Iron metabolism in patients with anorexia nervosa: elevated serum hepcidin concentrations in the absence of inflammation

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ABSTRACT

Background: Only a few studies based on small cohorts have been carried out on iron status in anorexia nervosa (AN) patients.

Objective: The aim of this study was to evaluate the role of hepcidin in hyperferritinemia in AN adolescents.

Design: Twenty-seven adolescents hospitalized for AN in the pediatric inpatient unit of Ambroise Paré Academic Hospital were enrolled in the study. The control group comprised 11 patients. Hematologic variables and markers of iron status, including serum hepcidin, were measured before and after nutritional rehabilitation.

Results: The mean age of patients was 14.4 y. Except for 2 AN patients and 1 control patient, all patients presented normal hemo-globin, vitamin B-12, and folate concentrations. Markers of inflammation and cytokines were normal throughout the study. None of the muscular lysis markers were elevated. Most AN patients had normal serum iron concentrations on admission. Serum ferritin concentrations were significantly higher in patients than in control subjects (198 compared with 49 μg/L, respectively; P < 0.001). The median hepcidin concentration was significantly higher in AN patients than in the control group (186.5 compared with 39.5 μg/L, respectively; P = 0.002). There was a highly significant correlation between ferritinemia and serum hepcidin concentrations (P < 0.0001). After nutritional rehabilitation, a significant reduction was observed (P = 0.004) in serum ferritin. Serum hepcidin analyzed in a smaller number of patients also returned to within the normal range.

Conclusions: Hepcidin and ferritin concentrations were higher in the serum of AN patients, without any evidence of iron overload or inflammation. These concentrations returned to normal after nutritional rehabilitation. These results suggest that nutritional stress induced by malnourishment in the hepatocyte could be yet another mechanism that regulates hepcidin.

INTRODUCTION

AN is a nutritional disorder that affects mostly adolescent girls and young women in Western societies. The incidence of AN is quite difficult to evaluate, but it varies from 8 of 100,000 persons/y in general medicine clinics to 270 of 100,000 girls between 15 and 19 y of age and 15.7 of 100,000 boys between 10 and 24 y of age in Finnish twins (1, 2). AN is associated with the highest mortality rate among all psychiatric illnesses (3). Other perturbations in hemodynamics (bradycardia), hematologic and endocrinologic variables, electrolyte balance, and bone metabolism contribute to the morbidity of AN. Most of these disturbances are reversible with the reinstitution of nutrition, at least in adults. But the consequences can be different in anorexic adolescent girls, especially for changes that pertain to growth, pubertal development, and bone mass.

Very few studies based on small cohorts of patients have been carried out on iron and hematologic status in AN patients.Normal serum iron and slightly elevated serum ferritin concentrations were the most striking results (4–7). However, only a limited number of variables of iron status were evaluated, and to our knowledge, none of these studies have addressed the changes induced by AN in hepcidin concentrations. Hepcidin was discovered in 2000 (8, 9) and was subsequently shown to be the master regulator of iron homeostasis in humans and other mammals (10, 11). Hepcidin acts as a negative regulator of iron absorption by duodenal enterocytes and of heme-iron recycling by tissue macrophages after phagocytosis of senescent red blood cells (12). Hepcidin exerts its control on plasma iron by binding to ferroportin, which is the sole iron exporter from mammalian...
cells. In macrophages, this interaction induces internalization and degradation of ferroportin (13, 14), whereas in duodenal enterocytes, hepcidin seems to trigger the inhibition of iron uptake rather than export (15). Thus, hepcidin maintains iron homeostasis by a hepcidin-ferroportin interaction that determines the flow of iron into the plasma. Hepcidin acts both as a regulator of iron stores and a regulator of iron delivery for erythropoiesis. Two different sensing mechanisms that are based either on the degree of transferrin saturation or the amount of tissue iron stores can trigger an increase in hepcidin expression after an iron overload (16). In contrast, iron deficiency, and all conditions that stimulate erythropoiesis (ie, bleeding, anemia, hypoxia, dyserythropoiesis, or erythropoietin injections) suppress hepcidin expression (17). It has also been suggested that muscle hypoxia could contribute to hepcidin downregulation, although this has not been fully shown. Finally, in inflammatory conditions, increased hepcidin expression, mostly mediated by IL-6, induces iron retention in macrophages and iron-restricted erythropoiesis (18).

The aim of the current work was to study iron metabolism in AN adolescents and to determine whether hepcidin plays a role in hyperferritinemia in this disease.

