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State of the Art Systematic Review of Bone Disease in Anorexia Nervosa

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Abstract

Objective—Low bone mineral density (BMD) is a known consequence of anorexia nervosa (AN) and is particularly concerning during adolescence, a critical time for bone accrual. A comprehensive synthesis of available data regarding impaired bone health, its determinants, and associated management strategies in AN is currently lacking. This systematic review aims to synthesize information from key physiologic and prospective studies and trials, and provide a thorough understanding of impaired bone health in AN and its management.

Method—Search terms included “anorexia nervosa” AND “bone density” for the period 1995–2015, limited to articles in English. Papers were screened manually based on journal impact factor, sample size, age of participants, and inclusion of a control group. When necessary, we included seminal papers published before 1995.

Results—AN leads to low BMD, impaired bone quality and increased fracture risk. Important determinants are low lean mass, hypogonadism, IGF-1 deficiency, and alterations in other hormones that impact bone health. Weight gain and menses restoration are critical for improving bone outcomes in AN. Physiologic estrogen replacement as the transdermal patch was shown to increase bone accrual in one study in adolescent females with AN; however, residual deficits persist. Bisphosphonates are potentially useful in adults with AN.

Discussion—To date, evidence suggests that the safest and most effective strategy to improve bone health in AN is normalization of weight with restoration of menses. Pharmacotherapies that show promise include physiologic estradiol replacement (as the transdermal estradiol patch), and in adults, bisphosphonates. Further studies are necessary to determine the best strategies to normalize BMD in AN.

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Keywords

anorexia nervosa; eating disorders; adolescents; bone density; bone microarchitecture; fracture; estrogen; menstruation; insulin like growth factor-1; bisphosphonates

Introduction

Anorexia nervosa (AN) is a very prevalent condition (0.2–1.0% per DSM IV and up to 4% per DSM-5¹) and is associated with significant morbidity and high mortality. An important comorbidity of AN is low bone mineral density (BMD) associated with an increased risk of fracture. However, a comprehensive synthesis of available data regarding the impact of AN on not only areal BMD, but also volumetric BMD and bone quality, and the determinants of these bone changes is lacking. In addition, clinicians are in need of direction regarding management strategies for low BMD in AN and a systematic review of possible therapeutic strategies is also currently lacking. This systematic review aims to synthesize information from key physiologic and prospective studies and important clinical trials performed in the last two decades and to provide a comprehensive understanding of bone consequences of AN and management of low BMD. This review examines the impact of AN on bone, factors contributing to low bone density in AN, and possible therapeutic strategies to improve bone mass in this condition.

Methods for Selection of Articles

In order to report key and up-to-date information regarding bone metabolism in adolescents with AN, we reviewed articles dating between 1995 and 2015. A thorough literature search was completed using PubMed and the database of the National Library of Medicine. Search terms included “anorexia nervosa” AND “bone density” (bone mineral density*, bone density*) for the period between 4/1/1995 and 4/20/ 2015 and limited to articles in English. The initial search yielded 286 papers. Papers were further screened manually based on the impact factor of the journal, numbers of subjects studied, age of participants (adolescents or adults) and whether or not the study included a control group. We also included seminal papers that were published before April 1995. The term “seminal” refers to classic papers that have served as a model for other papers and/or present an influential view on bone metabolism in AN. To hone in on treatment studies, we added “treatment” (therapy*, trial*, therapeutics*) to the search terms, and focused on prospective studies and randomized controlled trials during the subsequent manual search.

Impact of Anorexia Nervosa on Bone

The peak age of onset of AN is during adolescence, the period during which 40–60% of peak bone mass is normally accrued. Failure to achieve peak bone mass during adolescence secondary to a disease like AN can have life-long implications for bone health. Large scale epidemiological studies have demonstrated that patients with a past history of AN have a 2 to threefold increased risk of bone fracture.^{2,3} Increased fracture risk may even develop during the adolescent years. One study found that the lifetime prevalence of prior fracture in adolescents with active AN was 60% higher than that in normal-weight controls, and the

fracture incidence peaked after the diagnosis of AN.⁴ Patients with bulimia nervosa and subclinical eating disorders who have a prior history of AN or amenorrhea may also be at increased fracture risk.^{3,5}

