Preservation of Neuroendocrine Control of Reproductive Function Despite Severe Undernutrition

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Anorexia nervosa (AN) is characterized by low weight and self-imposed caloric restriction and leads to severe bone loss. Although amenorrhea due to acquired GnRH deficiency is nearly universal in AN, a subset of patients maintains menses despite low weight. The mechanisms underlying continued GnRH secretion despite low weight in these patients and the impact of gonadal hormone secretion on bone mineral density (BMD) in such eumenorrheic, low-weight patients remain unknown. We hypothesized that 1) eumenorrheic women with AN would have higher body fat and levels of nutritionally dependent hormones, including leptin and IGF-I, than amenorrheic women with AN and comparable body mass index; and 2) BMD would be higher in these women. We also investigated whether the severity of eating disorder symptomatology differed between the groups. We studied 116 women: 1) 42 low-weight women who fulfilled all Diagnostic and Statistical Manual of Mental Disorders (fourth edition) diagnostic criteria for AN, except for amenorrhea; and 2) 74 women with AN and amenorrhea for at least 3 months. The two groups were similar in body mass index (17.1 ± 0.2 vs. 16.8 ± 0.2 kg/m²), percent ideal body weight (78.2 ± 0.8% vs. 76.7 ± 0.8%), duration of eating disorder (70 ± 13 vs. 59 ± 9 months), age of menarche (13.2 ± 0.3 vs. 13.5 ± 0.2 yr), and exercise (4.5 ± 1.0 vs. 4.2 ± 0.5 h/wk). As expected, eumenorrheic patients had a higher mean estradiol level (186.6 ± 19.0 vs. 59.4 ± 2.5 nmol/liter; P < 0.0001) than amenorrheic subjects. Mean percent body fat, total body fat mass, and truncal fat were higher in eumenorrheic than amenorrheic patients (20.9 ± 0.9% vs. 16.7 ± 0.6% [P = 0.0001]; 9.8 ± 0.5 vs. 7.8 ± 0.3 kg [P = 0.0009]; 3.4 ± 0.2 vs. 2.7 ± 0.1 kg [P = 0.006]). The mean leptin level was higher in the eumenorrheic compared with the amenorrheic group (3.7 ± 0.3 vs. 2.8 ± 0.2 nmol/ml; P = 0.04). Serum IGF-I levels were also higher in the eumenorrheic than in the amenorrheic group (41.8 ± 3.7 vs. 30.8 ± 2.3 nmol/liter; P = 0.02). There were only minor differences in severity of eating disorder symptomatology, as measured by the Eating Disorders Inventory, and where differences were observed, eumenorrheic subjects manifested more severe symptomatology than amenorrheic subjects. Mean BMD at the posterior-anterior and lateral spine were low in both groups, but were higher in patients with eumenorrhea than in those with amenorrhea (posterior-anterior spine T-score, −0.9 ± 0.1 vs. −1.9 ± 0.1 [P < 0.0001]; lateral spine T-score, −1.2 ± 0.1 vs. −2.3 ± 0.2 [P < 0.0001]). In contrast, preservation of menstrual function was not protective at the total hip (total hip T-score, −0.9 ± 0.1 vs. −1.1 ± 0.1; P = 0.27), trochanter, or femoral neck. In summary, patients with eumenorrhea had more body fat and higher serum leptin levels than their amenorrheic counterparts of similar weight. Moreover, reduced bone density was observed in both groups, but was less severe at the spine, but not the hip, in women with undernutrition and preserved menstrual function than in amenorrheic women of similar weight. Therefore, fat mass may be important for preservation of normal menstrual function in severely undernourished women, and this may be in part mediated through leptin secretion. In addition, nutritional intake and normal hormonal function may be independent contributors to maintenance of trabecular bone mass in low-weight women. (J Clin Endocrinol Metab 89: 4434–4438, 2004)
have a different effect on bone mass. We hypothesized that low-weight, eumenorrheic women would have a higher mean bone density than amenorrheic women of similar weight. We therefore compared two groups of women with comparable body mass indexes (BMIs); one group with preserved hypothalamic-pituitary-gonadal function, and the other with amenorrhea.