SUBJECTS AND METHODS

Patients
Between January 2008 and June 2009, 27 consecutive adolescents (24 females and 3 males) hospitalized in the pediatric inpatient unit for restrictive AN in Ambroise Paré Academic Hospital were enrolled in the study. All participants or their relatives were informed and agreed to participate in the study. AN was diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (19).

The age- and sex-matched control group comprised 11 patients (10 females and 1 male) who were hospitalized for acute troubles other than malnutrition, such as a mood disorder or a suicide attempt. The control group had no history of eating disorders and did not suffer from any inflammatory disease.

Clinical data collected at arrival included sex, age (y), weight (kg), height (m), duration of illness before hospitalization for AN, and only phosphorus and multivitamin supplements were described. None of the inpatients were receiving any treatment (iron supplements or oestroprogestative contraception), and only phosphorus and multivitamin supplements were administered during the weight gain.

Hematologic and biological variables
Blood samples were drawn in the fasting state on the morning after admission and after partial rehabilitation. We measured hemoglobin, MCV, leukocytes, platelets, vitamin B-12, and folate. For the assessment of iron status, we measured serum iron, ferritin, transferrin, and sTfR (NLatex sTfR, BNProspec; Siemens). Transferrin saturation (%) was calculated by using the following formula:

\[ \text{[Serum iron (µmol/L) ÷ transferrin (g/L)] × 4} \]

Routine assays were used to measure inflammatory markers including CRP, haptoglobin, and orosomucoid; markers of myolysis such as CK, LDH, and cardiac troponin isomer I; and liver enzymes (alanine aminotransferase and aspartate aminotransferase). The percentage of glycosylated ferritin was measured as previously described (21).

Assay of proinflammatory cytokines
Quantification of various cytokines in serum was done by using a cytometric bead array. A Human Inflammatory Cytokines Kit (BD Biosciences) was used according to the manufacturer’s instructions to simultaneously detect human IL-8, IL-6, IL-1β, IL-10, IL-12p70, and TNF-α as previously described (22). Briefly, a mixture of 6 capture-bead populations with distinct PerCP.Cy5 fluorescence intensities coated with antibodies specific for the mentioned cytokines was mixed with each sample of serum and standard followed by PE-conjugated detection antibodies. Fluorescence acquisition was performed in a FACsCanToI flow cytometer (BD Biosciences), and the results were analyzed by using FCAP Array software (BD Biosciences). The concentration for each cytokine in serum was determined by interpolation from the corresponding standard curve. The range of detection was 20–5000 pg/mL for each cytokine.

Hepcidin assay
All AN patients (except for one individual) and 11 control subjects had determination of serum hepcidin concentrations at the time of hospitalization. Three patients had another hepcidin assay at discharge after nutritional rehabilitation. A competitive ELISA was used to measure hepcidin in serum samples frozen and stored at −80°C (23). Briefly, duplicate 10-µL aliquots of plasma were diluted 1:10 in phosphate-buffered saline, pH 7.4, and the refolded, bioactive form of hepcidin was measured by using previously described rabbit polyclonal antibodies (Intrinsic LifeSciences). HPLC-purified, synthetic, bioactive hepcidin (Bachem Biosciences Inc) was used as reference material for the construction of duplicate 12-point standard curves that were included on each assay plate. Standard curves were fitted with GraphPad Prism software (GraphPad Software). The fitted curve was then used to convert sample absorbance readings to hepcidin concentrations expressed as micrograms of hepcidin per liter of plasma.

Statistical analyses
Statistical analyses were performed with SPSS software (version 18; IBM Corp). Clinical, hematologic, and biological data were compared between patients and control subjects by using a non-parametric test (Mann-Whitney U test for independent samples). Significance was set at \( P < 0.05 \) for all comparisons. Univariate and multivariate analyses were used to determine the correlation between the iron-status variable and anthropometric characteristics. All results are expressed as the median (IQR).
Control subjects [median: 264,000 (219,000–296,000)] (anorexic patients [median: 231,000 (161,000–256,000)] than in bin concentrations were normal. Platelet counts were lower in folate rates. There was no sign of hemolysis because haptoglobin who presented normal MCV, hemoglobin, vitamin B-12, and except for 2 AN patients and one control subject who were Table 2

