Steroid metabolism and excretion in severe anorexia nervosa: effects of refeeding\textsuperscript{1,2}

Wassif S Wassif, Declan M McLoughlin, Royce P Vincent, Simon Conroy, Gerald FM Russell, and Norman F Taylor

ABSTRACT

Background: To our knowledge, changes in steroid metabolism in subjects with anorexia nervosa (AN) after weight gain have not been elucidated.

Objective: We characterized urinary steroid excretion and metabolism in AN patients and investigated the effects of refeeding.

Design: In an intervention study, we recruited 7 women with life-threatening weight loss upon admission and after a median [interquartile range (IQR)] of 95 d (88–125 d) of intensive refeeding; 15 age-matched women were recruited as control subjects. The major urinary metabolites were quantified in 24-h collections by capillary gas chromatography. A single examinee measured weights, heights, and skinfold thicknesses.

Results: The median (IQR) age of patients was 24 y (21–26 y), and the duration of AN was 4.0 y (3.3–8.0 y). Body mass index (BMI; in kg/m\(^2\)) increased from 12.8 (12.7–13.1) to 18.6 (18.0–19.6) after refeeding (P < 0.0001). Steroid values [median pre-, post-refeeding (P value)] were as follows: androgen metabolites [472, 1017 µg/24 h (0.93)], cortisol metabolites [1960, 3912 µg/24 h (0.60)], and ratios of androsterone (5α/etiocholanolone (5β) [0.28, 0.63 (<0.001)], 5α-5β-tetrahydrocortisol [0.20, 0.48 (0.02)], tetrahydrocortisols/tetrahydrocortisone [0.87, 0.61 (0.09)], 20-hydroxy-/20-oxometabolites [0.29, 0.47 (0.01)], and 20x-/20β-reduced cortisol metabolites [1.18, 1.89 (≥1.00)]. BMI change was positively correlated with 5α-5β-tetrahydrocortisol (r = 0.95, P < 0.001). Before refeeding, the following metabolites were lower in patients than in control subjects: androsterone, 5α-tetrahydrocortisol, α-cortolone and α-cortol, 5α-/5β-tetrahydrocortisol, androsterone/etiocholanolone, and 20-hydroxy/20-oxocortic (all P < 0.05). After refeeding, all steroid metabolites in patients were at concentrations that were comparable with those in control subjects.

Conclusions: Significant changes in urine steroid-metabolite excretion occurred upon starvation, which were reversed upon refeeding. For cortisol, there were decreases in 5α-/5β-tetrahydrocortisol and 20-hydroxy-/20-oxometabolites; for androgen, there was a decrease in androsterone/etiocholanolone.


INTRODUCTION

The eating disorder anorexia nervosa (AN) is an important and often underrecognized cause of a wide range of morbidity (1–3). AN often runs a protracted course, and in severe cases, the mortality rate is high (ie, ≤18% after ≥20 y of the illness (4, 5). During the early stages of weight loss, the negative energy balance leads to a depletion of mainly fatty tissue. In very severe cases, a protein-energy malnutrition may be apparent (6).

Many endocrine abnormalities occur in AN patients, including hypogonadotropic hypogonadism, hypercortisolemia, growth hormone resistance, and low thyroid-hormone concentrations, and these mediate the clinical manifestations of this disease (7). Although, in many respects, endocrine changes in AN represent a physiologic adaptation to starvation, some persist after recovery and might contribute to susceptibility to an AN recurrence (7).

The cortisol production rate and circadian rhythm are normal in AN subjects, but the metabolic clearance rate is decreased (8, 9), which results in hypercortisolism with, as in Cushing’s disease, elevated concentrations of serum and urine cortisol and the lack of suppression of serum cortisol by dexamethasone (10). This effect has been attributed to the hypersecretion of corticotropin-releasing hormone in AN subjects (11), whereas other factors that can influence cortisol concentrations, such as cortisol-binding globulin and corticotropin concentrations, are similar in AN and normal-weight subjects (12). In wasted subjects, urinary cortisol excretion in response to corticotropin was diminished compared with that in normal subjects (13). AN subjects do not develop the common clinical features of hypercortisolism, and it may be that a paucity of metabolic substrates in AN accounts for the lack of cushingoid features in AN subjects (14).