**Subjects and Methods**

**Subjects**

We studied a total of 116 women recruited from the community through advertisements and referrals from healthcare providers. Seventy-four women were confirmed to have AN, as defined by the Diagnostic and Statistical Manual of Mental Disorders (fourth edition; DSM-IV) (1). This included intense fear of gaining weight, emphasis on body shape, weight less than 85% ideal body weight (IBW) as determined by the 1959 Metropolitan Life Tables, and lack of menses for at least 3 months (11). We also studied 42 women who fulfilled all DSM-IV criteria for AN, except that they maintained normal menstrual function. Patients receiving estrogens were excluded. Current or past use of medications known to affect bone density, including glucocorticoids, bisphosphonates, and anticonvulsants, were also exclusion criteria.

**Methods**

This study was approved by the institutional review boards at Massachusetts General Hospital and Massachusetts Institute of Technology, and written informed consent was obtained from all subjects. All data were collected during one outpatient visit, which included bone mineral density (BMD) determination performed at the Massachusetts Institute of Technology Clinical Research Center. Nutritional evaluation, including weight in a gown, height, frame size, and BMI, was performed by research dieticians for all study participants. Dieticians also administered a standardized calcium food questionnaire to determine calcium intake. A study investigator conducted interviews with all patients to determine menstrual history, illness duration, medication use, and diagnosis of AN. Subjects classified as eumenorrheic reported they were having regular menstrual cycles. The Eating Disorder Inventory (EDI) was administered to patients studied after March 21, 2001 (32 amenorrheic and 24 eumenorrheic subjects) to determine the severity of psychiatric symptoms related to the eating disorder. Body composition and BMD at the posterior-anterior (PA) lumbar spine (L1-L4), lateral spine, left total hip, femoral neck, trochanter, radius, and total body were measured using dual energy x-ray absorptiometry (DXA) with a Hologic 4500 densitometer (Hologic, Inc., Waltham, MA). This technique has a precision of 0.01 g/cm² at the lumbar spine, 3% for fat mass, and 1.4% for lean body mass (12, 13). A blood sample was collected, and serum was stored at −80°C for measurement of estradiol, FSH, leptin, and IGF-I.

**Assays**

Serum estradiol was measured by double-antibody RIA, with an intraassay coefficient of variation of 3.2–5.3% (Diagnostic Systems Laboratories, Webster, TX). Serum leptin levels were determined by RIA (Linco Research, Inc., St. Louis, MO), with an intraassay coefficient of variation of 3.4–8.3% and a sensitivity of 0.5 ng/ml. Serum IGF-I was measured by immunoradiometric assay, with an intraassay coefficient of variation of 3.9–7.0% (Diagnostic Systems Laboratories).

**Statistical analysis**

JMP Statistical Discoveries, version IV, was used for statistical analysis (SAS Institute, Inc., Cary, NC). An outlier analysis was performed on the amenorrheic group for estradiol and FSH. Sixteen subjects of 90 were determined to be outliers, defined as at least 2 sd greater than the mean, and were excluded from further analysis. Clinical characteristics and bone densities were compared by ANOVA. All variables were tested for normality by the Shapiro-Wilke test. For all variables that were not normally distributed, the Wilcoxon rank-sum test was used to assess statistical significance. Univariate and multivariate regression analyses were performed to investigate determinants of serum leptin. The following variables were entered into the model: total fat mass (kilograms) and total truncal fat (kilograms). Statistical significance was defined as $P \leq 0.05$. Data are reported as the mean ± sem.

**Results**

**Clinical characteristics of study subjects**

The clinical characteristics of eumenorrheic subjects ($n = 42$) were compared with those of amenorrheic subjects ($n = 74$), all of whom fulfilled DSM-IV criteria for AN, except for amenorrhea in the eumenorrheic patients (Table 1). The percent IBW, BMI, duration of AN, age of menarche, and hours per week of exercise were similar between the groups.

**Body composition**

Body composition was compared between the groups (Table 1). Fat mass, truncal fat mass, and percent body fat were significantly higher in the eumenorrheic compared with the amenorrheic subset despite comparable BMI and percent IBW. Eumenorrheic subjects had significantly more truncal fat than amenorrheic subjects.