Hematologic and biological data

<table>
<thead>
<tr>
<th></th>
<th>Anorexic patients (n = 27)</th>
<th>Control subjects (n = 11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/L)</td>
<td>132 (126–140)²</td>
<td>134 (125–138)</td>
<td></td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>91.4 (88.0–93.3)</td>
<td>86.8 (84.7–94.15)</td>
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<tr>
<td>Haptoglobin (g/L)</td>
<td>0.51 (0.17–0.72)</td>
<td>0.47 (0.35–0.70)</td>
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<tr>
<td>LDH (IU/L)</td>
<td>158 (136–183.5)</td>
<td>140 (129.5–193.5)</td>
<td></td>
</tr>
<tr>
<td>ASAT (IU/L)</td>
<td>26.0 (20.0–36.0)</td>
<td>20.5 (18.0–27.3)</td>
<td></td>
</tr>
<tr>
<td>ALAT (IU/L)</td>
<td>26.0 (21.0–32.0)</td>
<td>14.5 (10.5–26.0)</td>
<td></td>
</tr>
<tr>
<td>CK (IU/L)</td>
<td>60 (31–103)</td>
<td>41 (37.5–85.5)</td>
<td></td>
</tr>
<tr>
<td>Vitamin B-12 (ng/L)</td>
<td>747 (589–944)</td>
<td>633 (372–1178)</td>
<td></td>
</tr>
<tr>
<td>Folate (µg/L)</td>
<td>8.09 (5.67–11.4)</td>
<td>6.96 (3.91–16.8)</td>
<td></td>
</tr>
</tbody>
</table>

¹ Data were compared between patients and control subjects by using a nonparametric test (Mann-Whitney U test for independent samples). Significance was set at P < 0.05 for all comparisons.
² Median; IQR in parentheses (all such values).

RESULTS

Anthropometric and clinical characteristics of the study population

Hospitalization of the 27 AN patients enrolled in the study was required because of medical needs such as bradycardia (<40 beats/min), systolic pressure <90 mm Hg, temperature <35°C, or refusal to eat. Clinical and anthropometric data of patients and control subjects are shown in Table 1. The patient group had a mean age of 14.4 y and consisted of 24 girls and 3 boys. As expected, anorexic patients had significantly lower BMI than did age- and sex-matched adolescents (P < 0.001). The mean (±SD) duration since diagnosis of AN was 10 ± 9.6 mo. All of the anorexic girls were premenarchal or amenorrheic, whereas in the control group, 9 girls were menarchal, and 3 girls were premenarchal.

Hematologic and biological data

The median values of hematologic and biological variables in patients at the time of hospitalization are shown in Table 2. Except for 2 AN patients and one control subject who were moderately anemic, there was no sign of anemia in AN patients who presented normal MCV, hemoglobin, vitamin B-12, and folate rates. There was no sign of hemolysis because haptoglobin concentrations were normal. Platelet counts were lower in anorexic patients [median: 231,000 (161,000–256,000)] than in control subjects [median: 264,000 (219,000–296,000)] (P = 0.05). All of these correlations were similar regarding all AN patients or only girls.

Several markers of inflammation were tested in all AN patients (orosomucoid and a panel of cytokines), and CRP was measured in 12 subjects only. All of these data were within the normal range. Concentrations of all proinflammatory or antiinflammatory cytokines that were assayed (IL-1β, IL-6, IL-8, IL-10, IL-12p70, and TNF-α) were below the lower concentration of detection in AN patients as well as in control subjects (see supplemental material under “Supplemental data” in the online issue).

None of the muscular lysis markers were affected as shown by normal CK, troponin I (<0.02 µg/L), and LDH concentrations except for one anorexic girl who had high plasma CK activity (547 UI/L) but with no other lysis marker.

Iron status

Iron-status variables are shown in Table 3. Most AN patients had normal serum iron concentrations on admission, and there was no significant difference between patients and control groups. There was a trend toward lower serum transferrin concentrations in AN patients, which resulted in higher transferrin saturation, but these differences were not significant. Similarly, sTfR concentrations were lower in patients, which suggested that there was a perfect match between iron availability and erythropoiesis. Serum ferritin concentrations were significantly higher in patients than in control subjects [median: 198 µg/L (136–319 µg/L) compared with 49 µg/L (21–76 µg/L); P < 0.001]. Sixteen patients had abnormally high serum ferritin concentrations (>150 µg/L, and as high as 1400 µg/L). However, ferritin glycosylation, which was assayed on a subset of 24 patients, was within the normal range [75% (68–78%)]. Serum ferritin concentrations were not correlated with BMI, either expressed as the SD from the norm (Figure 1A) or as the rate of weight loss (ΔBMI/mo; not shown). However, serum transferrin concentrations were correlated with the rate of weight loss by using either univariate or multivariate models (P = 0.05).

