Decreased Nocturnal Oxytocin Levels in Anorexia Nervosa Are Associated With Low Bone Mineral Density and Fat Mass

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ABSTRACT

Objective: Anorexia nervosa is characterized by self-induced starvation and associated with severe bone and fat loss. Oxytocin is a peptide hormone involved in appetite and energy homeostasis. Recent data show that oxytocin has an anabolic effect on bone and stimulates osteoblast function. There is limited information about oxytocin levels or their relationship to decreased bone mineral density in anorexia nervosa. Our objective was to investigate the relationship between oxytocin levels, bone mineral density, and body composition in women with anorexia nervosa.

Method: We studied 36 women, mean ± SEM age 27.6 ± 1.3 years: 17 with *DSM-IV* anorexia nervosa and 19 healthy controls in a cross-sectional study. Oxytocin levels were determined from pooled serum samples obtained every 20 minutes from 8 PM to 8 AM during an inpatient overnight visit. Fasting leptin levels were measured. Bone mineral density at the anterior-posterior and lateral spine and hip and body composition were assessed by dual energy x-ray absorptiometry. The study was conducted from September 2004 to June 2008.

Results: Subjects with anorexia nervosa versus healthy controls had lower mean ± SEM oxytocin levels (14.3 ± 1.5 vs 31.8 ± 5.1 pg/mL, $P = .003$), leptin levels (2.7 ± 0.5 vs 11.4 ± 1.1 ng/mL, $P < .0001$), bone mineral density (anterior-posterior spine: 0.83 ± 0.02 vs 1.04 ± 0.03; lateral spine: 0.63 ± 0.02 vs 0.81 ± 0.02; total hip: 0.79 ± 0.03 vs 0.97 ± 0.03 g/cm^2, $P < .0001$), and fat mass (8.8 ± 0.6 vs 19.7 ± 0.9 kg, $P < .0001$). Oxytocin levels were associated with bone mineral density at the anterior-posterior ($r = 0.40$, $P = .02$) and lateral ($r = 0.36$, $P = .04$) spine, fat mass ($r = 0.42$, $P = .01$), and leptin levels ($r = 0.55$, $P = .001$).

Conclusions: Overnight secretion of oxytocin in women with anorexia nervosa is decreased compared with healthy women. Low oxytocin levels are associated with decreased bone mineral density and body fat and may contribute to anorexia nervosa–induced bone loss.

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Anorexia nervosa is a psychiatric illness affecting up to 1% of college-aged women, characterized by self-induced starvation and associated with severe bone loss. Oxytocin, a peptide hormone synthesized and secreted centrally in the supraoptic and paraventricular nuclei of the hypothalamus, is stored and released into the peripheral circulation via the posterior pituitary gland. Experiments using animal models indicate that oxytocin may be involved in appetite[1–4] and energy regulation.[5,6] Recent studies have shown that oxytocin may also play an important anabolic role in bone homeostasis, promoting osteogenesis over adipogenesis[7] and osteoblast in favor of osteoclast activity.[4] The low bone mass in anorexia nervosa is characterized by marked inhibition of bone formation markers consistent with impaired osteoblast function. The role of oxytocin in fat distribution and bone mineral density has not been well explored in humans. There are limited data on oxytocin levels in anorexia nervosa, and the potential role of oxytocin as a mediator of bone loss in this population is unknown.

We hypothesized that oxytocin levels would be lower in women with anorexia nervosa compared to healthy women and would be associated with low bone mineral density, fat mass, and leptin levels. We therefore investigated oxytocin levels in women with anorexia nervosa compared to healthy women. We determined the relationship between oxytocin and bone mineral density at the anterior-posterior and lateral spine and total hip, fat mass, and leptin levels.

METHOD

Subjects

We studied 36 women: 17 with anorexia nervosa and 19 healthy controls. All subjects were recruited from the community through advertisements and referrals from health care providers. Subject clinical characteristics, bone mineral density, and leptin levels were previously reported in subsets of anorexia nervosa and healthy control subjects.[8–10] Pooled oxytocin levels from overnight sampling and its relationship to bone density, fat mass, and leptin levels in these subjects have not been previously reported.

