Basal metabolic rate in anorexia nervosa: relation to body composition and leptin concentrations[1–3]

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ABSTRACT

Background: Leptin is thought to represent a peripheral signal involved in the regulation of energy balance. Its action has been studied in animals and obese subjects. Little is known about leptin's role during negative energy balance.

Objective: The objective was to evaluate the relation between energy turnover, body composition, and plasma leptin concentrations in anorexia nervosa (AN).

Design: Sixteen weight-stable women with AN were compared with 22 control subjects and 14 rehabilitated AN patients (R-AN). Basal metabolic rate (BMR) was measured by indirect calorimetry; fat-free mass (FFM) and fat mass (FM) were calculated according to a 4-compartment model. Plasma leptin was determined by radioimmunoassay.

Results: The BMR of AN patients (2.73 ± 0.37 kJ/min) was significantly lower than that of control subjects (3.45 ± 0.34 kJ/min) ($P < 0.001$), even after adjustment for FFM (2.92 ± 0.33 kJ/min in AN patients and 3.30 ± 0.26 kJ/min in control subjects; $P < 0.004$). Plasma leptin concentrations in AN patients were 76% lower than in control subjects, even after body fat was controlled for. In R-AN patients, BMR was not significantly different from that of control subjects and leptin concentrations were generally close to normal. Plasma leptin concentrations correlated significantly with FM ($r^2 = 0.53$, $P < 0.0000$) and BMR, even after adjustment for FFM ($r^2 = 0.21$, $P < 0.0003$).

Conclusions: BMR and plasma leptin concentrations are depressed in patients with AN; this is not explained by body-composition changes. The relation between leptin and BMR suggests that leptin plays a role in the energy sparing response to exposure to chronic energy deficiency. The return of BMR to normal and the significant increase in leptin concentrations in R-AN patients suggests a full reversibility of this adaptation mechanism. *Am J Clin Nutr* 2000;71:1495–502.

KEY WORDS Basal metabolic rate, leptin, body composition, fat-free mass, anorexia nervosa, Italy, women

INTRODUCTION

Anorexia nervosa (AN) is an emerging nutritional disorder that affects mostly adolescent and young adult females in Western societies. Patients with AN are severely undernourished because of voluntary restriction of food intake that lasts several months or even years (1). Alterations in energy metabolism are among the more constant results of energy restriction. Many studies invariably showed a reduced basal metabolic rate (BMR) in subjects with AN (2–6) and in experimental semistarvation studies of well-nourished adult volunteers (7–9), in chronically undernourished populations of developing countries (10–12), and in obese patients undergoing therapeutically restricted diets (13–15). The main controversy remains whether the decrease in BMR is due to a change in body composition or whether it represents a down-regulation of cellular metabolism.

Several physiologic mechanisms have been proposed to explain these changes in energy expenditure. Factors such as hormonal concentrations and substrate oxidation rates may operate and interact to influence metabolic processes. Energy deficit reduces activity of the sympathetic nervous system, alters peripheral thyroid metabolism, and lowers insulin secretion (16). Several studies have indicated that leptin might play a role in the complex mechanism that regulates energy balance. Leptin (also known as the *ob* gene product) is a protein whose expression is mainly localized in adipose tissue, from which it is secreted into the circulation and transported to the hypothalamic area, where it is presumed to act as a lipostatic mechanism through modulation of satiety signals and sympathetic nervous system–mediated energy expenditure (17). Plasma leptin concentrations increase in the fed state and decrease rapidly during nutritional deprivation (18–19). Long-term leptin administration was shown to markedly decrease food consumption, decrease body weight and fat mass, and increase energy expenditure in *ob/ob* mice (20–22). In humans, circulating leptin concentrations appear to be highly correlated with adipose tissue mass (19).

Several studies showed that plasma leptin concentrations are elevated in most obese people, which implies that obesity might be associated with leptin insensitivity due to several mechanisms, such as a leptin-receptor defect (23), impaired postreceptor signal transduction, and alteration of transport capacity across the

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blood-brain barrier (24). On the other hand, a significant decrease in plasma leptin concentration has been shown to occur in AN (25, 26) and during dietary treatment of obesity (27, 28). It has been suggested that this fall in leptin might be involved in the neuroendocrine adaptation to starvation (29). An inverse association was found between leptin concentrations and BMR in obese subjects (30, 31); however, this relation was not observed in other studies (32, 33). A return to normal BMR after refeeding was shown in adults (8, 9), in an undernourished population (34), and in subjects with AN (35–38). Similarly, leptin concentrations were reported to increase with weight gain (26, 39). However few studies addressed the role of leptin in the regulation of energy expenditure in humans. The aim of the present study was to examine the effect of chronic energy undernutrition on energy turnover and plasma leptin concentrations in patients with AN and to explore the relation between body composition, BMR, and plasma leptin.

SUBJECTS AND METHODS

Subjects

Twenty-eight women aged 17–37 y were recruited from the outpatient clinics for eating disorders of the University of Rome, La Sapienza. All women met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria (40) for AN. A first group of 16 patients with AN had a body mass index (BMI; in kg/m^2) <17 and had been weight stable for ≥3 mo before the study, as assessed by clinical report. Eight of these subjects had AN of the restricting type and the other 8 had the binge-eating or purging type of AN. The duration of AN ranged from 6 mo to 12 y ($\bar{x}$ ± SD: 4.5 ± 4.2 y). A second group consisted of 14 recently rehabilitated AN patients (R-AN; BMI > 18.5 for ≥1 y). This group had a history of AN ($\bar{x}$ ± SD: 5.3 ± 3.2 y) and a mean BMI, at their lowest weight, of 14.3 ± 2.4, as assessed by clinical report. A last group of 22 women of normal weight (BMI: 18.5–24.9), who were free of a history of eating disorders, served as control subjects and were recruited from the staff and students of the National Institute of Nutrition.