The major methods of assessing bone health are described in Table 1. All methods are only surrogate measures of bone fragility and each method has advantages and limitations. The preferred method of assessing bone health in clinical practice is dual energy X-ray absorptiometry (DXA) because of its precision, availability, reproducibility, speed, ease, low radiation exposure, relatively low cost and reference data. DXA measures bone mineral content (BMC) and two dimensional areal bone mineral density (aBMD). Prepubertal bone accrual is primarily due to an increase in bone size during linear growth, whereas pubertal bone accrual is due to both increases in linear growth and volume. AN can cause pubertal delay and interruption of linear growth. In addition, young people who develop AN during childhood or early adolescence have not yet reached their peak bone mass. Therefore, a young person with AN may not have had the gains in bone size, geometry, and density that occur in healthy young people.⁶ Finally, there are limitations when conceptualizing and defining BMD abnormalities in children and adolescents using cross-sectional Z-scores. This may lead to inclusion of large numbers of normal children when using specific cut offs of Z-scores to define abnormalities, and does not take into consideration the trajectory of change in young people sampled from a normally distributed population.^{4,7} Clearly, longitudinal data are needed. One must be mindful of these factors when interpreting DXA findings in this population.

Controversy persists about the optimal method for adjusting for variations in bone size, body composition, and maturity. The Pediatric Position Development Conference (PDC) of the International Society of Clinical Densitometry (ISCD) guidelines recommend that BMC or BMD in children and adolescents should be compared with that of a reference database of healthy individuals of similar gender, age and race/ethnicity (reported as the Z-score), and should be adjusted for height in those with delayed growth or puberty.⁸ Appropriate interpretation of DXA results relies on the use of BMC or BMD Z-scores as opposed to T-scores, which compare DXA measures to a standard adult reference point and are thus not relevant in children.⁹ Further, the ISCD recommends that the term “osteopenia” (milder deficits) only be used to describe deficits in bone mass in adults. This label should not be used in children and adolescents. A DXA measurement with a Z-score of -2 should be labeled “below the expected range for age”. The revised PDC guidelines suggest that a diagnosis of osteoporosis in children and adolescents requires (i) the occurrence of one or more vertebral compression (crush) fractures in the absence of local disease or high energy trauma, or (ii) in the absence of vertebral compression fractures, the presence of both a significant fracture history (two or more long bone fractures by the age of 10 years, or three or more long bone fractures at any age up to age 19 years) AND a BMD Z-score of -2 .¹⁰ In premenopausal women and men less than 50 years, a diagnosis of osteoporosis requires a BMD Z-score of -2 and presence of risk factors for fracture or secondary causes of osteoporosis.

Other methods used to assess bone mass include quantitative computed tomography (QCT) and peripheral QCT (pQCT) (Table 1). Unlike DXA, both methods measure true volumetric

BMD. QCT provides a three-dimensional assessment of the structural and geometric properties of bone, and a separation of cortical and trabecular bone. A major disadvantage of axial QCT is the high-radiation dose, making it unsuitable for use in children and adolescents. pQCT permits a three-dimensional analysis of appendicular bones by using a lower radiation dose than axial QCT. The usual sites measured are the nondominant distal tibia and radius. High resolution pQCT also allows assessment of the microstructure of bone. These methods are not widely used in clinical practice due to lack of accessibility, higher doses of radiation, and standardization of scan acquisition.

Effect of Anorexia Nervosa on Dual Energy X-Ray Absorptiometry Measures of Areal Bone Mineral Density