Subjects with anorexia nervosa met *DSM-IV* criteria, including intense fear of gaining weight, emphasis on body shape, weight less than 85% of ideal body weight as determined by the 1983 Metropolitan Life tables,[11] and amenorrhea for at least 3 consecutive months.

Healthy controls were 90%–120% of ideal body weight and reported regular menstrual cycles. Healthy controls had no history of amenorrhea or disordered eating.

All subjects had normal thyroid function tests. Subjects were excluded if they had any condition known to affect bone metabolism other than anorexia nervosa or history of diabetes mellitus. Additional exclusion criteria included active abuse of drugs or alcohol, use of medication known to affect bone metabolism within 3 months (including estrogen), use of depot medroxyprogesterone within 6 months, use of a bisphosphonate within a year, and pregnancy or breastfeeding within 6 months of the study.

Design

This study was approved by the institutional review boards of Partners Health Care, Inc, and Massachusetts Institute of Technology. Written informed consent was obtained from all subjects prior to any procedures. All subjects were admitted to the Clinical Research Center of Massachusetts General Hospital, Boston, for an outpatient screening visit and an inpatient overnight visit. The study was conducted from September 2004 to June 2008.

At the screening visit, height, weight, and elbow breadth were measured by research dietitians, blood was drawn for screening laboratory tests, and a comprehensive history and physical examination were performed. Exercise patterns and alcohol intake were assessed. Percentage of ideal body weight was calculated as described above. Body mass index was obtained by dividing the weight in kilograms by the square of height in meters. Frame size was determined by comparing elbow breadth to race-specific norms derived from the US Health and Nutritional Examination Survey I.[12]

During the inpatient overnight visit for frequent sampling, percentage of ideal body weight and BMI were reevaluated. Medical history and physical examination were performed. Bone mineral density at the anterior-posterior and the lateral spine and total hip and body composition were assessed by dual-energy x-ray absorptiometry (Hologic 4500, Hologic, Inc, Waltham, Massachusetts). This technique has a precision of 0.01 g/cm^2 at the lumbar spine and 3% for fat mass.[13] Subjects had blood samples drawn every 20 minutes from 8 PM to 8 AM. Overnight serum samples were pooled for oxytocin levels. Fasting leptin and estradiol levels were obtained at 7:45 AM. Healthy controls presented for the overnight visit during the follicular phase of the menstrual cycle.

Biochemical Analysis

Serum samples were stored at −80°C until analysis. Oxytocin levels were measured following extraction using an enzyme immunoassay kit from Assay Designs (Ann Arbor, Michigan). The intra-assay coefficient of variation was 8.7%–12.4% and the inter-assay coefficient of variation was 5.2%–14.5%. The sensitivity was 11.7 pg/mL. Leptin levels were measured using a radioimmunoassay kit from LINCO Research, a division of Millipore Inc (St Charles, Missouri). The intra-assay coefficient of variation was 3.4%–8.3% and the inter-assay coefficient of variation was 3.6%–6.3%. The sensitivity was 0.5 ng/mL. Serum estradiol levels were measured using a paramagnetic particle chemiluminescent immunoassay using the Assay Immunoassay Systems from Beckman Coulter (Fullerton, California). The total coefficient of variation was ≤ 21%, and the lower limit of detection was 20 pg/mL.

Data Analysis

JMP Statistical Discoveries (version 5.01; SAS Institute, Inc; Cary, North Carolina) was used for statistical analyses. Clinical characteristics, hormone levels, and measures of bone density and body composition were compared using the student *t* test. Variables that were not normally distributed were log transformed. Linear regression analyses were used to investigate the associations between oxytocin levels and bone density, body composition, and leptin levels. Multivariate least-square 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.