All subjects were measured in the fasting state early in the morning. BMR and body-composition measurements were conducted on the same day to minimize within-subject biological variability. Dual-energy X-ray absorptiometry (DXA) and blood collection for leptin assay were performed, within the next 3 d, in the Department of Medical Physiopathology of the University of Rome, La Sapienza. Control subjects and R-AN patients were studied between the 6th and 12th days of their menstrual cycles; all the AN patients were amenorrheic. The study protocol was reviewed and approved by the ethics committee of the University of Rome, La Sapienza. All subjects gave written, informed consent to participate in the study.

Basal metabolic rate

BMR was measured in triplicate (CV < 2%) by open-circuit indirect calorimetry under standardized conditions with Douglas bags. The measurements were made at the National Institute of Nutrition at 0800 after 10–12 h of fasting and ≥30 min of resting, in absolute quietness and at thermic neutrality (the temperature inside the room was 22–25°C). Expired air was collected for 10 min. The volume of expired air was measured on a calibrated wet gas meter (SIM Brunt, Milan, Italy), analyzed for oxygen content with Servomex 1100 A (Taylor Instrument Analytics Ltd, Sussex, United Kingdom), and analyzed for carbon dioxide content with a Morgan infrared analyzer (PK Morgan Ltd, Chatham, Kent, United Kingdom). The gas analyzers were calibrated daily with certified gas mixtures (pure nitrogen and atmospheric air for Servomex and a mixture of 6.60% carbon dioxide in nitrogen for the carbon dioxide analyzer). The metabolic rate was calculated by Weir's equation (41).

Body composition

Body fat was derived according to a 4-compartment model that requires measurements of body volume, total body water (TBW), total-body bone mineral mass, and body weight. We used the equation proposed by Fuller et al (42), with body volume measured by underwater weighing. TBW was derived by impedance analysis with use of Kushner's equation (43), which was validated in patients with AN (44), and total-body bone mineral mass was measured by DXA. The propagated measurement error for this method is 3.0% of fat weight (45).

Underwater weighing

Body density was determined by using underwater weighing as described by Durnin and Rahaman (46), with simultaneous measurement of residual lung volume by using the nitrogen dilution technique (47). The subjects were measured in the fasting state after voiding, having refrained from intense exercise and diuretics over the previous 24 h. To reduce gastrointestinal gas, the subjects were asked to consume a low-fiber, meat-free diet during the 4 d before the test and took an antiflatulent (160 mg activated dimethyl-polysiloxanes/d; Warner Lambert Consumer Healthcare S Com pA, Milan, Italy). Body density measurements were repeated until a difference of ±1.5 g/L between any 3 replicates was obtained (corresponding to ≈0.4% of fat).

Bioelectrical impedance

Whole-body impedance was measured with an impedance analyzer (Human Im Scan, Dietosystem, Milan, Italy). Signal and detecting electrodes were positioned according to the recommended protocol on each subject's right wrist and right ankle (48). The measurements were made 10 min after the subjects lay supine on a nonconductive surface with their legs slightly divaricated and their arms next to, but not touching, their trunks. Calibration of the analyzer was checked daily by using a standard resistor. TBW was estimated by using Kushner's equation (43). SEs of repeated measurements for 10 subjects were 7 Ω for impedance.

Dual-energy X-ray absorptiometry

DXA measurements were made by using a total body scanner (model QDR-4500W; Hologic, Walthman, MA) according to a previously published procedure (49). Total-body bone mineral mass was derived according to the computer algorithms provided by the manufacturer. The within-subject day-to-day CV for total-body bone mineral mass is <0.1%.

Anthropometric measurements

Height and weight were measured according to the standard procedure (50). Height was measured to the nearest 0.1 cm with a wall-mounted Holtain stadiometer (Holtain Ltd, Crosswell, Crymych, United Kingdom). Body weight was recorded to the nearest 0.01 kg by using a calibrated computerized digital balance (K-Tron P1-SR; K-Tron SA, Hasler Division, Colombier, Switzerland); each subject was barefoot and wore a light bathing suit.

TABLE 1
Characteristics of study patients[1]

	Patients with AN[2] (n = 16)	Rehabilitated AN patients[3] (n = 14)	Control subjects[3] (n = 22)
Age (y)	25 ± 5	24 ± 5	26 ± 6
Weight (kg)[4]	41.6 ± 4.9[5,6]	51.5 ± 5.5[7]	56.9 ± 5.1
Height (cm)	163.7 ± 5.9	160.5 ± 4.7	164.6 ± 6.2
BMI (kg/m^2)[4]	15.5 ± 1.2[5,6]	20.0 ± 1.6	21.0 ± 1.5
Fat mass			
(kg)[4]	6.8 ± 3.3[5,6]	13.6 ± 4.8	15.7 ± 3.7
(%)[4]	16.1 ± 6.7[5,6]	26.0 ± 7.3	27.4 ± 4.8
Fat-free mass			
(kg)[4]	34.7 ± 3.5[5,6]	37.9 ± 3.8[7]	41.2 ± 3.2
(%)[4]	83.9 ± 6.7[5,6]	74.0 ± 7.3	72.6 ± 4.8

[1] $\bar{x}$ ± SD. AN, anorexia nervosa.
[2] BMI < 17.
[3] BMI: 18.5–24.9.
[4] Significant difference among groups, $P < 0.0000$ (ANOVA).
[5,7] Significantly different from control subjects (Tukey's honestly significant difference test): [5] $P < 0.0001$, [7] $P < 0.05$.
[6] Significantly different from rehabilitated AN patients, $P < 0.01$ (Tukey's honestly significant difference test).

