Chronic Starvation Secondary to Anorexia Nervosa Is Associated With an Adaptive Suppression of Resting Energy Expenditure

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Background: Chronic starvation is accompanied by a reduction in resting energy expenditure (REE). It is not clear whether this is due mainly to a reduction in body mass or also involves a significant reduction in the cellular metabolic rate of the fat-free mass (FFM).

Objectives: The main goal was to compare measured REE (REEm) with REE predicted by dual-energy X-ray absorptiometry modeling of organ-tissue mass (REEp) in malnourished patients with severe anorexia nervosa (AN) and in healthy lean control subjects. REE adjusted for FFM and fat mass was also compared between the groups.

Design: This was a cross-sectional study of 30 patients with AN and 25 lean control subjects. REE was measured by indirect calorimetry. Body composition was modeled using dual-energy X-ray absorptiometry, and REE was predicted for each group based on organ-tissue mass.

Results: REEm was significantly lower than REEp in subjects with AN (854 ± 41 vs 1080 ± 25 kcal/d, P < .001), but not in control subjects. In addition, REE adjusted for both FFM and fat mass was significantly lower in the subjects with AN (1031 ± 37 vs 1178 ± 32 kcal/d, P < .01). Finally, compared with the lean control subjects, both organ and skeletal muscle mass were approximately 20% smaller in subjects with AN.

Conclusions: Chronic starvation is accompanied by a significant reduction in the metabolic rate of the FFM. The organs and/or tissues accounting for this are unknown. In addition, this study suggests that protein is mobilized proportionately from organs and skeletal muscle during starvation. This too may be an adaptive response to chronic starvation. (J Clin Endocrinol Metab 99: 908–914, 2014)

Obesity and starvation represent the 2 extremes of disordered energy balance. Obesity occurs only if energy intake consistently exceeds total daily energy expenditure. Likewise, weight loss occurs only if energy intake is less than energy expenditure. Despite the obesity epidemic in the developed world, there is evidence that body weight is regulated (1, 2). For example, it is estimated that the average adult consumes 18 000 pounds of food between the ages of 18 and 65 but will gain only 1 to 2 pounds per year (2). This remarkable fact suggests that a regulatory system is present to control both energy intake and expenditure. In addition, there is evidence that body composition is defended. For example, weight cycling does not appear to alter percent body fat (3, 4) and weight regain after semistarvation appears to restore the individual’s prestarvation body composition (5). Older adults, however, may recover less fat-free mass (FFM) during weight regain (6).

Animal and human studies of obesity vastly outnumber studies of starvation. Because it represents an extreme challenge, the study of starvation may provide deeper insights into the systems that regulate body weight and com-

Abbreviations: AN, anorexia nervosa; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; EE, energy expenditure; FFM, fat-free mass; FM, fat mass; LBM, lean body mass; MRI, magnetic resonance imaging; REE, resting energy expenditure; REEm, measured resting energy expenditure; REEp, predicted resting energy expenditure.
position. Improved understanding of the regulatory systems that defend body weight and composition during starvation could one day allow for manipulation of these pathways to assist weight loss.

In the United States, primary starvation is extremely rare, but severe and chronic semistarvation is seen in individuals with anorexia nervosa (AN). AN is a psychiatric disorder characterized by a marked and sustained reduction of caloric intake (7). Thus, although it cannot provide much insight into how energy intake adapts to chronic starvation, it can serve as a model of adaptations in energy expenditure. Down-regulation of cellular metabolism is one mechanism that could limit the loss of body mass during starvation, and this adaptation should be reflected in measured resting energy expenditure (REE) adjusted for body mass and composition.