The usual sites measured are the lumbar spine, hip and total body (or preferably total body less head). In adults, a 1 SD reduction in BMD is associated with a twofold increased risk of fracture. In children and adolescents there is no specific threshold below which a fracture is more likely to occur, but there is an increasing body of knowledge associating low BMD with fractures. Multiple cross-sectional and longitudinal studies have consistently shown reductions in BMD in AN, both in adults^{11,12} and in adolescents.^{13–23} Reduced bone mass is not limited to girls, but is also seen in boys with AN.^{24,25} Both cortical and trabecular bone sites are affected but there is preferential loss of trabecular bone which is more metabolically active and has a higher turnover rate. The lumbar spine which has a greater proportion of trabecular bone is more frequently affected than the hip or total body. Prospective studies demonstrate that adult women with active disease lose bone mass at the rate of 2.5% per year.¹² In a longitudinal case-controlled study, Soyka et al. showed that adolescent girls with AN prospectively followed for 12 months had persistently low BMD at follow-up despite weight gain, while healthy adolescents continued to accrue bone.¹⁴ These findings, combined with those examining markers of bone turnover in AN (discussed later), suggest that adults with AN lose bone mass whereas adolescents with AN have reduced bone formation in addition to increased^{19,39} or decreased^{26,27} bone resorption. Studies evaluating adults who have recovered from adolescent-onset AN demonstrate persistent deficits in BMD up to 21 years after full recovery from the eating disorder.^{28,29}

Effect of Anorexia Nervosa on Peripheral QCT (pQCT) and High Resolution pQCT Measures of Volumetric Bone Density, Bone Geometry, and Microarchitecture

A cross-sectional study of 36 adult women with AN demonstrated significant deficits in volumetric BMD, trabecular number, trabecular density and cortical thickness compared to age-matched controls.³⁰ These findings confirmed the fact that both cortical and trabecular bone are compromised in AN. High resolution peripheral quantitative computed tomography (HR-pQCT) measures small regions of the distal tibia and radius and can evaluate bone microarchitecture as well as bone strength. Adolescent girls with AN have reductions in the number of trabeculae, decreased thickness of trabeculae and a paradoxical increase in bone marrow adipose tissue, compared to healthy controls.^{31–33} Finite element analysis (FEA) is a computer-based modeling technique used to reconstruct 3-dimensional images of the bone in order to estimate bone strength by calculating the predicted load necessary to fracture bone. Failure load, estimated by FEA, is lower in girls with AN, indicative of reduced bone strength.³³

Effect of Anorexia Nervosa on Bone Turnover Markers

Measurements of markers of bone formation and resorption are useful to understand the pathophysiology of disturbances in bone health and to assess dynamic responses to specific interventions before the changes become apparent using DXA or pQCT. Osteocalcin (OC) and bone specific alkaline phosphatase (BSAP) are serum markers of bone formation that are released at different stages of osteoblast proliferation and differentiation. Since OC is incorporated into the bone matrix and is later released into the circulation during bone resorption, it can also be considered a marker of bone turnover. Type I collagen C-terminal telopeptide (ICTP), cross-linked C-telopeptide (CTX), and cross-linked N-telopeptide (NTX) are markers of bone resorption that can be measured in the serum or urine. In adults with AN markers of bone formation are reduced and markers of bone resorption are increased suggesting reduced bone formation as well as increased bone degradation.^{34,35} In adolescents with AN, only one study had a control group and in that study both markers of bone formation and resorption were reduced, suggesting suppression of bone turnover.¹⁴ Other uncontrolled studies in adolescents with AN have found evidence of increased bone resorption in addition to reduced markers of bone formation.^{20,36}

Determinants of Impaired Bone Health in Anorexia Nervosa

Determinants of low BMD and impaired bone microarchitecture in AN include changes in body composition and numerous endocrine alterations (Fig. 1). Importantly, these endocrine changes are primarily adaptive; however, together they have a significant negative impact on bone.^{37,38} This section will review the many factors that contribute to impaired bone health in AN.

Changes in Body Composition

Decreased Body Mass Index (BMI) and Lean Mass—Both BMI and lean mass are important determinants of BMD.^{14,16,18,24,25,36,39–42} Low BMI in AN is typically associated with lower lean mass than seen in normal-weight controls, and with many hormone alterations (described subsequently) that in turn can impact bone. The positive effect of lean mass on bone has been attributed to the pull of muscle on bone having bone anabolic effects. Further, increased mechanical loading, which is anabolic to bone, may cause an increase in lean mass. Adolescents with AN have lower BMI and lean mass than controls, both of which are strongly associated with lower areal BMD at multiple sites^{16,25} and impaired hip structural parameters.⁴¹ Similar data are reported in adults with AN.¹¹ A longer duration of illness predicts lower areal BMD,^{18,24,43} and also impaired bone microarchitecture and volumetric BMD at the distal radius.³³ In addition, in girls with AN, an increase in body weight following treatment of AN is associated with an increase in lean body mass, which in turn predicts an increase in bone density measures.^{14,44}

