Plasma Sodium Level Is Associated With Bone Loss Severity in Women With Anorexia Nervosa: A Cross-Sectional Study

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ABSTRACT

Background: Anorexia nervosa is a psychiatric disorder characterized by restrictive eating, low body weight, and severe bone loss. Recent data show a deleterious relationship between low circulating sodium levels and bone mass, and relative or absolute hyponatremia is a known complication of anorexia nervosa. Clinical studies of other medical conditions associated with hyponatremia suggest that detrimental effects of low sodium levels on health are seen even within the normal range. We hypothesized that women with anorexia nervosa and relatively low plasma sodium levels would have lower bone mineral density (BMD) than those with higher plasma sodium levels.

Method: In a cross-sectional study (January 1, 1997–December 31, 2009) of 404 women aged 17 to 54 years (mean ± standard error of the mean [SEM] age = 25.6 ± 0.3 years) who met *DSM-IV* criteria for anorexia nervosa, we measured BMD using dual-energy x-ray absorptiometry. Bone mineral density was compared in women with plasma sodium levels < 140 mmol/L (midpoint of normal range) versus those with plasma sodium levels ≥ 140 mmol/L and in women with hyponatremia (plasma sodium < 135 mmol/L) versus those without. The study was conducted at the Neuroendocrine Unit of Massachusetts General Hospital, Boston.

Results: Women with plasma sodium levels < 140 mmol/L had significantly lower BMD and *t* and *z* scores versus those with plasma sodium levels ≥ 140 mmol/L at the anterior-posterior (AP) spine (mean ± SEM *z* scores = −1.6 ± 0.1 vs −1.3 ± 0.1, $P = .004$) and total hip (mean ± SEM *z* scores = −1.2 ± 0.1 vs −0.9 ± 0.1, $P = .029$). In a model controlling for age, BMI, psychiatric drug use, and disease duration, differences in BMD and *t* and *z* scores remained significant at the AP spine. Women with hyponatremia had significantly lower BMD and *t* and *z* scores versus those without hyponatremia at the AP spine (mean ± SEM *z* scores = −2.2 ± 0.3 vs −1.3 ± 0.1, $P = .009$), lateral spine (mean ± SEM *z* scores = −2.4 ± 0.4 vs −1.5 ± 0.1, $P = .031$), and total hip (mean ± SEM *z* scores = −2.5 ± 0.5 vs −1.0 ± 0.1, $P < .0001$). In a model controlling for age, BMI, psychiatric drug use, and disease duration, differences in BMD and *z* and *t* scores remained significant at all sites.

Conclusions: These data suggest that relative plasma sodium deficiency may contribute to anorexia nervosa–related osteopenia.

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Anorexia nervosa is a psychiatric disorder characterized by restrictive eating, low body weight, and severe bone loss. In a study of 130 women with anorexia nervosa and a mean age of 24 years old, Grinspoon et al[1] found that more than 90% had osteopenia and nearly 40% had osteoporosis at 1 or more skeletal sites. Consistent with these data, Miller et al[2] reported that only 14% of 214 ambulatory young women with anorexia nervosa had normal bone mineral density (BMD) at all sites and 30% reported a history of bone fracture. The risk of fractures in women with anorexia nervosa is up to 7 times that of age-matched healthy women.[3] Anorexia nervosa–induced bone loss in adult women reflects a decrease in bone formation and increase in bone resorption, which has been attributed to nutritional deficiencies and endocrine abnormalities, including hypoestrogenemia, growth hormone resistance, and hypercortisolemia.[4] Recent reports indicate that hyponatremia, a complication of anorexia nervosa,[2] has deleterious effects on bone.[5–10] Verbalis et al[5] demonstrated that experimentally induced hyponatremia in rats results in a marked reduction in BMD and trabecular and cortical parameters. Clinical studies of other medical conditions associated with hyponatremia suggest that detrimental effects of low sodium levels on health are seen even within the normal range.[11–14] We hypothesized that women with anorexia nervosa and relatively low plasma sodium levels would have lower BMD than those with higher plasma sodium levels, suggesting that sodium deficiency may contribute to the profound bone loss seen in this disorder.

