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Bone Metabolism in Anorexia Nervosa

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Abstract

Anorexia nervosa (AN), a psychiatric disorder predominantly affecting young women, is characterized by self-imposed chronic nutritional deprivation and distorted body image. AN is associated with a number of medical co-morbidities including low bone mass. The low bone mass in AN is due to an uncoupling of bone formation and bone resorption, which is the result of hormonal adaptations aimed at decreasing energy expenditure during periods of low energy intake. Importantly, the low bone mass in AN is associated with a significant risk of fractures and therefore treatments to prevent bone loss are critical. In this review, we discuss the hormonal determinants of low bone mass in AN and treatments that have been investigated in this population.

Keywords

Anorexia nervosa; bone mineral density

Introduction

Anorexia nervosa (AN) is a psychiatric disease characterized by self-induced starvation coupled with a fear of gaining weight and a distorted body image [1]. AN predominantly affects young women and has a lifetime prevalence of 2.2% [2] but the disease also affects adolescent and adult males [3]. An increasing number of women over the age of 35 are also being treated for AN [4] and therefore the epidemiology of the disease may be shifting in the coming years.

AN has the one of the highest mortality rates of any psychiatric disorder [5] and is associated with a significant number of medical complications, including bradycardia, hypotension, anemia and the most common finding -- low bone mass [6]. Nearly 50% of women with AN have bone mineral density (BMD) values more than one-standard deviation below an age-comparable mean and an additional 30% have BMD values more than 2.5 standard deviations below an age-comparable mean [7, 6]. This low bone mass is associated with an increased risk of fracture. Thirty percent of women with AN report a history of a fracture [6] and a population-based retrospective study demonstrated the cumulative incidence of fracture to be 57%, even many years after the diagnosis of AN [8]. Importantly, a prospective study of young-women with AN demonstrated a seven-fold increased risk of

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Conflict of Interest

Human and Animal Rights and Informed Consent
All studies by PK Fazeli and A Klibanski involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

fracture as compared to normal-weight controls [9]. Therefore, the low bone mass in AN is clinically significant.

There are a number of mechanisms which contribute to this low bone mass. As AN in characterized by decreased nutrient intake, it has been hypothesized that decreased intake of calcium and vitamin D may be important mediators of bone loss. However, girls and women with AN have higher intakes of both calcium and vitamin D, predominantly through supplements, as compared to normal weight controls and therefore this is not an important cause of bone loss in this disease [10, 11]. The bone loss in AN is the consequence of a response by hormonal pathways, including neuroendocrine axes and appetite-regulating hormones, to preserve energy and decrease energy expenditure in a state of nutritional deprivation. In adults with AN, the result is an uncoupling of bone formation and bone resoprtion with a profound decrease in bone formation and an increase in bone resorption [12, 13]. We will review these hormonal changes, their effects on BMD and potential treatment options below.

Hormonal mediators of the low bone mass in AN

Anorexia nervosa is a state of growth hormone resistance

States of nutritional deprivation are characterized by growth hormone (GH) resistance. Individuals with AN have elevated levels of GH coincident with low levels of insulin-like growth factor I (IGF-I) – an important anabolic hormone which mediates many of the growth-promoting actions of GH in the periphery, including bone metabolism [14-17]. IGF-I levels are extremely sensitive to nutritional cues – acute nutritional deprivation, in the form of four days of fasting, results in a 50% decrease in IGF-I levels [18]. Chronic nutritional deprivation, as seen in AN, also results in similarly low IGF-I levels – levels in AN are approximately 50% of those of normal-weight women [19]. The low IGF-I levels in AN also respond acutely to re-feeding with IGF-I levels increasing by approximately 50% after only three days of hyper-alimentation therapy [20]. Growth hormone resistance is likely an adaptive response to the state of under-nutrition. Low IGF-I levels preserve energy by decreasing expenditures on growth, including expenditures on the growth and maintenance of bone mass. Elevated GH levels are likely the result of both positive feedback on the pituitary from the low IGF-I levels [21], as well as ghrelin-stimulated GH secretion. Levels of ghrelin – an appetite-stimulating (orexigenic) hormone secreted by cells in the fundus of the stomach – are elevated in AN [22-24]. Ghrelin receptors stimulate GH secretion and the elevated ghrelin levels in states of fasting and chronic under-nutrition may be an important means of maintaining euglycemia [25]. Elevated GH levels may also be important for mobilizing fat stores in states of nutritional deprivation [26]. Therefore elevated GH levels in AN may be necessary for energy mobilization, while the low IGF-I levels help decrease energy expenditure.