Leptin

After the subjects fasted overnight, blood samples were collected for leptin assay. Plasma leptin was measured by using a commercially available radioimmunoassay kit (Linco Research, St Charles, MO), as described elsewhere (51). The intra- and interassay CVs were 3.5% and 4.2%, respectively. All measurements were performed in duplicate.

Statistical analysis

Statistical analyses were performed by using COMPLETE STATISTICAL SYSTEM (StatSoft, Inc, Tulsa, OK). The data were first tested for normal distribution by using the Shapiro-Wilk test for normality. Leptin concentrations were not normally distributed, so a Kruskal-Wallis test was used to compare leptin concentrations among groups. The logarithm of leptin (log leptin) was normally distributed and was used for regression analyses. Relations among log leptin concentration and body composition or BMR were determined by using regression analyses. Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were used to determine intergroup differences in body composition and BMR (52). Results are presented as group means and SDs. A level of significance of $P < 0.05$ was used for all data analyses.

RESULTS

The physical and body-composition characteristics of the subjects are presented in **Table 1**. The mean ages and heights of the 3 study groups were similar. The mean BMI of the AN patients (15.5 ± 1.2) indicates the severe grade of these patients' undernutrition. The fat mass of the AN patients (6.8 ± 3.3 kg) was 58% and 50% lower, respectively, than the fat mass of the control subjects (15.7 ± 3.7 kg) and of the AN-R group (13.6 ± 4.8 kg). The FFM of AN patients (34.7 ± 3.5 kg) was 15% less than that of the control subjects. The R-AN patients had a fat mass that was ≈16% less and a FFM (37.9 ± 3.8 kg) that was 7% less than that of the control subjects.

The BMR data for all 3 groups are shown in **Table 2**. The mean absolute BMR (in kJ/min) was significantly lower (by 21%) in AN patients than in control subjects. R-AN patients had an intermediate BMR that was significantly higher than that of AN patients (by 17%) but only 7% lower than that of the control subjects. BMR was significantly correlated with FFM and body weight. The regression equation showed that 62% of the variance in BMR was attributed to differences in body weight (**Figure 1**). When BMR was regressed against FFM, 48% of the variance was explained by FFM (Figure 1). There was no significant difference between regression lines (BMR against body weight and FFM) of different groups (data not shown). When BMR was expressed per unit of body weight or per unit of FFM, no significant differences between the 3 groups were observed. Adjustment by ANCOVA for FFM reduced the differences but did not eliminate them (AN group, −10%; R-AN group, −3%). There were no significant differences in BMR within the same analysis with body weight as the covariate. Respiratory quotients were similar among the 3 groups, indicating no significant difference in substrate utilization.

TABLE 2
Basal metabolic rate (BMR) of the 3 study groups[1]

	Patients with AN[2] (n = 16)	Rehabilitated AN patients[3] (n = 14)	Control subjects[3] (n = 22)
BMR			
(kJ/min)[4]	2.7281 ± 0.3691[5,6]	3.2254 ± 0.4082	3.4516 ± 0.3405
(kJ·kg body wt^{-1}·min^{-1})	0.0658 ± 0.0067	0.0629 ± 0.0071	0.0608 ± 0.0052
(kJ·kg FFM^{-1}·min^{-1})	0.0789 ± 0.100	0.0855 ± 0.0111	0.0839 ± 0.0065
ANCOVA-adjusted means			
Body weight (kJ/min)	3.1146 ± 0.2824	3.1932 ± 0.3433	3.1911 ± 0.2781
FFM (kJ/min)[7]	2.9207 ± 0.3327[8,9]	3.2459 ± 0.3834	3.2985 ± 0.2579
Respiratory quotient	0.80 ± 0.06	0.81 ± 0.05	0.82 ± 0.04

[1] $\bar{x}$ ± SD. AN, anorexia nervosa; FFM, fat-free mass.
[2] BMI < 17.
[3] BMI: 18.5–24.9.
[4,7] Significant difference among groups (ANOVA): [4] $P < 0.00000$, [7] $P < 0.002$.
[5,8] Significantly different from control subjects (Tukey's honestly significant difference test): [5] $P < 0.001$, [8] $P < 0.004$.
[6,9] Significantly different from rehabilitated AN patients (Tukey's honestly significant difference test): [6] $P < 0.002$, [9] $P < 0.03$.

