phase 2			
	Insulin	Glucose	Leptin	Cortisol
<i>Men</i>				
Desire to eat	0.09	0.07	-0.42	0.68*
Hunger	0.11	0.02	-0.35	0.57
Fullness	0.26	0.02	0.68*	-0.78**
PFC <sup>a</sup>	-0.07	0.05	-0.33	0.91**
<i>Women</i>				
Desire to eat	0.41	-0.66	0.59	0.60
Hunger	0.40	-0.63	0.54	0.55
Fullness	-0.43	0.71 <sup>b</sup>	-0.35	0.13
PFC <sup>a</sup>	0.21	-0.18	0.37	0.06

\* \*\* $P<0.05$  and  $0.01$ , respectively.

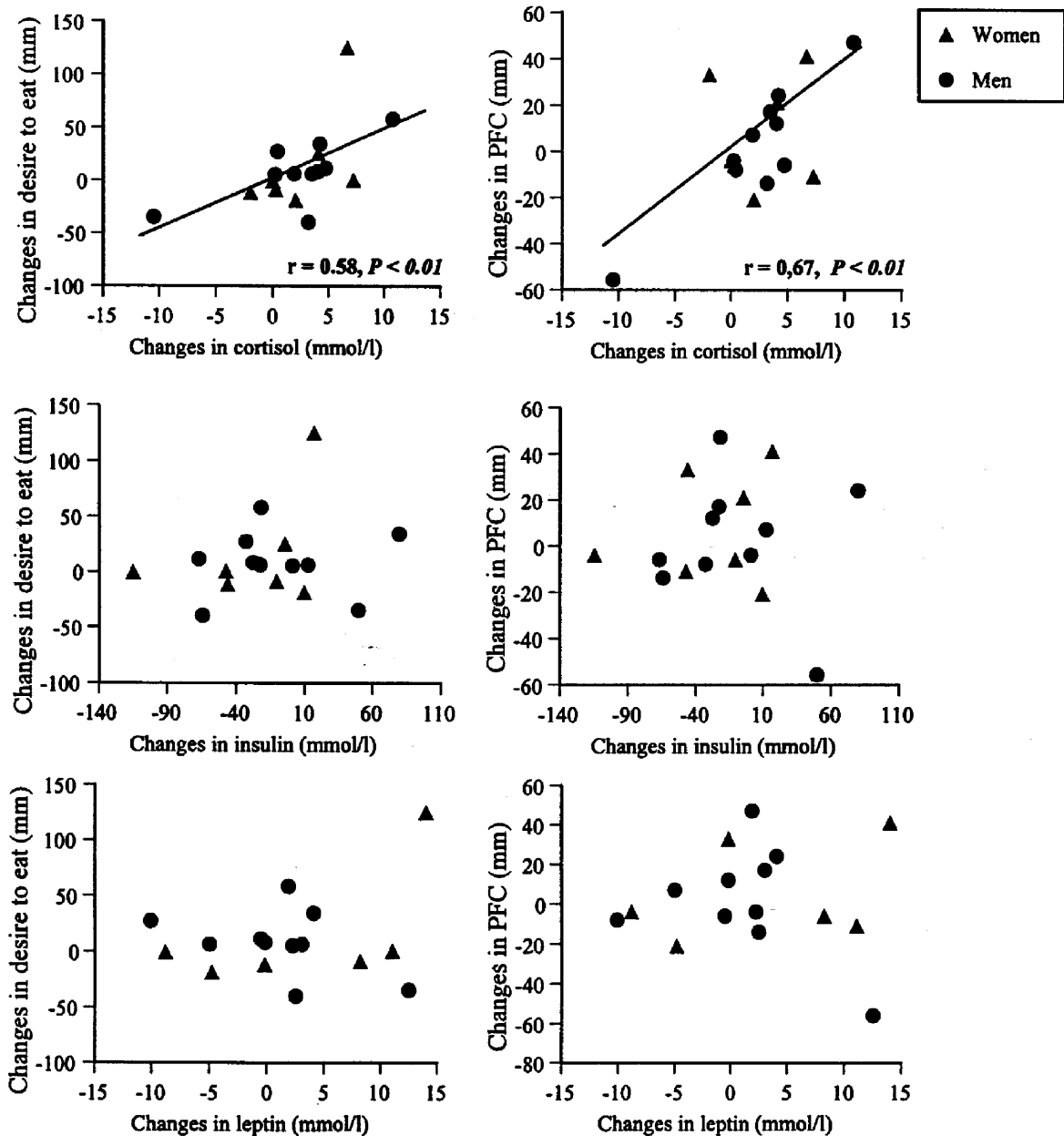
<sup>a</sup>PFC=prospective food consumption.