Altered cortisol metabolism may explain the diminished cortisol metabolic clearance rate in AN subjects. Although the conjugation status is unchanged (15), 5α-reduction and 11-dehydrogenation are diminished (16). Oxidoreduction at C11 may be a more influential determinant of the clearance rate (17). We presented a detailed study of steroid metabolism in AN patients on the basis of analysis of urinary steroid metabolites.

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We examined the hypothesis that such changes are dependent on fat mass and that these changes will be normalized during weight gain as a result of refeeding.

SUBJECTS AND METHODS

Ethics approval

All enrolled patients provided fully informed consent to participate in the study, and the study was approved by the Maudsley Hospital Ethics Committee (London, United Kingdom).

Patient and control details

Patients were recruited over a 2-y period from the Eating Disorders Unit at the Maudsley Hospital, London. Seven women were studied upon admission when they were severely underweight and showed features of anorectic myopathy. The structural muscular abnormalities in these patients were previously reported (18, 19), and the steroid data were published in abstract form (20). Patients were reassessed after weight gain and thus acted as their own control subjects. Fifteen age-matched woman of normal weight were used as control subjects for steroid-excretion studies.

Refeeding program

Patients followed an intensive in-patient refeeding program that was designed for those whose self-induced weight loss had reached a degree at which their physical health and life were in danger. Some patients who were reluctant to stay in the hospital for treatment were compulsorily detained under the UK Mental Health Act 1983. During the first week, 1200–1500 kcal/d of a normal diet was given. From the second week, 3000 kcal/d of a normal diet was provided until discharge. During the period of weight gain, all patients in the program ate together. Nobody could leave the table until the last eater had finished. Patients also participated in individual and group psychotherapy sessions. This scheme continued until target weights had been reached. Patients were not informed of their target weights or of their current weights until target weights had been achieved. For an additional 2 wk until discharge, patients received the same diet but were free to eat where they wanted.

Urinary steroid profiling

Urinary steroid profile analysis in 24-h urine collections was used to obtain direct assessments of daily production rates of androgen metabolites (total AMs) (androsterone and etiocholanolone) and cortisol metabolites (total CMs) (tetrahydrocortisone, androgen metabolites (total AMs) (androsterone and etiochola-

Comparison of steroid production and urinary steroid profile analysis in AN before and after refeeding showed significant changes that were used to evaluate the hypothesis that such changes are dependent on fat mass and that these changes will be normalized during weight gain as a result of refeeding.

Statistics

All data were expressed as medians (interquartile ranges). The distribution of all variables was tested by using the Shapiro-Wilk W test. Data were compared by using one-factor analysis of variance, the Kruskal-Wallis test, or the Mann-Whitney U test where appropriate. The Mann-Whitney pairwise test was used to compare between groups, and significance was obtained with analysis of variance, with Bonferroni correction for 3 comparisons. Spearman’s rank correlation was used to examine relations of steroid metabolites and anthropometric data. Differences were considered significant at \( P < 0.05 \). All statistical analyses were done with Analyze-it software (version 2.21; Microsoft, Leeds, United Kingdom).

RESULTS

Data on age and changes in body mass index (BMI; in kg/m\(^2\)) with refeeding are shown in Table 1. Significant changes were observed in BMI and all other anthropometric indexes after refeeding (Table 2).

Urinary steroid profile

Values for the major urinary total AMs and CMs are shown in Table 2 for AN patients (before and after refeeding) and control subjects. Total excretions are also shown for the listed androgen and CMs and ratios of metabolites that were chosen to express the major routes of peripheral steroid metabolism.

