Factors associated with the increase in resting energy expenditure during refeeding in malnourished anorexia nervosa patients

Virginie Van Wymelbeke, Laurent Brondel, Jean Marcel Brun, and Daniel Rigaud

ABSTRACT

Background: In malnourished anorexia nervosa (AN) patients, body-weight gain during refeeding is slowed by an increase in resting energy expenditure (REE).

Objective: The objective of the study was to identify factors associated with the increase in REE during refeeding.

Design: Before and 8, 30, and 45 d after the beginning of refeeding, REE was studied by indirect calorimetry in 87 female AN patients (x ± SD age: 23.4 ± 7.9 y; body mass index (in kg/m²) 13.2 ± 1.3). Energy intake, body composition (by bioelectrical impedance analysis), physical activity, smoking behavior, abdominal pain, anxiety, depressive mood, serum thyrotropin and thyroid hormone, and urinary catecholamines were measured. REE was also evaluated in 18 patients after 1 y of recovery.

Results: By day 8, REE increased from 3.84 ± 0.6 to 4.36 ± 0.59 MJ/d (P < 0.01). This increase (13.4%) was significantly (P < 0.01) greater than that expected on the basis of the increase in fat-free mass (FFM: 1.6%). Thereafter, the ratio of REE to FFM remained high, and, in multivariate analysis, was significantly related to 4 factors: energy intake (P < 0.01), anxiety (P < 0.01), abdominal pain (P < 0.05), and depressive mood (P < 0.05). The ratio also increased significantly with physical activity (P < 0.01) and cigarette smoking (P < 0.02). This rise in REE leveled off after recovery from AN.

Conclusion: In AN patients, the rise in REE observed during refeeding was independently linked to anxiety level, abdominal pain, physical activity, and cigarette smoking, and it contributed to resistance to weight gain. Am J Clin Nutr 2004;80:1469–77.

KEY WORDS Energy expenditure, anorexia nervosa, malnutrition, anxiety, mood, depression, metabolism

INTRODUCTION

Anorexia nervosa (AN) mostly affects women aged 15–35 y in Western societies. Because they severely restrict their food intake and engage in physical activity, AN patients are undernourished and maintain a very low weight with a negative energy balance. In treating AN patients, a major goal is to correct malnutrition by means of refeeding.

It has been shown that the energy requirement for body-weight gain is higher than would be expected on the basis of the cost of energy storage (1–3). Overexpenditure, proposed by Neumann et al (4) in 1902 as the reason for this discrepancy, has been described by numerous others in both normal-weight and overweight subjects: that is, a 20–50% increase in energy intake (EI)—that is, an increase above the energy balance—induced a 6–15% increase in 24-h energy needs (5–9) and a 5–27% increase in resting energy expenditure (REE) (10–14). In female AN patients, great differences between predicted and measured values of REE have been found (15, 16). Little is known about the changes that occur during refeeding, but it is possible that these changes contribute to the difficulty of weight gain among AN patients. Plate et al (17) found lower REE in AN patients on admission than after recovery. This “starved” REE was lower than that observed in healthy volunteers (18–21) or in bulimia nervosa patients (22). An increase in REE was described in AN patients during refeeding (18, 20, 22). This phenomenon was attributed to changes in body composition (13), because fat-free mass (FFM) plays a significant role in REE in humans (23–25).

In AN patients, whereas FFM increased, factors such as an increase in physical activity (2, 11) or in diet-induced thermogenesis (DIT; 12, 20) could be involved in the lack of weight gain. We found a large increase in DIT in AN patients after 1 wk of refeeding (12). Russell et al (20) found that AN patients had a higher basal respiratory quotient (RQ; which probably reflected net lipogenesis) and a lower REE before refeeding, as well as a paradoxically higher DIT after a 100-g oral glucose load, than did nonanorexic patients after feeding and control subjects.

An increase in physical activity with refeeding is expected in AN patients, who are known to initiate physical hyperactivity so as not to put on weight. In malnourished AN patients, little is known about the effect of psychological factors, such as mood changes (anxiety or depressive mood), on REE during refeeding. Moreover, energy metabolism can be severely altered by smoking, dieting, or exercising (26, 27). It has also been shown that eating-disorder patients are more anxious (28) and have greater deficits in emotional functioning (29) than do healthy subjects.

The aim of the study was to investigate in 87 malnourished AN patients the role of several factors, such as EI, physical activity,
smoking, and mood changes on variations in REE and on body composition, digestive symptoms, and thyroid hormone concentrations during refeeding and after recovery.

