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Anorexia Nervosa and Bone

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Abstract

Anorexia nervosa (AN), a psychiatric disorder characterized by altered body image, food restriction and low body weight, is associated with low bone mineral density and increased fracture risk. Despite broadening the definition of AN in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, the prevalence of low bone mass remains high, suggesting we continue to capture individuals at high risk for bone loss. Many of the endocrine disturbances adaptive to the state of chronic starvation are thought to be causal in impaired skeletal integrity in females and males with AN. Understanding mechanisms responsible for impaired bone quality is important given the disease's severity and chronicity. Further research is needed to formulate optimal treatment strategies to reduce fracture risk.

Keywords

Anorexia nervosa; Bone mineral density; Osteoporosis

1. Epidemiology of anorexia nervosa

Anorexia nervosa (AN) is a psychiatric disorder characterized by altered body image, food restriction and low body weight. In 2013, the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) broadened the diagnostic criteria for AN by making the weight criteria less stringent and removing the requirement for amenorrhea [1]. This has increased the prevalence of AN among female adolescents by about 50%, ranging from 0.8 to 1.7%[2–4]. In addition, the diagnosis of 'atypical AN' was created within the Other Specific Feeding or Eating Disorders (OSFED) category for those individuals who are not low weight but meet AN psychological criteria[1]. AN is associated with increased fracture risk in females[5], including those with normal bone mineral density (BMD)[6]. Less is known about fracture risk in males with AN, although one study reported a higher fracture risk among males >40 years old compared with controls[7]**.

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Conflicts of interest: none.

2. Bone mineral density

Multiple studies have shown reductions in spine and hip BMD in both adolescents and adults with AN. In the first report of BMD across the AN spectrum, the presence of a BMD Z-score <−1 at any site was comparable between women with AN and atypical AN (80% vs 69%)[8]**. In contrast, more severe bone loss, i.e. BMD Z-score <−2, was more common in women with AN compared to atypical AN (44% vs 25%, p=0.01). These prevalence rates are similar to women with AN using DSM-IV criteria[9],suggesting that the high prevalence of low bone mass persists despite new diagnostic criteria. In addition, women with atypical AN are also at high risk for bone loss.

In the first study to evaluate sex differences in BMD among adolescents with AN using DSM-5 criteria, similar percentages of males and females had a BMD Z-score <−1 at the spine (48 vs 45%) or hip (44 vs 45 %)[10]**. These data confirm a prior study of adolescent boys with AN using DSM-IV criteria[11], again suggesting that broadening the diagnostic criteria for AN has not changed the prevalence of low bone mass.

3. Bone microarchitecture and estimated bone strength

Two DXA-derived parameters, hip structural analysis (HSA) and trabecular bone score (TBS), provide information about bone structure and strength. HSA reports hip structural geometry and estimated strength; both correlate with 3-D quantitative CT[12] and fracture risk[13,14]. HSA parameters have been reported to be impaired in both women[15] and male adolescents[16] with AN. TBS also correlates with fracture risk[17] and in one study, TBS showed evidence of degraded microarchitecture in over 40% of female adolescents with AN[18]*.

Impaired cortical and trabecular microarchitecture and lower estimated bone strength, using high resolution peripheral quantitative CT (HR-pQCT), have been reported at the distal radius in adolescent girls with AN[19]. Whether weight-bearing would overcome the detrimental effects of AN at the distal tibia was investigated by Singhal *et al.* who reported that female adolescents and young adults with AN had greater cortical porosity and lower total and cortical volumetric BMD (vBMD), cortical thickness, trabecular number and strength estimates than controls[20]**. In contrast, DiVasta *et al.* reported lower trabecular, but higher cortical, vBMD as assessed by pQCT in adolescent girls with AN compared to controls[21]. These results could be due to differences in site assessed, techniques and disease severity. Singhal *et al.* also investigated individual trabeculae segmentation in their cohort, and reported a preferential preservation of rod-like (versus plate-like) trabecular bone in AN, which was associated with lower strength estimates, and consistent with reports that more rod-like trabeculae are detrimental to bone strength[22]. Lastly, this paper demonstrated that bone strength estimates are associated with cortical and trabecular microarchitecture independent of areal BMD (aBMD). Both the peripheral and axial skeleton are compromised in women with AN. Vertebral BMD and estimated strength measured by QCT are impaired in women with both AN and atypical AN compared to controls[23]*.