Total AMs

Total AM values of AN patients before \([1960 (1904–3613) \mu g AMs/d, P = 0.09]\) or after refeeding \([1017 (638–1446) \mu g AMs/d, P = 0.24]\) were not different from values in the control group \([1725 (1238–2411) \mu g AMs/d]. There was no change (\(P = 0.93\)) in AM values of AN patients after refeeding compared with at admission.

Total CMs

Total CM values of AN patients before \([3912 (2870–4777) \mu g CMs/d, P = 0.09]\) or after \([3912 (2870–4777) \mu g CMs/d, P ≥ 1.00]\)
refeeding were not different from values in the control group [4181 µg CMs/d (3426–5217 µg CMs/d). There was no change (P = 0.60) in CM values after refeeding compared with at admission.

Markers of steroid metabolism

Changes in steroid metabolism with refeeding were expressed as steroid-metabolite ratios in Figure 1, and values are shown in Table 2.

### TABLE 1

Patient clinical details and BMI upon admission and after intensive inpatient refeeding

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (y)</th>
<th>Duration of AN</th>
<th>Admission BMI</th>
<th>Post-refeeding BMI</th>
<th>Duration of refeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>4.0</td>
<td>12.9</td>
<td>20.2</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>13.0</td>
<td>12.6</td>
<td>17.6</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>10.0</td>
<td>12.7</td>
<td>15.0</td>
<td>119</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>1.7</td>
<td>13.3</td>
<td>21.1</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>4.0</td>
<td>11.6</td>
<td>18.6</td>
<td>144</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>6.0</td>
<td>12.8</td>
<td>18.4</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>2.5</td>
<td>13.5</td>
<td>19.0</td>
<td>130</td>
</tr>
</tbody>
</table>

Median (IQR) 24 (21–26) 4 (3.3–8.0) 12.8 (12.7–13.1) 18.6 (18–19.6) 95 (88–125)

1 AN, anorexia nervosa; IQR, interquartile range.

### TABLE 2

Anthropometric variables and steroid metabolites in patients with anorexia nervosa (AN) upon admission (pre) and after refeeding (post) and age-matched control subjects (C)