<sup>b</sup> $P=0.07$ .

**Table 2** Comparison of VAS measurements calculated as area under the curve in response to a test meal before and after phase 1 as well as after phase 2

Variables	Before phase 1		After phase 1		After phase 2	
	Men	Women	Men	Women	Men	Women
Desire to eat	867 ± 315	1499 ± 627	1330 ± 437	1561 ± 604	1436 ± 530	1544 ± 695
Hunger	956 ± 334	1546 ± 621	1379 ± 469	1494 ± 615	1506 ± 535	1532 ± 701
Fullness	7402 ± 480	6665 ± 867	6998 ± 491	7261 ± 713	6898 ± 638	7210 ± 678
PFC <sup>a</sup>	1122 ± 333	2055 ± 744	1497 ± 439	1507 ± 599	1529 ± 504	1749 ± 696

Mean = s.e.m. PFC=prospective food consumption;  $n=10$  men and  $7$  women, respectively.



**Figure 2** Correlation analysis between changes in fasting desire to eat and prospective food consumption (PFC) and changes in fasting cortisol, insulin and leptin in response to an 18-week low-fat diet-exercise follow-up in obese men ( $n = 10$ ) and women ( $n = 7$ ) having initially undergone 15 weeks of drug therapy.

state. However, a test meal of a given caloric content seems to exert a similar influence over these variables in the postprandial period once the reduced-obese state is achieved. Furthermore, the inter-subject variability in the changes of VAS variables in response to this program permitted us to investigate the contribution of hormonal adaptations to weight loss to these variations. In this sense, it would seem that changes in appetite scores that occur during weight loss are partly explained by changes in fasting plasma cortisol.

The most consistent finding of this study is the increase of baseline appetite across the intervention in both men and women. Indeed, as shown in Figure 1, the desire to eat, hunger and PFC were all increased after phase 1 and to a further extent after phase 2. These results are in accordance with those of Keim

*et al.*<sup>18</sup> who have found an increase in day long VAS AUC for desire to eat and hunger after 2 and 8 weeks of energy restriction and physical activity. Furthermore, our results show that these increased feelings of appetite persist beyond 12 weeks, as demonstrated in the latter study, since our intervention lasted approximately 33 weeks. These findings are important since appetite feelings might dictate the quantity and the quality of the foods that will be prepared and consumed during the day. Thus, it can easily be speculated that individuals with increased appetite before the initiation of a meal would rather choose readily accessible processed foods which generally have a high fat and sucrose content. Moreover, it is also possible that the amount of food prepared would be commensurate with the appetite scores. This is in agreement with recently reported results which have

shown that after an initial weight loss induced over 2 months by an energy restricted diet, hunger as measured by the Dutch Eating Behaviour Questionnaire scores was a significant predictor of weight regain over a 14 month period.<sup>28</sup> Beyond these observations, it would have been expected that, after drug therapy, the low-fat diet–exercise follow-up would have at least partly corrected for the increase in appetite scores noted after weight loss since the exercise prescription was of 72% and 52% of  $\text{VO}_2$  max for men and women, respectively,<sup>19</sup> and that high-intensity exercise seems to reduce *ad libitum* energy intake in the postexercise period in lean healthy men.<sup>29</sup> However, the fact that an increase in appetite scores was still observed during phase 2 is somewhat in agreement with the observation that the anorectic effect of strenuous physical exercise is not necessarily observed in obese individuals.<sup>30</sup> From this, it can be argued that the gender difference in exercise intensity which was observed during phase 2 of this weight loss–weight maintenance program probably did not affect appetite responses differently between men and women. In this regard, it is also important to consider that a delay of at least 48 h elapsed between the last bout of exercise and VAS measurements, which might be sufficient to lose a possible acute anorectic effect of exercise.

Another issue which needs to be discussed is the fact that, despite a different weight loss, the increases in appetite scores as measured by VAS scale were quite similar between men and women. It should however be kept in mind that no associations were observed between changes in body weight and changes in appetite-related variables. In this context, it is tempting to speculate that one of the reasons why women generally lose less body weight than do men during weight loss programs is because comparable metabolic adaptations to prevent further weight loss occur in women at a lesser amount of weight lost. This fits well with our results since we document an increase in appetite-related variables which is related to an increase in circulating plasma cortisol more particularly during phase 2. Despite a difference in changes of body weight and composition, the increase in the main predictor of changes in appetite-related scores, ie cortisol levels in this case, was remarkably similar between men and women. Hence, we can speculate that a lesser weight loss in women than in men might trigger a similar increase in cortisol levels which is in turn associated to similar increases in appetite-related scores more particularly when a resistance to further loss of fat is achieved.