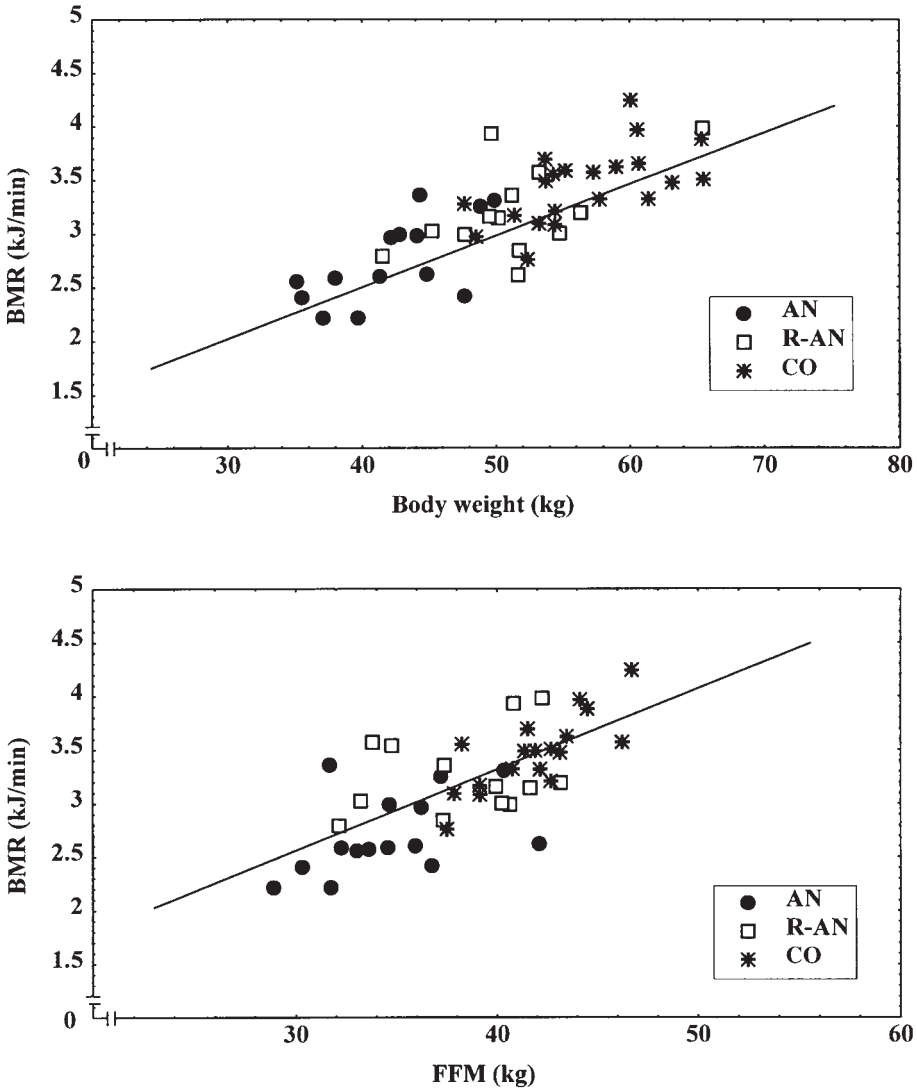

FIGURE 1. Regression of basal metabolic rate (BMR) on body weight ($r^2 = 0.62$, $P < 0.0000$) and on fat-free mass (FFM) ($r^2 = 0.48$, $P < 0.0000$) in patients with anorexia nervosa (AN), rehabilitated AN patients (R-AN), and control subjects (CO).

The next step in the analysis involved evaluating the differences in leptin concentrations and their relation with BMR. Leptin plasma concentrations of the study subjects are shown in **Table 3**. Leptin concentrations were lowest in the AN patients (1.9 ± 1.5 μg/L), the maximum difference being 76%. R-AN patients appeared to have the highest absolute concentrations (8.4 ± 10.5 μg/L). The difference between groups persisted when leptin concentrations were adjusted for fat mass. The logarithm of leptin concentration was significantly correlated across groups with body fat mass (**Figure 2**). Although the slope for AN patients was not significantly different from that for control subjects and R-AN patients, the intercept was slightly significantly different ($P < 0.04$). A positive correlation was found also between the logarithm of leptin concentration and BMR (**Figure 3**, top). The slope and intercept of the regression line for AN patients were not significantly different from those for control subjects and R-AN patients, possibly because of the wide scatter of the points and the relatively small number of subjects in each group. The correlation with BMR persisted after statistical adjustment for FFM and the slight apparent individual regression lines of the 3 groups disappeared (Figure 3, bottom). In a stepwise regression analysis, with BMR as the dependent variable and FFM and leptin as the independent variables, the final model included both terms as significant variables, which together accounted for 58% of the variation in BMR (**Table 4**).

DISCUSSION

The results of this study showed that AN is accompanied by a marked reduction in BMR. The BMRs of the AN patients in our study, when expressed in absolute terms, were 21% lower than those of a comparable group of healthy women. This result appears to be mostly, but not entirely, explained by the large reduction in body weight (15.4 kg) and FFM (6.2 kg). When

TABLE 3
Leptin plasma concentrations of the 3 study groups[1]

	Patients with AN[2] (n = 16)	Rehabilitated AN patients[3] (n = 14)	Control subjects[3] (n = 22)
		$\mu g/L$	
Leptin[4]	1.9 ± 1.5[5,6]	8.4 ± 10.5	7.8 ± 3.0
Log leptin[7]	0.15 ± 0.35[5,6]	0.75 ± 0.40	0.87 ± 0.14
Log leptin adjusted for body fat[7]	0.34 ± 0.34[5,8]	0.71 ± 0.32	0.75 ± 0.32

[1] $\bar{x}$ ± SD. AN, anorexia nervosa.
[2] BMI < 17.
[3] BMI: 18.5–24.9.
[4] Significant difference among groups, $P < 0.0000$ (Kruskal-Wallis test).
[5] Significantly different from control subjects, $P < 0.0001$ (Tukey's honestly significant difference test).
[6,8] Significantly different from rehabilitated AN patients (Tukey's honestly significant difference test): [6] $P < 0.0001$, [8] $P < 0.001$.
[7] Significant difference among groups, $P < 0.0000$ (ANOVA).

these differences were taken into account, BMR adjusted by ANCOVA for FFM was still lower in AN patients than in control subjects (by 11%). This persistent difference suggests that the metabolic activity of the active tissue mass may have been reduced. In most of the studies of energy expenditure in AN patients, there was no decrease in BMR (2, 3, 35, 38, 53). However, the findings of the present study agree with the results obtained by Keys et al (8) in individuals undergoing experimental semistarvation, by Scalfi et al (6), and by Vaisman et al (4) in AN patients. In the Minnesota study (8), BMR fell by 39% in absolute terms (kJ/d) and by 19% and 16% when BMR was expressed per kilogram of body weight or per kilogram of FFM, respectively. Scalfi et al (6) observed a similar reduction of FFM-adjusted BMR (≈16%) in a group of women with AN who were similar in age and BMI to the women in the present study. In adolescent girls with AN, Vaisman et al (4) showed that BMR was 28% lower than that of control subjects even when expressed per unit of lean body mass.