<table>
<thead>
<tr>
<th></th>
<th>C (n = 15)</th>
<th>AN pre (n = 7)</th>
<th>AN post (n = 7)</th>
<th>ANOVA</th>
<th>C vs pre</th>
<th>Pre vs post</th>
<th>C vs post</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>25 (21–27)</td>
<td>24 (21–26)</td>
<td>24 (21–26)</td>
<td>0.14</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>20.2 (19.2–20.7)</td>
<td>12.8 (12.7–13.1)</td>
<td>18.6 (18.0–19.6)</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>TST (mm)</strong></td>
<td>—</td>
<td>3.1 (2.9–4.5)</td>
<td>14.3 (13.8–14.6)</td>
<td>&lt;0.001</td>
<td>—</td>
<td>&lt;0.001</td>
<td>—</td>
</tr>
<tr>
<td><strong>MAC (cm)</strong></td>
<td>—</td>
<td>15.4 (15.2–16.1)</td>
<td>24.1 (23.5–25.1)</td>
<td>&lt;0.001</td>
<td>—</td>
<td>&lt;0.001</td>
<td>—</td>
</tr>
<tr>
<td><strong>MTC (cm)</strong></td>
<td>—</td>
<td>29.0 (28.6–29.8)</td>
<td>39.5 (39.1–40.4)</td>
<td>&lt;0.001</td>
<td>—</td>
<td>&lt;0.001</td>
<td>—</td>
</tr>
<tr>
<td><strong>Steroid metabolites (μg/d)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total AMs</td>
<td>1725 (1238–2411)</td>
<td>472 (340–1052)</td>
<td>1017 (638–1446)</td>
<td>0.09</td>
<td>0.09</td>
<td>0.93</td>
<td>0.24</td>
</tr>
<tr>
<td>Andro</td>
<td>774 (509–1306)</td>
<td>123 (73–238)</td>
<td>261 (239–641)</td>
<td>0.003</td>
<td>0.003</td>
<td>0.27</td>
<td>0.12</td>
</tr>
<tr>
<td>Etoio</td>
<td>966 (729–1156)</td>
<td>387 (247–814)</td>
<td>651 (395–858)</td>
<td>0.39</td>
<td>0.30</td>
<td>≥1.00</td>
<td>0.48</td>
</tr>
<tr>
<td>Total CMs</td>
<td>4181 (3426–5217)</td>
<td>1960 (1904–3613)</td>
<td>3912 (2870–4777)</td>
<td>0.10</td>
<td>0.09</td>
<td>0.60</td>
<td>≥1.00</td>
</tr>
<tr>
<td>THE</td>
<td>1642 (1455–2049)</td>
<td>876 (776–1569)</td>
<td>1695 (188–1989)</td>
<td>0.34</td>
<td>0.24</td>
<td>0.78</td>
<td>≥1.00</td>
</tr>
<tr>
<td>5α-THF</td>
<td>506 (291–632)</td>
<td>118 (87–219)</td>
<td>265 (235–412)</td>
<td>0.001</td>
<td>0.002</td>
<td>0.09</td>
<td>0.18</td>
</tr>
<tr>
<td>5β-THF</td>
<td>836 (611–981)</td>
<td>725 (555–1087)</td>
<td>730 (513–841)</td>
<td>0.49</td>
<td>≥1.00</td>
<td>≥1.00</td>
<td>0.63</td>
</tr>
<tr>
<td>α-Cortolone</td>
<td>586 (507–760)</td>
<td>207 (186–345)</td>
<td>538 (422–733)</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>0.33</td>
<td>≥1.00</td>
</tr>
<tr>
<td>β-Cortolone and β-cortol</td>
<td>457 (389–617)</td>
<td>195 (164–478)</td>
<td>380 (329–685)</td>
<td>0.27</td>
<td>0.36</td>
<td>0.60</td>
<td>≥1.00</td>
</tr>
<tr>
<td>α-Cortol</td>
<td>180 (146–221)</td>
<td>114 (89–141)</td>
<td>146 (121–179)</td>
<td>0.01</td>
<td>0.006</td>
<td>0.21</td>
<td>0.21</td>
</tr>
</tbody>
</table>

5α- and 5β-reductase activities

<table>
<thead>
<tr>
<th></th>
<th>C (n = 15)</th>
<th>AN pre (n = 7)</th>
<th>AN post (n = 7)</th>
<th>ANOVA</th>
<th>C vs pre</th>
<th>Pre vs post</th>
<th>C vs post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andro/etio</td>
<td>0.81 (0.70–1.11)</td>
<td>0.28 (0.27–0.35)</td>
<td>0.63 (0.59–0.71)</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
<td>0.012</td>
<td>0.36</td>
</tr>
<tr>
<td>5α/5β-reductase</td>
<td>0.60 (0.39–0.69)</td>
<td>0.20 (0.13–0.21)</td>
<td>0.48 (0.45–0.57)</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
<td>0.02</td>
<td>0.99</td>
</tr>
</tbody>
</table>

11β-HSD activities

<table>
<thead>
<tr>
<th></th>
<th>C (n = 15)</th>
<th>AN pre (n = 7)</th>
<th>AN post (n = 7)</th>
<th>ANOVA</th>
<th>C vs pre</th>
<th>Pre vs post</th>
<th>C vs post</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF/THE</td>
<td>0.69 (0.58–0.75)</td>
<td>0.87 (0.76–0.97)</td>
<td>0.61 (0.58–0.65)</td>
<td>0.04</td>
<td>0.48</td>
<td>0.09</td>
<td>0.21</td>
</tr>
</tbody>
</table>
| 20α and 20β HSD activities
| 20-OH/20α-oxo        | 0.41 (0.38–0.45) | 0.29 (0.23–0.32) | 0.47 (0.42–0.55) | 0.001  | 0.006   | 0.012 | 0.69 |
| 20α-Cortolone + 20β-cortol + 20β-cortolone | 1.73 (0.94–2.09) | 1.18 (1.17–1.66) | 1.89 (1.61–2.02) | 0.33   | 0.45     | ≥1.00       | ≥1.00     |

