Increase in diet-induced thermogenesis at the start of refeeding in severely malnourished anorexia nervosa patients 

Maryam Moukaddem, Alain Boulanger, Marian Apfelbaum, and Daniel Rigaud

ABSTRACT Many reports describe the difficulty for anorexia nervosa patients to gain weight during refeeding. To assess whether an increase in diet-induced thermogenesis (DIT) participates to this resistance, we studied DIT by indirect calorimetry in 11 severely malnourished anorexia nervosa patients [body mass index (BMI; in kg/m²) = 13] to accomplish two purposes: 1) to compare DIT in a strict semistarvation state with that obtained after 1 wk refeeding, when metabolism is shifted to a dynamic trend toward regaining weight, without significant change in body composition; 2) to study the effect on DIT of two energetic loads representing each one-third of the energy intake during semistarvation and refeeding, respectively: 1.25 and 2.92 MJ. To avoid bias, the two liquid loads were infused intragastrically in a random double-blind fashion. A significant increase in DIT during refeeding was observed for the two loads (204 ± 23 kJ for the 1.25-MJ liquid meal and 482 ± 78 kJ for the 2.92-MJ one, P < 0.02). The higher the load, the larger the increase with refeeding (P < 0.001). This increment in DIT exceeded the increase in active lean body mass and was poorly correlated with lean body mass. These results provide clear evidence of a strong cellular "waste" mechanism in anorexia nervosa patients during the early phase of refeeding, which enhances the adaptative resistance to overfeeding that we have already shown for resting energy expenditure. Am J Clin Nutr 1997;66:133–40.

KEY WORDS Energy expenditure, anorexia nervosa, starvation, malnutrition, diet-induced thermogenesis, lean body mass, refeeding

INTRODUCTION

Anorexia nervosa is an eating disorder that affects as many as 1% of adolescent and young adult females in the Western world. It is a condition in which a severe voluntary restriction of food results in major weight loss and several physical and psychologic stigmata (1–3). Previous studies of anorexia nervosa patients have shown that this weight loss is related to a great reduction in lean body mass (LBM) leading to severe malnutrition.

A consistently reported finding in these patients is their ease at maintaining low body weight, and the fact that they apparently require high energy intakes to gain weight (4–8). For instance, Dempsey et al (5) and Walker et al (6) observed that energy requirements necessary to promote weight gain in anorexia nervosa patients were more important in the first 15 d of treatment (32.6 kJ/g body wt gain) than during the subsequent 20 d (23 kJ/g). Indeed, most of the published studies reported energy intake as high as 13–15 MJ/d for a body weight gain varying from 150 to 250 g/d. On the other hand, even to stabilize the target weight achieved by these patients, some investigators reported a 40% increase in their energy needs compared with control subjects. Contrasting with these observations, the resting energy expenditure (REE) has been reported to be lower than expected in semistarved anorexia nervosa patients (4, 5, 9), so that weight gain should have been relatively easy.

To explain increased metabolic needs during the refeeding process in anorexia nervosa patients, one can hypothesize an increase in energy expenditure resulting in a "waste" phenomenon. Many studies have investigated changes in REE during refeeding compared with the semistarved state (5, 10–13). Recent studies (13, 14) reported an 8–10% increase in REE in the early phase of refeeding and a 25–30% increase in REE with high energy input during a later phase of renutrition. However, these increments could not completely explain the high energy requirement necessary for substantial gain in body weight and LBM.

Increased metabolic needs could therefore be related to an increase in diet-induced thermogenesis (DIT). Although studies were flourishing on the DIT of control and obese subjects, there is only a scarce amount of data available on DIT in anorexia nervosa patients and only one complete report on the change in DIT during refeeding (20). The main reason is the difficulty in handling these psychologically fragile patients under strict protocol conditions. Furthermore, the results of these few studies on DIT in anorexia nervosa patients are contradictory (11, 15–21). Some of these reports did not show any impairment of DIT (11), whereas others described a higher thermic response to either glucose or a mixed meal compared with control subjects (21). These conflicting results may be partly due to differences in the nutritional status of the patients.