**SUBJECTS AND METHODS**

**Patients**

Eighty-seven malnourished AN patients were studied [age: 23.4 ± 7.9 y; body mass index (BMI; in kg/m²): 13.2 ± 1.3]. All were women and fulfilled the criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders, as described by Polito et al (19). These patients had the restrictive form of the disease [no vomiting (as determined by inquiries) and normal serum sodium, potassium, and amylase concentrations]. All patients had low EI and had lost ≥4 kg in the previous 3 mo. The noninclusion criteria were bulimia, binge eating, purging or vomiting, any medication known to modify REE, and inflammatory processes—ie, C-reactive protein concentration > 10 mg/L or sedimentation rate > 15 mm.

For purposes of comparison with the AN population, 48 healthy, nonanorexic women with the same characteristics (age: 24.8 ± 8.2 y; BMI: 21.4 ± 2.6) were recruited from medical students and medical staffs during the same period. None had eating disorders, and all had stable body weight. Their body composition was in the normal range [FFM: 82 ± 6%; fat mass (FM): 18 ± 4%].

**Experimental design**

The 87 female AN patients were hospitalized for tube feeding and renutrition for ≥2 mo. The following variables were measured ≥4 times during tube feeding: EI [oral food intake plus enteral nutrition (EN) mixtures], body weight and body composition, body temperature, REE, physical activity, mood, abdominal pain, cigarette smoking, nutritional status, serum TSH and thyroid hormones, and catecholamines in plasma. Each variable was measured before refeeding, on “spontaneous” oral intake while the patient remained in hospital, and after 8, 30, and 45 d of refeeding that consisted of EN and dietary advice to increase food intake. In addition, the same measurements were made in 52 patients after 75 days of refeeding and in 18 patients after 1 y of complete recovery. Recovery was defined as stable and normal BMI (>18.5), normal EI (>1.5 × REE), disappearance of fear of eating and of becoming fat, and normal eating behavior at the 1-y visit, without relapse in the previous 2 mo.

Mean daily EI was calculated during the 8 d before hospital admission and then during the whole period of refeeding. Oral food intake was assessed each day by a well-trained dietitian from records kept by the patient of meal and between-meal food items and from the difference between the portion presented and the remaining quantities. The reliability and coherence of dietary information were cross-checked through overlapping questions to the staff regarding the food that remained on the serving tray.

Nutritional data were computerized by using a compilation of food tables adapted to the foods purchased by the hospital (BIL.NUT-SCDA software, version 2002; Nutrisoft, Cerelles, France).

EN was given to each patient via a 9-gauge nasogastric tube. It consisted of Normoreal (Sodietal, St-Malo, France), which was composed of whole protein (15% total EI), polysaccharides (55%), triacylglycerols (30%; long-chain triacylglycerols provided 63% of that amount), minerals, vitamins, and trace elements. The diet had an energy content of 4.18 kJ/mL (1 kcal/mL) and an osmolarity of 250 mOsm/L. It was infused for 6–8 h/d (the tube was left in place around-the-clock for 7–8 wk, according to the weight gain). The volume remaining in each EN bottle was noted daily. To compare the data, total daily EI (oral intake plus EN) was expressed as a relative value, ie, the ratio of EI to the energy needs for weight maintenance, or 1.3 × REE.

Body weight and body temperature were noted every morning between 0730 and 0830 while the subjects were fasting and after bladder emptying. Fat mass (FM) was evaluated from skinfold-thickness measurements and bioelectrical impedance analysis (BIA). Measurements of skinfold thickness were made by using a metallic Harpenden caliper twice at 4 sites (biceps, triceps, subscapular, and suprailiac areas). Body density was calculated from the logarithm of the sum of the 4 site values, and then FM was estimated from density (30). BIA measurements made by using a portable two-frequency (50 kHz and 1 MHz) analyzer (IMP BO 1; l’Impulsion, Caen, France) had previously been validated in normal subjects by densitometry (31). FMF was calculated as the difference between body weight and FM. Because anthropometry seemed to underestimate FMF, whereas BIA overestimated FMF in malnourished patients, and because we observed a good correlation between FMF and the anthropometric and BIA data in the 87 AN patients (r = 0.926, P < 0.001), we expressed FMF as the mean of the results of the 2 methods.

The indirect calorimetry technique that we used has been reported previously (12, 32). Oxygen consumption (VO₂) and carbon dioxide production (VCO₂) were measured by using open-circuit indirect calorimetry with a ventilated-hood system (mean flow rate: 50 ± 5 L/min). Oxygen concentration was assessed by using a differential paramagnetic analyzer (Klogor, Lannion, France), and carbon dioxide concentration was measured by using an infrared analyzer (Hartmann and Braun Instruments, Frankfurt, Germany). Gas flow was measured with the use of a linear mass flow meter (Setaram, Lyon, France), and raw data were recorded online every 30 s. Gas exchanges were calculated as the product of gas flow and the differences between both oxygen and carbon dioxide concentrations in room air and expired gas [eg, gas flow × ([ApVO₂ in – [ApVO₂ out]), by using continuous monitoring of gases at the inlet and the outlet of the ventilated hood. Corrections were made for the effects of the RQ on gas flow measurements. Before each measurement, the system was calibrated with 21% oxygen and a mixture of 99% nitrogen and 1% carbon dioxide. The system was checked regularly by burning butane: the mean recovery of oxygen and carbon dioxide was 98 ± 1% and 99 ± 1%, respectively, and the RQ for butane was 0.614 ± 0.003. REE was calculated from VO₂, VCO₂, and daily urinary nitrogen output according to Ben Porat et al (33).