4. Skeletal integrity in recovery

Impaired skeletal integrity and increased fracture risk are often long-term comorbidities in AN. Studies have demonstrated that women continue to have reduced BMD 9[24] and 21 years[25] after the onset of recovery from AN. Mueller *et al.* reported that women in recovery from AN for a mean of 27 years have reduced trabecular vBMD at the distal tibia compared to controls[26]*. These data support the concept that impaired skeletal integrity persists despite recovery.

5. Determinants of skeletal integrity

5.1. Body composition

Body weight and body composition are important determinants of skeletal integrity. Muscle has an anabolic effect on bone through mechanical loading and muscle-bone hormonal crosstalk. Low lean body mass has been associated with impaired BMD, bone microarchitecture and estimated bone strength in females with AN[27,28] (Figure 1). More recently, the effect of muscle strength on skeletal health in women with AN has been investigated by calculating maximal voluntary ground reaction forces (F_{m1LH}), a measure of bone strength that includes skeletal muscle force production. Mueller *et al.* demonstrated that variability in tibial vBMC is largely explained by F_{m1LH}, and that women with a history of AN, but currently in recovery, have lower tibial vBMC and F_{m1LH} than controls[26]*.

A relatively new area of investigation is bone marrow fat, which is paradoxically elevated in women with AN despite reduced total body fat[29,30] (Figure 1). Higher preadipocyte factor 1 (Pref-1) levels, which is a negative regulator of osteoblast and adipocyte differentiation, is associated with higher marrow fat content and lower bone mass in women with AN[31]. Bredella *et al.* demonstrated an inverse relationship between marrow fat content and BMD at multiple skeletal sites[30,32], as well as between marrow fatty acid saturation and BMD[33]. The relationship between marrow fat and BMD in adolescents is more complex, as both marrow fat and BMD normally increase rapidly during adolescence[34]. Ecklund *et al.* reported a positive relationship between marrow fat and BMD in younger female adolescents with AN [35]. Faje *et al.* reported that although Pref-1 levels are comparable in adolescent girls with AN and controls, Pref-1 levels decrease after treatment with transdermal estradiol, and correlate inversely with changes in BMD, suggesting that Pref-1 may mediate the effects of transdermal estradiol on BMD[36].

5.2. Nutrition

The prevalence of vitamin D deficiency in AN largely depends on the use of supplements. Vitamin D deficiency was reported to be much less common among adolescents with AN than healthy youths[37], in part due to the high prevalence of supplementation. A more recent study in found that approximately 60% of females with AN had 25OHvitD levels <30 ng/mL and 36% were <20 ng/mL[38]. Hip BMD was significantly lower in subjects with 25OHvitD levels <12 vs ≥20 ng/mL. A 20-week observational study demonstrated that weight gain was associated with an increase in spinal BMD only in females with AN who

had 25OHvitD levels ≥30 ng/mL[39]*. Maintaining adequate 25OHvitD levels during treatment may be important to maximize gains in BMD.

In healthy adolescents and adults, mechanical loading (i.e. exercise) has beneficial effects on bone. In contrast, in individuals with AN who are in a state of energy deficit, exercise has deleterious effects on bone because caloric expenditure further worsens the energy deficit. Resting energy expenditure (REE_m), or basal metabolic rate, decreases as an adaptive response to energy deficit. Maimoun *et al.* reported that REE_m in women with AN was positively correlated with bone formation markers and negatively correlated with bone resorption markers[40]. However, in individuals in recovery from AN, high bone loading activities may help increase bone accrual[41].