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The major purpose of this study was to determine whether DIT increases in severely malnourished anorexia nervosa patients soon after the start of the refeeding process and whether this could account for their difficulty in even maintaining body weight during the early phase of the renutrition program. For this purpose, we studied the DIT of severely malnourished anorexia nervosa patients in response to two energy loads at two well-defined periods so as to provide two very homogenous conditions: 1) a strict semistarvation state, by including only restrictive anorexia nervosa patients losing body weight just before the study; and 2) the beginning of the refeeding program (day 7–8) with strictly controlled energy input. Two liquid meals were selected to represent one-third of the energy intake of the patients during the semistarvation state and during the beginning of refeeding, respectively: 1.25 and 2.92 MJ. To avoid any fear of energy intake, these loads were infused intragastrically in random order and in a double-blind fashion.

Another aim was to see whether such a change in DIT was only a predictable result of the increase in LBM or could be related to an early appearance of a “waste” phenomenon. The question is important to improve the nutritional program of anorexia nervosa patients and to search for the underlying biochemical mechanisms involved in pathologic leanness.

SUBJECTS AND METHODS

Subjects

Twelve anorexic patients were selected according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, diagnosis for anorexia nervosa (22) and to the following criteria: 1) On admission to the hospital, all patients were still dieting, ingesting <4000 kJ/d, and had severe clinical signs of malnutrition. The length of dieting before hospitalization was ≥ 8 mo. 2) All patients claimed to have recently reduced or even ceased their physical activities because of weakness. 3) None of the patients had symptoms of binge eating, purging, or induced vomiting. 4) There was no lifetime history of major depression and none of them had been taking psychopharmacologic drugs or hormones before our study. Moreover, all patients had been amenorrheic for 6 mo to 6 y. Their ages ranged from 15 to 32 y and the mean duration of their illness ranged from 8 mo to 7 y (median: 2.8 y).

Exclusion criteria were regular vomiting or bulimia, a past history of endocrinopathies, chronic organic diseases, or drug or alcohol addiction. A major exclusion criterion was any start of refeeding or any body weight gain in the past week. One patient was excluded for this reason.

The research protocol was duly explained to the subjects who gave informed consent. Study procedures were approved by the Bichat Hospital Ethical Committee.

Experimental protocol design

The protocol is divided into two distinct phases.

Period 1: Denutrition phase

The study started soon after hospital admission (within 3 d) so that REE and DIT could be measured in a strict semistarvation state. Before refeeding, the patients were not asked to increase their food intake so as to keep them on the same nutritional baseline. Moreover, they were familiarized with the calorimetry equipment, which happened to be on the same hospital floor as their bedrooms; therefore, the stress-dependent energy expenditure due to transport or environmental influences was strongly minimized.

Nasogastric tubes were indicated for enteral feeding. To avoid any stress, the tube was positioned 12 h before the beginning of the experimental period. On the test day, subjects were awakened at 0800. After emptying their bladders, body temperature was noted and body weight was determined to the nearest 0.05 kg. Then, the patients were assigned to rest in bed. Body composition was estimated by bioelectrical impedance analysis and anthropometric skinfold thickness measurements.

Energy expenditure experiments were carried out at 1100 after a 12-h fast. After determination of premeal baseline metabolic rate (PMR), one of the two liquid meals was administered intragastrically in 25–30 min by nasogastric tube. To avoid time bias, as well as anxiety symptoms related to high-energy loads, the liquid diets were administered intragastrically in a double-blind randomized fashion so that the patient was convinced that all diets were of the same energy content. We called them “dietetic beverages.” Each patient had four tests in one of the four possible combinations (ABAB, ABBA, BABA, or BABA). The energy content of these energy loads was selected to represent one-third of their energy intake during semistarvation and refeeding, respectively. The load consisted of Megareal (Sodietal Laboratories, Ploudaniel, France). It contains 5.85 MJ/L in sterile bottles, with 20% whole protein, 45% polysaccharides, and 35% tricaplyglycerols (66% being polyunsaturated fatty acids); its osmolality was 300 mOsm/kg.