Changes in Marrow and Brown Fat—Fat mass is markedly decreased in AN, and is associated with lower bone density measures. In addition, regional fat, particularly marrow adipose tissue, has been inversely associated with bone density in AN, in both adolescents and adults.^{32,45} This is consistent with the concept of a common progenitor stem cell in the marrow being able to differentiate along the osteoblast or adipocyte pathways. In fact,

preadipocyte factor-1 (Pref-1), a transcription factor that preferentially stimulates the progenitor stem cell to differentiate along the adipocyte pathway, is increased in adults (though not in adolescents) with AN^{46,47} and decreases following estrogen replacement in adolescents with AN.⁴⁶ In addition, brown fat has been positively associated with cross-sectional dimensions of bone⁴⁸ and BMD measures,⁴⁹ and is less likely to be visible in women with AN compared with controls.⁴⁹

Changes in Hormone Profiles

AN, a state of severe energy deprivation, leads to changes in many endocrine axes, and most of these changes are physiologic adaptive changes aimed at either (i) energy conservation (through suppression of the hypothalamic-pituitary-gonadal axis, thus avoiding energy utilization in activities such as procreation) or (ii) activation of pathways that (a) cause an increase in energy intake (though an increase in appetite stimulating hormones and a decrease in appetite inhibiting hormones), or (b) mobilize substrates to increase energy availability for vital functions (such as through activation of the glycogenolytic and lipolytic pathways by cortisol and growth hormone respectively).^{37,38} However, the majority of these endocrine changes have a deleterious effect on bone, leading to decreased bone formation or increased bone resorption or both, and consequent low bone density.^{37,38}

Hypothalamic-Pituitary-gonadal (HPG) Axis—The state of low energy availability in AN has an inhibitory effect on the HPG axis, resulting in varying degrees of menstrual dysfunction, the most extreme being a state of amenorrhea. Hypogonadism leads to low levels of the gonadal steroids, estrogen and testosterone, both of which have a key role in bone metabolism. Estrogen is essential for inhibiting bone resorption and may also impact bone formation by inhibiting sclerostin secretion, a factor that inhibits osteoblast differentiation.⁵⁰ One study has reported increased sclerostin levels in adults with AN.⁵¹ However, sclerostin levels do not differ in girls with AN compared with controls, and do not change following estrogen replacement.⁵² Estrogen primarily inhibits bone resorption by inhibiting the secretion of inflammatory cytokines and RANKL, which otherwise increase osteoclastic activity, and increasing the secretion of osteoprotegerin (OPG), which inhibits osteoclasts.⁵³ Levels of inflammatory cytokines, such as IL-6, are increased in AN,⁵⁴ however, OPG levels are also increased,^{27,55,56} likely a compensatory phenomenon. However, studies have also reported a decrease in the ratio of OPG/ RANKL in AN, which may contribute to bone loss.^{56,57} Testosterone (levels of which are low in AN) has antiresorptive effects on bone (both direct and through aromatization to estrogen) and a direct anabolic effect on bone formation.

Adolescent girls and boys with AN have lower levels of estrogen and testosterone than controls,^{14,25} and these hormonal changes are important predictors of low BMD and impaired hip structure in AN.⁴¹ In adolescent girls with AN, a longer duration of amenorrhea (>6 months in one study¹⁸) and later menarchal age are important determinants of the extent of bone density impairment.^{16,18,39,43} Similar associations have been reported in adults with AN.⁵¹ One study has reported an association of lower lumbar BMD Z-scores with carriers of the A allele for estrogen receptor alpha (ESR1) (rather than the G allele).⁵⁸