IGF-I has significant bone anabolic effects and the low levels of IGF-I are therefore an important contributor to the low bone mass in AN. IGF-I is a chemotactic factor which induces osteoblast recruitment [27] and in cultured rat calvaria, stimulates DNA synthesis and increases bone collagen content [28]. The effects of treatment with recombinant human IGF-I on bone turnover markers and BMD have been investigated in AN. Recombinant human IGF-I increases levels of bone formation markers in girls and women with AN [29-31], and in women with AN increases lumbar spine BMD by 1.8% when used in conjunction with oral contraceptive pills. [29].

The mechanism responsible for the GH resistance state in AN is unknown, but recent studies suggest that fibroblast growth factor 21 (FGF-21) and sirtuin 1 (SIRT1) may play important roles. FGF-21 is a hormone produced in the liver [32] and adipocytes [33]. Transgenic

FGF-21 mice have phenotypic characteristics similar to women with AN – they weigh less and have a lower core body temperature than wild-type litter mates [34, 35], and importantly, they are GH resistant with elevated levels of GH and low levels of IGF-I [36]. The mechanism by which FGF-21 transgenic mice become GH resistant is thought to be a decrease in STAT5 – a transcription factor important in GH signaling [36]. In adolescent girls with AN, FGF-21 levels are higher than normal-weight controls after controlling for body fat and insulin resistance – two important factors which may affect FGF-21 levels [37]. There is also a significant association between FGF-21 levels and GH area under the curve and an inverse association between elevated FGF-21 levels and IGF-I [37], suggesting that FGF-21 may be an important mediator of GH resistance in AN.

SIRT1 is a histone deacetylase which promotes fatty acid oxidation and gluconeogenesis during fasting and nutrient deprivation [38]. Similar to FGF-21, SIRT1 is thought to be an important mediator of GH resistance by decreasing STAT5 phosphorylation [39]. During a 48 hour fast, mice that lacked SIRT1 had higher GH-dependent increases in IGF-I and higher IGF-I mRNA levels compared to wild-type mice, suggesting that SIRT1 may be an important factor in GH resistance during starvation [39].

Lastly, low insulin levels, which are characteristic of states of under-nutrition, may also play a role in GH resistance. In animal models, GH receptor expression is reduced in low insulin states and expression is increased in response to insulin therapy [40]. GH receptor up-regulation by insulin has also been demonstrated in *in vitro* models [41]. Therefore low insulin levels may also play a role in the GH resistance state of AN.

Hypogonadotropic hypogonadism

Amenorrhea due to hypogonadotropic hypogonadism is a common finding in women with AN. Amenorrheic women with AN have low amplitude luteinizing hormone (LH) pulsatility, which is a secretory pattern similar to that of pre-pubertal girls and this abnormal pattern normalizes with weight recovery [42]. The LH response to gonadotropin-releasing hormone (GnRH) is normal with a normal or exaggerated follicle-stimulating hormone response and therefore an abnormal GnRH secretory pattern is the likely cause of amenorrhea in AN [43-46]. Similar to the effects of estrogen deficiency in post-menopausal women, hypogonadotropic hypogonadism results in an increase bone resorption [47]. One might expect that estrogen replacement in women with AN would result in increases in BMD but two randomized, placebo-controlled studies have demonstrated that oral contraceptives do not improve BMD [48, 29], except in the subset of women who were very low weight (less than 70% of ideal body weight) in a post-hoc analysis. Recently, a study investigating the effects of physiologic estrogen replacement in adolescent girls with AN demonstrated a 2.6% increase in spine BMD after 18 months of treatment [49] (Figure 1). This finding suggests that physiologic doses of estrogen – which in the majority of girls in the study consisted of 100 μg of transdermal 17β-estradiol applied twice weekly -- but not the supraphysiologic doses of estrogen in oral contraceptive pills, may be beneficial for the treatment of the low bone mass in AN.