Clinical Points

- Oxytocin is a peptide hormone involved in appetite as well as bone metabolism.
- Anorexia nervosa is characterized by restrictive eating, extremely low weight, and severe bone loss.
- Nocturnal oxytocin levels are low in women with anorexia nervosa and are positively associated with bone mineral density, suggesting that oxytocin deficiency may contribute to bone loss in this disorder.

RESULTS

Subject Characteristics

Subject characteristics are presented in Table 1. The groups did not significantly differ in age. As expected, body mass index, percentage of ideal body weight, and fat were lower in anorexia nervosa subjects than in healthy controls. Anorexia nervosa subjects reported more hours of exercise per week than did healthy controls. Five subjects with anorexia nervosa and no healthy controls reported a history of purging; no subjects reported purging in the prior 28 days.

Oxytocin and Bone Mineral Density

Oxytocin levels, estradiol levels, and bone mineral density results are presented in Table 2. Mean overnight oxytocin levels were lower in anorexia nervosa subjects than in healthy controls, and this difference remained significant after controlling for estradiol levels, months of amenorrhea, age of menarche, percentage of body fat, or hours of exercise per week. There was no significant difference in oxytocin levels in anorexia nervosa subjects with versus those without a history of purging. Bone mineral density and *Z* scores were lower in anorexia nervosa subjects than in healthy controls at all sites. The relationship between oxytocin and bone mineral density is presented in Table 3 and Figure 1. Oxytocin levels were positively associated with bone mineral density at the anterior-posterior and lateral spine, independent of estradiol levels.

Body Composition and Leptin

Fasting leptin levels are presented in Table 2. Mean fasting leptin levels were lower in anorexia nervosa subjects than in healthy controls. The relationship between oxytocin and measures of body composition and leptin levels

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Table 1. Subject Characteristics

Characteristic, mean ± SEM	Healthy Controls (n = 19)	Anorexia Nervosa (n = 17)	*P* Value
Age, y	27.5 ± 1.8	27.7 ± 1.9	.93
Body mass index	24.1 ± 0.5	18.1 ± 0.2	< .0001
Ideal body weight, %	104.8 ± 1.8	79.3 ± 0.7	< .0001
Fat, %	29.4 ± 1.1	17.2 ± 1.0	< .0001
Fat mass, kg	19.7 ± 0.9	8.8 ± 0.6	< .0001
Age at menarche, y	12.5 ± 0.3	13.1 ± 0.4	.18
Duration of amenorrhea, mo	0	65.8 ± 19.8	.0003
Exercise per week, h	3.3 ± 0.6	6.7 ± 1.1	.005
No. alcoholic drinks per week	1.8 ± 0.5	1.6 ± 0.5	.75

Abbreviation: SEM = standard error of the mean.

Table 2. Hormones and Bone Mineral Density

Variable, mean ± SEM	Healthy Controls	Anorexia Nervosa	*P* Value
Hormones			
12-hour pooled oxytocin, pg/mL	31.8 ± 5.1	14.3 ± 1.5	.003
Estradiol, pg/mL	47.1 ± 5.0	24.1 ± 4.1	.001
Fasting leptin, ng/mL	11.4 ± 1.1	2.7 ± 0.5	< .0001
Bone mineral density, g/cm^2			
Anterior-posterior spine	1.04 ± 0.03	0.83 ± 0.02	< .0001
Z score	−0.17 ± 0.25	−1.87 ± 0.22	< .0001
Lateral spine	0.81 ± 0.02	0.63 ± 0.02	< .0001
Z score	0.15 ± 0.29	−2.16 ± 0.28	< .0001
Total hip	0.97 ± 0.03	0.79 ± 0.03	< .0001
Z score	0.10 ± 0.25	−1.26 ± 0.21	.0003

Abbreviation: SEM = standard error of the mean.