Growth Hormone-Insulin-Like Growth Factor-1 (GH-IGF-1) Axis—GH, secreted by the pituitary gland, stimulates IGF-1 secretion in the liver and also locally in bone. GH and IGF-1 are important bone anabolic hormones. Together with the rising levels of the sex steroids during puberty, rising levels of GH and IGF-1 during adolescence cause the marked increase in bone accrual that characterizes puberty. AN is associated with significant increases in GH secretion, likely an adaptive mechanism to increase lipolysis and thus substrate availability for body functions.⁵⁹ However, decreased expression of the GH receptor in AN results in a state of GH resistance, such that despite increased GH secretion, levels of IGF-1 are very low.^{59–61} Thus, bone formation rates are decreased in adolescents with AN, associated with decreased bone turnover. In contrast to positive associations of GH concentrations with levels of bone turnover markers in healthy normal-weight adolescents, girls with AN show no association of GH concentrations with these markers, consistent with the state of GH resistance.⁵⁹ Furthermore, administration of supraphysiologic doses of GH to adult women with AN does not result in an increase in IGF-1 or in bone formation markers.⁶² These data support an important role for GH resistance and low IGF-1 levels in the state of impaired bone metabolism in AN.

Hypothalamic-Pituitary-Adrenal (HPA) Axis—AN is characterized by a state of relative hypercortisolemia, and high cortisol levels have multiple deleterious effects on bone.⁶³ An increase in cortisol is again adaptive; high cortisol levels increase gluconeogenesis and thus increase availability of substrate for vital functions. However, in AN, an increase in cortisol is associated with decreased bone formation and increased bone resorption, and with decreased bone density.⁶³ High cortisol levels also have an inhibitory effect on the HPG axis, impair calcium absorption from the gut and the renal handling of calcium, and inhibit OPG and increase RANKL secretion, both of which increase osteoclastic activity.

Adipokines (Leptin and Adiponectin) and Appetite Regulating Hormones (Leptin, Ghrelin, and Peptide YY)—Leptin and adiponectin are hormones secreted by adipocytes that have important effects on bone. Leptin also inhibits appetite, and levels of leptin are appropriately low in AN.⁴⁰ Peripheral leptin increases osteoblastic activity and bone formation, and low leptin levels are associated with low bone density and increased fracture risk in a healthy population.⁶⁴ Adiponectin, in contrast, is deleterious to bone,⁶⁴ and high adiponectin for fat mass in AN is associated with lower bone density.⁴⁰ Ghrelin is an appetite stimulating hormone secreted by the stomach that is appropriately high in AN.⁶⁵ Ghrelin also stimulates osteoblastic activity. However, unlike normal-weight girls, in whom ghrelin levels are positively associated with bone density, girls with AN demonstrate no associations of ghrelin with bone, suggestive of a resistance to ghrelin.⁶⁵ Peptide YY is an anorexigenic hormone with deleterious effects on bone⁶⁶ that is paradoxically high in AN, and is associated with lower levels of bone turnover markers and lower bone density.^{40,67}

Others (Insulin, Amylin, Oxytocin)—Insulin and amylin are secreted in equimolar concentrations by the pancreas and are bone anabolic. Similarly, oxytocin is also bone anabolic.⁶⁸ Insulin,⁴⁰ amylin,⁶⁹ and oxytocin⁷⁰ are all lower in AN than in controls associated with lower bone density.

Medications

Insufficient intake of calcium and vitamin D can compromise bone density in healthy adolescents. While some studies suggest that girls with AN do better than normal-weight controls for calcium and vitamin D intake (from supplement use),^{71,72} other studies differ and report a high prevalence of vitamin D deficiency and insufficiency (8% and 22%) in this population.⁷³ One study reported that only 30% and 50% of healthy controls met the dietary reference intake (DRI) for calcium and vitamin D intake respectively, whereas 59% and 77% of girls with AN met these requirements.⁷¹ Calcium intake of <600 mg/day was associated with lower bone density measures in another study.^{18,24}

Long-term use of selective serotonin reuptake inhibitors (SSRIs) is associated with lower BMD in girls with AN, independent of duration of disease and duration of amenorrhea.⁷⁴ This may relate to effects of serotonin on bone as prolactin elevations are typically not high enough or sustained for long enough to cause menstrual dysfunction. In contrast, long-term use of risperidone can cause sufficient elevations in prolactin that patients develop menstrual dysfunction with subsequent effects on bone. Finally, medications such as valproic acid and carbamazepine can impact vitamin D metabolism and impact bone mineralization.