1 All values are medians; interquartile ranges in parentheses. TST, triceps skinfold thickness; MAC, midarm circumference; MTC, mid thigh circumference; Total CMs, androgen metabolites [androsterone (Andro) (5α + etiocholanolone (Etoio) (5β)]; Total CMs, cortisol metabolites; THE, tetrahydrocortisone; THF, tetrahydrocortisol; THF/THE, (5α-THF + 5β-THF)/THE; 20α and 20β, 20α and 20β reduced cortisol metabolites (cortols and cortolones); HSD, hydroxysteroid dehydrogenase; 20-OH/20α-oxo, 20-hydroxycortosteroid (cortolone + cortisol)/20-oxocorticosteroid (THE + THFs). Data were compared by using one-factor ANOVA, and the Mann-Whitney pairwise test was used to compare between groups; significance was determined by ANOVA with Bonferroni correction for 3 comparisons. Differences were considered significant at P < 0.05.
with that in control subjects [0.60 (0.39–0.69); \(P < 0.001\)]. There was a significant increase of the 5α/5β-tetrahydrocortisol ratio in AN patients after refeeding (to 0.48 (0.45–0.57); \(P = 0.02\)) with values that were similar to those of control subjects (\(P = 0.99\)).

Changes in these ratios were accounted for by the 5α-reduced component because androsterone and 5α-tetrahydrocortisol were significantly low in AN patients before refeeding (\(P = 0.003\) and 0.002, respectively) and were not different in AN patients after refeeding from those of control subjects. In contrast, the 5β-reduced components (etiocholanolone and 5β-tetrahydrocortisol) in AN patients showed no differences from those of control subjects.

### 11β-Hydroxysteroid dehydrogenase activity

The tetrahydrocortisols/tetrahydrocortisone ratio was similar in AN patients before refeeding [0.87 (0.76–0.97)] compared with that in control subjects [0.69 (0.58–0.75), \(P = 0.48\)] and did not change after refeeding (\(P = 0.003\) and 0.002, respectively) and were not different in AN patients after refeeding from those of control subjects. In contrast, the 5β-reduced components (etiocholanolone and 5β-tetrahydrocortisol) in AN patients showed no differences from those of control subjects.

### 20α- and 20β-Hydroxysteroid dehydrogenase activities

The 20-OH/20-oxo ratio was significantly low in AN patients before refeeding [0.29 (0.23–0.32)] compared with that in control subjects [0.69 (0.58–0.75), \(P = 0.48\)] and did not change after refeeding (\(P = 0.003\) and 0.002, respectively) and were not different in AN patients after refeeding from those of control subjects. In contrast, the 5β-reduced components (etiocholanolone and 5β-tetrahydrocortisol) in AN patients showed no differences from those of control subjects.

### Relation of steroid metabolism and body indexes

Correlations of steroid and body indexes were examined. No significant relations were shown before refeeding. After refeeding (Table 3), a significant correlation (\(r = 0.89, P = 0.01\)) was observed for BMI and the 5α/5β-tetrahydrocortisol ratio. Because patient numbers in this study were relatively small, we considered whether changes in steroid and body indexes would show closer relations. Changes in 5α/5β-tetrahydrocortisol was significantly correlated with changes in both body weight and BMI (\(r = 0.84, P = 0.02,\) and \(r = 0.95, P < 0.001\), respectively; Figure 2). No other changes showed significant correlation.