Table 3. Correlations Between Oxytocin and Bone Mineral Density, Body Composition, and Leptin

Variable	*r*	*P* Value
Bone mineral density		
Anterior-posterior spine	0.40	.02
Lateral spine	0.36	.04
Hip	0.14	.43
Body composition and leptin		
Body mass index	0.49	.003
Total body mass	0.39	.02
Fat mass	0.42	.01
Percentage of fat	0.39	.02
Truncal fat	0.46	.005
Extremity fat	0.36	.03
Lean body mass	0.21	.23
Leptin	0.55	.001

are presented in Table 3 and Figure 2. Oxytocin levels were positively associated with percentage of fat, fat mass, truncal fat, extremity fat, and fasting leptin levels, independent of estradiol levels.

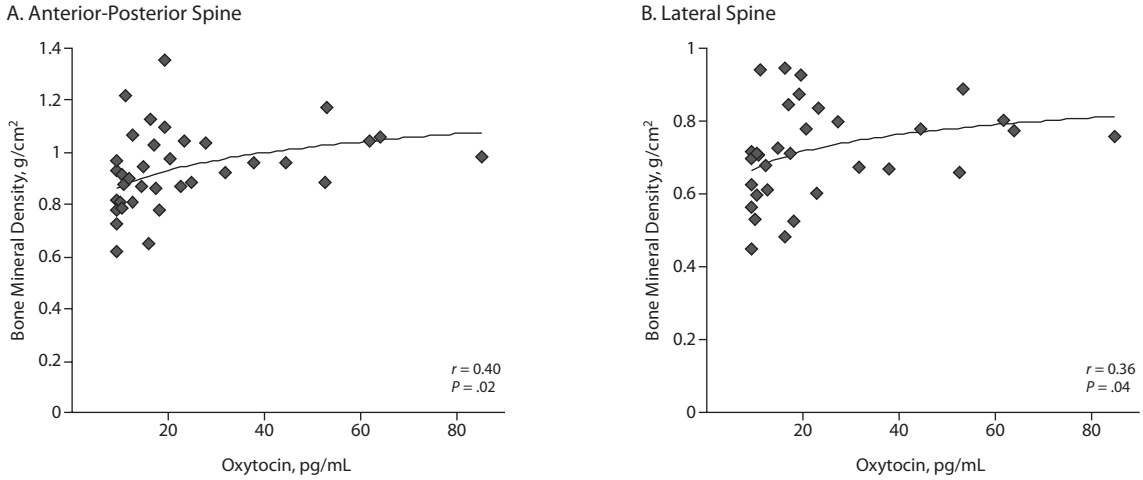
DISCUSSION

We demonstrated decreased oxytocin levels in women with anorexia nervosa compared to healthy controls. Furthermore, we found that mean overnight serum oxytocin levels were associated with bone mineral density, fat mass, and leptin levels. These relationships were independent of levels of estradiol, a key regulator of oxytocin secretion.

Oxytocin, a 9 amino acid peptide hormone produced in the hypothalamus and released into the peripheral circulation via the posterior pituitary, is widely known for its important role in parturition and milk letdown. Studies in animal models suggest that oxytocin also plays a role in the regulation of food intake. Intracerebroventricular and intraperitoneal administration of oxytocin to fasting rats resulted in dose-dependent decreased food intake and an increase in the time before eating.[1,14] When an oxytocin antagonist was given prior to administration of intracerebroventricular oxytocin, these effects were reversed.[1] Oxytocin is thought to be involved in leptin signaling. The leptin receptor has been identified on oxytocinergic cells in the supraoptic and paraventricular nuclei of the hypothalamus.[15] In fasting mice, oxytocin messenger ribonucleic acid (mRNA) levels were reduced, and administration of leptin increased oxytocin mRNA transcripts.[16] An oxytocin antagonist reversed the anorexigenic effects of intraventricular leptin administration in rats.[17] In contrast to this line of evidence, several studies of rats have shown increases in food intake, weight, and fat with subcutaneous or central administration of oxytocin.[2,3,18] Furthermore, increased food intake has been reported after intraventricular administration of oxytocin to oxytocin and oxytocin receptor knockout mice.[4] Therefore, although oxytocin appears to be an important modulator of appetite in animals, the specific effects are unclear.