Serum hepcidin concentrations were assayed at admission by using a recently described sensitive ELISA (23). Mean hepcidin was significantly higher in AN patients than in the control group [186.5 µg/L (99.8–278.5 µg/L) compared with 39.5 µg/L (30.0–64.5 µg/L); P = 0.002]. There was a highly significant correlation...
between ferritinemia and serum hepcidin concentrations ($r^2 = 0.478$, $P < 0.0001$; Figure 1B) regarding the whole anorectic population or girls only ($P = 0.01$).

Effect of nutritional rehabilitation on ferritin and hepcidin

Serum ferritin and hepcidin concentrations were assayed for several patients at discharge after nutritional rehabilitation (Table 4). There was a spectacular drop in these 2 markers, which both returned to normal values (Figure 2). These changes were highly significant for ferritinemia (Figure 2A), but the small amount of serum available for hepcidin determination (Figure 2B) did not allow statistical analysis. In the 7 patients, BMI (±SD) changed from $-2.66 ± 0.5$ to $-1.2 ± 0.7$ after nutrition rehabilitation. These weight gains were also highly significant ($P = 0.028$; Wilcoxon’s test), although BMI did not fully return to normal values.

DISCUSSION

In this article we report a comprehensive analysis of iron metabolism in 27 patients who were hospitalized for undernutrition because of AN and did not receive iron supplementation. To our knowledge, our results show, for the first time, that serum ferritin concentrations are elevated in AN patients and correlate with serum ferritin concentrations. This increase in hepcidin and ferritin values did not appear to be due to inflammation because proinflammatory cytokines were undetectable, including IL-6. Both markers returned to within the normal range after partial nutritional rehabilitation.

Iron deficiency is relatively frequent in the non-AN adolescent female population. By contrast, numerous studies have reported a normal iron status in AN patients (4, 5, 24). In this study, serum iron status at admission was within the normal range. Several authors showed that AN patients have dietary iron intake significantly lower than that of normal subjects (25, 26). In other studies, dietary iron intakes of AN patients did not differ from those of control subjects, although greater total iron intake in the AN group resulted from greater iron supplementation than in healthy subjects (27). Furthermore, the absence of iron deficiency could also be partly explained by the amenorrheic condition of the anorexic girls that preserves iron stores (28). There was a moderate reduction in serum transferrin concentrations in our patients, which probably accounted for the slightly higher transferrin saturation than in control subjects, although the values remained within the normal range. This increase in transferrin saturation might have contributed to a better efficacy of iron delivery to the developing erythroid cells, as testified by the normal soluble transferrin receptor concentrations and absence of anemia. Both the hemoglobin concentration and MCV were normal in AN patients as previously reported (29, 30). It is likely that the reduction of blood volume that has been reported in malnourished patients (29) and the presence of amenorrhea at admission contribute to maintaining a normal hematocrit through a reduction in red blood cell mass. Anemia was reported in 38.6% of AN patients by Miller and al (31) and in 22% of AN patients by

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Anorexic patients ($n = 27$)</th>
<th>Control subjects ($n = 11$)</th>
<th>Normal range</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron (µmol/L)</td>
<td>13.8 (12.1–16.0)</td>
<td>12.0 (7.2–24.8)</td>
<td>11–27</td>
<td>NS</td>
</tr>
<tr>
<td>Transferrin (g/L)</td>
<td>1.73 (1.65–2.03)</td>
<td>2.2 (2.1–2.6)</td>
<td>1.9–3.04</td>
<td>NS</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>32.0 (26.0–37.0)</td>
<td>21.0 (11.5–48.5)</td>
<td>20–40</td>
<td>NS</td>
</tr>
<tr>
<td>sTfR (mg/L)</td>
<td>1.1 (0.95–1.30)</td>
<td>1.38 (1.33–1.75)</td>
<td>1.0–1.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Ferritin (µg/L)</td>
<td>198 (136–319)</td>
<td>49 (21–76)</td>
<td>20–150</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepcidin (µg/L)</td>
<td>186.5 (99.8–278.5)</td>
<td>39.5 (30.0–64.5)</td>
<td>28–245</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*1 Data were compared between patients and control subjects by using a nonparametric test (Mann-Whitney $U$ test for independent samples). Significance was set at $P < 0.05$ for all comparisons.