It is also important to consider the effect of prescription and non-prescription drugs on skeletal integrity. Selective serotonin re-uptake inhibitors (SSRI) have been associated with lower BMD[42] and increased fracture risk in females with AN[7,43]**. A recent meta-analysis reported high levels of smoking in individuals with AN[44], which has been associated with lower bone mass. Alcohol abuse has been independently associated with an increased fracture risk in females and males with AN[7]**.

5.3. Onset and duration of disease

Adolescence is a period of high bone turnover, with bone formation exceeding bone resorption as peak bone mass accrues[45]. In contrast, adolescents with AN have both decreased bone formation and resorption[46], causing compromise of peak bone mass accrual. In contrast, adult women with AN have decreased bone formation and increased bone resorption, resulting in loss of established bone mass. For both groups, changes in bone mass may occur relatively rapidly, often within the first year of disease[47]. Moreover, duration of illness is associated with lower BMD in both male[48] and female adolescents[49] and women[5], and more impaired bone microarchitecture in females[19], suggesting that bone loss continues throughout the course of the illness[49].

5.4. Hypothalamic-pituitary-gonadal axis

The energy deficit associated with nutritional deprivation in females with AN often results in hypothalamic amenorrhea, which contributes to impaired skeletal integrity (Figure 1). Leptin, which is positively associated with fat mass, is a proposed regulator of kisspeptin neurons in the hypothalamus, which signal to GnRH neurons[50]. Although abnormal leptin and kisspeptin signaling are major regulators of hypothalamic amenorrhea, there is no a clear cut-off in serum leptin levels between women with AN who are amenorrheic and those who are eumenorrheic of comparable low weight and psychopathology [51], suggesting other mechanisms may contribute, such as underlying genetic susceptibility of the hypothalamic-pituitary-gonadal axis to nutritional deprivation.

Hypothalamic amenorrhea results in low estradiol and androgen levels in females with AN[52]. Estradiol inhibits bone resorption by inhibiting receptor activator of nuclear factor k B ligand (RANKL) secretion, which increases osteoclastogenesis and osteoclastic activity, and increasing osteoprotegerin (OPG) secretion[53], a factor that inhibits osteoclastogenesis and osteoclast activity. Estrogen stimulates bone formation by inhibiting sclerostin secretion,

a factor that inhibits osteoblast differentiation[54]. Consistent with these data, decreased ratios of OPG/RANKL[55] and increased sclerostin levels[56] have been reported in women but not adolescents with AN [57]. Numerous studies have reported that a longer duration of amenorrhea is associated with worse skeletal integrity[5,15,23]*, as is a history of amenorrhea in those who are currently eumenorrheic[8,58]**. However, bone resorption is higher in adult amenorrheic women with AN than postmenopausal women, suggesting other factors contribute to increased bone resorption in AN[59]. The contribution of hypogonadism to impaired skeletal integrity in males with AN is less well understood.

5.5. GH- IGF-1 axis

Chronic nutritional deprivation in AN is a state of acquired growth hormone (GH) resistance, characterized by increased GH and decreased insulin-like growth factor 1 (IGF-1) secretion[60,61] (Figure 1). GH and IGF-1 stimulate osteoblast differentiation while inhibiting osteoclast differentiation, and GH independently stimulates osteoblast proliferation[62]. Accordingly, low serum levels of IGF-1 in women with AN are associated with low levels of bone formation markers [46,63], low BMD[46] and impaired bone microarchitecture[64].

5.6. Hypothalamic-pituitary-adrenal axis

In at least one-third of women with AN, the hypothalamic-pituitary-adrenal axis is in a chronically stimulated state due to the stress of chronic nutritional deprivation[65,66] (Figure 1). Cortisol decreases bone formation and increases bone resorption, in part by inhibiting osteoprotegerin and increasing RANKL secretion[67]. Hypercortisolemia is inversely associated with BMD in females with AN[65,66].

