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Bone health in anorexia nervosa

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Abstract

Purpose of review—Anorexia nervosa is associated with low bone mineral density (BMD), concerning for an increased risk of fractures, and decreased bone accrual in adolescents, concerning for suboptimal peak bone mass. This review discusses causes of impaired bone health in anorexia nervosa and potential therapeutic strategies.

Recent findings—Low BMD in anorexia nervosa is consequent to decreased lean mass, hypogonadism, low insulin-like growth factor-1 (IGF-1), relative hypercortisolemia and alterations in hormones impacted by energy availability. Weight gain causes some improvement in bone accrual, but not to the extent observed in controls, and vitamin D supplementation does not increase BMD. Oral estrogen is not effective in increasing BMD, likely from IGF-1 suppressive effects. In contrast, transdermal estrogen replacement is effective in increasing bone accrual in adolescents with anorexia nervosa, although not to the extent seen in controls. Recombinant human IGF-1 increases bone formation in adolescents, and with oral estrogen increases BMD in adults with anorexia nervosa. Bisphosphonates increase BMD in adults, but not in adolescents, and should be used cautiously given their long half-life.

Summary—Further investigation is necessary to explore therapies for low BMD in anorexia nervosa. Weight gain is to be encouraged. Transdermal estrogen in adolescents, and bisphosphonates in adults, have a potential therapeutic role.

Keywords

anorexia nervosa; bone density; bone microarchitecture; gonadal steroids; growth hormone; insulin-like growth factor-1

Introduction

Anorexia nervosa occurs in 0.2–4% of adolescent girls and college-aged young women, and low bone mineral density (BMD) is a common complication of this disorder. Adolescence is a critical time for bone accrual and attainment of peak bone mass, an important determinant of future bone health and fracture risk. Anorexia nervosa commonly begins during adolescence and is associated with low BMD and decreased bone accrual rates during the critical pubertal years, raising concerns regarding acquisition of peak bone mass. This

review discusses the impact of anorexia nervosa on bone metabolism, factors contributing to low BMD, potential therapeutic strategies and highlights recent advances.

Impact of anorexia nervosa on bone metabolism

Anorexia nervosa has a profound impact on bone metabolism in adults and adolescents.

Bone mineral density

Adolescents with anorexia nervosa have lower BMD, as assessed by dual energy X-ray absorptiometry (DXA), than normal-weight adolescents of comparable age and maturity, and have decreased rates of bone accrual [1,2]. Up to 50% of adolescent girls with anorexia nervosa have Z-scores of less than -1 at one site at least, and 11% have Z-scores of less than -2 [3]. Although there are fewer data in boys with anorexia nervosa than in girls, available studies are even more concerning with 70% of boys having Z-scores of less than -1 at at least one site [1]. Height-adjusted measures of BMD, including spine bone mineral apparent density and whole body bone mineral content/height, are lower in anorexia nervosa than that in controls, as are measures of spine BMC for bone area (suggestive of lighter bones) and whole body bone area for height (indicative of thinner bones) [2]. Adolescence is a particularly critical time for developing anorexia nervosa, and BMD is lower in women developing anorexia nervosa during adolescence compared with those who develop this in adulthood, even when the duration of amenorrhea is comparable [4]. Recent studies corroborate these data and indicate that adult women with a history of menstrual dysfunction and restrictive eating disorders in adolescence have a high prevalence of low BMD [5]. These data speak to the permanent effects anorexia nervosa can have on adult bone mass throughout life, even if there is recovery. Additionally, in contrast to normal-weight adolescents who steadily accrue bone through puberty, bone accrual in girls with anorexia nervosa at least often plateaus [2]. Thus, there is an increasing gap between BMD in normal adolescents and girls with anorexia nervosa. BMD shows even greater compromise in adults with anorexia nervosa, and 92% have osteopenia and 38% have osteoporosis at at least one site [6].