There are several possible explanations for these discrepancies in findings. First, note that the studies that did not find a decrease in BMR did not use ANCOVA. It is well known that the normalization procedure of dividing energy expenditure measurements by body weight or FFM is mathematically biased (52). In the present study, although BMR did not differ significantly among groups when expressed per kilogram of body weight or per kilogram of FFM, we found a significantly lower BMR after adjustment, by ANCOVA, for FFM differences. The FFM compartment is composed of tissues and organs that differ profoundly in their metabolic activity. Elia (54) estimated that 40% of the body weight of a man is represented by muscle, which contributes only 22% of BMR, whereas visceral organs account for >60% of BMR. Organ mass has been shown to be inversely related to FFM (55); therefore, it is to be expected that BMR reflects this diversity of proportion (56). The relative proportion of the various components of FFM changes in relation to the intensity and duration of energy deprivation (57). In mild-to-moderate energy deficiency, muscle mass is more likely to be lower than normal than is nonmuscle or visceral mass, whereas in the more severe forms of energy deficiency, such as found in AN patients with low BMIs (<16), mobilization of tissues from visceral mass may dominate. Thus, it is possible that the lower FFM-adjusted BMR of the AN patients in the present study might reflect a prevalent loss of visceral tissue. Weight stability of AN patients is also an important variable in the study of energy metabolism. Although the subjects in the present study were weight stable at a low BMI (<17) ≥1 y before the study, the other studies did not find lower BMRs and did not report on the stability of their subjects.

AN patients were found to have plasma leptin concentrations that were 76% lower than those of control subjects. These results agree with the findings of other investigators (25, 26, 58), who found that AN patients of similar age and BMI had plasma leptin concentrations that were 70%, 77%, and 70% lower, respectively, than those of control subjects. Plasma leptin concentrations in the present study remained lower even when adjusted for fat mass, suggesting that leptin secretion might not depend entirely on the size of the fat mass. Both insulin and glucocorticoids have

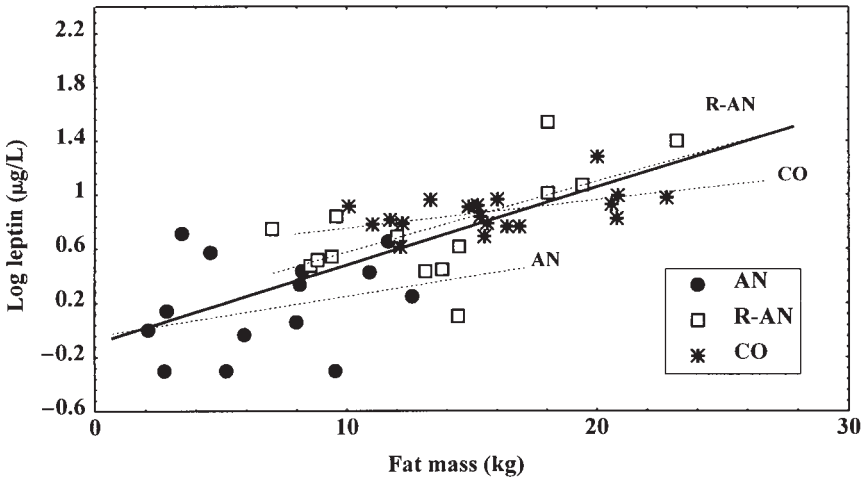

FIGURE 2. Relation between leptin and fat mass in patients with anorexia nervosa (AN), rehabilitated AN patients (R-AN), and control subjects (CO). The regression line for the whole group is shown as a solid line: the logarithm of leptin concentration is strongly correlated with fat mass ($r^2 = 0.53$, $P < 0.0000$).