Levels of testosterone, another gonadal steroid, are also low in women with AN [50, 51] and these low levels predict low BMD [51]. Therefore, one might expect that testosterone replacement would result in increases in BMD in women with AN. A randomized, placebo-controlled study investigating the effects of 12 months of testosterone replacement in women with AN demonstrated no improvements in BMD [52], suggesting that other factors may play a more significant role in the bone loss in AN.

Disruption of the hypothalamic-pituitary-adrenal axis

Adrenal androgen precursor levels are also low in AN. Dehydroepiandrosterone (DHEA) levels are decreased in women with AN [53] and are a predictor of low BMD [51] and increased bone resorption [54]. The effects of DHEA replacement on BMD in AN have been investigated. Twelve months of treatment with DHEA does not improve BMD as compared to placebo [55], whereas DHEA given in conjunction with oral contraceptives for 18 months results in maintenance of BMD in girls and women with AN [56], again suggesting that factors other than androgens play a more significant role in the low bone mass state of AN.

Girls and women with AN have elevated cortisol levels [57, 58], which are an important contributor to the low bone mass in AN; elevated 12-hour pooled cortisol levels are associated with low BMD in AN even after controlling for duration of amenorrhea and IGF-I levels, suggesting an important independent effect of hypercortisolemia [58]. Cortisol levels are likely increased due to activation of a stress response induced by chronic nutritional deprivation and are also a means of maintaining euglycemia via a counter-regulatory response pathway [59], but decreased metabolic clearance of cortisol has also been reported [60]. Elevated cortisol levels affect BMD in a number of ways. First, hypercortisolemia may decrease calcium absorption in the intestine [61]. Elevated cortisol levels also decrease bone formation; glucocorticoid receptors found on osteoblasts may reduce osteoblast proliferation [62] and elevated cortisol levels may inhibit GH secretion and decrease IGF-I synthesis in bone [63]. In adolescent girls with AN, the relationship between elevated cortisol levels and decreased bone formation is evident from the fact that high cortisol levels are associated with lower levels of osteocalcin and C-terminal propeptide Type 1 procollagen – markers of bone formation [57]. Lastly, hypercortisolemia also increases bone resorption; elevated cortisol levels may increase bone resorption via parathyroid hormone (PTH) by increasing PTH receptor expression on osteoblasts [64] and also by decreasing gonadotropin secretion [65], thereby contributing to the state of hypogonadotropic hypogonadism characteristic of AN.

Non-thyroidal illness syndrome

Women with AN have thyroid hormone levels consistent with the non-thyroidal illness syndrome, previously called the euthyroid-sick syndrome. In AN, levels of T4 and T3 are low or low-normal, with elevated levels of reverse T3 and normal levels of thyroid stimulating hormone (TSH) [66-69]. In AN, low T3 levels are due in part to decreased peripheral conversion of T4 to T3 [66, 67]. Exogenous TRH stimulation results in a delayed but quantitatively appropriate TSH response [67, 70, 71], suggesting that decreased TRH stimulation from the hypothalamus is contributing to the non-thyroidal illness state. These mechanisms -- which are likely an adaptive response allowing the body to decrease its metabolic rate and therefore energy expenditure, as suggested by the fact that increases in T3 with weight recovery are associated with increases in resting energy expenditure [72] -- reverse with weight gain [70, 73].

States of hyperthyroidism have been associated with loss of bone mass [74], therefore whether the non-thyroidal illness syndrome contributes to the low bone mass in AN is controversial. Thyroid hormone receptor knockout mice exhibit decreased trabecular BMD and elevated levels of marrow fat [75], similar to women with anorexia nervosa [76]. Thyroid hormone receptors are found on osteoblasts [77] and levels of IGF-I, an important stimulator of bone formation, increase after treatment of hypothyroidism [78], both of which suggest that thyroid hormone may be an important contributor to bone mass. Yet, although there is some evidence suggesting that low levels of thyroid hormone may contribute to the low bone mass in AN, the fact that that the non-thyroidal illness syndrome results in a decrease in energy expenditure and treatment would disadvantageously increase energy

expenditure in a state of under-nutrition, makes thyroid hormone a highly undesirable treatment option in AN.