*2 Median; IQR in parentheses (all such values).

*3 Transferrin saturation was calculated by using the following formula: [serum iron (µmol/L) ÷ transferrin (g/L)] × 4.

*4 sTfR, soluble transferrin receptor.

**FIGURE 1.** Correlation between serum ferritin and BMI or serum hepcidin in 27 AN patients. Values were obtained at the time of admission in AN patients. Serum ferritin was plotted against BMI expressed as the SD from the norm (A) or against serum hepcidin (B). Serum ferritin values did not correlate with BMI (SD) but showed a highly significant correlation with serum hepcidin ($P < 0.0001$, $R^2 = 0.47$). Univariate and multivariate analyses were used to determine correlation between the iron-status variable and anthropometric characteristics. AN, anorexia nervosa.
Misra and al (32). Previous studies have shown contradictory results regarding serum transferrin with either normal (33) or lower concentrations at admission that increased after refeeding (34, 35). Therefore, the correlation between transferrin concentration and speed of weight loss indicated that serum transferrin might be a marker of protein nutritional status similar to serum prealbumin.

The only biological variables that differed significantly between anorexic and control subjects were serum ferritin and hepcidin concentrations, which were higher in AN patients than in control subjects and returned to normal after nutritional rehabilitation. High serum ferritin concentrations have already been reported by other authors (4–7). It has been proposed that the contraction of circulating blood volume induced the destruction of red blood cells, iron release, and subsequent increased ferritin synthesis (5). However, our data do not support this hypothesis because we found no sign of hemolysis (haptoglobin and LDH within the normal range). We ruled out all the other known causes of high ferritin concentrations. There was no sign of inflammation because CRP, orosomucoid, and glycosylated ferritin values were normal. All proinflammatory cytokines, including IL-6, were below detectable amounts. Data regarding inflammatory markers in AN are contradictory, with both increased and normal amounts of IL-6 reported (27, 36, 37).

Liver disease, which can affect ferritin concentrations, was also excluded. Indeed, we showed a lower incidence of liver dysfunction in our study than in a previous report (38), probably because of the recent emaciation of our patients compared with patients reported in the literature. Tajiri et al (6) described a case of one AN girl who had a high serum ferritin concentration and nonalcoholic steatohepatitis accompanied by necroinflammatory changes. Liver-biopsy specimens showed iron deposits and peroxidized lipid products in hepatocytes. Excess iron deposition could cause oxidative stress. However, there was no evidence of liver disease or disturbed hepatic function in our study population. In addition, normal serum iron concentrations and transferrin saturation did not argue in favor of liver-iron overload.

The elevated serum hepcidin concentrations shown in AN patients are very intriguing, especially because these values were highly correlated with serum ferritin values. It is likely that a common and new mechanism underlies this concomitant increase in ferritin and hepcidin. There are several pathological conditions in which ferritin and hepcidin concentrations are correlated, although the mechanisms that underlie these correlations are notably different. Tissue-iron overload is known to stimulate intracellular ferritin synthesis by an iron-mediated posttranscriptional regulation (39), with a parallel increase in serum ferritin concentrations. Hepcidin synthesis and secretion by hepatocytes is also stimulated by iron overload by the activation of the bone morphogenic protein/hemojuvelin pathway (see reference 14 for review). In inflammatory conditions, hepcidin synthesis is strongly stimulated by IL-6 (40) through a Janus kinase 2/signal transducer and activator of transcription 3 signaling pathway, and high serum hepcidin concentrations result in macrophage iron retention and stimulation of intracellular ferritin. Iron sequestration in macrophages is a major