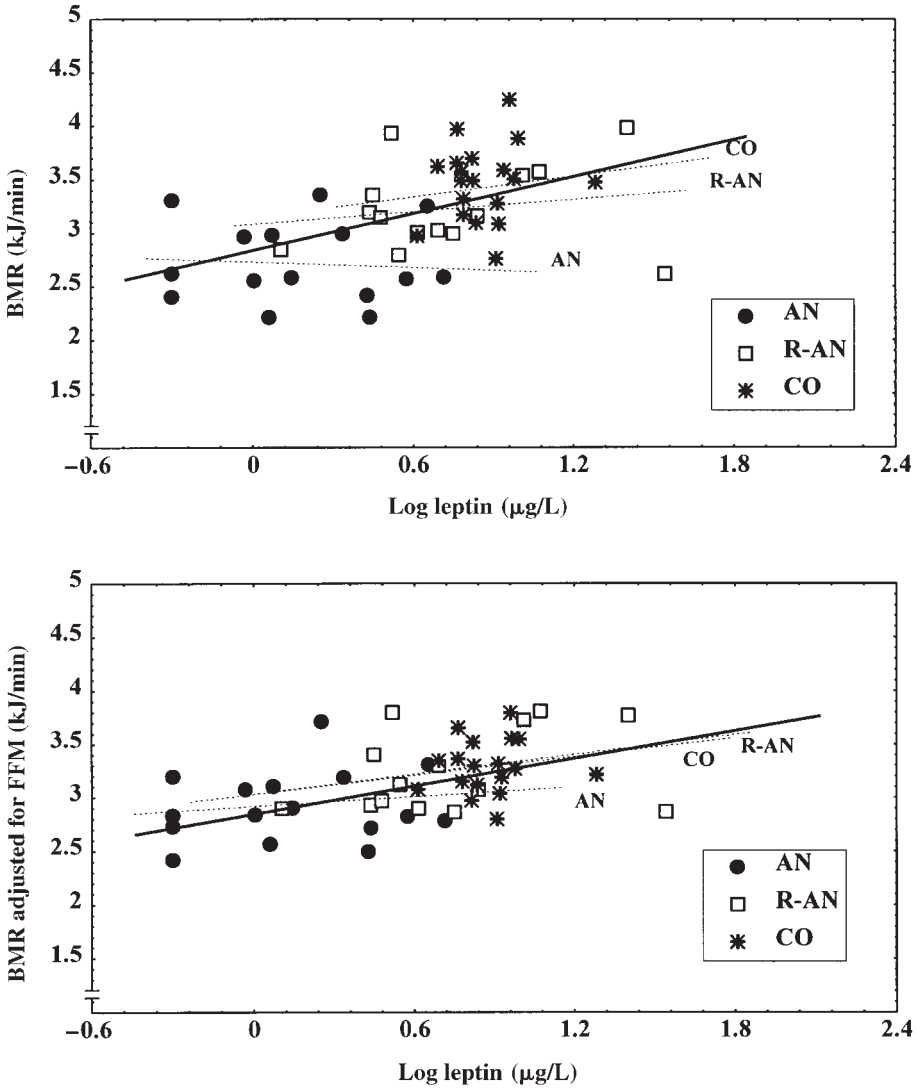

FIGURE 3. Relation between basal metabolic rate (BMR) and plasma leptin concentrations in patients with anorexia nervosa (AN), rehabilitated AN patients (R-AN), and control subjects. The regression line for the whole group is shown as a solid line: BMR is strongly correlated with the logarithm of leptin concentration as an absolute value (top: $r^2 = 0.28$, $P < 0.00006$) or adjusted for fat-free mass (FFM; bottom: $r^2 = 0.21$, $P < 0.0003$).

been proposed as having a stimulatory effect on the expression of the *ob* gene (59). In the subjects in the present study, leptin was positively correlated with BMR. To our knowledge, there are no reports in the literature on the relations between BMR and leptin in AN patients because most results were obtained in obese people. Moreover, conflicting results were obtained. In some of these studies, there was a positive relation between leptin and BMR (60, 61), others found a negative relation (30, 31), and others (32, 33) found no relation at all. In animal models, leptin appears to stimulate energy expenditure through mechanisms that may involve suppression of neuropeptide Y secretion and thus activation of the sympathetic nervous system (62).

TABLE 4
Stepwise regression analyses between basal metabolic rate (dependent variable) and fat-free mass (FFM) and leptin plasma concentration (independent variables)

Variable	R^2	Intercept	Slope	Standardized regression coefficient	Partial *r*	*P*
FFM (kg)	—	—	0.064	0.587	0.65	0.0000
Log leptin (μg/L)	—	—	0.3608	0.324	0.42	0.001
Total	0.58	0.5011	—	—	—	0.0000

Leptin is also known to determine changes in the expression of uncoupling proteins, which have been implicated in mitochondrial oxidative phosphorylation (63).

Rehabilitation is an important phase of AN because it is during this phase that the lost functions and tissues are restored to normal or near-normal conditions. Recovery appears to be influenced by several factors, such as age, duration of AN, and the refeeding protocol used. Ideally, the recovery process should be studied with a longitudinal design. Despite the cross-sectional nature of the present study, the findings show that the BMR and leptin concentrations of the subjects who had anthropometrically recovered for ≥1 y returned to near normal, suggesting full reversibility of the changes produced by AN. It is interesting to note that there was a high interindividual variability in leptin concentrations in the R-AN patients in our study; in some cases, these concentrations exceeded the concentrations of control subjects. The direct causes of this remain to be identified. As pointed out by other authors, large increases in leptin concentrations during weight restoration could be due to disproportionate accumulation of fat during this phase (64). Moreover, a disregulation of leptin after weight gain in patients with AN was supposed by Eckert et al (26) with the hypothesis that plasma leptin concentrations during nutritional rehabilitation could be related to neuroendocrine abnormalities during weight loss.

In conclusion, this study showed that there is a relation between BMR and leptin concentration, both of which are lower in AN patients than in healthy control subjects. The study also showed that the decrease in BMR observed in AN patients cannot be fully explained by a modification in the composition of FFM, a residual 30% being explained by plasma leptin concentrations. In animal models, mechanisms have been shown to exist (such as suppression of neuropeptite Y secretion and uncoupling mitochondrial oxidative phosporylation) that might be involved in the modulation of the relation between BMR and leptin in AN subjects.