It is also intriguing to observe a positive relationship between changes in PFC and changes in fat mass in men in response to phase 1. However, this observation does not necessarily contradict the main finding of this study. Indeed, it would seem that the increases in appetite scores which occurs during weight loss are best predicted by increases in cortisol levels and not by weight loss *per se*. In this context, if cortisol levels

increase to a greater extent in some individuals than in others during weight loss, it would be expected that these particular individuals would lose less fat because of the influence that cortisol seems to exert over subjective feelings of hunger and satiety and possibly on food intake.

The recent discovery of the *Ob* gene product, leptin,<sup>31</sup> has brought new insights into the regulation of energy balance. Even if this hormone does not seem to be acutely affected by food intake,<sup>5,32</sup> it has been shown to fluctuate considerably with body weight variations<sup>5</sup> and prolonged energy deficit.<sup>33</sup> Since leptin has been shown to reduce food intake in animals,<sup>8</sup> it is also probable that it might affect energy balance in humans. Even if leptin levels do not seem to be associated with hunger and desire to eat in obese women, be it in the fasting state or after exposure to food,<sup>32</sup> other results have demonstrated that, in response to prolonged energy deficit induced either by caloric restriction,<sup>16</sup> or caloric restriction and aerobic activity,<sup>18</sup> changes in hunger–satiety feelings were related to changes in leptin. Our results do not show as strong a relationship between changes in leptin and changes in VAS scores. However, our results are partly in accordance with those of Heini *et al*,<sup>16</sup> who reported that leptin seems to be a satiety hormone since fullness was significantly associated with changes in leptin in the present study.

The fact that in women a negative association was observed between changes in fasting plasma insulin and changes in variables of VAS measured as AUC is in accordance with the idea that insulin might affect appetite-related variables<sup>15</sup> and food intake<sup>9</sup> by modulating the expression of neuropeptide Y.<sup>10</sup> Results from a decade ago have also emphasized the importance of changes in blood glucose in regards to eating behavior.<sup>12,13</sup> More recent results have shed some new light on this issue since Heini *et al*,<sup>15</sup> have demonstrated that changes in glucose and insulin seem to predict changes in appetite-related variables. Even if our data do not provide statistical support to these latter results, it nevertheless appears that changes of VAS variables also seem to be associated with variations in fasting plasma glucose in women.

On the basis of our results, it would seem that the most consistent predictor of changes in appetite-related scores, be it at baseline or in response to a test meal, is the change in fasting cortisolemia. Indeed, as shown in Figure 2, an increase in fasting cortisol seems to better predict an increase of fasting desire to eat and PFC when compared to changes in insulinemia or leptinemia. To our knowledge, this is the first paper to report such findings in humans having undergone a weight loss intervention program. Convincing demonstrations of the effects of glucocorticoids on food intake in animals have, however, been reported.<sup>34,35</sup> Whether or not these results can be transposed to humans remains unclear, but our results seem to support observations from the animal literature. It is however unclear as to why cortisol comes

out as such a strong predictor of changes of VAS variables. Since glucocorticoids are involved in glucose homeostasis, and that weight loss is accompanied by important changes in glucose metabolism, changes in cortisol might reflect an attempt at re-establishing glucose homeostasis by increasing food intake. Noteworthy is the fact that an increase in hypothalamic–pituitary–adrenal axis activity, as indicated by an increase in circulating plasma cortisol, might reflect an increase in the level of stress. Even if the role of stress in the development of obesity remains to be determined, there is some evidence to the effect that stress can trigger episodes of feeding in animals<sup>36</sup> and that some animals display a considerable stress response when food deprived.<sup>37</sup> From these observations, it might be speculated that energy-restricted humans might respond similarly to a prolonged energy deficit as do animals and, for undetermined reasons, increase their food intake to alleviate this stressful status.

In summary, our results demonstrate that weight loss is accompanied by an increase in appetite-related variables in the fasting state. Moreover, based on our results the most consistent predictor of these changes seems to be changes in fasting plasma cortisol. More studies need to be performed to further clarify how cortisolemia is implicated in the control of energy balance in the reduced obese state and to what extent these changes are acutely affected by food intake. Hence, nutritional strategies must be developed to prevent the overfeeding which might result from these increased appetite scores, otherwise a very plausible scenario is weight regain as is most often seen in reduced obese individuals.