**Hormone levels**

Mean serum estradiol and FSH levels were higher in the eumenorrheic group, as expected (Table 1). Mean leptin levels (Table 1 and Fig. 1) were higher in the eumenorrheic compared with the amenorrheic group (3.7 ± 0.3 vs. 2.8 ± 0.2 ng/ml; $P = 0.04$). Leptin levels correlated strongly with body fat mass ($r = 0.75$; $P < 0.0001$) and truncal fat ($r = 0.76$; $P < 0.0001$). In a multivariate regression analysis, truncal fat determined 64% of the variability in leptin levels ($r^2 = 0.64$; $P = 0.04$) when truncal fat and total fat were both entered into the model. IGF-I levels (41.8 ± 3.7 vs. 30.8 ± 2.3 nmol/liter; $P = 0.02$) were higher in the eumenorrheic compared with the amenorrheic group (Table 1). The mean sp of IGF-I for age (z-score) was 0.7 ± 0.3 in the eumenorrheic group and −0.5 ± 0.2 in the amenorrheic group ($P = 0.001$). IGF-I levels were below the age-appropriate means in 73% of amenorrheic subjects, but in only 37% of eumenorrheic subjects ($P = 0.001$).

**TABLE 1. Clinical characteristics and serum hormone levels of study subjects: amenorrheic vs. eumenorrheic**

| Variable                        | Amenorrheic | Eumenorrheic |
|---------------------------------|-------------|--------------|
| Age (yr)                        | 24.4 ± 0.7  | 28.3 ± 1.3*  |
| Duration of eating disorder (mos) | 59 ± 9      | 70 ± 13      |
| Age of menarche (yr)            | 13.5 ± 0.2  | 13.2 ± 0.3   |
| Exercise (h/wk)                 | 4.2 ± 0.5   | 4.5 ± 1.0    |
| Weight (kg)                     | 45.6 ± 0.7  | 46.5 ± 1.0   |
| % IBW                           | 76.7 ± 0.8  | 78.2 ± 0.8   |
| BMI (kg/m²)                     | 16.8 ± 0.2  | 17.1 ± 0.2   |
| Total fat mass (kg)             | 7.8 ± 0.3   | 9.8 ± 0.5*   |
| Body fat (%)                    | 16.7 ± 0.6  | 20.9 ± 0.9*  |
| Truncal fat (kg)                | 2.7 ± 0.1   | 3.4 ± 0.2*   |
| Lean mass (kg)                  | 36.6 ± 0.6  | 34.7 ± 0.8*  |
| Estradiol (nmol/liter)          | 59.4 ± 2.5  | 186.6 ± 19.0*|
| FSH (IU/liter)                  | 4.8 ± 0.2   | 6.2 ± 0.6*   |
| Leptin (ng/ml)                  | 2.8 ± 0.2   | 3.7 ± 0.3*   |
| IGF-I (nmol/liter)              | 41.8 ± 3.7  | 30.8 ± 2.3   |

$^a P \leq 0.05$.  
$^b P = 0.001$.  
$^c P < 0.01$.
Bone density

Mean bone densities at all sites in each subset (eumenorrheic and amenorrheic) were below normal (mean T-score range, −0.5 to −2.3; Fig. 2). Absolute BMD and T-scores were significantly lower at the PA and lateral spine, total body, and radius in amenorrheic compared with eumenorrheic patients. After controlling for age at eating disorder diagnosis, the difference in BMD between the groups remained significant at all skeletal sites. Bone density did not differ between the groups at the hip (Fig. 2). Sixty-one percent of amenorrheic patients had osteoporosis compared with 24% of eumenorrheic women. The mean calcium intake was lower in the eumenorrheic than in the amenorrheic group (996 ± 117 vs. 1477 ± 110 mg; P = 0.01). The difference was accounted for by lower dietary calcium intake among the eumenorrheic subjects (521 ± 60 vs. 902 ± 69 mg; P = 0.001), because calcium intake from supplements did not differ between the groups (468 ± 100 vs. 560 ± 70 mg; P = 0.32). BMD at the PA spine correlated with percent IBW (r = 0.33; P = 0.003), estradiol (r = 0.33; P = 0.001), fat-free mass determined by DXA (r = 0.31; P = 0.001), months since last menstrual period (r = −0.27; P = 0.003), and IGF-I (r = 0.21; P = 0.04).