REFERENCES

1. Casper RC. The pathophysiology of anorexia nervosa and bulimia nervosa. Annu Rev Nutr 1986;6:299–316.
2. Ljunggren H, Ikkos D, Luft R. Basal metabolism in women with obesity and anorexia nervosa. Br J Nutr 1961;15:21–33.
3. Melchior JC, Rigaud D, Rozen R, Malon D, Apfelbaum M. Energy expenditure economy induced by decrease in lean body mass in anorexia nervosa. Eur J Clin Nutr 1989;43:793–9.
4. Vaisman N, Rossi MF, Corey M, Clarke R, Goldberg E, Pencharz PB. Effect of refeeding on the energy metabolism of adolescent girls who have anorexia nervosa. Eur J Clin Nutr 1991;45:527–37.
5. Casper RC, Schoeller DA, Kushner R, Hnilicka J, Gold ST. Total daily energy expenditure and activity level in anorexia nervosa. Am J Clin Nutr 1991;53:1143–50.
6. Scalfi L, Di Biase G, Sapio C, Coltorti A, Contaldo F. Bioimpedance analysis and resting energy expenditure in undernourished and refed anorectic patients. Eur J Clin Nutr 1993;47:61–7.
7. Harris JA, Benedict FG. Biometric studies of basal metabolism in man. Washington, DC: Carnegie Institute of Washington, 1919. (Publication no. 297.)
8. Keys A, Brozek J, Henschel A, Taylor HL. The biology of human starvation. Minneapolis: University of Minnesota Press, 1950.
9. Grande F, Anderson JT, Keys A. Changes in metabolic rate in man in semistarvation and refeeding. J Appl Physiol 1958;12:230–8.
10. Soares MJ, Shetty PS. Basal metabolic rate and metabolic economy in chronic undernutrition. Eur J Clin Nutr 1991;45:363–73.
11. Piers LS, Shetty PS. Basal metabolic rates of Indian women. Eur J Clin Nutr 1993;47:586–91.
12. Ferro-Luzzi A, Petracchi C, Kuriyan R, Kurpad AV. Basal metabolism of weight-stable chronically undernourished men and women: lack of metabolic adaptation and ethnic differences. Am J Clin Nutr 1997;66:1086–93.
13. Garrow JS, Webster JD. Effects on weight and metabolic rate of obese women of a 3.4 MJ (800 kcal) diet. Lancet 1989;1:1429–31.
14. Heshka S, Yang MU, Wang J, Burt P, Pi-Sunyer FX. Weight loss and change in resting metabolic rate. Am J Clin Nutr 1990;52:981–6.
15. Kraemer WJ, Volek JS, Clark KL, et al. Physiological adaptations to a weight-loss dietary regimen and exercise programs in women. J Appl Physiol 1997;83:270–9.
16. Shetty PS. Adaptation to low energy intakes: the responses and limits to low intakes in infants, children and adults. Eur J Clin Nutr 1999;53:S14–33.
17. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homolog. Nature 1994;372:425–32.
18. Maffei M, Halaas J, Ravussin E, et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med 1995;11:1155–61.
19. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996;334:292–5.
20. Pelleymounter MA, Cullen MJ, Baker MB, et al. Effects of the obese gene product on body weight on body weight regulation in ob/ob mice. Science 1995;269:540–3.
21. Hwa JJ, Fawzu AB, Graziano MP, et al. Leptin increases energy expenditure and selectively promotes fat metabolism in ob/ob mice. Am J Physiol 1997;272:R1204–9.
22. Döring H, Schwarzer K, Nuesslein-Hildesheim B, Schmidt I. Leptin selectively increases energy expenditure of food-restricted lean mice. Int J Obes Relat Metab Disord 1998;22:83–8.
23. Clement K, Vaisse C, Lahlou N, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998;392:398–401.
24. Caro JF, Kolaczynski JW, Nyce MR, et al. Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. Lancet 1996;348:159–61.
25. Grinspoon S, Gulick T, Askari H, et al. Serum leptin levels in women with anorexia nervosa. J Clin Endocrinol Metab 1996;81:3861–3.
26. Eckert ED, Pomeroy C, Raymond N, Kohler PF, Thuras P, Browers CY. Leptin in anorexia nervosa. J Clin Endocrinol Metab 1998; 83:791–5.
27. Boden G, Chen X, Mozzoli M, Ryan I. Effect of fasting on serum leptin in normal human subjects. J Clin Endocrinol Metab 1996; 81:3419–23.
28. 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.
29. Ahima RS, Prabakaran D, Mantzoros C, et al. Role of leptin in the neuroendocrine response to fasting. Nature 1996;382:250–2.
30. Niskanen L, Haffner S, Karhunen LJ, Turpeinen AK, Miettinen H, Uusitupa MIJ. Serum leptin in relation to resting energy expenditure and fuel metabolism in obese subjects. Int J Obes Relat Metab Disord 1997;21:309–13.
31. Bobbioni-Harsch E, Assimacopoulos-Jeannet F, Lehman T, Münger R, Allaz AF, Golay A. Leptin plasma levels as a marker of sparing-energy mechanisms in obese women. Int J Obes Relat Metab Disord 1999;23:470–5.
32. Kennedy A, Gettys TW, Watson P, et al. The metabolic significance of leptin in humans: gender-based differences in relationship to adiposity, insulin sensitivity and energy expenditure. J Clin Endocrinol Metab 1997;82:1293–300.
33. Rosenbaum M, Nicolson M, Hirsch J, Murphy E, Chu F, Leibel R. Effects of weight change on plasma leptin concentrations and energy expenditure. J Clin Endocrinol Metab 1997;82:3647–54.