REE was assessed in a noiseless room at 22–24 °C between 0800 and 0930. The patients were asked to fast overnight for ≥12 h (EN stopped at 2000), to rest in bed, and to refrain from smoking. After a 30-min equilibration period on bed rest, REE was measured for 20–30 min while the subject remained in a bedrest position. Measured and estimated values of REE were expressed as kJ/d and kJ · kg FFM⁻¹ · d⁻¹, respectively. Estimated REE was obtained from actual weight by using the formula of Harris and Benedict (34).
Smoking data were given by the patient according to 4 classes: no smoking, 1–5 cigarettes/d, 6–10 cigarettes/d, and > 10 cigarettes/d. The patient’s level of physical activity during hospitalization was estimated by questionnaire and by interviewing the medical team and was categorized into the following 4 classes: low activity (< 1 h equivalent walking/d), normal activity (1.1–2 h/d), high activity (2.1–3 h/d), and very high activity (> 3 h walking/d, no sitting for meals or reading).

The patient’s depressive mood, anxiety, and abdominal pain (4 classes for each item on a simple analog scale) were arbitrarily assessed according to the patient’s answers to questions. With respect to depression and anxiety, the question was, “Are you depressed (anxious)?” This question was followed by another: “If the answer is yes, how depressed (anxious) have you felt in the last 3 d?” With respect to abdominal pain, the question was, “Have you had a stomach ache after the meal? If yes, what was the intensity of the pain?” There were 4 suggested answers: none, a little, high, and very high. A preliminary test was done in 14 AN patients to validate the questionnaire by testing the variance of their answers to the questions about physical activity, depressive mood, anxiety, and abdominal pain. The result was < 0.12 with good reproducibility.

These simple questions were preferred over more complicated questionnaires that were not validated for short periods of study. Moreover, the question on abdominal pain was chosen because we had observed in another group of AN patients that abdominal pain was related to anxiety (unpublished data). The scores for physical activity, smoking, depressive mood, anxiety, and abdominal pain in each patient were stable between day 8 and day 45.

Medicines that the patients took were noted. The doses of hypnotics, anxiolytics, and antidepressants were reduced as often as possible. Of the 87 patients, 15 took such medication.

The plasma concentrations of urea, sodium, potassium, creatinine, and protein were measured every week with the use of the Technicon SMA 6 (Technicon, Paris), as were serum TSH and thyroid hormones [free triiodothyronine (T3) and free thyroxine (T4)]. Urine was collected over a 3-d period every week for measurements of daily creatinine output (mean of the 3 days’ output), per reference 35. All values are expressed as percentage of normal values; 35) and also to evaluate 24-h urinary adrenalin and noradrenalin output by HPLC (36).

**Statistical analysis**

The EI value was the mean of the daily values of the week preceding the REE measurement. FM and FFM were the mean values obtained by anthropometric and BIA methods. To compare REE at different periods of refeeding, REE was also expressed as EI, BMI (kg/m²), and FFM (kg). FM and FFM were the mean values for each patient. To analyze the relation between physical activity, smoking, anxiety, and depressive mood or abdominal pain on the one hand and REE or REE:FFM on the other hand, we performed multiple linear regression analysis by including EI, physical activity, smoking, anxiety, depressive mood, body-weight change, thyroid hormones, and catecholamines in the model. A P value < 0.05 was considered significant. These analyses were performed using the MGLH module of SYSTAT software (version 8.0; SYSTAT Inc, Evanston, IL).

**RESULTS**

The clinical characteristics of the female AN patients are summarized in Table 1. Before refeeding, the patient’s mean body weight tended to decrease (−0.24 ± 0.17 kg within the first 3–4 d), and the mean body temperature (36.6 ± 0.2 °C) and oral intake (3.440 ± 1.233 MJ/d) remained low. Oral intake was near that of the last week at home (3.285 ± 1.342 MJ/d). The mean REE:FFM in AN patients tended to be lower (118 ± 13), albeit not significantly, than that in the 48 normal women of the same age who were used as a control group (131 ± 15 kJ · kg FFM⁻¹ · d⁻¹).