A new finding of importance in understanding the pathogenesis of low bone mass in anorexia nervosa is work done investigating marrow fat in this disorder. Women with anorexia nervosa have higher marrow fat at the spine and hip than normal-weight controls despite having lower visceral and subcutaneous fat, and higher marrow fat is associated inversely with measures of BMD [7]. This is consistent with emerging knowledge regarding the bone-fat connection. Osteoblasts and adipocytes arise from a common progenitor cell, and factors that increase adipogenesis often concomitantly decrease osteoblastogenesis and *vice versa*. Pref-1, an epidermal growth factor-like protein that regulates adipogenesis and osteoblastogenesis, is higher in women with anorexia nervosa than in controls and correlates positively with marrow fat and inversely with spine BMD [8]. In adolescents with anorexia nervosa, data indicate preferential conversion of red (hematopoietic) marrow to yellow (fatty) marrow, suggestive of increased differentiation along the adipocyte lineage [9].

Surrogate markers of bone turnover

Adolescents with anorexia nervosa have lower levels of surrogate markers of bone formation and resorption than normal-weight controls, indicating a coupled decrease in bone turnover [1,10]. This is in contrast to normal-weight adolescents, who have increased levels of markers of bone turnover, particularly in earlier puberty, consistent with increased bone modeling. This is also in contrast to adults with anorexia nervosa, who have a decrease in bone formation markers, but an increase in bone resorption markers [11,12*].

Bone microarchitecture and strength

In addition to low DXA measures of BMD, adolescents with anorexia nervosa have impaired bone microarchitecture. Bone trabecular volume and trabecular thickness are lower and trabecular separation higher [as measured using flat-panel ultra-high-resolution volume computed tomography (CT)] in girls with anorexia nervosa than controls even when BMD measures do not differ [13]. Impaired bone microarchitecture raises concerns regarding fracture risk independent of low BMD. In addition to these changes, adults with anorexia nervosa have decreased trabecular number [14,15] and decreased cortical thickness [15]. Recent data show that there is a decrease in bone strength in anorexia nervosa, as indicated by lower measures of stiffness and failure load, using finite element analysis [16**].

Impact of weight gain and resumption of menses

Optimally, adolescents and adults with anorexia nervosa should be under the care of a multidisciplinary team working on therapeutic strategies for weight gain. These measures must be strongly encouraged and can lead to an improvement in bone accrual in adolescents (1.4% over a year at the spine compared with a 0.3% decrease in those not gaining weight or resuming menses, and a 3% increase in normal-weight controls) [2]. However, residual deficits persist and prevent complete ‘catch-up’.

In adults with anorexia nervosa, weight gain and menses resumption are associated with a 3% annual increase in BMD at the spine and 2% at the hip, compared with an annual decrease in BMD of about 2.5% at both sites in those who do not recover [17]. Weight gain alone is predictive of increases in hip BMD, whereas menstrual recovery alone predicts increases in spine BMD. Similar data have been reported for women with anorexia nervosa followed over a 2-year period; women who gained weight had a 4 and 3% increase in hip and femoral neck BMD, respectively; and those who resumed menstrual function had an increase in spine, total hip and femoral neck BMD of 4, 3 and 3%, respectively [18]. Olmos *et al.* [19] reported an increase in BMD by 1.6, 4.4 and 1.3% at the femoral neck, total hip and spine, respectively, in anorexia nervosa women who gained weight.

Pathophysiology contributing to impaired bone metabolism in anorexia nervosa

There are several factors that contribute to impaired bone metabolism in anorexia nervosa (Fig. 1).

Body composition changes

Mechanical loading has bone anabolic effects, and important determinants of low BMD in anorexia nervosa include decreased BMI and lean body mass [1,17]. Prospective increases in lean mass are associated with increases in bone turnover markers and BMD [17,20].

Endocrine changes

Anorexia nervosa is associated with changes in many hormonal axes that impact bone. These include the hypothalamic–pituitary–gonadal axis, the growth hormone (GH)–insulin-like growth factor-1 (IGF-1) axis and the hypothalamic–pituitary–adrenal axis. Changes occur in many hormones impacted by energy status, such as peptide YY (PYY), leptin, ghrelin, insulin and adiponectin, which may affect bone.

Hypogonadism—Severe undernutrition in anorexia nervosa leads to altered patterns of luteinizing hormone pulsatility and low levels of gonadal steroids [21]. Gonadal steroids have important effects on bone metabolism. In early puberty, rising estrogen levels in girls

and aromatization of testosterone to estrogen in boys impact GH secretion [22]. Rising pubertal GH levels are associated with increases in bone modeling [23], whereas estrogen inhibits osteoclastic bone resorption [24]. Girls and boys with anorexia nervosa have lower levels of estradiol and testosterone than do controls [1,2], and these are important determinants of lower BMD, as are older age at menarche and longer duration of amenorrhea. Additionally, prospective increases in testosterone predict prospective increases in BMD [20]. Similarly, adult women with anorexia nervosa have low androgens levels, which predict low BMD [25] and impaired microarchitecture [14].