At this time, the energy-related adaptations to starvation are not completely understood (8, 9). Several studies have suggested that cellular metabolism is suppressed during starvation secondary to AN (10–12). In addition, in the Minnesota Starvation Experiment, REE adjusted for FFM was found to be significantly lower during chronic starvation compared with baseline values (13). However, other studies, including the largest study of energy expenditure in AN, have found no such adaptations in REE (14–16). Of note, almost all of these studies used suboptimal measurements of body composition, such as anthropometrics and body impedance analysis. Because FFM is the major determinant of REE (17), it is essential that FFM be accurately measured. Today, dual x-ray absorptiometry (DXA) is routinely used to accurately and reliably measure 3 compartments of the body: FFM, fat mass (FM), and bone mass.

In addition, a 5-compartment model of body composition has recently been developed using DXA (18). Specifically, skeletal muscle mass, adipose tissue mass, brain mass, bone mass, and “residual mass” can now be estimated for each sex by DXA. In this model, lean mass of the extremities is used to calculate skeletal muscle mass, and the organs, such as the liver, heart, and kidneys, are included in the residual mass, which is calculated by subtracting the mass of the bone, brain, skeletal muscle, and adipose tissue from total body weight. This model, therefore, allows for the FFM to be subdivided into low metabolic rate skeletal muscle and high metabolic rate residual mass. This “DXA modeling” has led to new insights into the relationship of body composition to energy expenditure (18, 19). For example, it has long been established that mammals with a larger FFM have a lower REE per kilogram of FFM than do those with a smaller FFM (20). DXA modeling has helped explain this finding by demonstrating that a larger FFM is associated with a larger proportion of low metabolic rate skeletal muscle and a smaller proportion of high metabolic rate residual mass (21). Thus, DXA modeling has shown that the composition of the FFM itself is the major determinant of REE.

In addition, although it is clear that adipose tissue accounts for most body mass lost during starvation (22), the effect of starvation on the composition of the FFM itself has not been well studied. Again, the FFM is made up of low metabolic rate skeletal muscle and high metabolic rate organs such as the brain, heart, liver, and kidneys. Therefore, the amount of protein mobilized from these different parts of the lean body mass (LBM) during starvation will affect energy expenditure, functional status, and survival.

In this study, we used DXA modeling to determine whether there is evidence for a significant and adaptive suppression of energy expenditure during the starvation of AN and to gain insight into the composition of the FFM itself during this chronic starvation. The body composition of lean control subjects was used as the “baseline” body composition for the patients with AN for the latter aim.

Subjects and Methods

This is a cross-sectional study using data obtained from 2 populations: patients with severe AN admitted to the eating disorder medical stabilization unit at Denver Health Medical Center and lean healthy control subjects. A waiver of consent was granted for the patient data, and the lean control subjects provided formal consent as part of a separate study. REE was measured by indirect calorimetry after an overnight fast in both groups and within the first 48 hours of hospitalization in all patients with AN with the exception of those requiring tube feedings or total parental nutrition at the time of admission. In most patients with AN admitted to the unit, weight history was self-reported and so could be unreliable. Body composition was measured within the first 72 hours of admission by DXA. The healthy lean control subjects underwent indirect calorimetry and DXA scanning as part of a research protocol.

In all subjects, body weight was measured to the nearest 0.5 kg on a calibrated scale with subjects wearing only a hospital gown. Body composition was measured by DXA (Hologic). The system software provides estimates of total and regional fat, lean soft tissue, and bone mineral mass. The coefficient of variation for repeated measures is 1.1% for lean soft tissue, 2.1% for fat mass, and 1.3% for bone mineral mass.

For DXA analysis of body composition, estimates were made of the amount of fat and lean soft tissue in the trunk and extremities. The trunk was defined as the region that extended from the level of the superior aspect of the iliac crest and passed through the hip joint. The arm included the...
entire shoulder, arm, and forearm. The leg included the entire hip, thigh, and lower leg.

