Published in final edited form as:

J Clin Psychiatry. 2011 November ; 72(11): 1546–1551. doi:10.4088/JCP.10m06617.

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 its relationship to decreased bone mineral density (BMD) in anorexia nervosa. Our objective was to investigate the relationship between oxytocin levels, BMD and body composition in women with anorexia nervosa.

Method—We studied 36 women, mean age 27.6±1.3 years: 17 with anorexia nervosa (AN) and 19 healthy controls (HC) in a cross-sectional study. Oxytocin levels were determined from pooled serum samples obtained every 20 minutes from 8pm to 8am. Fasting leptin levels were measured. BMD at the anterior-posterior (AP) and lateral spine and hip, and body composition were assessed by dual energy X-ray absorptiometry.

Results—Mean oxytocin levels (14.3±1.5 vs. 31.8±5.1 pg/mL, $p=0.003$), leptin levels (2.7±0.5 vs. 11.4±1.1 ng/mL, $p<0.0001$), BMD (AP 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/cm², <0.0001), and fat mass (8.8±0.6 vs. 19.7±0.9 kg, $p<0.0001$) were lower in AN vs. HC. Oxytocin levels were associated with BMD at the AP ($r=0.40$, $p=0.02$) and lateral ($r=0.36$, $p=0.04$) spine, fat mass ($r=0.42$, $p=0.01$), and leptin levels ($r=0.55$, $p=0.001$).

Conclusion—Overnight secretion of oxytocin in AN is decreased compared with healthy women. Low oxytocin levels are associated with decreased BMD and body fat and may contribute to anorexia nervosa-induced bone loss.

Keywords

Anorexia Nervosa; Oxytocin; Bone; Fat; Leptin

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The authors report no financial or other relationship relevant to the subject of this article.

Introduction

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 adipogenesis⁷ and osteoblast in favor of osteoclast activity⁴. 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 (AP) and lateral spine and total hip, fat mass, and leptin levels.

Method

Subjects

We studied 36 women: 17 with anorexia nervosa (AN) and 19 healthy controls (HC). All subjects were recruited from the community through advertisements and referrals from healthcare providers. Subject clinical characteristics, bone mineral density and leptin levels were previously reported in subsets of AN and HC subjects^{8, 9}. 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 AN met DSM-IV criteria, including intense fear of gaining weight, emphasis on body shape, weight less than 85% of ideal body weight (IBW) as determined by the 1983 Metropolitan Life tables¹⁰, and amenorrhea for at least three consecutive months.

HC were 90–120% of IBW 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 AN or history of diabetes mellitus. Additional exclusion criteria included active abuse of drugs or alcohol, use of medication known to affect bone metabolism within three months (including estrogen), use of depot medroxyprogesterone within six months, use of a bisphosphonate within a year, and pregnancy or breastfeeding within six months of the study.

Methods

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 for an outpatient screening visit and an inpatient overnight visit.

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 exam were performed. Exercise patterns and alcohol intake were assessed. Percent 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-I¹¹.

During the inpatient overnight visit for frequent sampling, % IBW and BMI were reevaluated. Medical history and physical exam were performed. Bone mineral density at the AP and lateral spine and total hip and body composition were assessed by dual-energy X-ray absorptiometry (Hologic 4500, Hologic, Inc., Waltham, MA). This technique has a precision of 0.01 g/cm² at the lumbar spine and 3% for fat mass¹². Subjects had blood samples drawn every twenty minutes from 8pm to 8am. Overnight serum samples were pooled for oxytocin levels. Fasting leptin and estradiol levels were obtained at 745am. HC 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, MI). The intra-assay coefficient of variation (CV) was 8.7–12.4% and the inter-assay CV 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, MO). The intra-assay CV was 3.4–8.3% and the inter-assay CV 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, CA). The total CV was 12–21% and the lower limit of detection was 20pg/mL.

Data Analysis

JMP Statistical Discoveries (version 5.01; SAS Institute, Inc., Cary, NC) 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 two-tailed P-value < 0.05. Data are reported as mean ± SEM.

Results

Subject Characteristics

Subject characteristics are presented in Table 1. The groups did not significantly differ in age. As expected, body mass index, %IBW, and fat were lower in AN than HC. The hours of exercise per week reported was greater in AN than HC. Five subjects with AN and no HC 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 AN than HC, and this difference remained significant after controlling for estradiol levels, months of amenorrhea, age of menarche, percent body fat or hours of exercise per week. There was no significant difference in