Exercise

A few studies have reported that lower exercise activity is associated with lower BMD in males and females with AN.^{18,24,36} A recent study has concluded that effects of exercise on BMD in AN are dependent on the type of mechanical loading and stage of illness, such that excessive moderate loading exercise in an ill patient increases the risk for low BMD, whereas during and after recovery, high bone loading activities may contribute to increased accrual.⁷⁵ In this study, moderate bone loading exercise included walking, hiking, using the elliptical trainer, stair climbing, baseball, softball, ice hockey, inline skating, alpine, cross country or water skiing, snowboarding, horseback riding, boxing, and recreational volleyball and dance, activities common in AN. High bone loading exercise included running, competitive dancing and volleyball, gymnastics, figure skating with jumps, high impact aerobics, basketball, soccer, tennis, squash, ultimate Frisbee, jump rope and jumping jacks. The deleterious effects of exercise on bone in ill patients may be attributable to further weight loss from exercise induced caloric expenditure, or further impairment in energy availability status with exercise. In addition, estrogen is permissive for the effects of the mechanostat on bone,^{53,76} and the beneficial effects of exercise on bone may not be evident in amenorrheic women, whereas recovery of weight and menses following nutritional rehabilitation would be an appropriate milieu for these beneficial effects.

Management of Bone Disease in Anorexia Nervosa

Assessing Bone Health in Anorexia Nervosa

History and Physical Examination—A comprehensive skeletal assessment in AN should start with a comprehensive history and complete physical examination. The history should focus on length of illness of the eating disorder; menstrual history including age of menarche, last normal menstrual period, frequency of menses, changes in menses, and medications including hormonal contraceptives; type, duration, intensity and frequency of

physical activity; 24-h recall of dietary history with a specific focus on total energy intake and calcium and vitamin D; family history of osteoporosis; prior history of stress fractures or fractures sustained after minimal trauma; past or current history of known medical condition(s) associated with low BMD; past or current exposure to medications (e.g., glucocorticoids, anticonvulsants) known to impact bone density and cigarette and alcohol use.

Weight and height should be measured and BMI (kg/m^2) calculated and plotted on a growth curve to identify any changes or falling off of percentiles for any of these parameters. In addition, the clinician should determine the adolescent's sexual maturity rating to assess whether puberty is proceeding normally.

Techniques for Assessing Bone Density—Dual Energy X-ray Absorptiometry (DXA): As described above, in the clinical setting, DXA remains the preferred method for assessing bone density. In growing children, optimal sites for such scans include the lumbar spine and total body less head (TBLH), and BMC and BMD or both may be assessed. In children with short stature or growth delay, it is important to adjust for height using measures of spine bone mineral apparent density, or the height Z-score (the latter can be used for both sites).⁸ After growth is complete and in adults, the hip may also be assessed for BMD. BMC or BMD Z-scores should be based on the mean for an appropriate reference population and take into consideration age, gender, and race/ethnicity.^{8,9}

Currently, there is a lack of scientific evidence guiding existing recommendations on when to order a DXA and how frequently to follow abnormal results with repeat DXA scans in AN. The PDC of the ISCD recommends that DXA be performed in children and adolescents with chronic diseases including AN *'when the patient may benefit from interventions to decrease their elevated risk of a clinically significant fracture and the DXA results will influence that management'* and that *'the timing of the first DXA scan, and the number of areal BMD reevaluations depend on the magnitude of the ongoing risk of fracture, the magnitude of low BMD, the BMD trajectory, and periods when significant clinical changes are expected'*.⁷⁷ In children and adolescents, some groups, based on consensus, recommend that DXA scans be obtained when amenorrhea occurs for six months or more and be repeated annually.^{78,79} The National Osteoporosis Society (NOS) in the United Kingdom suggests that the appropriate interval between scans to monitor a response to osteoporosis treatment or to monitor changes in BMD is determined by the concept of the 'least significant change in BMD' and the anticipated change over time. The monitoring time interval is the expected time in years necessary to identify a change between two measures that exceeds measurement error and depends on age, sex and site measured. In healthy children between 6 and 15 years the mean monitoring time interval is <1 year⁸⁰ but increases in older adolescents and young adults. In adults with osteoporosis, the NOS recommends that follow-up BMD scans occur no more frequently than every two years.⁸¹ However, in situations where clinically expected rates of change are greater than what is normally expected, a shorter follow-up interval should be considered. One such clinical situation might be young women with AN who are unable to maintain or sustain their weight and remain amenorrheic. Until such time that there are evidence-based guidelines, clinicians should use their clinical judgment in combination with expert recommendations to