34. Soares MJ, Kulkarni RN, Piers LS, Vaz M, Shetty PS. Energy supplementation reverses changes in the basal metabolic rates of chronically undernourished individuals. Br J Nutr 1992;68:593–602.
35. Stordy BJ, Marks V, Kalucy RS, Crisp AH. Weight gain, thermic effect of glucose and resting metabolic rate during recovery from anorexia nervosa. Am J Clin Nutr 1977;30:138–46.
36. Vaisman N, Rossi MF, Goldberg E, Dibden LJ, Wykes LJ, Pencharz PB. Energy expenditure and body composition in patients with anorexia nervosa. J Pediatr 1988;113:919–24.
37. Krahn DD, Rock C, Deckert RE, Nairn KK, Hasse SA. Changes in resting energy expenditure and body composition in anorexia nervosa patients during refeeding. J Am Diet Assoc 1993;93: 434–8.
38. Platte P, Pirke KM, Trimborn P, Pietsch K, Krieg JC, Fichter MM. Resting metabolic rate and total energy expenditure in acute and weight recovered patients with anorexia nervosa and in healthy young women. Int J Eat Disord 1994;16:45–52.
39. Morgan JF, Bolton J, Sedgwick PM, Patel S, Lacey JH, Conway GS. Changes in plasma concentrations of leptin and body fat composition during weight restoration in anorexia nervosa. J Clin Endocrinol Metab 1999;84:2257 (letter).
40. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994.
41. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol 1949;109:1–9.
42. Fuller NJ, Jebb SA, Laskey MA, Coward WA, Elia M. Four-compartment model for the assessment of body composition in humans: comparison with alternative methods and evaluation of the density and hydration of fat-free mass. Clin Sci 1992;82:687–93.
43. Kushner RF, Schoeller DA, Fjeld CR, Danford L. Is the impedance index (ht^2/R) significant in predicting total body water? Am J Clin Nutr 1992;56:835–9.
44. Scalfi L, Bedogni G, Marra M, et al. The prediction of total body water from bioelectrical impedance in patients with anorexia nervosa. Br J Nutr 1997;78:357–65.
45. Heymsfield SB, Wang ZM, Withers R. Multicomponent molecular-level models of body composition analysis. In: Roche A, Heymsfield SB, Lohman T, eds. Human body composition. Champaign, IL: Human Kinetic Publishers, 1996:129–48.
46. Durnin JVGA, Rahaman MM. The assessment of the amount of fat in the human body from measurements of skinfold thickness. Br J Nutr 1967;21:681–9.
47. Rahn F, Fenn WO, Otis AB. Daily variations of vital capacity, residual air and expiratory reserve including a study of residual air method. J Appl Physiol 1949;1:725–36.
48. Deurenberg P. International consensus conference on impedance in body composition. Age Nutr 1994;5:142–5.
49. Fabbri A, Giannini D, Aversa A, et al. Body fat distribution and responsiveness of the pituitary-adrenal axis to corticotropin-releasing hormone stimulation in sedentary and exercising women. J Endocrinol Invest 1999;22:377–85.
50. Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Champaign, IL: Human Kinetics Books, 1988.
51. Isidori AM, Caprio M, Strollo F, et al. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. J Clin Endocrinol Metab 1999;84:3673–80.
52. Ravussin E, Bogardus C. Relationship of genetics, age and physical fitness to daily energy expenditure and fuel utilization. Am J Clin Nutr 1989;49:968–75.
53. Obarzanek E, Lesem MD, Jimerson DC. Resting metabolic rate of anorexia nervosa patients during weight gain. Am J Clin Nutr 1994; 60:666–75.
54. Elia M. Organ and tissue contribution to metabolic rate. In: Kinney JM, Tucker HN, eds. Energy metabolism. Tissue determinants and cellular corollaries. New York: Raven Press, 1992:61–72.
55. Garby L, Lammert O. An explanation for the non-linearity of the relation between energy expenditure and fat-free mass. Eur J Clin Nutr 1992;46:235–6.
56. Censi L, Toti E, Pastore G, Ferro-Luzzi A. The basal metabolic rate and energy cost of standardised walking of short and tall men. Eur J Clin Nutr 1998;52:441–6.
57. Barac-Nieto M, Spurr GB, Lotero H, Maksud MG. Body composition in chronic undernutrition. Am J Clin Nutr 1978;31:23–40.
58. Balligand JL, Brichard SM, Brichard V, Desager JP, Lambert M. Hypoleptinemia in patients with anorexia nervosa: loss of circadian rhythm and unresponsiveness to short-term refeeding. Eur J Endocrinol 1998;138:415–20.
59. Blum WF, Englaro P, Attanasio AM, Kiess W, Rascher W. Human and clinical perspectives on leptin. Proc Nutr Soc 1998;57:477–85.
60. Niklas BJ, Toth MJ, Poehlman ET. Daily energy expenditure is related to plasma leptin concentrations in older African-American women but not men. Diabetes 1997;46:1389–92.
61. Jorgensen JOL, Vahl N, Dall R, Christiansen JS. Resting metabolic rate in healthy adults: relation to growth hormone status and leptin levels. Metabolism 1998;47:1134–9.
62. Mistry AM, Swick AG, Romsos DR. Leptin rapidly lowers food intake and elevates metabolic rates in lean and ob/ob mice. J Nutr 1997;127:2065–72.
63. Porter RK, Andrews JF. Effects of leptin on mitochondrial “proton leak” and uncoupling proteins: implications for mammalian energy metabolism. Proc Nutr Soc 1998;57:455–60.
64. Mantzoros C, Flier JS, Lesem MD, Brewerton TD, Jimerson DC. Cerebrospinal fluid leptin in anorexia nervosa: correlation with nutritional status and potential role in resistance to weight gain. J Clin Endocrinol Metab 1997;82:1845–51.