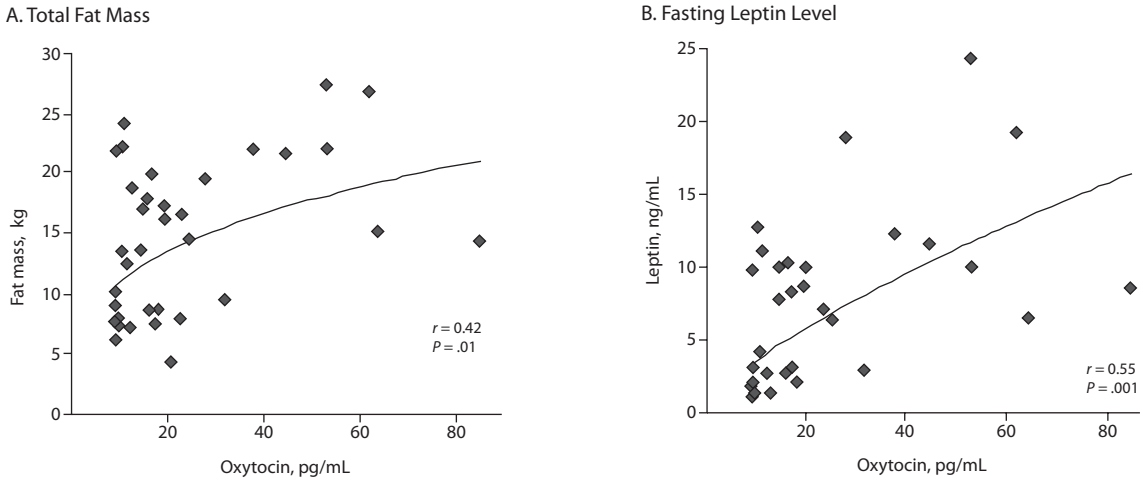
There are some data in the literature that have primarily focused on cerebrospinal fluid levels of oxytocin that raise the possibility of an "oxytocin-deficient state" in anorexia nervosa. In a study of 5 women with restrictive anorexia nervosa, cerebrospinal fluid oxytocin levels were lower than in healthy controls.[19] In contrast, cerebrospinal fluid oxytocin levels in women with bulimic subtype anorexia nervosa did not differ from the controls in this study. Frank et al[20] demonstrated that cerebrospinal fluid oxytocin levels were comparable in 10 recovered women with bulimic subtype anorexia nervosa and controls. However, women with active anorexia nervosa and those with restrictive subtype were not studied.[20] Chiodera et al[21] investigated the plasma oxytocin response to stimulation in 7 women with anorexia nervosa and controls. They found that stimulation was suppressed at the time of hospitalization, improved with partial weight recovery, and normalized with full weight recovery.[21] No published study has looked at oxytocin secretion in a well-defined cohort with active disease. Although oxytocin is produced in the hypothalamus, it is secreted into the periphery via the posterior pituitary and can be measured in the blood. Our study averages 36 serum samples over 12 hours for an integrated measure of oxytocin in a much larger patient sample than previously studied. We demonstrated lower levels of mean 12-hour serum oxytocin levels in women with anorexia nervosa compared to healthy controls, confirming that there is a state of relative oxytocin deficiency in anorexia nervosa compared to young healthy women. It is unclear whether oxytocin deficiency is an adaptive response to the energy deficit associated with chronic

Figure 1. Correlations Between Overnight Pooled Oxytocin Levels and Bone Mineral Density at the (A) Anterior-Posterior Spine and (B) Lateral Spine[a]



[a]There were positive correlations between overnight pooled oxytocin levels and bone mineral density at the anterior-posterior spine and lateral spine.

