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Hyponatremia and decreased bone density in adolescent inpatients diagnosed with anorexia nervosa

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ABSTRACT

Objective: Recent studies demonstrated an association between low serum sodium levels and reduced bone density. Patients with anorexia nervosa (AN) are at greater risk for osteoporosis as well as for hyponatremia. The aim of the present study was to assess the association between hyponatremia and bone mineral density (BMD) in a large cohort of adolescent inpatients with AN.
Methods: A historic cohort study of 174 adolescent females (mean age 15.7 ± 1.8 y) hospitalized because of AN between 2003 and 2013. Demographic and clinical data, including age, psychiatric comorbidity, anthropometric measurements, laboratory tests, and BMD scores were obtained from the patients' medical charts.
Results: Mean lumbar spine BMD z-score of the patients was lower than expected in the normal population (mean −1.5 ± 1.2) and positively correlated with body mass index standard deviation score ($r = 0.42$, $P < 0.0001$). Sixty-four participants (36.8%) had at least one episode of hyponatremia during the year preceding the BMD measurement. These participants had a significantly lower lumbar spine BMD z-score (−1.8 ± 1.2 versus −1.3 ± 1.2, $P = 0.01$) compared with participants with no hyponatremia. Lumbar spine BMD z-score was also positively correlated with the levels of free triiodothyronine ($r = 0.16$, $P = 0.038$), 17 b-estradiol ($r = 0.23$, $P = 0.005$), and luteinizing hormone ($r = 0.25$, $P = 0.001$), and negatively correlated with cortisol levels ($r = 0.33$, $P < 0.0001$). Having at least one episode of hyponatremia, BMI z-score and cortisol levels were identified as independent predictors of BMD z-score ($P < 0.001$, $P < 0.001$, and $P = 0.034$, respectively).
Conclusions: Hyponatremia may be associated with decreased bone density in adolescent females with AN. Additional studies are required to evaluate whether the correction of hyponatremia will improve BMD.

Introduction

Anorexia nervosa (AN) carries a high rate of morbidity, with osteoporosis being one of its major complications [1,2]. Considerable reduction of bone mass has been reported even in young adolescents with AN [3], and the risk of fracture is significantly higher compared to healthy controls [4]. AN-related bone loss has been attributed to nutritional deficiencies, reduction in lean body mass [5,6], and changes in hormones involved in bone metabolism [1,7]. Gathering knowledge about the determinants of impaired bone mineral density (BMD) in AN is essential to

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develop appropriate therapeutic strategies to optimize bone quality.

Recent population studies have shown that even mild hyponatremia may be associated with low BMD and bone fractures [8–18]. Most of the studies assessing the association between hyponatremia and impaired bone density have included mainly elderly people, in whom hyponatremia is a common finding. These epidemiologic and observational findings are supported by animal-model studies demonstrating increased osteoclastic bone resorption in response to low extracellular sodium levels [11,19]. This effect is consistent with reports indicating that approximately one-third of total-body sodium is stored in bone [20] and that the release of sodium from bone during prolonged deprivation requires the resorption of bone matrix [11,19,21].

Patients with AN are at risk for hyponatremia because of several processes: inappropriate secretion of vasopressin (syndrome of inappropriate antidiuretic hormone secretion); excessive water consumption; electrolyte disturbances due to inadequate nutrition and purging behaviors; impaired renal sodium reabsorption in the setting of malnutrition; and the use of psychotropic medications, potentially resulting in syndrome of inappropriate antidiuretic hormone secretion or polydipsia [22–26]. To our knowledge, only one previous study investigated the association between low sodium plasma levels and bone density in female patients with AN [27]. In this cross-sectional study of women ages 17 to 54 y, lower sodium level was associated with lower BMD. The effect of sodium level on BMD of adolescents with AN has not yet been evaluated.

The aim of the present study was to assess the possible contribution of hyponatremia to impaired bone density in a large cohort of female adolescents hospitalized because of AN. In addition, we assessed hormonal risk factors for osteoporosis.

Materials and methods

Patients

The study was approved by the Institutional Review Board at the Sheba Medical Center. All adolescent females ages 10 to 19 y diagnosed with AN who were hospitalized in the Pediatric Psychosomatic Department of The Edmond and Lily Safra Children's Hospital between 2003 and 2013 and who had BMD measurements available were included in the study. For patients who had more than one hospitalization during the study period, only data from the first hospitalization were used. Demographic and clinical data, including age, anthropometric measurements, laboratory data, and psychiatric comorbidity were obtained from the patients' medical charts.

Diagnosis of an eating disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th ed (DSM-IV) [28] and of other lifetime DSM-IV Axis I psychiatric morbidity was established using the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P Version 2.0) [29]. Participants were interviewed independently by two highly experienced child and adolescent psychiatrists. The degree of diagnostic interrater reliability (according to the correlation coefficient procedure) between the two raters was $r = 0.92$. The diagnoses of AN and of other psychiatric comorbid disorders were finalized in clinical meetings of the department's team. For the present study, we included patients who fit the diagnostic criteria of AN according to the DSM-V [30].