METHOD

Subjects

Four hundred four women (18–54 years of age) who completed a screening visit between January 1, 1997, and December 31, 2009, in the Neuroendocrine Unit at the Massachusetts General Hospital for studies involving bone density determinations in adult women with anorexia nervosa were included in the study. Subjects met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, criteria for anorexia nervosa (intense fear of gaining weight, emphasis on body shape, weight less than 85% of ideal body weight), except for amenorrhea. Women who were pregnant were excluded from the study. Participants were recruited through referrals from local eating disorder providers and on-line advertisements. Subject characteristics, sodium levels, and DXA results have been previously reported in subsets, but the relationship between plasma sodium levels and bone density has not been described.[1,2,15–22]

Clinical Points

- Women with anorexia nervosa are at risk for hyponatremia and severe osteopenia.
- Animal models suggest that hyponatremia results in bone loss.
- Women with anorexia nervosa and lower plasma sodium levels have more severe bone loss than those with higher plasma sodium levels.
- Relatively low plasma sodium levels may contribute to anorexia nervosa–induced bone loss.

Procedures

The study was approved by the Partners Institutional Review Board and complied with the Health Insurance Portability and Accountability Act[23] guidelines. Written informed consent was obtained from all participants.

Subjects had a complete medical history and physical examination performed by a physician, physician's assistant, or nurse practitioner at the Massachusetts General Hospital Clinical Research Center. Height was measured as the mean of 3 readings on a single stadiometer. Elbow breadth was measured using calipers and compared to norms based on the first National Health and Nutrition Examination Survey (NHANES-I) data[24] (for estimation of frame size). Participants were weighed on an electronic scale while wearing a hospital gown. Body mass index (BMI) was calculated using the formula *weight (kg)/height (meter^2)*; percentage of ideal body weight was calculated based on 1983 Metropolitan Life Height and Weight Tables.[25] Bone mineral density at the anterior-posterior (AP) spine (L1–L4), lateral spine (L2–L4), and total hip was determined using DXA (Hologic QDR 4500, Waltham, Massachusetts). This technique has a precision of 0.01 g/cm^2 at the lumbar spine.[26] Plasma sodium levels were measured by the MGH clinical pathology laboratories using a Roche/Hitachi fully automated chemistry analyzer (Roche Diagnostics, Indianapolis, Indiana; normal range, 135–145 mmol/L) and closely monitored for consistency over the study time frame.[27]

Data Analysis

JMP Statistical Discoveries (Version 9.0.0; SAS Institute, Inc, Cary, North Carolina) was used for statistical analyses. Clinical characteristics and measures of BMD were compared using the Student *t* test. Multivariable least-squares analyses were constructed to control for potential confounders. Statistical significance was defined as a 2-tailed P value < .05. Data are reported as mean ± standard error of the mean (SEM).

RESULTS

Subject Characteristics: Women With Sodium Levels at or Above vs Below 140 mmol/L

Subject characteristics are presented in Table 1. Mean ± SEM age of subjects was 25.6 ± 0.3 years. Twenty-three percent of subjects with anorexia nervosa reported binge/purge activity. Mean ± SEM plasma sodium levels did not differ significantly between those who purged and those who did not (140.6 ± 0.3 mmol/L vs 140.6 ± 0.2 mmol/L, respectively; P = .94). One hundred seventeen of the 404 women had plasma sodium levels below 140 mmol/L (the midpoint of the normal range). Women with sodium levels below 140 mmol/L were older and reported greater duration of anorexia nervosa than those with plasma sodium levels at or above 140 mmol/L. A greater percentage of the women with plasma sodium levels below 140 mmol/L reported current psychiatric medication use than those with sodium levels at or above 140 mmol/L (66% vs 49%, P = .002). Fifty percent of subjects with plasma sodium levels below 140 mmol/L were treated with SSRIs compared to 37% of those with plasma sodium levels at or above 140 mmol/L (P = .01). The percentage of subjects treated with antipsychotics (16% vs 13%, P = .33) did not differ significantly between those with plasma sodium levels below 140 mmol/L and those at or above 140 mmol/L. BMI, age of diagnosis, estrogen use (oral or transdermal), and age at menarche did not differ significantly between the groups. Sixty-four percent of those with plasma sodium levels greater than or equal to 140 mmol/L and 64% of those with plasma sodium levels less than 140 mmol/L were amenorrheic (P = .96).

Subject Characteristics: Women With Versus Without Hyponatremia

Twelve of the 404 women were hyponatremic (plasma sodium level less than 135 mmol/L). Women with hyponatremia were older, had lower BMI, and reported greater duration of anorexia nervosa than those without hyponatremia. A greater percentage of the women with hyponatremia reported current psychiatric medication use than those without hyponatremia (83% vs 53%, P = .04). In women with hyponatremia versus those without, the percentage of subjects treated with selective serotonin reuptake inhibitors (SSRIs) (58% vs 40%, P = .22) and antipsychotics (33% vs 13%, P = .08) did not significantly differ. Age at diagnosis, estrogen use (oral or transdermal), and age at menarche did not differ between the groups. Seventy-five percent of those with hyponatremia and 64% of those without were amenorrheic (P = .41).