The two different energy loads were administered blindly, in a random order, with a 2-d interval: the 2.92-MJ Megareal and the same liquid diet diluted in pure water to obtain 1.25 MJ in the same final volume.

Period 2: Refeeding phase

Both loads were administered with the same procedure. This second set of experiments was conducted 6–8 d after the second semistarvation load. The renutrition program included enteral nutrition by nasogastric tube as well as three meals and two snacks per day devised to produce a weight gain of ~250 g/d. To minimize increases in body water between the two periods, a low-sodium diet was prescribed. Enteral nutrition consisted of Normoreal (Sodietal Laboratories), which contains 4.18 MJ/L, with 15% whole protein, 55% polysaccharides, and 30% tricaplyglycerols (63% being polyunsaturated fatty acids); its osmolality was 250 mOsm/L with minerals, vitamins, and trace elements as recommended. It was infused for 12–14 h/d by automatic pump. The enteral nutrition was stopped at 2200 in the evening preceding each experiment. The patients were instructed to dramatically increase their food intake. All meals and snacks were supplied by the Bichat Hospital’s kitchen. Subjects were discreetly watched by the nurses for 1 h after the meals and in the bathrooms at all times to prevent vomiting.

Over the study period, energy intake was monitored by a registered dietitian who recorded the amount of food leaving the kitchen. Whatever remained on the tray was measured and subtracted from the initial amount. The grams of protein, carbohydrate, and fat were calculated from food-composition tables and the energy content of the food was determined by using the Atwater factors of 4, 4, and 9 kJ, respectively, for the three categories.
Body composition

Body composition was assessed by bioelectrical impedance analysis and double checked by anthropometric data. These techniques were routinely performed once a week on our anorexic patients. For bioelectrical impedance we used a portable two-electrode impedance analyzer (IMP BO 1; l’Impulsion, Caen, France) (23).

Duplicate measures of skinfold thicknesses were performed at the four classic sites and results were converted into density according to the equations of Durnin and Womersley (24) and Brozek et al (25). LBM was calculated by subtracting fat mass from body weight.

Metabolic rate measurements

Premeal basal metabolic rate

Energy expenditure was measured by open-circuit indirect calorimetry with a ventilated-hood system (mean flow rate: 70 ± 5 L/min). Oxygen concentrations were assessed by the use of a differential paramagnetic analyzer (Klogor Inc, Lannion, France), and carbon dioxide concentrations with an infrared analyzer (Hartman and Braun Instruments, Frankfurt, Germany). Gas flow was measured with a linear mass flow meter (Setaram, Lyon, France). Raw data were continuously recorded and computerized on-line every minute. Gas exchanges were calculated as the product of gas flow times the difference in both oxygen and carbon dioxide concentrations in room air and expired gas by continuously monitoring gases at the inlet and outlet of the ventilated hood. Corrections were made for effect of respiratory quotient (RQ) on gas flow measurements. The system was checked regularly by burning butane: the mean recoveries of oxygen and carbon dioxide were 98 ± 1% and 99 ± 1%, respectively. RQ for butane was 0.6138 ± 0.003 (n = 4). Before each measurement session the system was calibrated with 99% nitrogen and 1% dioxide.

PMR measurements were made at 1100 with subjects in bed rest position in a noiseless room at 22–24 °C; the patient was allowed to read or to listen to music. Respiratory gases were analyzed for 35–40 min, but only the results from the final 20 min were averaged for the calculation of energy expenditure. REE was calculated from oxygen consumption (VO2), carbon dioxide production (VCO2) and daily urinary nitrogen output according to Ben Porat et al (26). Measured and estimated values of REE were expressed as kJ/d, kJ · kg LBM−1 · d−1, and as a percentage of the value expected from LBM. Urinary nitrogen output was measured by chemiluminescence.