### TABLE 4
Clinical and biological characteristics of the follow-up cohort

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>BMI (kg/m²)</th>
<th>Ferritin (µg/L)</th>
<th>Hepcidin (µg/L)</th>
<th>Duration since admission (mo)</th>
<th>BMI (kg/m²)</th>
<th>Ferritin (µg/L)</th>
<th>Hepcidin (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>16.0 (−1.7)</td>
<td>213</td>
<td>158</td>
<td>18</td>
<td>17.6 (−1.2)</td>
<td>21</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>13.6 (−2.7)</td>
<td>310</td>
<td>296</td>
<td>11</td>
<td>20.6 (0)</td>
<td>34</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>12.8 (−2.7)</td>
<td>287</td>
<td>201</td>
<td>22</td>
<td>17.7 (−1.1)</td>
<td>165</td>
<td>78</td>
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<tr>
<td>9</td>
<td>10.8 (−3.1)</td>
<td>178</td>
<td>292</td>
<td>6</td>
<td>13.6 (−1.8)</td>
<td>68</td>
<td>77</td>
</tr>
<tr>
<td>24</td>
<td>11.2 (−3.5)</td>
<td>136</td>
<td>110</td>
<td>2</td>
<td>13.4 (−1.7)</td>
<td>44</td>
<td>ND</td>
</tr>
<tr>
<td>25</td>
<td>14.2 (−2.4)</td>
<td>556</td>
<td>294</td>
<td>12</td>
<td>16.3 (−1.9)</td>
<td>210</td>
<td>ND</td>
</tr>
<tr>
<td>26</td>
<td>12.7 (−2.5)</td>
<td>465</td>
<td>779</td>
<td>14</td>
<td>17.6 (−0.6)</td>
<td>31</td>
<td>14</td>
</tr>
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1 Mean; SD from the norm in parentheses (all such values).
2 ND, not determined.

![FIGURE 2](https://academic.oup.com/ajcn/article-abstract/95/3/548/4626041/552)

**FIGURE 2.** Changes in serum ferritin or hepcidin concentrations after nutritional rehabilitation. Serum ferritin (A) and hepcidin (B) concentrations were assayed at admission and at discharge after nutritional rehabilitation. Only 3 patients had both ferritin and hepcidin determinations, and these patients are identified by the same symbols in A and B. The significance of changes in serum ferritin was analyzed by using the Wilcoxon’s test and was shown to be highly significant (P = 0.004). The number of paired hepcidin determinations was too small to allow statistical analysis.
determinant of the anemia of chronic disorders (18). However, none of our AN patients had detectable amounts of IL-6 or of any other proinflammatory cytokine. As mentioned, we also think we can rule out the presence of excess body iron in these patients. Arruda et al (41) have recently reported that vitamin A deficiency in rats increases liver hepcidin expression. However, it has been reported that AN patients do not suffer from vitamin A deficiency (24). Nevertheless, it has been shown that hepcidin can also be produced by adipocytes (42), but the decrease in fat proportion in AN patients would be expected to reduce rather than increase this source of hepcidin. However, other endocrine perturbations have been described in AN patients including the perturbations of endocrine function of adipose tissue such as decreased circulating leptin concentrations as a consequence of changes of fat mass (43–47). AN in adolescence is associated with specific changes in regional body composition. Furthermore, in contrast to other malnutrition states, weight loss and low BMI in anorexic patients mostly result from fat depletion rather than from protein depletion (30). Chung et al (48) have shown that leptin upregulates hepatic hepcidin expression in vitro through the Janus kinase 2/signal transducer and activator of transcription 3 signaling pathway. However, our malnourished patients were expected to have low serum leptin concentrations, as previously described (43–47).

It is tempting to speculate that the nutritional stress induced by malnourishment at the level of the hepatocyte might stimulate both L-ferritin (the major determinant of serum ferritin) and hepcidin gene expression. This hypothesis is also supported by the observation that serum ferritin and hepcidin concentrations return to normal after weight gain, which probably reflects the changes in metabolism triggered by nutritional rehabilitation and partial anthropometric recovery. Although our study sample was relatively small, the changes in ferritinemia for our 7 patients were large enough to achieve significance. The changes occurred despite the fact that the AN patients remained amenorrheic and still had low BMI at discharge. Nova et al (4) hypothesized that high ferritin values might represent an adjustment in the process of adaptation to low calorie intakes. Subsequently, whenever some weight is gained, ferritin concentrations decrease.

To our knowledge, we show, for the first time, that both hepcidin and ferritin are increased in the serum of AN patients, which is a situation reminiscent of either iron overload or inflammation. However, we could rule out both these conditions in AN patients. The observation that ferritin and hepcidin returned to normal after partial nutritional rehabilitation suggests that these biological markers could be used as markers of disease severity, and nutritional stress induced by malnourishment in the hepatocyte could be a new mechanism that regulates hepcidin. Finally, our study of iron metabolism in AN patients shows that iron supplementation is not necessary in individuals with AN, even in patients with severe undernutrition.

The authors’ responsibilities were as follows—SP-M, BC, CB, and HP: conducted research and wrote the manuscript; MS: performed statistical analyses; MH-N, YA, CM-S, MD, and MW: provided essential reagents and analyzed data; and CS: designed the research. None of the authors had a conflict of interest.

REFERENCES