The patients included in the study had no evidence of organic brain disorders, schizophrenic-spectrum disorders, substance-use disorders, or any significant medical or neurologic disorder, including those with the potential to affect food consumption, weight, and bone metabolism (e.g., diabetes mellitus, primary thyroid disorders, or chronic inflammatory diseases).

Anthropometric measurements

Standing height was measured to the nearest 0.1 cm, using a wall-mounted stadiometer, and body weight was obtained to the nearest 0.1 kg, with the patient wearing a hospital gown and without any footwear. For the sake of reducing internal variability, all measurements were taken during the morning hours, using standardized procedures. Body mass index (BMI) was calculated based on the formula weight (kg)/height $(m)^2$. Height, weight, and BMI standard deviation scores were calculated using age and sex-specific growth data (based on the Centers for Disease Control and Prevention's Year 2000 Growth Charts) found adequate for assessing Israeli children and adolescents [31].

Laboratory tests

Blood samples for sodium, calcium, phosphate, alkaline phosphatase, 25-hydroxy vitamin D, thyroid function tests, cortisol, prolactin, follicle stimulating hormone, luteinizing hormone (LH), and 17 b-estradiol (E2) were obtained upon admission to the Pediatric Psychosomatic Department as part of routine care. Samples were obtained between 07:00 h and 09:00 h after an overnight fast. In addition, all sodium measurements obtained during the year preceding the BMD measurement were retrieved from the patients' electronic charts. For the purpose of data analysis, we documented the presence of episodes of hyponatremia, defined as serum sodium concentration $\leq$136 mmol/L [32], and grouped all patients with at least one episode of hyponatremia. In addition, all sodium measurements available for each patient before the BMD study were averaged ("average sodium").

Serum sodium, calcium, phosphate, and alkaline phosphatase were measured using an autoanalyzer (AU2700, Olympus, Hamburg, Germany). Levels of 25-hydroxy vitamin D were determined using the LIAISON (DiaSorin, Saluggia, Italy) competitive two-step chemiluminescent immunoassay. Thyrotropin, free triiodothyronine, and free thyroxin were measured by UniCel DxI 800 Access Immunoassay System (Beckman Coulter Inc., Brea, CA, USA). Cortisol, prolactin, follicle stimulating hormone, LH, and E2 were measured by a chemiluminescent method (IMMULITE 2000, Diagnostic Products Corporation, Los Angeles, CA, USA).

Bone mineral density

BMD at the lumbar spine (L1–L4) was evaluated using dual-energy x-ray absorptiometry (DXA) (Lunar Prodigy, GE Medical Systems, Madison, WI, USA) as part of patients' routine care. BMD is expressed in grams per square centimeter and in terms of z-scores (i.e., the difference between the BMD of the patient and the average BMD of age- and sex-matched controls divided by the standard deviation of the control group).

Data analysis

The initial analysis included estimations of mean, standard deviations, and frequency distribution. Comparisons between subgroups of patients were made using the unpaired t test for continuous variables and the Pearson χ^2 test for categorical variables. Pearson correlation coefficients were calculated to study the relationship between potential continuous predictors. Variables significantly associated with BMD z-score were included in regression models to examine independent predictors of decreased BMD z-score. Results were considered significant if the two-sided P value was <0.05. Calculations were performed using SPSS Statistics 23.0 (IBM, Armonk, NY, USA), a statistical software package.

Results

The study included 174 patients. Their characteristics are presented in Table 1. Mean age at the time of BMD measurement was 15.7 ± 1.8 y (range 9.7–19.6) and illness duration at that time was 2.2 ± 1.5 y. Fifty-nine patients (34.9%) had regular menstruation, 21 (12.4%) were premenarche, 7 (4.1%) had primary amenorrhea (defined as age >15 y with no menses), and 82 (48.5%) had secondary amenorrhea. The mean duration between cessation of menstruation and BMD measurement was 0.9 ± 0.6 y.

Ninety-two girls (52.9%) were diagnosed with depressive disorders, 16 (9.2%) with anxiety disorders, 21 (12.1%) with obsessive compulsive disorder, and 11 (6.3%) with attention deficit hyperactivity disorder. The patients were not treated with psychotropic medications in the first month of their hospitalization, the time when DXA was performed.

Lumbar spine BMD z-score of the patients was lower than expected in the normal population (-1.5 ± 1.2) and positively correlated with BMI standard deviation ($r = 0.42$, $P < 0.0001$) (Fig. 1).

Patients had a mean of 5.5 ± 3.6 measurements of sodium during the year preceding the DXA. Looking at all measurements,