Postprandial measurements

To avoid any stress induced by swallowing a high-energy meal, the patients had absolutely no idea of the composition of the load. Another reason is that the complete protocol involved a questionnaire designed to study the load-related changes in hunger, body image, gastric feelings, and variations in mood. The analysis of this questionnaire will be published elsewhere.

Energy measurements started at the half-way point of administration of the meal and lasted 5 h. Each measure lasted 35–40 min/h, but only the results from the final 20 min were recorded. For ethical reasons, the patients were relieved from the hood for 15–20 min between measures although they were instructed to remain at bed rest. The length of the postprandial period was limited to 5 h because we regularly observed a significant increase in restlessness and energy expenditure after the fifth hour. Besides, this time interval covered almost all of the incremental postprandial area above baseline (27).

Statistical analysis

The thermic effect of the meal (TEM) was defined as the increase in energy expenditure at rest integrated over 5 h after the nasogastric infusion of the liquid meal (11). All analyses were performed with SYSTAT software for a microcomputer by using the MGLH module (Systat Inc, Evanston, IL). Results are expressed as means ± SEMs.

To compare the REE values from the two periods taking into account the change in LBM, we determined the REE expected from the LBM in a group of 58 malnourished anorexia nervosa patients; the regression formula was as follows: REE = −37 + (29.6 × LBM). The intercept was not significantly different from zero (r2 for identity = 0.68, P < 0.001). Thus, this data validates the use of the ratio of REE to LBM in our results. To determine significance in differences between variables before and during refeeding, P < 0.05.

Table 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the 11 anorexic patients before and during refeeding(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Semistarvation</td>
</tr>
<tr>
<td>Age (y)</td>
<td>23.55 ± 1.28</td>
</tr>
<tr>
<td>Duration of the disease (y)</td>
<td>2.45 ± 0.56</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.4 ± 1.91</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>33.7 ± 1.3</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>12.9 ± 0.34</td>
</tr>
<tr>
<td>Body weight (% of ideal)</td>
<td>61.5 ± 1.6</td>
</tr>
<tr>
<td>Body surface area (m(^2))</td>
<td>1.27 ± 0.03</td>
</tr>
<tr>
<td>Lean body mass (kg)(^1)</td>
<td>29.4 ± 1.1</td>
</tr>
<tr>
<td>Fat mass (kg)(^2)</td>
<td>4.30 ± 0.50</td>
</tr>
<tr>
<td>Total body water(^3)</td>
<td>24.9 ± 0.72</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>36.5 ± 0.2</td>
</tr>
<tr>
<td>Creatinine-height index (% of N)</td>
<td>64.8 ± 3.2</td>
</tr>
</tbody>
</table>

\(^1\) ± SD.

\(^2\) Significantly different from semistarvation, P < 0.05.

\(^3\) Determined by two-frequency bioelectrical impedance and double-checked by anthropometry. A good correlation (r = 0.81, P < 0.001) was found between anthropometry and impedance for lean body mass.

Table 2

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Average daily energy and macronutrient intakes during hospitalization in 11 anorexia nervosa patients(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intakes</td>
</tr>
<tr>
<td>Energy (MJ/d)</td>
<td>3.28 ± 1.34</td>
</tr>
<tr>
<td>(kcal/d)</td>
<td>783 ± 60</td>
</tr>
<tr>
<td>(kJ · kg body wt(^{-1}· d(^{-1}))</td>
<td>99 ± 7.65</td>
</tr>
<tr>
<td>Protein (g/d)</td>
<td>37.6 ± 18.6</td>
</tr>
<tr>
<td>Fat (g/d)</td>
<td>28 ± 15.9</td>
</tr>
<tr>
<td>Carbohydrates (g/d)</td>
<td>95.1 ± 49.2</td>
</tr>
</tbody>
</table>

\(^1\) ± SD.

\(^2\) By both oral and tube feeding.

\(^3\) All refeeding values significantly different from semistarvation and preadmission, P < 0.05.
and after the liquid meal loading, data were analyzed by using a repeated two-way analysis of variance (ANOVA).