### Acknowledgements

This research was supported by grants from Servier Canada and FCAR Québec.

### References

- 1 Leaf A, Weber PC. A new era for science in nutrition. *Am J Clin Nutr* 1987; **45**: 1048–1053.
- 2 Blundell J, Burley VJ, Cotton JR, Lawton CL. Dietary fat and control of energy intake: evaluating the effects of fat on meal size and postmeal satiety. *Am J Clin Nutr* 1993; **57**: 772S–778S.
- 3 Lawton CL, Burley VJ, Wales JK, Blundell JE. Dietary fat and appetite control in obese subjects: weak effects on satiety. *Int J Obes* 1993; **17**: 409–416.
- 4 Aronne LJ, Mackintosh R, Rosenbaum M, Leibel RL, Hirsch J. Autonomic nervous system activity in weight gain and weight loss. *Am J Physiol* 1995; **269**: R222–R225.
- 5 Considine RV, Shina MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohanessian JP, Marco CC, McKee LJ, Bauer TL, Caro JF. Serum immunoreactive-leptin concentrations in normal-weight and obese subjects. *N Engl J Med* 1996; **334**: 292–295.
- 6 Goldstein DJ. Beneficial health effects of modest weight loss. *Int J Obes* 1992; **16**: 397–415.
- 7 Bray GA. Food intake, sympathetic activity, and adrenal steroids. *Brain Res Bull* 1993; **32**: 537–541.
- 8 Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* 1995; **269**: 543–546.
- 9 Schwartz MS, Figlewicz DP, Baskin DG, Woods SC, Porte D. Insulin in the brain: a hormonal regulator of energy balance. *Endocrinol Rev* 1992; **13**: 387–414.
- 10 Schwartz MW, Sipols AJ, Marks JL, Sanacora G, White JD, Scheurink A, Kahn SE, Baskin DG, Woods SC, Figlewicz DP, Porte D. Inhibition of hypothalamic neuropeptide Y gene expression by insulin. *Endocrinology* 1992; **130**: 3608–3616.
- 11 Wing RR, Klein R, Moss SE. Weight gain associated with improved glycemic control in population-based sample of subjects with type I diabetes. *Diabetes Care* 1990; **13**: 1106–1109.
- 12 Campfield LA, Smith FJ. Functional coupling between transient declines in blood glucose and feeding behavior: temporal relationships. *Brain Res Bull* 1986; **17**: 427–433.
- 13 Campfield LA, Smith FJ. Transient declines in blood glucose signal meal initiation. *Int J Obes* 1990; **14**: 15–31.
- 14 Weinsier RL, Neslon KM, Hensrud DD, Darnell BE, Hunter GR, Schutz Y. Metabolic predictors of obesity. *J Clin Invest* 1995; **95**: 980–985.
- 15 Heini AF, Kirk KA, Lara-Castro C, Weinsier RL. Relationship between hunger-satiety feelings and various metabolic parameters in women with obesity during controlled weight loss. *Obes Res* 1998; **6**: 225–230.
- 16 Heini AF, Lara-Castro C, Kirk KA, Considine RV, Caro JF, Weinsier RL. Association of leptin and hunger-satiety ratings in obese women. *Int J Obes* 1998; **22**: 1084–1087.
- 17 Raynaud E, Brun JF, Perez-Martin A, Sagnes C, Boularan AM, Fedou C, Mercier J. Serum leptin is associated with the perception of palatability during a standardized high-carbohydrate breakfast test. *Clin Sci (Colch)* 1999; **96**: 343–348.
- 18 Keim NL, Stern JS, Havel PJ. Relation between circulating leptin concentrations and appetite during a prolonged, moderate energy deficit in women. *Am J Clin Nutr* 1998; **68**: 794–801.
- 19 Doucet E, Imbeault P, Almeras N, Tremblay A. Physical activity and low-fat diet: is it enough to maintain weight stability in the reduced-obese individual following weight loss by drug therapy and energy restriction? *Obes Res* 1999; **7**: 323–333.
- 20 Khan MA, Herzog CA, St Peter JV, Hartley GG, Madlon-Kay R, Dick CD, Asinger RW, Vessey JT. The prevalence of cardiac valvular insufficiency assessed by transthoracic echocardiography in obese patients treated with appetite-suppressant drugs. *N Engl J Med* 1998; **10**: 713–718.
- 21 Weissman NJ, Tighe JFJ, Gottdiener JS, Gwynne JT. An assessment of heart-valve abnormalities in obese patients taking dexfenfluramine, sustained-release dexfenfluramine, or placebo. Sustained-release dexfenfluramine study group. *N Engl J Med* 1998; **10**: 725–732.
- 22 Prud'homme D, Langlais M, Samson MP, Gallagher P, Turcotte J, Tremblay A, Després J-P. Lack of major cardiac valvular abnormalities in asymptomatic obese men and women following a 3-month fenfluramine or dexfenfluramine treatment. *Int J Obes* 1999; **23**: S175.
- 23 Hill AJ, Blundell JE. The effects of a high-protein or high-carbohydrate meal on subjective motivation to eat and food preferences. *Nutr Behav* 1986; **3**: 133–144.
- 24 Arvaniti K, Richard D, Tremblay A. Reproducibility of energy and macronutrient intake and related substrate oxidation rates in a buffet-type meal. *Br J Nutr* (in press).
- 25 Richterich R, Dauwwalder H. Zur bestimmung der plasmaglukose-konzentration mit der hexokinase-glucose-6-phosphat-deshydrogenase-methode. *Schweiz Med Wochenschr* 1971; **101**: 615–618.
- 26 Desbuquois B, Aurbach GD. Use of polyethylene glycol to separate free and antibody-bound peptide hormones in radioimmunoassays. *J Clin Endocrinol Metab* 1971; **37**: 732–738.