5.7. Alterations in appetite-regulating hormones

Appetite-regulating hormones are altered in AN and may contribute to impaired skeletal integrity (Figure 1). Low nocturnal serum oxytocin levels are associated with decreased spine BMD, as well as some measures of impaired hip structure and strength in women with AN, independent of BMI[68]. In women with AN, hypoleptinaemia is associated with lower femoral neck and spine BMD, as well as abnormalities in bone microarchitecture, independent of BMI[64]. Serum peptide tyrosine tyrosine (PYY) levels, an anorexigenic hormone, are inappropriately elevated in females with AN[73]. PYY is thought to inhibit osteoblastic activity while increasing osteoclastic activity[74]. Consistent with these data, mean overnight PYY levels are negatively associated with BMD in women with AN, independent of BMI[73].

6. Management of low bone mass

The most effective therapy to improve skeletal integrity in AN is successful treatment of the underlying eating disorder to reverse many of the adaptive hormone changes associated with active disease. In one study, women with AN who gained weight and resumed menses had a mean annual increase in hip BMD of 1.8% and spine BMD of 3.1%[75] (Table 1). In contrast, those who remained low weight and amenorrheic had a mean annual decline in hip BMD of – 2.4% and spine BMD of –2.6%. Even weight gain, on the order of 5–10% of

body weight, may improve bone turnover markers[40]. Importantly, weight gain and resumption of menses may not normalize BMD in all women[76], especially for those who develop active disease during adolescence.

Oral estrogen is not effective in increasing BMD in adults[77–79], likely in part because oral estrogen decreases IGF-1 production by the liver[80] (Table 1). In contrast, physiological transdermal estrogen replacement with cyclic progesterone has been shown to increase spine and hip BMD in adolescent girls with AN[82] although BMD is not normalized[82] (Table 1). In addition, androgen or androgen precursor replacement, in the form of testosterone or DHEA, does not improve BMD[83,84] (Table 1). Although oral estrogen is not effective in increasing BMD in women with AN, recombinant human IGF-1 (rhIGF-1) administered in combination with oral contraceptives increased mean spine BMD by 2.8% vs placebo untreated women, in whom BMD decreased, in a randomized controlled trial[85] (Table 1).

Both antiresorptive and anabolic therapies have been evaluated in females with AN. In a randomized controlled trial, oral bisphosphonates increased mean spine BMD by 3.2% and total hip BMD by 1.9% after 12 months compared with placebo in women with AN[83] although no effect was seen in adolescent girls with AN[86] (Table 1). Although there is more recent safety data suggesting that bisphosphonates may be safe in women of childbearing age[87], data suggest that these drugs do cross the placenta[88].

Because bone formation is decreased in AN, anabolic strategies have been investigated. Fazeli *et al.* showed that 6 months of teriparatide, in a small randomized controlled trial of women with AN, increased spine BMD by 6–10%[89] (Table 1). However, an FDA warning advises that this medication should not be prescribed to patients who are at increased risk for osteosarcoma, including adolescents with open epiphyses.

7. Conclusion

Impaired skeletal integrity, defined as low BMD, impaired bone microarchitecture and increased fracture risk, is highly prevalent in both AN and atypical AN. A history of low weight and amenorrhea are important determinants of impaired skeletal integrity, even for those who are currently normal weight and eumenorrheic. Other hormone factors that may contribute to impaired skeletal integrity include GH resistance, hypercortisolemia, and changes in appetite-regulating hormones. Understanding the mechanisms responsible for bone loss in individuals with AN may provide insight into new therapies, which is a critical unmet need as there are currently no FDA-approved medications to treat bone loss in AN. Further research regarding the pathophysiology and treatment of bone loss in adolescent boys and men with AN is also needed.