Acquired resistance to growth hormone and low insulin-like growth factor-1 levels—Girls with anorexia nervosa have low IGF-1 despite high GH levels, indicative of an acquired nutritional hepatic GH resistance [26]. Additionally, GH-binding protein levels are low in anorexia nervosa, suggestive of decreased GH receptor expression [27]. High GH levels are consequent to increased basal GH secretion and increased pulse frequency and are predicted by lower BMI, fat mass and glucose [26]. High 24-h median GH and low fasting IGF-1 have similarly been reported in adults with anorexia nervosa compared with controls [12*].

GH levels are positively associated with ghrelin, a GH secretagogue, and inversely with IGF-1, likely from reduced feedback inhibition at the hypothalamus and pituitary [26,28]. Higher GH levels in anorexia nervosa are consistent with an adaptive response to relatively lower glucose levels as well as low IGF-1 levels, given that GH is a counterregulatory hormone with gluconeogenic and lipolytic effects. A potential mediator of GH resistance in anorexia nervosa is fibroblast growth factor-21 (FGF-21), levels of which are higher in anorexia nervosa than that in controls [29*]. FGF-21 transgenic mice have increases in GH and decreases in IGF-1, and induce GH resistance by inhibiting signal transducer and activator of transcription-5 [30]. Peroxisome proliferator-activated receptor- γ agonists, which promote the mesenchymal progenitor cell to differentiate along the adipogenic rather than the osteoblastic lineage, also induce hepatic FGF-21 production [31]. FGF-21 induces ketogenesis [31], and increases in FGF-21 may, thus, mediate hepatic resistance to GH in anorexia nervosa, but may also be adaptive to a state of starvation and increase ketogenesis as a source of alternative fuel.

Whereas GH is positively associated with surrogate markers of bone formation and resorption in healthy adolescents, these associations are absent in girls with anorexia nervosa, indicating bone resistance to GH [26]. This is corroborated by a study in adult women with anorexia nervosa in whom administration of supraphysiological doses of recombinant human GH (rhGH) for 3 months compared with placebo did not increase IGF-1 or bone formation markers [32*], despite a significant decrease in fat mass in women receiving rhGH. In addition to GH, IGF-1 has direct bone anabolic effects, and low IGF-1 in girls with anorexia nervosa is associated with low levels of bone formation markers, and prospective increases in IGF-1 are associated with increases in surrogate bone formation markers [20]. Low IGF-1 also predicts impaired microarchitecture in adults with anorexia nervosa [14].

Relatively hypercortisolemia

Adolescents with anorexia nervosa have higher serum and urinary cortisol than controls, and increased cortisol is consequent to increased cortisol pulse frequency and a longer half-life [33]. Higher cortisol is associated with lower BMI and fat mass, and lower glucose, consistent with an adaptive response to the state of undernutrition as cortisol is gluconeogenic. Higher cortisol levels are also associated with lower BMD and inversely with bone turnover markers [33]. Similarly, adults with anorexia nervosa have higher mean

24-h serum cortisol [12*] and 12-h overnight pooled cortisol levels [34] compared with controls, and higher cortisol levels are predictive of lower spine and hip BMD [34] as well as lower extremity lean mass in anorexia nervosa, which may also impact bone [35].

Hormones impacted by energy status

A normal adaptive response to a state of severe undernutrition would be to stimulate orexigenic hormones (such as ghrelin), and inhibit anorexigenic hormones (such as leptin and PYY). Consistent with this, anorexia nervosa girls have higher ghrelin and lower leptin levels than controls [28,36], and high ghrelin [37] and low leptin levels have been reported in anorexia nervosa adults [12*,14,38].