**DXA modeling of organ-tissue mass**

Through the use of DXA-derived measurements, the mass of each organ-tissue component was calculated in kilograms (18):

- Brain mass = 0.005 × skull area + 0.2 × sex + 0.24
- Skeletal muscle mass = lean tissue in extremities × 1.13 - 0.02 × age + 0.61 × sex + 0.97
- Bone mass = 1.85 × bone mineral content
- Adipose tissue mass = 1.18 × fat mass
- Residual mass = body weight - (brain + skeletal muscle + adipose + bone)

where sex = 0 for female and 1 for male.

The DXA-derived measurements used in these equations are as follows: skull area, which was used to predict brain mass, was provided by the software system in square centimeters. The lean soft tissue mass, which was used to predict skeletal muscle mass, was calculated as the sum of lean tissue in the arms and legs. Total body fat and bone mineral content measurements from DXA were used to calculate total adipose mass and bone mass, respectively. Residual mass was calculated by subtracting the masses of the brain, adipose tissue, skeletal muscle, and bone from total body weight.

**Organ-tissue energy model**

The energy expenditure (EE) of each organ-tissue component (kilocalories per day) is calculated by multiplication of the mass of the body component by a specific $\kappa$ value that represents the metabolic rate (kilocalories per kilogram per day) of each organ-tissue (18). Presented by Elia in 1992 (23), these $\kappa$ values come from experimental work in both humans and animals. Seven organs and tissues in adults were assigned specific metabolic rates, and these rates continue to be used as reference values today (24). Because the sum of the masses of the 5 components gives the total body mass, the sum of the 5 EE components gives predicted whole-body EE (kilocalories per day):

$$EE = 240 \times \text{brain mass}$$

$$EE_{SM} = 13 \times \text{skeletal muscle mass}$$

$$EE_{bone} = 2.3 \times \text{bone mass}$$

$$EE_{AT} = 4.5 \times \text{adipose tissue mass}$$

$$EE_{RM} = 43 \times \text{residual mass}$$

**Study design**

Charts from patients with severe AN who underwent measurement of REE and body composition at Denver Health Medical Center were abstracted for this analysis. Body composition of these patients was compared with that of a cohort of lean women from a protocol performed at the Colorado Clinical and Translational Sciences Institute at the University of Colorado Denver. Institutional review board approval was obtained.

**Statistical methods**

Statistical analyses were performed with the use of SAS (version 9.2; SAS Institute). Group characteristics were compared with the use of $t$ tests. The analysis of REE consisted of the following steps:

1. First, measured REEs were compared between the 2 groups with the use of $t$ tests. This REE data are presented in kilocalories per day unadjusted for body weight or composition.
2. To determine whether the observed differences in measured REE (REE$_m$) were due to differences in the composition of the FFM, we compared the mean predicted REE (REE$_p$) with the REE$_m$ in each group with the use of $t$ tests. REE$_p$ was calculated using the mass of each body component multiplied by the specific metabolic rate for each body component (18):

$$REE_p = \text{bone mass} \times \kappa_{bone} + \text{skeletal muscle mass} \times \kappa_{SM} + \text{residual mass} \times \kappa_{RM} + \text{adipose tissue mass} \times \kappa_{AT} + \text{brain mass} \times \kappa_{brain}$$

3. We also used multiple regression analysis to compare measured REEs between groups adjusted for differences in the FFM and for differences in the FFM and FM together. All subjects were used in these regression models, whereby REE$_m$ was regressed on group membership, FFM, and FM. FFM and FM were used as adjustment variables (ie, the impact of FFM and FM was not allowed to differ by group).

**Results**

Subject characteristics and body composition are shown in Table 1. All subjects were women, and subjects with AN were somewhat older than control subjects ($P = .07$). Analyses with and without adjustment for age were performed, and because all conclusions were the same, the unadjusted results are presented for simplicity. Body weight, body mass index (BMI) (kilograms per meter squared), body fat percentage, total FM, and FFM were all significantly lower in subjects with AN ($P < .01$) than in control subjects.