- 27 Couillard C, Mauriege P, Prud'homme D, Nadeau A, Tremblay A, Bouchard C, Despres JP. Plasma leptin concentrations: gender differences and associations with metabolic risk factors for cardiovascular disease. *Diabetologia* 1997; **40**: 1178–1184.
- 28 Paman WJ, Saris WH, Westtererp-Plantenga MS. Predictors of weight maintenance. *Obes Res* 1999; **7**: 43–50.
- 29 Imbeault P, Saint-Pierre S, Almeras N, Tremblay A. Acute effects of exercise on energy intake and feeding behaviour. *Br J Nutr* 1997; **77**: 511–521.
- 30 Kissileff HR, Pi-Sunyer FX, Segal K, Meltzer S, Foelsch PA. Acute effects of exercise on food intake in obese and nonobese women. *Am J Clin Nutr* 1990; **52**: 240–245.
- 31 Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994; **372**: 425–432.
- 32 Karhunen L, Haffner S, Lappalainen R, Turpeinen A, Miittinen H, Uusitupa M. Serum leptin and short-term regulation of eating in obese women. *Clin Sci* 1997; **92**: 573–578.
- 33 Scholz GH, Englaro P, Thiele I, Scholz M, Klusmann T, Kellner K, Rascher W, Blum WF. Dissociation of serum leptin concentration and body fat content during long term dietary intervention in obese individuals. *Horm Metab Res* 1996; **28**: 718–723.
- 34 Arvaniti K, Deshaies Y, Richard D. Effect of leptin on energy balance does not require the presence of intact adrenals. *Am J Physiol* 1998; **275**: R105–111.
- 35 Dagnault A, Deshaies Y, Richard D. Effects of the 5-hydroxytryptamine agonist D, L-fenfluramine on energy balance in rats: influence of gender. *Int J Obes* 1993; **17**: 367–373.
- 36 Burlet C. Stress and feeding behavior. *Ann Endocrinol* 1988; **49**: 141–145.
- 37 Timofeeva E, Richard D. Functional activation of CRH neurons and expression of the genes encoding CRH and its receptors in food-deprived lean (*Fa/?*) and obese (*fa/fa*) Zucker rats. *Neuroendocrinology* 1997; **66**: 327–340.

**Appendix A** Composition of the breakfast meal test in men and women

Foods	Weight (g)	Proteins (g)	CHO (g)	Fat (g)	Energy kJ (kcal)
Wholewheat bread	55	6.9	31.2	1.9	712 (170)
Smooth peanut butter	17	4.3	3.2	8.6	448 (107)
Strawberry jam (Kraft)	20	0.1	14	0	234 (56)
Mozzarella cheese, 17% m.f.	50	13.7	1.6	8.6	582 (139)
Butter	10	0.1	0	8.1	306 (73)
Orange juice	150	1	16.2	0.1	293 (70)
Milk, 2% m.f. <sup>a</sup>	200	6.7	9.6	3.8	414 (99)
Total women	302 g	26.1 g	66.2 g	27.3 g	2575 (615)
Total men	502 g	32.8 g	75.8 g	31.1 g	2989 (715)

<sup>a</sup>Milk was only included in the test meal for men. m.f. = milk fat.