Abbreviations

AN	anorexia nervosa
BMD	bone mineral density
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition

OSFED	Other Specific Feeding or Eating Disorders
HSA	hip structural analysis
TBS	trabecular bone score
HR-pQCT	high resolution peripheral quantitative CT
vBMD	volumetric BMD
aBMD	areal BMD
F_{m1LH}	maximal voluntary ground reaction forces
Pref-1	preadipocyte factor 1
REE_m	resting energy expenditure
SSRI	selective serotonin re-uptake inhibitors
RANKL	receptor activator of nuclear factor k B ligand
OPG	osteoprotegerin
GH	growth hormone
IGF-1	insulin-like growth factor 1
PYY	peptide tyrosine tyrosine
rhIGF-1	recombinant human IGF-1

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Highlights

1. Anorexia nervosa (AN) is associated with low bone density (BMD) and increased fracture risk
2. Endocrine dysregulation in AN is mostly adaptive to chronic undernutrition and contributes to low BMD
3. Although weight and gonadal recovery may improve bone health, BMD and fracture risk may not normalize
4. There are no FDA-approved therapies to treat low BMD in AN, which is a critical unmet need

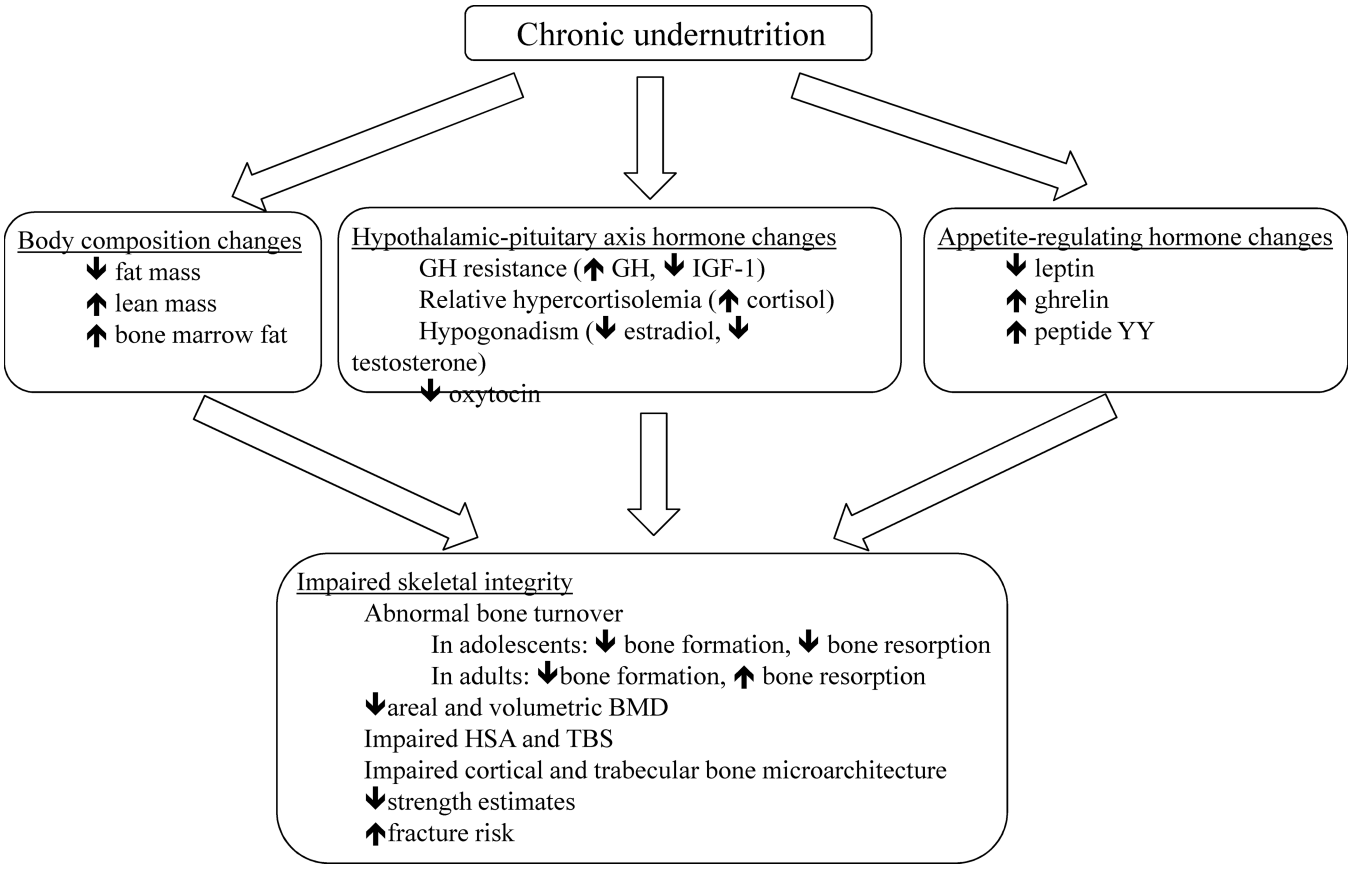

Figure 1. Summary of endocrine dysregulation in individuals with anorexia nervosa and its effects on skeletal integrity.

Endocrine dysregulation in anorexia nervosa is mostly adaptive to the state of chronic undernutrition. Body composition changes, hypothalamic-pituitary axis hormone changes and appetite-regulating hormone changes all contribute to impaired skeletal integrity. GH: growth hormone. IGF-1: insulin-like growth factor 1. HSA: hip structural analysis. TBS: trabecular bone score.

Table 1.

Summary of therapies for low bone mass in adolescent girls and women with anorexia nervosa

Therapy	Study Design	Subject Characteristics	Control Group(s)	Duration of Treatment	Outcome(s)	Reference
Weight gain and restoration of menses	Prospective observational	75 females ages 18–40yo	none	mean 13.5 mo (6–69 mo)	Weight gain and menstrual recovery resulted in annual mean increase of 3.1% in spine BMD and 1.8% in hip BMD compared to an annual decrease of 2.6% in spine BMD and 2.4% in hip BMD in those who did not gain weight or recover menses	Miller 2006