<table>
<thead>
<tr>
<th>Table 1. Subject Characteristics and Body Composition</th>
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<tbody>
<tr>
<td><strong>Patients With AN (n = 30)</strong></td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Body weight, kg</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
</tr>
<tr>
<td>Body fat, %</td>
</tr>
<tr>
<td>FM, kg</td>
</tr>
<tr>
<td>FFM, kg</td>
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</tbody>
</table>

Data are means ± SD or median (range).

* Significant differences of at least $P < .01$. Comparisons between groups were done with $t$ tests.
The measured and predicted REE are presented in Table 2. In subjects with AN, REEm was significantly lower than REEp (P < .01), and the mean difference was 226 kcal/d. In contrast, the mean difference between REEm and REEp was only 49 kcal/d in the healthy control subjects, and REEm was significantly higher than REEp (P = .04). As expected, REEm and REEp were both significantly lower in subjects with AN than in lean control subjects. REEm was on average 536 kcal/d lower in the subjects with AN. Although the metabolic rates assigned to each organ/tissue are well established in the literature (24), we conducted a sensitivity analysis to test whether study conclusions may have been affected by the specific values used. We therefore reanalyzed the data assuming a 10% variation in the assigned metabolic rates and observed that the pattern of findings did not change.

Using standard regression analysis to adjust REE for body composition, REEm was significantly lower in subjects with AN after adjustment for FFM as a whole and after adjustment for both FFM and FM. The mean difference in REE between the groups was 147 kcal/d after adjustment for both FFM and FM. The β coefficients for FFM and FM representing change in REEm per 1-kg change in FFM and FM are also presented in Table 2.

On average, REEm was >500 kcal/d lower in the subjects with AN before any adjustments. Taken together, the above data demonstrate that there was a reduction in REE of about 250 to 350 kcal/d in the subjects with AN with chronic starvation due simply to their smaller body mass. However, the smaller body mass of the subjects with AN could not account for all of the difference in REEm between the groups. Therefore, it appears that there was also an adaptive suppression of energy expenditure in the subjects with AN, amounting to about 150 to 250 kcal/d.

Table 3 presents the DXA-modeled mass and predicted EE of brain, bone, skeletal muscle, adipose tissue, and residual mass in the 2 groups. As expected, adipose tissue mass was much lower in subjects with AN than in control subjects. Skeletal muscle mass and residual mass were 21% and 25% smaller in the subjects with AN, respectively.

The smaller residual mass of the subjects with AN accounted for about 50% of the reduction in REE due to the overall smaller body mass of the subjects with AN (~150 kcal/d). An additional combined “savings” of ~100 kcal/d could be attributed to the smaller skeletal muscle mass and adipose tissue mass of the subjects with AN.

**Discussion**

In this study, REEm was significantly lower in women with chronic starvation secondary to anorexia nervosa than in healthy lean control subjects. DXA modeling of organ-tissue mass predicted that REEs in the healthy control

### Table 2. Measured and Predicted REE

<table>
<thead>
<tr>
<th></th>
<th>Patients With AN</th>
<th>Lean Control Subjects</th>
<th>β Coefficient for Adjustment Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>REEm, kcal/d</td>
<td>854 ± 41a</td>
<td>1390 ± 35b</td>
<td></td>
</tr>
<tr>
<td>REEp, kcal/d</td>
<td>1080 ± 25a</td>
<td>1341 ± 26b</td>
<td></td>
</tr>
<tr>
<td>REEm (kcal/d) adjusted for</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFM</td>
<td>1005 ± 34a</td>
<td>1209 ± 28b</td>
<td>32.64 ± 3.57</td>
</tr>
<tr>
<td>FFM and FM</td>
<td>1031 ± 37a</td>
<td>1178 ± 32b</td>
<td></td>
</tr>
<tr>
<td>FFM</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FM</td>
<td></td>
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</tbody>
</table>

Data are means ± SE. Values within a row but with different superscripts are significantly different (P < .01). Comparisons between groups were done with t tests or multiple regression analysis.