Appetite regulating hormones

Hypoleptinemia

Girls and women with AN have decreased levels of subcutaneous and visceral adipose tissue. Levels of leptin, an anorexigenic hormone secreted by adipose tissue, primarily subcutaneous adipose tissue, are low in AN [79, 80]. Leptin is likely the key mediator between energy expenditure and hypogonadotropic hypogonadism in AN; women with AN who are not amenorrheic have higher leptin levels as compared to those who are amenorrheic [81]. Importantly, low leptin levels are associated with low BMD [82] and abnormalities in microarchitectural parameters [83] in AN. Administration of recombinant human leptin to women with hypothalamic amenorrhea results in increased levels of osteocalcin and bone-specific alkaline phosphatase – two markers of bone formation, although a major effect of treatment was weight loss [84]. Therefore, although leptin may be a mediator of the low bone mass in AN and treatment with recombinant human leptin may stimulate bone formation, this is not an appropriate potential treatment for individuals with AN, given the associated weight loss.

Elevated Peptide YY levels

Peptide YY (PYY) is another anorexigenic hormone but contrary to what we might expect in normal physiology, levels are elevated in girls and women with AN [85, 86] and therefore may contribute to the decreased nutrient intake characteristic of AN. In animal models, mice lacking PYY's receptor – the Y2 receptor – have increased trabecular bone parameters [87], suggesting that PYY may be a negative regulator of trabecular bone. In girls and women with AN, PYY has also been shown to be inversely associated with BMD [86, 88] suggesting that this may be an important mediator of the low bone mass in AN.

Elevated ghrelin levels

Levels of ghrelin, an appetite-stimulating hormone secreted by cells in the stomach, are elevated in girls and women with AN [22-24] and ghrelin levels decrease with weight gain in AN [22]. Ghrelin induces GH secretion and therefore the elevated ghrelin levels in AN also contribute to the higher GH levels characteristic of the GH resistance state. In animal and *in vitro* models, ghrelin stimulates bone formation. Ghrelin's receptor, the growth hormone secretagogue receptor 1a, is present in rat osteoblast-like cells and treatment with ghrelin results in a dose-dependent increase in the osteoblast-like cells [89]. In rats, ghrelin administration also increases BMD [89] and in humans, a significant positive association between BMD and ghrelin is observed in normal-weight adolescent girls -- even after controlling for cortisol levels, body composition and GH/IGF-I levels -- but not in girls with AN [90]. In fact, in girls with AN, ghrelin is inversely associated with BMD [88]. Therefore the association between ghrelin and BMD may be disrupted in AN.

Adiponectin

Although adiponectin is secreted by adipocytes, levels are lower in obesity as compared to normal-weight individuals. In AN, levels of adiponectin have been shown to be higher, lower and comparable to normal-weight controls [91-93] but after controlling for fat-mass, levels have been shown to be higher in AN [91]. Adiponectin may also be a mediator of low bone mass in AN. Adiponectin stimulates RANK-ligand, an osteoclast activator, and also decreases osteoprotegrin – a decoy receptor for RANK-ligand which inhibits its osteoclast-activating effects [94]. In girls with AN, adiponectin has been shown to be inversely

associated with BMD [91], again suggesting that this adipokine may be an important contributor to the bone loss characteristic of AN.

Potential treatments for the low bone mass in AN (Table 1)