Severity of psychiatric symptoms

Eating disorder symptomatology (Table 2) was evaluated by administering the EDI, a 64-item, self-report questionnaire with eight subscales (14). Drive for thinness (P = 0.02) and body dissatisfaction (P = 0.003) were more severe in the eumenorrheic compared with the amenorrheic group. Likewise, eumenorrheic compared with amenorrheic subjects manifested greater interoceptive awareness (P = 0.01), confusion in recognizing and accurately responding to emotional states, including feelings of hunger and satiety (14). There were no other differences between the eumenorrheic and amenorrheic groups in any of the other five EDI subscales.

Discussion

Our data demonstrate that the relative sparing of fat mass may be critical to the preservation of menstrual function despite severe undernutrition in a subset of extremely low-weight women who fulfill all criteria for AN, except amenorrhea, and that this may be mediated by leptin secretion. In addition, this eumenorrheic subset has higher IGF-I levels than amenorrheic women with AN symptomatology, implying that despite comparable weight, nutritional status may be superior in women who maintain menstrual function. Psychiatric symptoms are unlikely to be a major contributor to maintenance of normal menstrual function, because we observed only minor differences between the groups, and where there were differences, eumenorrheic women had more severe symptoms. Our data also demonstrate that preservation of menstrual function appears to provide partial protection to the skeleton from severe bone loss despite undernutrition. However, significant bone loss still occurs in this low-weight group despite normal gonadal function. Therefore, low-weight and undernutrition, regardless of gonadal status, remain important risk factors for bone loss in young women.

Our data demonstrate significantly greater mean fat mass and percent body fat in low-weight eumenorrheic women compared with amenorrheic women despite similar weights. Therefore, relative sparing of fat mass may be a mechanism underlying preservation of menstrual function in markedly underweight women. As originally proposed by Frisch and McArthur (15), body fat may play a central role in permitting...
Di Carlo through which greater body fat mass leads to preservation of amenorrheic group with AN, and this may be a mechanism individual patient. There may be a total body or visceral fat threshold for each body fat mass, truncal fat, and percent body fat. Although there does not appear to be a threshold percent or absolute amount of body fat above which menstrual function occurs, there may be a total body or visceral fat threshold for each individual patient.

Mean leptin levels were higher in the eumenorrheic women with psychiatric characteristics of AN than in the amenorrheic group with AN, and this may be a mechanism through which greater body fat mass leads to preservation of ovulatory function in this population. To our knowledge, this has not been reported previously, although a small study by Di Carlo et al. (17) reported lower leptin levels in 14 women with AN and compared them to 11 constitutionally lean subjects with low weight and menses, but without the characteristic psychological manifestations of AN. Leptin, an adipocyte-derived hormone, has been posited to play an important permissive role in the neuroendocrine control of reproductive function, and its absence has been suggested to contribute to hypogonadism during starvation (18). Leptin decreases in starved mice in conjunction with delayed ovulation, and leptin administration prevents the ovulatory delay, suggesting that leptin may mediate the effects of starvation on the hypothalamic-pituitary-gonadal axis in mice (19). Our previous data demonstrated lower mean leptin levels in normal-weight women with hypothalamic amenorrhea compared with normal weight and body fat-matched controls (20), suggesting that leptin may also be an important mechanism underlying amenorrhea of hypothalamic origin, such as in AN. Recently, Chan et al. (18) demonstrated that hypogonadism associated with leptin deficiency during starvation in men can be reversed by the administration of recombinant leptin. Therefore, it has been hypothesized that leptin may play a seminal role in permitting normal reproductive function, and leptin deficiency may be the mechanism underlying hypogonadotropic hypogonadism due to starvation.