The effect of refeeding was tested by comparing values according to periods (semistarvation and refeeding) by using ANOVA with repeated measures. Significant differences between periods or loads were assessed by paired Student's t test with correction for experiment wise error or by the nonparametric paired test of Wilcoxon. Statistical significance was set at P < 0.05.

RESULTS

On admission, all patients displayed pathologic eating attitudes with a mean score on our meal test well above the cutoff point for anorexia nervosa. The mean weight loss was 37 ± 5.9% (± SEM) of the preillness weight (Table 1). LBM was very low, amounting to 87 ± 3% of body weight.

After 6 ± 2 d refeeding, a significant increase in body weight and LBM was observed, without changes in fat mass. As assessed by bioelectrical impedance analysis, the increase in LBM seemed related only to an increase in body water, data confirmed by sodium balance. A very good correlation (r = 0.81, P < 0.0001) was found between anthropometry and impedance for LBM.

The mean oral intake during the semistarvation period was below the energy needs for body weight maintenance and similar to that at preadmission (3285 ± 1342 kJ; Table 2). A 130% increase in total energy intake (including tube feeding) was obtained at the end of the first week as compared with intake at semistarvation (P < 0.0001).

The REE (measured at 0800) was low at inclusion in all patients as compared with predicted REE. After 1 wk of refeeding, body temperature increased from 36 ± 0.3 °C (days 0–2) to 37.2 ± 0.3 °C (days 7–10, P < 0.05). At the same time, although remaining low, REE increased by 8% (mean increase: 352 ± 74 kJ, P = 0.021). Similar data were observed for basal PMR measured at 1100 after ≥15 h of fasting: mean increase: 373 ± 78 kJ (P = 0.021). When the increase in body weight and LBM was taken into account, 1 wk of refeeding did not modify REE and PMR (Table 3). Expressed as the percentage of expected REE from LBM, a significant increase in REE was observed with the refeeding: 88 ± 9% before refeeding compared with 106 ± 11% after 1 wk of refeeding (P < 0.05).

The increase in VO₂ after the load began very early (Figure 1); the value obtained at the half-time infusion point was significantly higher than the PMR (P < 0.005). An increase of ≥10% was observed in 36 of the 44 occasions (81% of the tests, P < 0.001). In 8 of 44 occasions (18%), this value was

### Table 3

<table>
<thead>
<tr>
<th>Load and session</th>
<th>REE (kJ)</th>
<th>PMR (kJ)</th>
<th>DIT (0–300 min) (kJ)</th>
<th>LBM (kg)</th>
<th>REE:LBM</th>
<th>PMR:LBM</th>
<th>5-h DIT:LBM (kJ/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1254-kJ (300 kcal) load</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semistarvation</td>
<td>4316 ± 125</td>
<td>4155 ± 140</td>
<td>456 ± 44</td>
<td>29.35 ± 1.08</td>
<td>150 ± 3.8</td>
<td>142 ± 5.0</td>
<td>17.1 ± 1.45</td>
</tr>
<tr>
<td>Refeeding</td>
<td>4622 ± 135&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4601 ± 154&lt;sup&gt;2&lt;/sup&gt;</td>
<td>660 ± 47&lt;sup&gt;2&lt;/sup&gt;</td>
<td>31.75 ± 1.22&lt;sup&gt;2&lt;/sup&gt;</td>
<td>154 ± 3.5</td>
<td>142 ± 4.0</td>
<td>22.32 ± 1.95&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>2926-kJ (700 kcal) load&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semistarvation</td>
<td>4256 ± 138</td>
<td>4228 ± 151</td>
<td>718 ± 75</td>
<td>29.53 ± 1.12</td>
<td>148 ± 4.6</td>
<td>151 ± 5.34</td>
<td>23.24 ± 1.8</td>
</tr>
<tr>
<td>Refeeding</td>
<td>4655 ± 156&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4530 ± 160&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1200 ± 82&lt;sup&gt;2&lt;/sup&gt;</td>
<td>31.47 ± 1.15&lt;sup&gt;2&lt;/sup&gt;</td>
<td>155 ± 3.6</td>
<td>146 ± 3.4</td>
<td>40.94 ± 2.83&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> ± SEM. LBM, lean body mass.
<sup>2</sup> Significantly different from semistarvation phase: <sup>2</sup>P < 0.021, <sup>3</sup>P < 0.001.
<sup>3</sup> DIT rose significantly with the energy load during both study periods, P = 0.008.