### Table 3. Body Mass Components and REE Predictions From DXA Modeling

<table>
<thead>
<tr>
<th></th>
<th>Patients With AN</th>
<th>Lean Control Subjects</th>
<th>REEp, kcal/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>1.44 ± 0.02a</td>
<td>1.38 ± 0.02b</td>
<td>346 ± 4a</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>15.60 ± 0.45a</td>
<td>19.88 ± 0.47b</td>
<td>303 ± 6a</td>
</tr>
<tr>
<td>Bone</td>
<td>3.29 ± 0.12a</td>
<td>4.02 ± 0.11b</td>
<td>7.6 ± 0.3a</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>5.67 ± 0.38a</td>
<td>17.80 ± 1.01b</td>
<td>26 ± 2a</td>
</tr>
<tr>
<td>Residual mass</td>
<td>11.60 ± 0.49a</td>
<td>15.39 ± 0.43b</td>
<td>499 ± 21a</td>
</tr>
</tbody>
</table>

All values are means ± SE. Values within the same grouping (mass or REEp) and row with different superscript letters are significantly different (P < .01). Note that organ/tissue mass and REE are directly proportional; therefore, P values for each measure are the same.
subjects and subjects with AN should differ by 261 kcal/d because of differences in body mass and composition. However, measured REE was on average 536 kcal/d lower in the subjects with AN than in control subjects. In addition, measured REE was 226 kcal/d lower than predicted in the AN group. Together, these data suggest that there is a substantial down-regulation of cellular metabolism in the FFM during chronic and severe starvation, accounting for upward of 250 kcal/d.

However, when regression analysis was used to adjust REE for the FFM and FM, the estimated savings from adaptive thermogenesis fell to ~150 kcal/d. This is a significant amount of energy because it has been predicted that an energy imbalance of only 10 kcal/day can account for most of the weight gain experienced by the average individual during adulthood (25). Unfortunately, we were unable to determine which aspect of the FFM (residual mass vs skeletal muscle) might account for this reduction in REE.

Although this was not a longitudinal study of semistarvation, the comparison of body composition between the subjects with AN and the lean control subjects suggests that protein is mobilized equally from skeletal muscle and the residual mass during starvation. From a teleological perspective, this would appear to confer a survival advantage. For example, strength and mobility would be profoundly diminished early in starvation if most protein mobilized came from skeletal muscle. Likewise, early organ dysfunction could result if most of the protein mobilized came primarily from the organ mass.

Overall, our findings strongly suggest that cellular metabolism is suppressed in the organs and/or tissues of the FFM during chronic starvation to spare energy. This particular study suggests that 150 to 250 kcal/d were spared through adaptive thermogenesis in the starved subjects. However, it remains controversial as to whether or not a particular study suggests that 150 to 250 kcal/d were spared energy. This paradigm of FFM between patients with AN at nadir weight and control subjects (14). This study and the others referenced above suggest that the FFM does not down-regulate its metabolic rate to spare energy during severe starvation.

In contrast, data from the Minnesota Starvation Experiment suggest that the energy expended by the FFM is decreased during semistarvation (13). In this classic study, 32 young healthy men were semistarved for 24 weeks and then were refed in a controlled fashion over the next 12 weeks. On average, the men lost approximately 24% of their original body weight and REE per kilogram of LBM was significantly lower than prestarvation values. The reduction in REE was roughly 25%. In addition, the reduction in REE correlated with the percent decrease in the FM but not the FFM during the semistarvation period. In other words, those individuals who lost a greater proportion of body fat had a greater reduction in REE per kilogram of FFM. This finding suggests that the state of fuel stores in adipose tissue somehow regulates the cellular metabolic rate of the FFM.