**Effect of refeeding**

After 1 wk of refeeding (ie, on day 8), body temperature increased significantly (Table 2, P < 0.05), and total EI (oral intake plus EN) reached a mean of 2.5 times the initial intake (Table 3, P < 0.001). There was a significant (P < 0.001) change in body weight (+3.28 ± 2.1%) and FM (+6.5 ± 5.6%) but not in FFM (+3.1 ± 3.4%) and creatinine index (−1.8 ± 3.5%) (Table 2). At that time, the mean REE:FFM had increased significantly (11.7%; P < 0.001; Table 3). Such an increase in REE:FFM was noted in 78 of the 87 patients.

After 30 and 45 d of tube feeding, as compared with values obtained on day 8, total EI increased significantly (P < 0.001), reaching 3 times the spontaneous initial diet (Table 3). Body temperature remained significantly higher than that before refeeding (Table 2). Body weight, FFM, FM, and creatinine were all significantly (P < 0.001) higher than initial values (Table 2). During the same period, REE:FFM remained significantly higher than the initial value (Table 3, P < 0.001) but did not rise beyond the day 8 value.

When compared with the theoretical REE value expected on the basis of FFM, the mean REE was significantly higher after 1 wk of refeeding than before refeeding (P < 0.01; Table 3). The coefficient and the slope of the regression lines between REE and FFM changed significantly (P < 0.02) with refeeding: before refeeding, the REE was −37 + (121 × FFM) kJ, and on days 7, 9, and 11, the REE was 70 + (105 × FFM) kJ.

**TABLE 1**

Clinical characteristics and nutritional status of 87 malnourished female anorexia nervosa patients before refeeding

<table>
<thead>
<tr>
<th>Value</th>
<th>Average ± SD Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>23.4 ± 7.9 (16–47)</td>
</tr>
<tr>
<td>Duration of the disease (y)</td>
<td>4.1 ± 3.4 (0.7–29)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.0 ± 7.4 (148–178)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>35.8 ± 5.1 (27.9–47.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>13.2 ± 1.3 (10.2–15.4)</td>
</tr>
<tr>
<td>Weight loss (kg)</td>
<td>23.5 ± 3.9 (18.3–31.2)</td>
</tr>
<tr>
<td>Creatinine index (% of normal)²</td>
<td>62.4 ± 13.8 (37–91)</td>
</tr>
<tr>
<td>Intake before admission (KJ/d)³</td>
<td>3285 ± 1342 (1783–4615)</td>
</tr>
</tbody>
</table>

¹ All values are x ± SD; range in parentheses.
² Daily urinary creatinine output (mean of 3 days’ output), per reference 35.
³ Alimentary intake according to dietary recall (mean of 7 days’ intake).
Factors associated with increased resting energy expenditure

Multivariate analysis

In a model including body weight, time, body-weight change, EI, physical activity level, smoking, anxiety, depressive mood, free T3, free T4, TSH, and urinary adrenaline and noradrenaline, only 4 factors—EI (P < 0.01), anxiety (P = 0.01), depressive mood (P < 0.05), and abdominal pain (P < 0.05)—were significantly associated with REE:FFM. A significant association was found between anxiety and abdominal pain and between anxiety and physical activity level (both: P < 0.05).

Univariate analyses

The mean REE:FFM in 4 classes of total EI (oral intake plus EN) is shown in Figure 1, classified according to the energy requirement for weight maintenance. The lowest class (1.3 × REE) corresponded to intakes lower than those required to maintain weight. As shown, REE:FFM was significantly (P < 0.0001) related to total EI. This relation was observed throughout the study (P < 0.001, < 0.01, < 0.003, and < 0.01 on days 8, 30, 45, and 75, respectively). During the study period (75 d), an increase or a decrease in EI was associated with a similar trend of evolution in REE:FFM (P < 0.0001). For example, an increase in mean EI over that in the preceding period was associated with a significant (88%; P < 0.01) increase in REE:FFM in 77 of 87 patients. During refeeding, the weekly total EI fell below a value equal to 1.3 × REE on 19 occasions in 14 patients; their mean REE:FFM decreased to 120 ± 11 kJ · kg FFM⁻¹ · d⁻¹. This value is not significantly different from the value before refeeding (119 ± 14 kJ · kg FFM⁻¹ · d⁻¹) but is significantly (P < 0.001) lower than that observed in the same patients when their intake was >1.8 × REE (142 ± 9 kJ · kg FFM⁻¹ · d⁻¹). After verification for differences in BMI, FFM, and creatinine index in an ANCOVA, the relation between changes in REE:FFM and those in EI remained significant (P < 0.01).