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FIGURE 1. Change in oxygen consumption (VO₂) after infusion of the two intragastric loads (1.25 and 2.92 MJ) in semistarvation and during early refeeding in 11 anorexia nervosa patients. ▲, semistarvation, 1.25 MJ; △, semistarvation, 2.92 MJ; ■, refeeding, 1.25 MJ; □, refeeding, 2.92 MJ. ± SEM. Semistarvation significantly different from refeeding, P < 0.002.
the maximal one, whatever the phase and the load. At the half-time infusion point, the increase in $V_O_2$ from the premeal value for the 1.25-MJ load rose from 25.8 ± 15 (semistarvation phase) to 33 ± 11 mL/min (refeeding phase; $P < 0.02$); for the 2.92-MJ load the rise was from 31.8 ± 28 (semistarvation phase) to 40.1 ± 16 mL/min (refeeding phase; $P < 0.02$). One hour after the load, $V_O_2$ reached its maximal value in 70% of the patients. This increment was dependent on the load and the period (Figure 1; $P = 0.0001$). After 1 h, $V_O_2$ plateaued in all the experiments and in each patient.

As expected, the 5-h DIT was higher with the bigger load than with the smaller one. Before refeeding, the 2.92-MJ load DIT was 158% higher than the 1.25-MJ load DIT (Table 4; $P = 0.008$). During early refeeding, it became 181% higher than that of the smaller load ($P = 0.002$). The increase in heat production followed a different pattern with regard to energy intake: the $V_O_2$ (and thus DIT) plateaued for the 2.92-MJ load from 60 to 180 min whereas a $V_O_2$ peak was observed at 60 min for the 1.25-MJ load (Figure 1).

More interesting was the difference in DIT between the two phases for the same load. For all patients and for the two loads, DIT was significantly higher after than before refeeding (Figure 2 and Table 4). For both loads respectively, the 0–300 min DIT was 45% and 67% higher during early refeeding than before ($P < 0.002$). This energy expenditure represented 36% and 24% of the input of the low- and high-energy loads, respectively, in the semistarvation state, and 52% and 41% of these loads, respectively, in the refeeding phase.

When LBM values were derived from impedance data (Figure 3), DIT:LBM values were significantly higher after the start of refeeding than before it ($P < 0.01$, for the 1.25-MJ load, and $P < 0.001$ for the high-energy one). Use of data from anthropometry did not modify these results. The increment in DIT did not correlate with LBM change.

As shown in Figure 3, the RQ decreased significantly by the end of the load infusion as compared with preload values ($P = 0.007$). This was true for both periods and loads. The preprandial variation of RQ was not related to the load: similar values were noted for the two loads. Then RQ values rose significantly. The mean peak RQ value was obtained at 60–120 min, a little bit later with the 2.92-MJ load than with the low one.

Moreover, RQ was lower during semistarvation than with refeeding ($P < 0.05$; Figure 3).

**DISCUSSION**

In anorexia nervosa patients there are multiple components of the high energy needs observed by almost all workers (28–33). Among them is the increase in REE, the increase in physical activities that is allowed by energy replenishment, and the rise in DIT. The main result of the present study is the finding of a dramatic increase in DIT as soon as the beginning of renutrition for both loads and for all patients, contrasting with a small increase in REE and PMR.