In other studies of AN, REE per kilogram of FFM has been found to be significantly decreased during severe starvation. The largest such study included 34 patients with AN with a mean BMI of 15.5 kg/m² and 18 healthy control subjects with a mean BMI of 21.5 kg/m² (12). In this study, adjusted REE was decreased by about 18% compared with that in healthy control subjects. In the second largest study (11), 28 patients with AN and a mean BMI of 15 kg/m² were compared with 49 control subjects with a mean BMI of 22 kg/m². Adjusted REE was reduced by about 25% in those with AN. Both studies used skinfold thicknesses, either alone, or in combination with bioelectric impedance analysis to determine body composition. Other smaller studies have also suggested that cellular metabolism of the FFM is suppressed after extreme weight loss due to AN (10, 26). It is not clear whether there are significant sex differences in adaptations to weight loss.

There are several possible explanations for the conflicting data regarding REE during starvation. As mentioned previously, body composition was measured by less than optimal methods in most studies. In addition, the degree of starvation may have differed enough to account for the different findings. Interestingly, despite various degrees of weight loss, REE reductions of about 25% are frequently reported in studies that find adaptive reductions in EE with starvation. Perhaps one explanation for these findings is that individuals have a more or less robust energetic response to severe and chronic food deprivation, but also that down-regulation of REE is limited. Individuals probably differ in a number of ways that could affect survival during severe starvation, just as individuals appear to differ in important ways that make them more or less prone to weight gain in an obesogenic environment. Other possible adaptations to chronic food deprivation, such as reduced physical activity and reduced postprandial thermogenesis, were not measured in this study.
Several factors could reasonably be expected to play a role in the down-regulation of cellular metabolism during starvation. Thyroid function is an important regulator of metabolic rate. Hypothyroidism is associated with a significant reduction in REE, whereas hyperthyroidism is associated with a significant rise in REE (27). In one study, lower T₃ concentrations were associated with lower REE in subjects with AN and severe weight loss (11). The sympathoadrenal system also plays a role in REE. In the general population, activity of this system accounts for about 5% of REE (28). To our knowledge, the activity of the sympathoadrenal system has not been shown to be associated with REE in subjects with starvation.

Differences in REE adjusted for FFM during semistarvation could of course be due to differences within the FFM itself that are not detected by DXA modeling. In the current study, the mean residual mass of the women with AN was 3.8 kg smaller than that in healthy control subjects. DXA modeling cannot estimate the change in mass of the kidney, heart, and liver, the high metabolic rate organs included in this body mass component. In the DXA model, the “residual mass” is assigned a metabolic rate of 43 kcal/kg/d. However, the heart, liver and kidneys have estimated metabolic rates of 442, 201, and 442 kcal/kg/d, respectively. The mass of these organs could be reduced out of proportion to the reduction in the residual mass as a whole and thus lead to significant reductions in $\text{REE}_{m}$.

Study limitations

Many assumptions are involved in modeling REE from body composition analysis. For example, muscle mass is calculated from the lean soft tissue in the arms and legs as measured by DXA using equations derived from muscle mass measured by magnetic resonance imaging (MRI) scans in lean and overweight subjects. To our knowledge, this equation has not been validated in severely underweight subjects.

In addition, skull circumference determines brain mass in DXA modeling of organ/tissue mass. Therefore, significant changes in brain mass would not be accounted for by DXA modeling. A recent systematic review of structural MRI findings in eating disorders found no “unequivocal” evidence for gray or white matter volume loss, but some studies have found such changes (29). In AN, studies using MRI to calculate brain mass as well as the mass of other organs are needed to better understand both how starvation affects both REE and protein mobilization from skeletal muscle and organs. MRI measurement of individual organ/tissue mass is now being used to gain further insight into the metabolic rates of organs/tissues with aging and across the sexes (19, 24). Finally, subjects with AN were older than the control subjects. REE does decline with age, but this is mostly due to age-related declines in LBM. Only in advanced age is there a reduction in REE when adjusted for LBM (30). In conclusion, chronic starvation appears to be accompanied by a significant reduction in the metabolic rate of the FFM. However, the organs and/or tissues accounting for this are not known.

Acknowledgments

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