### DISCUSSION

Most of the medical conditions associated with AN are shown in uncomplicated starvation and are reversed by a return to a normal healthy diet and weight. Upon refeeding, a high proportion of the weight gain (77%) is due to fat (24). Fat gain in
women preserves the gynoid fat–distribution pattern, with no preferential deposition in central regions (25). The deposition of fat and lean tissue during weight recovery in healthy experimental subjects is mainly dependent on individual variations in the percentage of body fat before weight loss (26) and the same may apply to AN patients (27). A limitation of our study is that patient numbers were small, and there was a small spread of BMI values before refeeding. This probably explained our finding of a lack of correlation between some steroid variables and anthropometric data. Differences were considered significant at *P* < 0.05.

TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>Andro/etio</th>
<th>5α/5β-THF</th>
<th>THFs/THE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>(0.32) 0.49</td>
<td>(0.7) 0.08</td>
<td>(−0.35) 0.44</td>
</tr>
<tr>
<td>Change in body weight</td>
<td>(0.68) 0.09</td>
<td>(0.84) 0.018</td>
<td>(0.03) 0.95</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>(0.46) 0.3</td>
<td>(0.89) 0.007</td>
<td>(−0.36) 0.43</td>
</tr>
<tr>
<td>Change in BMI</td>
<td>(0.75) 0.05</td>
<td>(0.95) &lt;0.001</td>
<td>(0.12) 0.80</td>
</tr>
<tr>
<td>TST (mm)</td>
<td>(−0.21) 0.68</td>
<td>(0.56) 0.24</td>
<td>(0.35) 0.49</td>
</tr>
<tr>
<td>Change in TST</td>
<td>(−0.52) 0.29</td>
<td>(0.5) 0.31</td>
<td>(0.1) 0.86</td>
</tr>
<tr>
<td>MAC (cm)</td>
<td>(0.17) 0.76</td>
<td>(0.56) 0.24</td>
<td>(0.4) 0.44</td>
</tr>
<tr>
<td>Change in MAC</td>
<td>(−0.62) 0.19</td>
<td>(0.42) 0.4</td>
<td>(0.12) 0.83</td>
</tr>
<tr>
<td>MTC (cm)</td>
<td>(0.76) 0.08</td>
<td>(0.34) 0.5</td>
<td>(0.78) 0.07</td>
</tr>
<tr>
<td>Change in MTC</td>
<td>(−0.53) 0.28</td>
<td>(0.08) 0.94</td>
<td>(0.36) 0.49</td>
</tr>
</tbody>
</table>

1 All values are correlation coefficients (*r*; in parentheses) and probability values. Andro/etio, androsterone/etiocholanolone. 5α/5β-tetrahydrocortisol; THFs/THE, (5α-THF + 5β-THF)/tetrahydrocortisone; TST, triceps skinfold thickness; MAC, midarm circumference; MTC, midthigh circumference. Spearman’s rank correlation was used to examine relations of steroid metabolites and anthropometric data. Differences were considered significant at *P* < 0.05.

Although the cortisol secretion rate is generally normal in AN patients (29), the metabolic clearance rate is reduced and half-life is increased (8).

Starved patients showed reduced androsterone/etiocholanolone and 5α/5β-tetrahydrocortisol ratios, which were consistent with previous reports (7, 30). This was due to changes in the 5α-reduced components (see Results). Low ratios mimic findings in patients with 5α-reductase deficiency and during treatment with the 5α-reductase inhibitor finasteride. Steroid metabolic changes in AN patients are similar to those in hypothyroidism (30, 31). The 5α/5β-tetrahydrocortisol and androsterone/etiocholanolone ratios are significantly higher in hyperthyroid patients and significantly lower in hypothyroid patients than in normal subjects (31). This may be explained by anorexics essentially having hypothyroidism because of metabolic adaptation that lowers the resting energy expenditure during chronic starvation, which is reversible with refeeding (32).