TABLE 2
Body weight and body composition in the 87 female anorexia nervosa patients before and during refeeding

<table>
<thead>
<tr>
<th></th>
<th>Before refeeding</th>
<th>Day 8</th>
<th>Day 30</th>
<th>Day 45</th>
<th>Day 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature (°C)</td>
<td>36.6 ± 0.2</td>
<td>37.2 ± 0.3</td>
<td>37.4 ± 0.2</td>
<td>37.3 ± 0.3</td>
<td>37.2 ± 0.3</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>35.8 ± 5.1</td>
<td>37.0 ± 5.2</td>
<td>40.2 ± 4.9</td>
<td>41.6 ± 4.9</td>
<td>45.4 ± 4.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>13.3 ± 0.9</td>
<td>13.7 ± 0.9</td>
<td>14.9 ± 0.9</td>
<td>15.5 ± 0.9</td>
<td>16.9 ± 1.1</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>32.3 ± 3.8</td>
<td>33.2 ± 4.0</td>
<td>34.8 ± 3.6</td>
<td>35.6 ± 3.7</td>
<td>37.2 ± 3.5</td>
</tr>
<tr>
<td>FFM (% of BW)</td>
<td>90.5 ± 3.9</td>
<td>88.7 ± 3.8</td>
<td>86.8 ± 4.2</td>
<td>85.6 ± 3.8</td>
<td>83.1 ± 3.3</td>
</tr>
<tr>
<td>FM (kg)</td>
<td>3.5 ± 1.8</td>
<td>3.8 ± 1.7</td>
<td>5.4 ± 2.1</td>
<td>6.1 ± 2.0</td>
<td>7.7 ± 1.8</td>
</tr>
<tr>
<td>FM (% of BW)</td>
<td>9.5 ± 3.9</td>
<td>11.3 ± 3.8</td>
<td>13.2 ± 4.2</td>
<td>14.4 ± 3.8</td>
<td>16.9 ± 3.5</td>
</tr>
<tr>
<td>Creatinine index (%)</td>
<td>62.4 ± 13.8</td>
<td>61.4 ± 14</td>
<td>77.0 ± 15.7</td>
<td>84.9 ± 17.1</td>
<td>89.4 ± 15.3</td>
</tr>
</tbody>
</table>

1 All values are ± SD. FFM, fat-free mass; FM, fat mass; BW, body weight. Means in a row with different superscript letters are significantly different, P < 0.001 (creatinine index, P < 0.01) (ANOVA, followed by Student’s t test with adjustment for multiple comparisons).

2 Daily urinary creatinine output (24-h collection) from 3 d surrounding measurements of resting energy expenditure. Values are expressed as percentages of the normal value.

30, and 45, it was 659 + (50.6 × FFM), 743 + (50.1 × FFM), and 642 + (66.9 × FFM) kJ, respectively.

Significant correlations were observed between the REE and both FFM and creatinine index (r = 0.692 and r = 0.718, respectively; P < 0.001). After 75 d of refeeding, the mean REE:FFM did not differ significantly from that on day 45, but it was significantly higher than that obtained on day 8 (Table 3).

The nonprotein RQ increased slowly during the period of refeeding (Table 3) until day 30, and then it decreased. The value on day 30 was significantly (P < 0.05) higher than the value before refeeding.

TABLE 3
Mean daily energy inputs and resting energy expenditure (REE) in 87 malnourished female anorexia nervosa patients before and during refeeding

<table>
<thead>
<tr>
<th></th>
<th>Before refeeding</th>
<th>Day 8</th>
<th>Day 30</th>
<th>Day 45</th>
<th>Day 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy input²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tube feeding</td>
<td>0</td>
<td>5.597 ± 1.885</td>
<td>5.785 ± 1.250</td>
<td>2.774 ± 2.691</td>
<td>2.471 ± 1.124</td>
</tr>
<tr>
<td>Oral intake</td>
<td>3.440 ± 1.233a</td>
<td>3.010 ± 1.663a</td>
<td>4.819 ± 1.572a</td>
<td>7.745 ± 2.575a</td>
<td>8.458 ± 1.315a</td>
</tr>
<tr>
<td>Energy expenditure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REE</td>
<td>3.844 ± 0.670a</td>
<td>4.359 ± 0.541b</td>
<td>4.831 ± 0.517b</td>
<td>5.056 ± 0.539</td>
<td>5.484 ± 0.491</td>
</tr>
<tr>
<td>REE (% above day 0)</td>
<td>13.6 ± 3.3</td>
<td>25.2 ± 3.7</td>
<td>31.8 ± 6.2</td>
<td>42.7 ± 8.6</td>
<td></td>
</tr>
<tr>
<td>RQ</td>
<td>0.78 ± 0.03</td>
<td>0.84 ± 0.04</td>
<td>0.88 ± 0.07</td>
<td>0.85 ± 0.06</td>
<td>0.81 ± 0.05</td>
</tr>
<tr>
<td>REE:FFM</td>
<td>118 ± 13</td>
<td>131.8 ± 11b</td>
<td>135.7 ± 12b</td>
<td>138.6 ± 14b</td>
<td>147.8 ± 28a</td>
</tr>
<tr>
<td>(% above day 0)</td>
<td>—</td>
<td>11.7 ± 3.0</td>
<td>15.1 ± 3.6</td>
<td>16.8 ± 3.8</td>
<td>24.9 ± 4.5</td>
</tr>
<tr>
<td>(% above day 8)</td>
<td>—</td>
<td>3.1 ± 3.6</td>
<td>4.9 ± 5.2</td>
<td>10.6 ± 6.5</td>
<td></td>
</tr>
</tbody>
</table>