oxytocin levels in AN with vs. without a history of purging. Bone mineral density and Z-scores were lower in AN than HC 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 BMD at the AP 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 AN than HC. The relationship between oxytocin and measures of body composition and leptin levels are presented in Table 3 and Figure 2. Oxytocin levels were positively associated with %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 nine 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, 13}. When an oxytocin antagonist was given prior to administration of intracerebroventricular oxytocin, these effects were reversed¹. 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 hypothalamus¹⁴. In fasting mice, oxytocin mRNA levels were reduced and administration of leptin increased oxytocin mRNA transcripts¹⁵. An oxytocin antagonist reversed the anorexigenic effects of intraventricular leptin administration in rats¹⁶. 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, 17}. Furthermore, increased food intake has been reported after intraventricular administration of oxytocin to oxytocin and oxytocin receptor knockout mice⁴. 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 which have primarily focused on cerebrospinal fluid (CSF) 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 (CSF) oxytocin levels were lower than healthy controls¹⁸. In contrast, CSF oxytocin levels in women with bulimic subtype anorexia nervosa did not differ from the controls in this study. Frank et al. demonstrated that CSF 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 studied¹⁹. Chiodera et al. 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 recovery²⁰. 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 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 behavior²¹, and a relative oxytocin deficiency in anorexia nervosa may contribute to associated deficits in social functioning, which in turn predict poor outcome^{22, 23}.

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 amenorrhea²⁴, and prospective studies have found no benefit of estrogen replacement^{25–27}. Additional hormonal abnormalities, including hypercortisolemia and growth hormone resistance have been implicated in the pathogenesis of anorexia nervosa-induced bone loss²⁸. 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 osteoclasts²⁹ and osteoblasts^{4, 30}. 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 oxytocin³¹. Similarly in human osteoclast and preosteoclast cell cultures, oxytocin administration increases preosteoclast proliferation²⁹. Cultured human bone marrow stem cells preferentially differentiate into osteoblasts over adipocytes when exposed to oxytocin⁷. In rats, oxytocin treatment increases osteoblast proliferation and bone turnover, promoting net bone formation³². Oxytocin and oxytocin receptor knockout mice 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. investigated fasting morning oxytocin levels in postmenopausal women, and found that levels were 55% lower in the 20 subjects with osteoporosis than the 16 without osteoporosis⁷. 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 AN. 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 bone marrow fat and subcutaneous and total abdominal fat have been described³³. 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 AN has been hypothesized³³. 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^{14–16}, and that oxytocin may be involved in the regulation of leptin secretion³⁴. 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 AN 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.

Acknowledgments

We thank the nurses and bionutritionists in the Massachusetts General Hospital Clinical Research Center and the subjects who participated in the study.

This work was supported in part by the following grants: Investigator-initiated grant from Bioenvision. NIH: M01 RR01066, UL1 RR025758, and R01-DK052625. The Clinical Investigator Training Program: Harvard/MIT Health Sciences and Technology – Beth Israel Deaconess Medical Center, in collaboration with Pfizer Inc. and Merck & Co.

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A. **B.** **Figure 1.**

Oxytocin is associated with bone mineral density. There were positive correlations between overnight pooled oxytocin levels and bone mineral density at A.) the AP spine and B.) lateral spine.

A. **B.** **Figure 2.**

Oxytocin is associated with fat mass and leptin levels. There were positive correlations between overnight pooled oxytocin levels and A.) fat mass and B.) fasting leptin levels.

Table 1

Subject characteristics

	HC N=20	AN N=18	<i>p-values</i>
Age (years)	27.5±1.8	27.7±1.9	0.93
Body mass index	24.1±0.5	18.1±0.2	<0.0001
% Ideal body weight	104.8±1.8	79.3±0.7	<0.0001
% Fat	29.4±1.1	17.2±1.0	<0.0001
Fat mass (kg)	19.7±0.9	8.8±0.6	<0.0001
Age of menarche	12.5±0.3	13.1±0.4	0.18
Months of amenorrhea	0	65.8±19.8	0.0003
Hours exercise per week	3.3±0.6	6.7±1.1	0.005
No. alcoholic drinks per week	1.8±0.5	1.6±0.5	0.75

Means ± SEM

Table 2

Hormones and bone mineral density

	HC	AN	<i>p-values</i>
HORMONES			
12 hour pooled oxytocin (pg/mL)	31.8±5.1	14.3±1.5	0.003
Estradiol (pg/mL)	47.1±5.0	24.1±4.1	0.001
Fasting leptin (ng/mL)	11.4±1.1	2.7±0.5	<0.0001
BONE			
Bone mineral density (g/cm ²)			
AP spine	1.04±0.03	0.83±0.02	<0.0001
Lateral spine	0.81±0.02	0.63±0.02	<0.0001
Total hip	0.97±0.03	0.79±0.03	<0.0001
Z-scores			
AP spine	-0.17±0.25	-1.87±0.22	<0.0001
Lateral spine	0.15±0.29	-2.16±0.28	<0.0001
Total hip	0.10±0.25	-1.26±0.21	0.0003

Means ± SEM

Table 3

Correlations between oxytocin and bone mineral density, body composition and leptin

	r	p-value
Bone mineral density		
AP spine	0.40	0.02
Lateral spine	0.36	0.04
Hip	0.14	0.43
Body composition and leptin		
BMI	0.49	0.003
Total body mass	0.39	0.02
Fat mass	0.42	0.01
% Fat	0.39	0.02
Truncal fat	0.46	0.005
Extremity fat	0.36	0.03
Lean body mass	0.21	0.23
Leptin	0.55	0.001