There are 2 main 11β-hydroxysteroid dehydrogenase (HSD) enzymes: type 1 is predominant in the liver and acts as a reductase (converting cortisone to cortisol), whereas type 2 is predominantly renal and acts as a dehydrogenase (converting cortisol to cortisone). The cortisol metabolic clearance rate is greatly influenced by 11β-HSD activity. In most conditions in which the ratio of cortisol/cortisone metabolites changes (aside from specific enzyme deficiencies), such as differences of fat deposits and growth hormone status, it is the type 1 enzyme activity that is changed (33). Increased activity results in a lower clearance rate, whereas a decreased activity (or increased 11α-oxidation component of 11β-HSD) results in a higher clearance rate (8, 34). Previous studies of steroid excretion in AN patients have indicated a reduced activity of the 11-oxidation component of 11β-HSD (7, 31). This was supported in 6 out of 7 of our patients who showed higher ratios of tetrahydrocortisols/tetrahydrocortisone that diminished upon refeeding (Figure 1), but the presence of one patient with opposite changes rendered the changes for the majority nonsignificant. As in the situation with 5α-reductase, changes in 11β-HSD activity are similar to those in hypothyroidism, with a tetrahydrocortisols/tetrahydrocortisone ratio that is lower in hyperthyroid patients and higher in hypothyroid patients than in normal subjects (31). In specific type 2 enzyme deficiency (apparent mineralocorticoid excess), the tetrahydrocortisols/tetrahydrocortisone ratio is very high, but 5α-reduced steroids are also relatively increased and this is clearly a secondary phenomenon. In AN patients, the increase in the tetrahydrocortisols/tetrahydrocortisone ratio was accompanied by a decrease in 5α-reduction, and thus the latter clearly has another origin.

In contrast to AN patients, overweight individuals were shown to have enhanced AM and CM excretion and increased net 5α-reductase and 11-oxidation activities (8, 35). Adipose tissue samples taken from obese subjects showed an increased expression of 11β-HSD 1 (36), which would be expected to lead to an increased conversion of cortisone to cortisol and subsequently increased intracellular glucocorticoid reactivation and activity (37). A paradoxical net increase of urinary 11-oxo-/11-hydroxy CMs in the face of enhanced reactivation by adipose tissue may be explained by increased cortisol inactivation by the liver via decrease of 11β-HSD activity and an increase of 5α-reductase activities (38).

Weight-reducing diets for obese subjects were shown to diminish 5α-reductase and increase 11β-HSD1 activities (38). We
have shown that a high-calorie diet in AN patients achieved the opposite changes, with decrease of tetrahydrocortisols/tetrahydrocortisone (Table 2; Figure 1). Previous studies have shown that weight loss (39) and a low carbohydrate diet (38) were not associated with changes in 5α-reductase and 11β-HSD1 activities in adipose tissue. Hence, these changes are likely to predominantly occur in the liver.

In addition, we reported the novel finding, to our knowledge, that the 20-OH/20-oxo metabolite ratio was reduced in AN patients, which indicated a decreased 20-reduction over 20-dehydrogenation. This probably decreased the cortisol metabolic clearance rate. Refeeding significantly brought this ratio into the range of normal-weight subjects. The 20-OH/20-oxo metabolite ratio does not change in many clinical states but is increased in alcoholic liver disease. Zumoff et al (40) have ascribed this to the increased liver activity of 20-reductases. The fact that 20-reduction was decreased, whereas 11-reduction was increased, in patients with AN suggests that these changes were not due to a generalized change in the status of steroid oxidation compared with reduction.

In conclusion, numerous endocrine abnormalities occur in critically ill AN patients, and these largely reflect the endocrinology of reduced energy intake. In starvation, a lowered metabolic rate, decreased thyroid hormones, increased cortisol and growth hormone concentrations (which promote gluconeogenesis and a reduction of the peripheral use of glucose), and reduced fertility are all appropriate adaptations to an abnormal and highly stressful state. The changes we described in activities of the enzymes 5α-reductase, 11β-HSD1, and 20α- and 20β-HSD, were dominantly occur in the liver.

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