Ghrelin, leptin and PYY

A direct impact of ghrelin on bone is suggested by expression of ghrelin receptors on osteoblasts, and an increase in osteoblastic activity following ghrelin administration [39,40]. Additionally, ghrelin is a GH secretagogue, and ghrelin is positively associated with GH secretory parameters in anorexia nervosa [28]. Thus, ghrelin could impact bone metabolism directly and indirectly through its GH stimulatory effects. In our studies, ghrelin levels were positively associated with levels of bone formation markers in healthy girls, but not in anorexia nervosa [41]. This may indicate a direct tissue resistance to ghrelin, or resistance to GH, which is downstream of ghrelin. Effects of leptin on bone are still under investigation; however, leptin is stimulatory to limb bones and inhibitory to the spine in rodents [42,43]. Most human models, including anorexia nervosa, suggest positive associations of leptin and BMD, such that patients with lower leptin levels have lower BMD [38] and impaired bone microarchitecture [14].

In contrast to the expected adaptive response in a state of undernutrition, levels of PYY (an anorexigenic hormone) are high, related to lower BMI and fat mass [21,44]. PYY (acting via the Y2 receptor) has deleterious effects on bone, as suggested by increased bone formation in the Y2 receptor knockout mouse [45], and PYY is inversely associated with bone turnover markers in adolescents with anorexia nervosa [21,44]. Additionally, in adults with anorexia nervosa, higher PYY is inversely associated with BMD [46].

Other hormones

Insulin, which is bone anabolic, is decreased in anorexia nervosa and is positively associated with levels of bone formation markers in adolescents [21]. Similarly, amylin, which is cosecreted with insulin and increases bone formation and inhibits bone resorption in animal models [47,48], is positively associated with BMD in adults with anorexia nervosa, even after controlling for weight [49]. Levels of adiponectin, an adipokine, are low in obesity and high in anorexia nervosa. Adiponectin increases osteoclastic activity through effects mediated by osteoprotegerin and receptor activator of nuclear factor kappa-B ligand and may also affect osteoblastic activity [50,51]. We have reported inverse associations of adiponectin with spine BMD in anorexia nervosa, even after adjusting for covariates [21], consistent with other studies [52,53].

Psychotropic medications

Psychotropic medications are commonly prescribed in anorexia nervosa, and BMD is lower in adolescents and young adults with anorexia nervosa who take selective serotonin reuptake inhibitors (SSRIs) for more than 6 months [54]; duration of SSRI use is an independent predictor of BMD after controlling for covariates.

Potential therapeutic strategies

Although it is extremely important to emphasize recovery in anorexia nervosa, weight gain can be difficult to attain and sustain. Additionally, menstrual recovery may not occur for many months after weight normalizes, and not all hormonal changes reverse with weight gain. For example, our studies indicate higher cortisol levels even after these girls gain weight [33]. Consistent with these observations, although some improvement in bone accrual occurs with weight gain (and resumption of menses), these rates remain lower than in normal-weight controls, and ‘catch-up’ does not occur [2]. For this reason, it is important to develop therapeutic strategies that will optimize bone accrual in girls with anorexia nervosa and allow them to ‘catch-up’ with peers. This should allow for optimization of peak bone mass with positive implications for both current and future bone health.

Calcium and vitamin D supplementation

Normal vitamin D levels are necessary for optimizing BMD and, therefore, it is important to ensure adequate calcium and vitamin D intake in anorexia nervosa. However, intake of calcium and vitamin D is typically sufficient in anorexia nervosa from an increased intake of supplements [1,20], and prevalence of vitamin D deficiency is lower than that in controls (2% in anorexia nervosa versus 24% in controls) [55]. Additionally, administration of calcium and vitamin D does not increase BMD in anorexia nervosa [20,56]. Nevertheless, we recommend administration of 1200 mg of calcium and 600–800 IU of vitamin D in anorexia nervosa, particularly if intake through diet or supplements is low. Vitamin D levels should be checked, and therapeutic doses are necessary when levels are low.

Gonadal steroid replacement

Hypogonadism is an important cause of low BMD in anorexia nervosa; however, oral estrogen administration as an estrogen–progesterone combination pill does not increase BMD, possibly consequent to IGF-1 suppressive effects of oral estrogen [56,57]. Additionally, oral estrogen causes decreases in androgen levels in anorexia nervosa, which may also prevent beneficial effects [25]. We have recently shown that estrogen administration as a transdermal patch to anorexia nervosa girls with a mature bone age, and in small oral doses to girls with immature bone age, compared with placebo, causes a significant increase in BMD over an 18-month period in adolescent girls with anorexia nervosa, even after controlling for baseline age, weight changes, age at menarche and duration of amenorrhea. The net increase in spine and hip BMD compared with adolescents who receive placebo is 2.3 and 1.1%, respectively [58**]. However, bone accrual falls short of complete ‘catch-up’ and BMD remains lower than that in normal-weight controls. This is likely because estrogen replacement does not reverse other hormonal changes in anorexia nervosa that contribute to low BMD.