AN is a chronic disease and only approximately 50% of women with AN recover even many years after their initial diagnosis [95]. In those who gain weight and resume their menses, the mean annual increase in BMD is 1.8% at the hip and 3.1% at the spine [96]. In those who remain low weight and amenorrheic, the annual rate of decline is -2.4% at the hip and -2.6% at the spine [96]. Therefore finding an effective therapy for the treatment of bone loss in AN is critical. As previously discussed, supra-physiologic doses of estrogen, in the form of oral contraceptives, do not improve BMD as compared to placebo except in women who are very low weight [48, 29], whereas physiologic, primarily transdermal estrogen replacement in adolescents increases spine BMD by approximately 2.6% after 18 months of treatment [49] (Figure 1). Replacement of androgens, in the form of testosterone or DHEA, a pre-androgen, does not improve BMD as compared to placebo [52], although, when combined with an oral contraceptive, DHEA is able to maintain BMD in girls and women with AN [56]. The only other treatments which have demonstrated a benefit in adult women with AN are the anabolic agent, IGF-I, in combination with oral contraceptives, which increased spine BMD by 1.8% after 9 months [29] and risedronate, a bisphosphonate, which demonstrated a 2-4% increase in spine and hip BMD after 12 months of treatment [52]. Importantly, none of these therapies have led to normalization of BMD in girls or women with AN, and the effect of these treatments on fracture risk has not been investigated.

Conclusions

Anorexia nervosa, a state of chronic under-nutrition, is characterized by hormonal dysregulation which results in significant bone loss. The associated hormonal abnormalities, which include GH resistance, hypogonadotropic hypogonadism, hypercortisolemia, and the non-thyroidal illness syndrome, are likely an adaptive response to preserve energy in a state of chronic under-nutrition. The low bone mass, which is a consequence of this hormonal dysregulation, is clinically very important and associated with a significant increased risk of fracture [8]. There are currently no approved treatments for the bone loss associated with AN but a number of potential therapies have been investigated. Physiologic estrogen replacement in adolescents , bisphosphonates and the combination of recombinant human IGF-I and oral contraceptives in adults have been shown to increase BMD in AN by 1.8% to 4%. These treatments do not result in normalization of BMD and importantly, we do not know the effect of treatment on risk of fracture. Therefore further studies, are necessary to investigate potential treatment options for the bone loss associated with AN.

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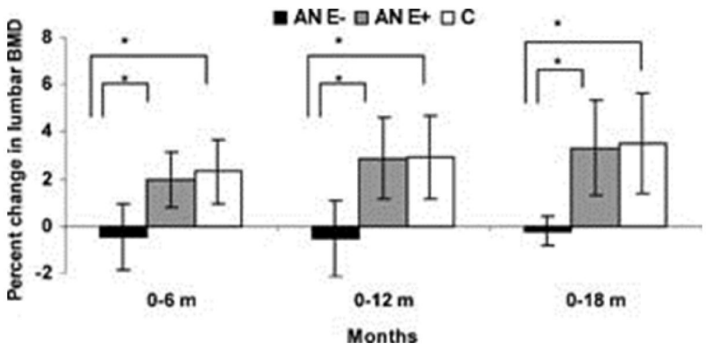

Figure 1.

Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa. Percent change in lumbar spine bone mineral density (LBMD) in adolescent girls with anorexia nervosa (AN) randomized to placebo (AN E–; black bars), girls with AN randomized to estrogen (AN E+; gray bars), and normal-weight control girls (C; white bars). AN E+ girls had significant increases in LBMD at 6, 12, and 18 months compared with AN E– girls. When compared with control girls, AN E– girls had significant decreases in LBMD at 6, 12, and 18 months, whereas AN E+ girls did not differ from control girls for changes in BMD over time. Analysis was performed for differences between means for pairs. *$p <$ 0.05. Borrowed with permission from [49] © 2011, John Wiley and Sons.

Table 1

Therapies that have been investigated to treat the low bone mass in anorexia nervosa and their effect on bone mineral density (BMD)

Therapy	Change in BMD	Duration of treatment	References
Oral contraceptives	No change compared to placebo except in women less than 70% ideal body weight	Mean of 1-1.5 years	[48, 29]
Physiologic estrogen replacement	2.6% increase in spine BMD	1.5 years	[49]
IGF-I + oral contraceptives	1.8% increase in spine BMD	9 months	[29]
Testosterone	No change compared to placebo	1 year	[52]
DHEA	No change compared to placebo	1 year	[55]
DHEA + oral contraceptives	Maintenance of BMD as compared to loss of BMD in placebo group	1.5 years	[55]
Bisphosphonates	2% increase in hip BMD 3-4% increase in spine BMD	1 year	[52]