1 All values are ± SD. RQ, respiratory quotient; FFM, fat-free mass. Means in a row with different superscript letters are significantly different, P < 0.001 (REE and REE:FFM at day 8, P < 0.05) (ANOVA, followed by Student’s t test with adjustment for multiple comparisons).

2 Values of energy inputs are the mean of the daily values of the week preceding REE measurements.
Cigarette smoking correlated positively with REE:FFM ($P < 0.02$): the values in the subjects smoking 6–10 cigarettes/d and $>10$ cigarettes/d were 21% and 17%, respectively, higher than those who did not smoke ($P < 0.05$ for both; Figure 2). Physical activity also correlated positively with REE:FFM ($P < 0.01$). As shown in Figure 3, the mean REE:FFM was $133 \pm 10$ kJ · kg FFM$^{-1}$ · d$^{-1}$ for the 2 classes with $\leq 1$ h and $1–2$ h activity/d and $147 \pm 12$ kJ · kg FFM$^{-1}$ · d$^{-1}$ for the 2 classes with $2.1–3.0$ h and $>3$ h activity, when pooled ($P < 0.02$).

In ANCOVA, anxiety levels correlated positively with REE:FFM ($P < 0.01$; Figure 4); there was a 31% increase between the classes with no anxiety or a little anxiety and the class with very high anxiety ($P = 0.001$). The level of depressive mood correlated negatively with the increase in REE:FFM: the REE:FFM was 15% lower in the subjects with very high depressive mood than in the subjects with no depressive mood ($P < 0.02$; Figure 5). Because 15 of the 87 patients took anxiolytic and antidepressant drugs, we analyzed the effect of this variable. When entered into the model, medication significantly amplified the effect of depressive mood or anxiety on REE:FFM ($P < 0.001$). Abdominal pain correlated positively with the increase in REE:FFM: REE:FFM was 26% higher in the pooled classes of subjects ($n = 22$) with high and very high anxiety ($163 \pm 17$ kJ · kg FFM$^{-1}$ · d$^{-1}$; $P < 0.01$) than in the pooled classes of subjects ($n = 65$) with no anxiety and a little anxiety ($129 \pm 13$ kJ · kg FFM$^{-1}$ · d$^{-1}$).

Other factors

Before refeeding, the free T3 concentration was low in 78 of 87 AN patients (89% of the cases)—the mean value was $3.2 \pm 0.6$ pmol/L, and the normal value was $>4$ pmol/L—whereas free T4 ($11 \pm 2.3$ pmol/L) and TSH ($1.8 \pm 0.9$ mU/L) were within the normal range ($8.5–18$ pmol/L and $0.25–3.5$ mU/L, respectively). At day 8, the free T3 concentration had increased to a mean low value of $3.6 \pm 0.4$ pmol/L ($P < 0.05$), and, after 45 days, it was normal ($5.1 \pm 0.9$ pmol/L; $P < 0.05$ compared with day 8 value). No correlation was found between REE:FFM or REE:FFM changes and concentrations of free T3, free T4, and TSH by using ANCOVA with repeated measures over time.

**FIGURE 1.** Relation between total energy intake and the ratio of resting energy expenditure to fat-free mass (REE:FFM) in 87 malnourished anorexia nervosa patients. Sample, number of determinations in each class of energy intake; E-REE, estimated REE. Total REE measurements on days 8, 30, 45, and 75 were $n = 84, 86, 83$, and 52, respectively. Error bars indicate SDs; bars with different letters are significantly different, $P < 0.001$ (analysis of covariance followed by Student’s $t$ test with adjustment for multiple comparisons).

**FIGURE 2.** Effect of smoking behavior on the ratio of resting energy expenditure to fat-free mass (REE:FFM) in 87 malnourished anorexia nervosa patients on day 30. Error bars indicate SDs; bars with different letters are significantly different, $P < 0.05$ (analysis of covariance followed by Student’s $t$ test with adjustment for multiple comparisons). $n =$ number of patients in each smoking category.