One study examined the impact of dehydroepiandrosterone administration on BMD in adolescent and young adult women with anorexia nervosa and reported no change in BMD after controlling for weight changes [59]. A study in adult anorexia nervosa women report a positive effect of replacement testosterone as a transdermal patch (versus placebo) on levels of bone formation markers [60], but not BMD [61**].

Replacement of insulin-like growth factor-1

Low IGF-1 is an important determinant of low BMD in anorexia nervosa, and short-term administration of replacement recombinant human IGF-1 (rhIGF-1) to adolescents with anorexia nervosa causes an increase in levels of bone formation, but not bone resorption markers, compared with those who do not receive rhIGF-1 [62]. Additionally, rhIGF-1 with an estrogen–progesterone combination pill causes a significant increase in BMD in adults

with anorexia nervosa compared with placebo, not seen with administration of estrogen or rhIGF-1 alone [63]. Studies have not examined the impact of long-term IGF-1 administration on bone in adolescents with anorexia nervosa.

Bisphosphonates

Bisphosphonates inhibit osteoclastic bone resorption, and oral intake of 35 mg of risedronate weekly for a year has been demonstrated to increase BMD at the posteroanterior spine by 3% and at the hip by 2% in adult women with anorexia nervosa (who have increased levels of bone resorption markers) [61**]. In contrast, adolescents with anorexia nervosa have decreased levels of bone turnover markers, and it is unclear whether similar effects may be expected in this younger population. In fact, one placebo-controlled study found no increases in spine BMD, and minimal increases in femoral neck BMD, in girls with anorexia nervosa who received alendronate compared with placebo [64]. Concerns persist regarding use of bisphosphonates in this younger population, given their extremely long half-life.

Exercise activity

Mechanical loading has beneficial effects on bone in healthy individuals. However, in one study, women with anorexia nervosa involved in moderate bone loading exercise had lower BMD than nonexercisers at the spine and whole body than nonexercisers [65]. In contrast, after recovery, women who engaged in high bone loading exercise had higher BMD at the femoral neck and whole body than nonexercisers. Thus, the beneficial effects of exercise on bone are lost in anorexia nervosa and may manifest only after recovery.

Conclusion

Anorexia nervosa is a complex condition of undernutrition associated with many hormonal alterations that impact bone metabolism. Low BMD and decreased bone accrual are characteristic of this condition, and therapeutic strategies to improve bone metabolism are limited. Further investigations are necessary to determine strategies that will allow for 'catch-up' of bone accrual rates and optimize peak bone mass and BMD.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 420).

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Key points

- In addition to decreased bone accrual rates and low bone density, anorexia nervosa is characterized by impaired bone microarchitecture and decreased bone strength (as assessed by finite element analysis).
- Determinants of impaired bone metabolism include changes in body composition, hypogonadism, a state of growth hormone resistance, relative hypercortisolemia and changes in other hormones that impact bone metabolism, such as leptin, peptide YY, adiponectin, insulin and amylin.
- Although it is important to encourage weight gain and menstrual recovery in anorexia nervosa, residual deficits persist in bone density and bone accrual rates even after weight gain and resumption of menstrual function.
- Although oral estrogen administered as an oral contraceptive pill does not increase bone density in anorexia nervosa, replacement doses of transdermal estrogen and low incremental doses of oral estrogen to mimic early pubertal rises in estrogen are effective in increasing bone density in adolescents with anorexia nervosa; however, residual deficits persist.
- Although bisphosphonates are effective in increasing spine and hip bone density in adults with anorexia nervosa and femoral neck bone density in adolescents, they should be used with caution in a young population, given their impact on bone turnover and their very long half-life.

AN, anorexia nervosa; GH, growth hormone, IGF-1, insulin-like growth factor-1; PYY, peptide YY.

Figure 1.

Pathophysiology contributing to impaired bone metabolism in adolescents and adults with anorexia nervosa