Bone Mineral Density: Women With Sodium Levels at or Above Versus Below 140 mmol/L

Table 1 and Figure 1 present differences in BMD and *t* and *z* scores based on plasma sodium levels. Women with plasma sodium levels below 140 mmol/L had lower BMD and lower *t* and *z* scores at the AP spine and total hip compared to those with sodium levels at or above 140 mmol/L. There was a trend toward lower BMD and *t* scores at the lateral spine in those with plasma sodium levels below 140 mmol/L compared to those at or above 140 mmol/L. In a model controlling for age, BMI, psychiatric drug use, and disease duration, differences remained significant at the AP spine. When the use of SSRIs and antipsychotics was substituted for psychiatric drug use in the model, the findings were similar.

Table 1. Demographic and Clinical Characteristics and Differences in Bone Mineral Density Based on Plasma Sodium Level[a]

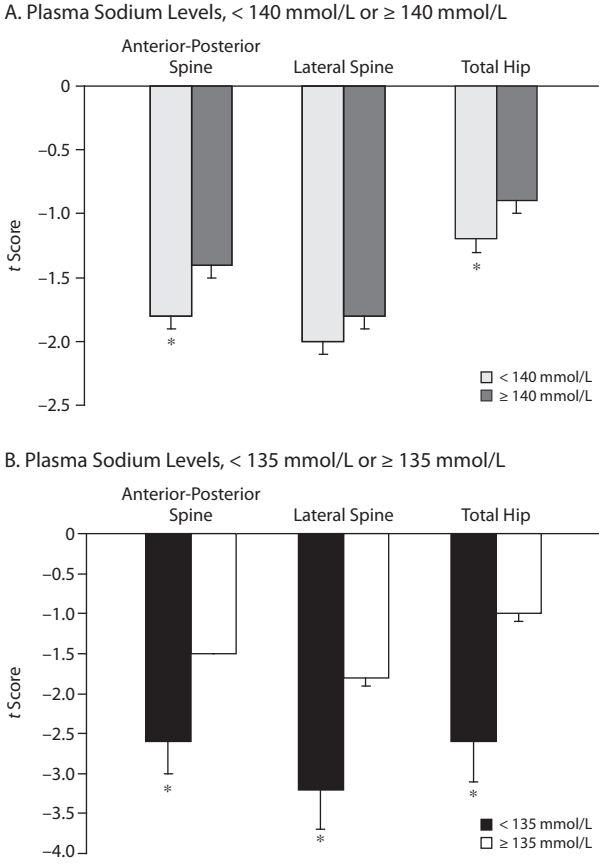
Characteristic	Plasma Sodium Level[b] Cutoff at Midpoint of Normal Range			Plasma Sodium Level[b] Cutoff at Low End of Normal Range		
	Sodium < 140 n = 117	Sodium ≥ 140 n = 287	*P* Value	Sodium < 135 n = 12	Sodium ≥ 135 n = 392	*P* Value
Age, y	27.5 ± 0.7	24.8 ± 0.4	.0005	31.3 ± 1.9	25.4 ± 0.3	.004
Body mass index, kg/m^2	16.9 ± 0.1	17.2 ± 0.1	NS	15.4 ± 0.6	17.2 ± 0.1	.0009
Height, cm	164.2 ± 0.7	164.7 ± 0.4	NS	164.1 ± 2.4	164.5 ± 0.3	NS
Age at diagnosis, y	20.3 ± 0.6	20.0 ± 0.4	NS	21.6 ± 1.9	20.0 ± 0.3	NS
Duration of anorexia nervosa, y	6.9 ± 0.7	4.9 ± 0.4	.007	9.7 ± 2.0	5.3 ± 0.4	.022
Age at menarche, y	13.4 ± 0.2	13.4 ± 0.1	NS	13.7 ± 0.6	13.4 ± 0.1	NS
Bone mineral density						
Anterior-posterior spine						
Bone mineral density	0.850 ± 0.011	0.891 ± 0.007	.002	0.774 ± 0.035	0.883 ± 0.006	.002
t Score	−1.8 ± 0.1	−1.4 ± 0.1	.004	−2.6 ± 0.4	−1.5 ± 0.0	.002
z Score	−1.6 ± 0.1	−1.3 ± 0.1	.004	−2.2 ± 0.3	−1.3 ± 0.1	.009
Lateral spine						
Bone mineral density	0.657 ± 0.010	0.675 ± 0.006	.095	0.581 ± 0.029	0.673 ± 0.005	.002
t Score	−2.0 ± 0.1	−1.8 ± 0.1	.093	−3.2 ± 0.5	−1.8 ± 0.1	.0008
z Score	−1.6 ± 0.1	−1.5 ± 0.1	NS	−2.4 ± 0.4	−1.5 ± 0.1	.031
Total hip						
Bone mineral density	0.790 ± 0.013	0.832 ± 0.113	.002	0.630 ± 0.036	0.825 ± 0.006	< .0001
t Score	−1.2 ± 0.1	−0.9 ± 0.1	.009	−2.6 ± 0.5	−1.0 ± 0.1	< .0001
z Score	−1.2 ± 0.1	−0.9 ± 0.1	.029	−2.5 ± 0.5	−1.0 ± 0.1	< .0001