Oral estrogen/ progestin	RCT	48 females ages 16–42yo	no medication	18 mo	Estrogen/progestin did not increase BMD vs no treatment	Klibanski 1995
	Prospective observational	50 females ages 12–21yo	no medication	mean 23.1 mo	Estrogen/progestin did not increase BMD vs no treatment	Golden 2002
	RCT	112 females ages 11–17yo	placebo	13 mo	Estrogen/progestin did not increase BMD vs placebo	Strokosch 2006
Physiologic transdermal estrogen replacement	RCT	110 females ages 12–18yo	placebo + 40 normal-weight controls	18 mo	Physiologic estradiol replacement increased spine and hip BMD vs placebo to approximate bone accrual rates in controls, but catch-up BMD did not occur	Misra 2011
Testosterone	RCT	77 females ages 19–49yo	placebo	12 mo	Testosterone did not increase BMD vs placebo	Miller 2011
DHEA	RCT	61 females ages 14–28yo	oral estrogen/ progestin	12 mo	After controlling for weight gain, no treatment effect was observed with either DHEA or oral estrogen/progestin	Gordon 2002
Recombinant hIGF-1 + oral estrogen/progestin	RCT	60 females ages 18–38yo	no treatment	9 mo	rhIGF-1 + oral estrogen/progestin increased spine BMD vs placebo	Grinspoon 2002
	Prospective	20 females ages 12–18yo	no treatment	7–9 days	rhIGF-1 caused an increase in bone formation markers vs no treatment	Misra 2009
Risedronate	RCT	77 females ages 19–49yo	placebo	12 mo	Risedronate increased spine and hip BMD vs placebo	Miller 2011
Alendronate	RCT	32 females ages 12–21yo	placebo	12 mo	Spine and hip BMD increased similarly in the alendronate and placebo groups. Within groups, spine and hip BMD increased significantly within the alendronate group, but not the control group.	Golden 2005
Teriparatide	RCT	32 females ages 32–58yo	placebo	6 mo	Teriparatide increased hip BMD vs placebo	Fazeli 2014

RCT: randomized controlled trial. DHEA: Dehydroepiandrosterone. hIGFl: human insulin-like growth factor 1.