Figure 2. Correlations Between Overnight Pooled Oxytocin Levels and (A) Fat Mass and (B) Fasting Leptin Levels[a]



[a]There were positive correlations between overnight pooled oxytocin levels and fat mass and fasting leptin levels.

starvation, or if oxytocin dysregulation is an etiologic factor in the development of anorexia nervosa. Low oxytocin levels may contribute to symptoms of anorexia nervosa through effects on appetite and food intake. In addition, oxytocin has been implicated in prosocial behavior,[22] and a relative oxytocin deficiency in anorexia nervosa may contribute to associated deficits in social functioning, which in turn predict poor outcome.[23,24]

Anorexia nervosa is characterized by central hypogonadism and decreased bone mineral density. The severity of bone loss is increased compared to women with normal-weight hypothalamic amenorrhea,[25] and prospective studies have found no benefit of estrogen replacement.[26–28] Additional hormonal abnormalities, including hypercortisolemia and growth hormone resistance, have been implicated in the pathogenesis of anorexia nervosa–induced bone loss.[29] There is a growing body of evidence indicating that oxytocin is an important hormone in bone remodeling. The oxytocin receptor has been found on human osteoclasts[30] and osteoblasts.[4,31] In a study of human osteoblast-like cells from an osteosarcoma cell line, oxytocin increased cell proliferation and protein synthesis. Administration of an oxytocin antagonist blocked the proliferative effects of oxytocin.[32] Similarly in human osteoclast and preosteoclast cell cultures, oxytocin administration increases preosteoclast proliferation.[30] Cultured human bone marrow stem cells preferentially differentiate into osteoblasts over adipocytes when exposed to oxytocin.[7] In rats, oxytocin treatment increases osteoblast proliferation and bone turnover, promoting net bone formation.[33] Oxytocin and oxytocin receptor knockout mice

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display marked osteoporosis. Peripheral administration of oxytocin to animal models of osteoporosis, including knockout mice or estrogen-deficient ovariectomized mice, increases osteoblast and osteoclast formation and microarchitecture while decreasing bone marrow adipocyte number.[4,7] A study by Elabd et al[7] investigated fasting morning oxytocin levels in postmenopausal women, and found that levels were 55% lower in the 20 subjects with osteoporosis than in the 16 without osteoporosis. There was no correlation with age, BMI, or weight. To the best of our knowledge, no other studies have examined the relationship between oxytocin levels and bone density in humans. Consistent with the concept that oxytocin regulates bone remodeling, our study showed a significant association between peripheral oxytocin levels and bone mineral density. This, along with lower levels of oxytocin in women with anorexia nervosa compared to controls, supports the hypothesis that oxytocin contributes to bone loss in anorexia nervosa. It is also possible that this relationship simply reflects a decrease in both oxytocin and bone mineral density due to low weight. Further studies are needed to establish causality.

Anorexia nervosa is characterized by low body fat and severe bone loss with increased bone marrow fat. Inverse correlations between bone marrow fat and bone mineral density and between bone marrow fat and subcutaneous and total abdominal fat have been described.[34] Given these relationships and the fact that adipocytes and osteoblasts develop from the same mesenchymal precursor cells in bone marrow, shunting of pluripotent marrow cells from osteogenic to lipogenic pathways in chronically starved patients with anorexia nervosa has been hypothesized.[34] We demonstrated an association between oxytocin and fat mass as well as leptin levels. Further investigation would be useful to determine the relationship between oxytocin and marrow fat. Previous studies suggest that leptin signaling may involve activation of oxytocin neurons[15–17] and that oxytocin may be involved in the regulation of leptin secretion.[35] It is possible that fat, leptin, and oxytocin share a common signaling pathway, or may independently indicate energy availability. In the case of women with anorexia nervosa, oxytocin deficiency may signal an energy deficit and lack of resources for bone formation. This is a cross-sectional study and causality cannot be determined.

In summary, we showed that oxytocin levels are decreased in women with anorexia nervosa compared to healthy controls and that these levels were positively associated with bone mineral density, fat mass, and leptin levels. Further investigation will be important to determine whether oxytocin deficiency resolves with recovery in anorexia or contributes to the pathophysiology of the disease.

Drug names: medroxyprogesterone (Depo-Provera and others).
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