**FIGURE 3.** Relation between total energy intake and the ratio of resting energy expenditure to fat-free mass (REE:FFM) in 87 malnourished anorexia nervosa patients. Sample, number of determinations in each class of energy intake; E-REE, estimated REE. Total REE measurements on days 8, 30, 45, and 75 were $n = 84, 86, 83$, and 52, respectively. Error bars indicate SDs; bars with different letters are significantly different, $P < 0.001$ (analysis of covariance followed by Student’s $t$ test with adjustment for multiple comparisons).
Urinary adrenalin and noradrenalin did not fluctuate significantly over time: the adrenalin concentration was 11.74 ± 6.45 μg/d before refeeding and 7.26 ± 7.03 μg/d after refeeding for 45 d, and the noradrenalin concentration was 58.7 ± 23 μg/d before and 64.2 ± 42.9 μg/d after refeeding for 45 d. These fluctuations did not correlate with either REE or REE:FFM (r = 0.12 and = 0.18, respectively).

Recovery

From the present cohort, 18 patients fulfilled the recovery criteria at the 1-y visit. BMI was 20.3 ± 1.6 (2) and consisted of 18% FM. Oral EI was 8.99 ± 1.45 MJ/d. Mean FFM-adjusted REE values were close to expected values according to the FFM of healthy subjects: 101 ± 8%. The REE:FFM (134 ± 16 kJ · kg FFM⁻¹ · d⁻¹) did not differ significantly from that obtained in the healthy age-matched women (131 ± 15 kJ · kg FFM⁻¹ · d⁻¹). A significant decrease in physical activity, anxiety, depressive mood, and abdominal pain was noted. There was no longer a relation between these factors and the REE:FFM. By contrast, a poor outcome was observed in 15 patients: loss of 7.2 ± 2.6 kg and BMI 15.5 ± 1.8 (FM: 12%). Their oral intake (no more tube feeding) was 5.93 ± 2.17 MJ/d. Their mean anxiety levels were high: 2.3 ± 0.5 (minimum: 0; maximum: 3). Their REE:FFM was significantly (P < 0.05) higher (148 ± 16 kJ · kg FFM⁻¹ · d⁻¹) than that expected according to their EI (123 ± 10 kJ · kg FFM⁻¹ · d⁻¹).

DISCUSSION

The present study showed that refeeding induced an increased in REE in malnourished AN patients. This increase remained significantly higher than baseline when FFM was taken into account (REE:FFM, or FFM-adjusted REE). It was related to the categories of smoking, physical activity, anxiety, depressive mood, and abdominal pain and to the previous week’s EI above energy need.

Before refeeding, the mean REE in our AN patients was low and not different from that observed by others (11, 37–40). The mean REE:FFM was near the lower limit of the normal values we found in healthy women.

An increase in REE during refeeding was also found by others (12, 13). It was explained in part by the rise in FFM and in muscle

![FIGURE 3](https://academic.oup.com/ajcn/article-abstract/80/6/1469/4690465/FIGURE_3.jpg)

**FIGURE 3.** Effect of physical activity on the ratio of resting energy expenditure to fat-free mass (REE:FFM) in 87 malnourished anorexia nervosa patients on day 30. Error bars indicate SDs; bars with different letters are significantly different, P < 0.01 (analysis of covariance followed by Student’s t test with adjustment for multiple comparisons). n = number of patients in each physical activity group.

![FIGURE 4](https://academic.oup.com/ajcn/article-abstract/80/6/1469/4690465/FIGURE_4.jpg)

**FIGURE 4.** Relation between anxiety and the ratio of resting energy expenditure to fat-free mass (REE:FFM) in 87 malnourished anorexia nervosa patients on day 30. Error bars indicate SDs; bars with different letters are significantly different, P < 0.01 (analysis of covariance followed by Student’s t test with adjustment for multiple comparisons). n = number of patients at each level of anxiety.
mass. The correlation between REE and FFM in the patients in the current study was close to that we observed in other AN patients (12, 13), in healthy normal-weight female subjects, and in obese patients ($r = 0.65; 5, 6, 8, 10, 14$). For 82% of the current patients, the variance in REE was explained by the FFM, which is in agreement with the literature (32, 41).

However, the rise in REE that we observed at the beginning of refeeding could not be explained by FFM. In fact, there was no increase in either FFM or muscle mass. Furthermore, the 1-wk increase in REE represented 31% of the total REE increase during the 2.5 mo of refeeding. These data suggest that, during overfeeding, the metabolic rate of FFM cells increases within a few days. This change may reflect different contributions of the different lean body masses to REE: for example, at rest, 100 g liver consumes 20 times as much oxygen as does 100 g muscle. Thus an increase of 100 g active liver mass could explain a 125 kJ/d rise in REE with no measurable change in FFM.