[a]Data are presented as mean ± standard error of the mean unless otherwise noted.
[b]Plasma sodium levels are presented as mmol/L.

Bone Mineral Density: Women With Versus Without Hyponatremia

Hyponatremic women had lower BMD and lower *t* and *z* scores at every site compared to those without hyponatremia (Table 1 and Figure 1). In a model controlling for age, BMI, psychiatric drug use, and disease duration, differences remained significant at all sites. When the use of SSRIs and antipsychotics was substituted for psychiatric drug use in the model, the findings were similar.

Figure 1. Differences in Mean Bone Mineral Density Based on Plasma Sodium Levels in Patients With Anorexia Nervosa[a]



[a]Error bars indicate standard error of the mean.
*$P < .01$.

DISCUSSION

In this cross-sectional study of more than 400 women with anorexia nervosa, we found that those with lower plasma sodium levels had more severe bone loss, independent of age, BMI, psychiatric medication use, and disease duration. Notably, these differences were evident within the normal plasma sodium range.

Hyponatremia, even when mild and asymptomatic, has been associated with increased risk of fractures in older adults.[7–10] NHANES-III participants 50 years of age or older who had hyponatremia were more likely to have osteoporosis at the femoral neck and total hip than those who had normal sodium levels.[5] Using a rat model for the syndrome of inappropriate antidiuretic hormone (SIADH), Verbalis et al[5] found that 3 months of hyponatremia (mean ± SEM sodium level = 110 ± 2 mmol/L) resulted in a 30% reduction in BMD compared to normonatremic controls. In addition, cortical and trabecular microarchitectural parameters were severely impaired in the chronically hyponatremic rats. Based on the findings of a 5-fold increase in osteoclast number per bone area, suggesting increased resorptive activity, and a relative decrease in concentration of the bone formation marker

osteocalcin in hyponatremic rats compared to controls, the authors concluded that chronic hyponatremia leads to bone loss through an uncoupling of bone resorption and formation.[5] Cellular and molecular studies have confirmed increased osteoclastic bone resorption in response to low extracellular sodium levels.[6] Resorption of sodium from bone is thought to be a mechanism to restore blood sodium levels to normal.[5,6] Recent research has called into question whether the established reference range for sodium is appropriate, given the increased morbidity and mortality seen in patients with relatively low sodium levels in the normal range.[11–14]

Women with anorexia nervosa are at risk for hyponatremia due to inappropriate secretion of vasopressin, a posterior pituitary peptide hormone that acts at the kidneys to increase resorption of free water.[28] Other contributors to low sodium levels in these women include excessive water consumption, hypovolemia due to inadequate nutrition and purging behaviors, impaired renal sodium reabsorption in the setting of malnutrition, and use of psychotropic medications that result in SIADH or polydipsia.[29–32] Given the prevalence of hyponatremia and osteopenia in women with anorexia nervosa, we studied whether relatively low plasma sodium levels in these women were associated with the severity of osteopenia. Whether we used a plasma sodium cutoff at the lower end or middle of the normal range, we found that those women with relatively lower plasma sodium levels had more severe bone loss, independent of potential confounders.

In our study, women with relatively low sodium levels tended to be older, with a longer duration of illness, and were more likely to report current use of psychiatric medications. Those with frank hyponatremia also had a lower mean BMI. Lower sodium levels may therefore reflect severity of illness in anorexia nervosa and/or use of psychiatric medications. Importantly, differences in BMD were still significant after controlling for these factors.

In summary, we report increased severity of bone loss in patients with lower plasma sodium levels, independent of age, BMI, psychiatric medication use, and disease duration. This is a cross-sectional study, and therefore causality cannot be determined. However, these data suggest that relatively low plasma sodium levels may contribute to the severe bone loss seen in women with anorexia nervosa.

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