The 8% REE increment that we observed could be criticized as low. However, these low values appeared to be coherent because REE and PMR were very close to each other and similar to previous results (5, 10–13, 19, 21). On the contrary, several workers observed a larger increase in REE (14, 20, 34). These discrepancies could be explained, as mentioned by Obarzanek et al (13), by differences in the duration and the energy input. For instance, Krahn et al (14) showed a rise in REE of 25–30% above predicted values during late refeeding on a 15-MJ/d energy intake. Obarzanek et al (13) observed a 23% increment in REE with 13-MJ/d intakes during a later phase of refeeding. By contrast, Vaisman et al (20), Dempsey et al (5), and Melchior et al (9) reported lower REE with intakes <9 MJ/d during early refeeding. When expressed as a function of LBM, the REE:LBM also appeared to be dependent on intakes: in our 11 anorexia nervosa patients, REE:LBM remained unchanged with 7–10-MJ/d intakes; Obarzanek et al (13) did not observe any increase in their 10 anorexia nervosa patients with 8-MJ intakes. The same authors and others found a significant increment in REE:LBM with inputs >12 MJ/d (5, 13, 14).

This lack of increase in REE:LBM, contrasting with the 8% increase in REE, could be related to the fact that the LBM increase during the early renutrition is mostly water.

We showed in the present study that the DIT in response to the lower load (1.25 MJ) was found to be 36% of the energy content of the load before refeeding, and as high as 52% (204 kJ) 1 wk later, whereas intakes achieved twice the REE. For the

**TABLE 4**

Overview of some studies on thermogenesis in anorexia nervosa patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Composition of the meal</th>
<th>DIT in semistarvation state $^{2}$</th>
<th>DIT in the refeeding state $^{2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stordy et al. 1977 (21)</td>
<td>Liquid glucose equivalent, 1.672 MJ (400 kcal)</td>
<td>Increased (332 kJ/150 min)</td>
<td>—</td>
</tr>
<tr>
<td>Contaldo et al. 1986 (15)</td>
<td>Mixed meal, 3.76 MJ, 16% P, 50% CHO, 34% F (900 kcal)</td>
<td>Decreased (no value given)</td>
<td>—</td>
</tr>
<tr>
<td>Vaisman et al. 1991 (20)</td>
<td>Mixed meal, 1.09 MJ, 22% P, 49% CHO, 29% F (260 kcal)</td>
<td>Decreased (152 kJ/120 min)</td>
<td>259 kJ/120 min</td>
</tr>
<tr>
<td>Casper et al. 1991 (11)</td>
<td>Liquid meal, 1.92 MJ (459 kcal)</td>
<td>Similar to control subjects</td>
<td>—</td>
</tr>
<tr>
<td>Scafﬁ et al. 1992 (35)</td>
<td>Mixed meal, 3.56 MJ, 16% P, 50% CHO, 34% F (850 kcal)</td>
<td>782 ± 102 kJ (240 min)</td>
<td>—</td>
</tr>
<tr>
<td>Kubota et al. 1993 (17)</td>
<td>Liquid glucose load, 0.836 MJ (200 kcal)</td>
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$^{1}$ P; protein; CHO, carbohydrate; F, fat. To convert kilocalories to kilojoules multiply by 4.184.

$^{2}$ Compared with control subjects.

$^{3}$ Compared with the semistarvation state.
higher load (2.92 MJ), DIT amounted to 24% and 41% of the energy input, respectively (477 kJ). In Table 4 we summarize data on DIT in anorexia nervosa patients. None of these studies examined the changes in DIT after refeeding, except the report of Vaisman et al (20). Using a 1-MJ mixed meal, these authors found results similar to ours: they observed a rise of 107 kJ in 2 h whereas we reported an increase of 200 kJ in 240 min (Figure 2).

A possible factor that may contribute to increased DIT with refeeding is the improvement in LBM: indeed, we found by ANOVA a slightly significant relation between 3-h DIT and LBM ($P < 0.052, F = 3.9$). However this dramatic increase in DIT with refeeding cannot be attributed only to the gain in LBM because the difference from prerefeeding values remained highly significant when DIT was expressed as a function of LBM ($P < 0.01$ for the low-energy load and $P < 0.001$ for the high-energy one). Similarly, Vaisman et al (20) reported a rise in DIT disproportionate to the one observed in LBM. This suggests that the efficiency of the lean tissue for energy processing was still poor during the early phase of refeeding. This may be partly due to the repletion of muscle and liver glycogen stores and enhancement of futile cycles as proposed by Newsholme (36).