However, this phenomenon could explain neither the mean 515 kJ/d increase in REE nor the $14 \text{kJ} \cdot \text{kgFMM}^{-1} \cdot \text{d}^{-1}$ increase in REE:FFM from baseline. The present study shows that 6 factors besides a more active liver mass could explain this increase during refeeding. The first of these factors was the total EI of the previous days, and there are 3 ways in which this factor could have affected the increase in REE:FFM. First, the 13.4% rise in REE:FFM observed after 1 wk of refeeding was related only to the EI ($P < 0.001$); second, changes in REE:FFM paralleled the level of EI, independently of time, body weight, creatinine index, and duration of refeeding; and third, any time that EI fell below the total needed for weight maintenance, REE:FFM decreased to prerefeeding values. Vaisman et al (38) showed an 18% higher REE:FFM during refeeding, as compared with admission values.

The second factor linked to the increase in REE:FFM is anxiety, which could be due to the patient’s fear of gaining weight. This mechanism seems to be maintained throughout the period of refeeding, as clearly suggested by the positive correlation that was found between anxiety level and REE:FFM in patients who had a poor outcome after discharge. Unfortunately, we did not find any correlation between adrenalin and noradrenalin concentrations and either anxiety or REE:FFM.

A third factor, the depressive state, may contribute to lower REE. Unfortunately, the effects of anxiety and depression on EE could not be precisely evaluated from our study because our scales were not exact enough. Further studies are needed.

The levels of physical activity and abdominal pain are another 2 of these potential factors. They could partly reflect the anxiety of such patients with respect to weight gain. Indeed, physical hyperactivity, frequent in AN patients, is one of the means by which these persons try lose weight. Such hyperactivity could induce an increase in muscle mass and thus could explain the increase in REE. Abdominal pain could also reflect the anxiety of the patients. We were unable to find any data in the literature to confirm or refute this or to suggest that abdominal pain could be correlated with REE. With respect to the data on physical activity, anxiety, depressive mood, and abdominal pain, we are aware that our analogic scales could appear to be very simple. But the results were logical and confirmed to the fact that anxiety increases EE in mice (43) and increases resting metabolic rate in men (44). Further studies are needed to confirm these observations.

Finally, there was also an interaction between REE:FFM and smoking status, such that nonsmokers and light smokers tended to have an REE:FFM 14% lower than that in the other 2 groups, who were heavier smokers. This could be a direct effect of smoking on REE or an indirect effect of a relation between smoking and activity levels or smoking and anxiety (45).

The biochemical mechanisms responsible for the increase in REE:FFM have not been elucidated so far. As was suggested by Casper et al (11), this rise does not seem to be linked to the increase in thyroid hormone concentrations in the blood. An increase in catecholamine secretion during refeeding could also be suspected (46, 47). It has been shown that sympathetic activity is reduced with undereating (48) and is increased with overeating in normal-weight subjects (49). Unfortunately, Johnston et al (47) observed low excretion of urinary norepinephrine metabolites in AN patients despite high EIs. Our results did not reinforce the idea that neither adrenalin nor noradrenalin contributes to the increase in REE. Among other possible mechanisms, a relation between REE and circulating leptin concentrations was examined during short-term (50) or long-term (21, 51) refeeding in AN patients; the authors of these reports concluded that leptin was unlikely to be responsible for the change in REE. However, Polito et al (19) found a positive relation between leptin and REE.
The biphasic evolution of the RQ is not easy to interpret. Initially, the RQ in AN patients was higher than that observed in normal, stable-weight subjects (ie, 0.72). This could be explained by the lack of lipid stores and the elevated amount of protein oxidation. During refeeding, the RQ in the AN patients increased, which suggests a shift to carbohydrate and protein oxidation related to the high concentration of protein (>2.5 g · kg⁻¹ · d⁻¹) and carbohydrate intakes. Thereafter, the RQ decline could be due to a relative increase in lipid oxidation.

In conclusion, the present study showed the role of factors such as anxiety, smoking, and activity level in the RQ increase. These factors could explain the resistance to overfeeding and weight gain in malnourished AN patients. Assuming a total daily EE of 1.4× RQ in such hospitalized patients (ie, 6500 kJ in 45 d), we estimated a daily EE cost of 29–30 kJ (ie, 7.0 kcal/d) for each gram of body-weight gain. This value is close to that found in AN patients by Walker et al (52)—ie, 6.4 kcal/g—but different from that obtained in healthy men and women by Forbes et al (49)—ie, 5.34 kcal/g. We suggest giving such patients, during their hospital stay, ~1.4× RQ plus 30 kJ/g so that they can achieve wanted body-weight gain. According to our results, a body-weight gain of 150 g/d requires the intake of not only the assumed 6500 kJ but also a further 4500 kJ (ie, 11 000 kJ, or 2630 kcal/d), or 300 kJ (ie, 75 kcal/kg body weight/d). One can understand why it is so difficult in such conditions to obtain a weight gain of >1 kg/wk. And thus, it is often unfair to accuse most of these AN patients of discarding their food when they do not gain body weight.

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