The bone loss at the spine, total body, and radius observed in low-weight women with eumenorrhea, although marked, does not appear to be as severe as in women of similar weight but with amenorrhea. Therefore, preserved gonadal function may be partially protective to skeletal health. Interestingly, our data from previous studies suggest that administration of exogenous estrogen/progestin combinations to amenorrheic women with AN does not appear to result in increases in bone density in this severely undernourished state (9, 10). It is also important to note that differences in bone density between the groups cannot be attributed to differences in calcium intake, because mean calcium intake in the eumenorrheic group was lower than that in the amenorrheic group. The presence of higher mean serum IGF-I levels in the eumenorrheic compared with the amenorrheic group probably reflects a relatively preserved nutritional status and also suggests a possible role for IGF-I in the preservation of bone mass in this group. IGF-I, which is secreted by the liver in response to GH secretion from the pituitary, has been shown to be a sensitive nutritional marker that decreases markedly with both acute and chronic starvation, including in women with AN (21, 22). AN is characterized by GH resistance, with high serum GH and low IGF-I levels, and IGF-I deficiency is probably an important mediator of undernutrition and a mechanism underlying bone loss in women with AN. IGF-I is a critical factor necessary for linear bone growth and maintenance of skeletal health in humans and, therefore, may be a contributory factor to the relative sparing of bone mass observed in low-weight, eumenorrheic women in this study. We have recently shown that administration of recombinant IGF-I in replacement doses is effective at increasing bone mass in women with AN, whereas estrogen therapy alone is minimally, if at all, effective (9, 10). The data from the study reported here suggest that severely undernourished women who remain eumenorrheic may experience a relatively less severe state of IGF-I deficiency and that the higher IGF-I levels may contribute to relative sparing of bone.

To our knowledge bone density in eumenorrheic, low-weight women with psychiatric manifestations of AN has not been investigated previously. Watson and Andersen (23) recently reported no difference in bone density at the lumbar spine or hip in 24 low-weight women with irregular menses and disordered eating behaviors compared with women who fulfilled all criteria of AN, including amenorrhea. The lack of difference in spine bone density between the groups in that study may be attributable to the smaller number of eumenorrheic subjects studied, the focus on subjects with irregular instead of regular menses (as in our study), or the less marked bone loss observed in their amenorrheic cohort than in the current study. For example, in the current study, we report a mean bone density 1.9 sd below the normal mean compared with 1.2 sd in the Watson study (23). The bone density of the AN group reported here is similar to that of our previously published data in a different group of women with AN (7).

Bone loss at the spine was more severe than at other skeletal sites, likely due to the higher proportion of trabecular bone than at other skeletal sites tested. Trabecular bone is more metabolically active than cortical bone and has been shown to be proportionately more affected in estrogen deficiency states, including menopause, than other skeletal sites (7, 24). Therefore, a greater impact of gonadal steroid deprivation at the spine than other sites, as observed in our data, is consistent with the hypothesis that estrogen deficiency is an important etiologic factor in the development of osteopenia in AN.

Eating disorder symptomatology, as measured by the EDI, was slightly more severe in the eumenorrheic than in the amenorrheic group, with significant differences in drive for thinness, body dissatisfaction, and interoceptive awareness. These data suggest that the severity of eating disorder symptomatology is unlikely to be a major underlying mechanism in the development of amenorrhea in low-weight women with eating disorders. These results are in concordance with...
other studies (23, 25) that report a lack of major psychiatric differences in women who fulfill all DSM-IV criteria of AN, including low weight and psychiatric symptoms, except for amenorrhea, and one study that reported a trend toward a greater severity of psychiatric comorbidities in a menstruating group (6). These published data demonstrate few significant differences in psychiatric comorbidities, demographics, ill history, or treatment response between amenorrheic and eumenorrheic women with all other manifestations of AN (23).

In conclusion, our data are consistent with the hypothesis that body fat and leptin may play a role in maintaining menstrual function in a subset of women with severe undernutrition and psychiatric manifestations of AN. We also demonstrate the importance of endogenous gonadal function and a possible role for maintenance of IGF-I secretion in the preservation of bone mass in women with AN. It should be noted, however, that bone density was low despite normal gonadal function and higher IGF-I levels in the eumenorrheic group, which highlights the importance of nutrition for maintenance of bone mass in this population. Additional studies are needed to determine the mechanisms of underlying preserved gonadal function in women with low weight and body fat.

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