The increase in DIT that we observed in anorexia nervosa patients could be compared with previous DIT studies in normal-weight experimentally overfed healthy subjects (31, 34, 35)....
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37), namely, ours in nine Cameroonian men (38): after a massive 28-MJ/d overfeeding period of 2 mo, the rise in DIT amounted to only 23.4% of the excess energy. This rise is much lower than that observed for our big load, for which the 5-h DIT represented 41% of the energy input.

From the analysis of other available reports on overfeeding, it seems that the highest DIT values are reported in studies in which carbohydrate is the main nutrient (39, 40). For instance, Schutz et al (40) fed for 7 d three lean men with increasing amounts of very-high-carbohydrate supplements and reported a DIT of 27%, which is the largest DIT reported in humans. Our findings (41%) exceed the range of this reported value, especially if we consider that our patients did not profit from a very-high-carbohydrate diet but were submitted to a strictly evaluated mixed-meal regimen.

It appears that malnourished anorexia nervosa patients are more responsive to overfeeding than are normal subjects. If we consider Figure 1, the rise in VO2 followed a specific pattern that can be explained by its two components: the first (the "early phase"), during which energy expenditure is rising; the second is the plateau of VO2. In the present study, the early phase of DIT began very soon, within the last 15 min of the intragastric load. This phase was obviously dependent on the period but not on the load: the VO2 increase was higher during the refeeding than during the semistarvation period but did not differ significantly, according to the load. This increase in VO2 may explain the decrease in RQ and could reflect a greater increment in fat-derived energy than in carbohydrate-derived energy (41, 42).

The factors that contribute to these early changes in VO2 and RQ are unknown. One reason could be the anxiety caused by the ingestion of the load. This anxiety-related stress probably increases the activity of many cycles involved in the mobilization and use of the various fuels of the body, especially fatty acids (37). The role of catecholamines and of the activation of the β-3 adrenergic system should be considered because these hormones mediate increases in the rate of many substrate cycles during the absorptive phase of the meal. A less plausible explanation could be a metabolic response to the entry of the nutrients into the body via the portal vein and the liver. This is unlikely for two reasons: 1) the first bolus of nutrients passed through the pylorus after ≥10 min in malnourished anorexia nervosa patients (43), and 2) gastric emptying is delayed in malnourished anorexia nervosa patients and was improved only after 4–6 wk of refeeding, as shown by Rigaud et al (44). Thus, this very early increase in energy expenditure after the load could be partly due either to the cephalic or to the gastric phases of the release of some regulatory peptides, or to the stress related to the meal in anorexia nervosa patients. Further studies are needed to answer this question. Nevertheless, the VO2 plateau appeared clearly to be in relation with the load. Yet, stress alone cannot account for this later part of the DIT. Metabolic pathways here play the major role. This suggests that futile cycles may be enhanced strongly by the start of refeeding.

In conclusion, a significant increase in DIT does occur in anorexia nervosa patients during the early phase of refeeding. This increment is not related to the increase in active LBM. It clearly has two components. The first one is the increase in energy intake: the higher the energy content of the meal, the higher the DIT. But the second component is the lower metabolic efficiency for a defined load, which occurs when refeeding is started. This is obvious for high loads (such as ours), for which the strong increase in DIT observed can partly explain the difficulty that anorexia nervosa patients have in gaining weight. But this increment in DIT also occurs for lower loads (such as our 1.25-MJ load): it is then quite obvious that in wasting ̃50% of its energy content, anorexia nervosa patients could have great difficulty just maintaining their body weight with the start of refeeding. Therefore, for these strong increases in the energy expenditure, the existence of some energy-wasting adaptive process can be legitimately considered. The question that arises is whether the disproportionate increase in DIT with renutrition is unique to anorexia nervosa patients, and whether it may be due to changes in release of metabolic regulatory peptides or to other biochemical deficiencies.

REFERENCES