determine when a young person with an eating disorder should have their bone density assessed by DXA and how often.

Management of Low Bone Density in Anorexia Nervosa

Table 2 summarizes observational studies of weight restoration and interventional studies in AN.

Weight Gain and Restoration of Menstrual Function—One of the primary goals of medical treatment for AN is weight restoration, and in females, the resumption of spontaneous menses. Likewise, evidence suggests that the safest and most effective strategy to improve bone density in AN is normalization of weight and restoration of menstrual function.

One study in adult women showed an increase in spine and hip BMD by 3.1 and 1.8% respectively, following weight gain and menstrual recovery in adult women with AN.¹² Earlier studies in adolescents with AN showed that patients with weight restoration had higher BMD than those who remained underweight. Despite this, greater than half of the patients had BMD Z-scores of less than -2.0 SD at follow-up.^{13,82,83} The studies suggest that bone density is not completely reversible and that residual deficits in BMD may persist even following full weight restoration and recovery from the illness. Of note, weight gain and restoration of menses does prevent further decreases in bone density.^{23,84,85} Together, these studies suggest that weight gain and resumption of menses is associated with the cessation of bone mass loss and possibly some improvement. For children and adolescents with AN, follow-up into adulthood is required to understand the long-term outcome of BMD in this population.

Calcium and Vitamin D—Calcium intake is extremely important for young people. Vitamin D is also important because it increases the gut's absorption of calcium and higher intakes are linked with lower risk for stress fractures among healthy adolescent females.⁸⁶ To date, there are no randomized controlled trials documenting that calcium and vitamin D supplementation alone is effective in increasing bone density in AN.^{14,71,87–89} However, given the known beneficial effects of calcium and vitamin D on bone mineralization in healthy young people, it is important to optimize the intake of these micronutrients in AN if suboptimal. Therefore, vitamin supplements are recommended, to ensure adequate amounts of calcium (1000–1200 mg/day of elemental calcium) and vitamin D (at least 600 IU per day and preferably 800 IU daily) as required for bone health.^{79,90}

Physical Activity—Healthy children involved in physical activity early in life improve their bone mass.⁹¹ In addition, adolescent athletes who have regular menses have been shown to a higher bone mass than sedentary controls. However, once they become amenorrheic, the protective effect of exercise is lost.⁹² To date, there is no evidence that high-intensity exercise in the context of weight loss and amenorrhea is protective to bone mass in AN. Of importance, recommending exercise needs to be weighed against the risk of fractures, delayed weight gain, and prolonged amenorrhea in AN. For those recovering from AN, advice about suitable activity levels should be sought from the person's treatment team.

The recommended level of activity will depend on the person's medical condition, whether they are able to gain weight appropriately or maintain their expected weight, and the status of the women's menstrual function.

Estrogen Replacement Therapy—The hypoestrogenic state commonly seen in AN is a risk factor for reduced BMD. Oral estrogen replacement therapies have been used to potentially improve bone density in adult women and adolescents with AN. Studies examining the effectiveness of oral contraceptives^{57,93–95} have not shown these preparations to be effective in this population.^{15,89,95} Klibanski et al. conducted a randomized placebo-controlled trial on the use of estrogen-replacement therapy in 48 adults with AN. Patients were followed for a mean of 1.5 years. At the end of the study period, there was no significant difference in BMD of the lumbar spine between the two groups. Only the most severely malnourished subjects (those <70% of ideal bodyweight) had a protective effect from oral estrogen.⁸⁹ A prospective observational study of 50 adolescent females with AN who were followed for 1–3 years demonstrated that at 1-year follow-up, there were no significant differences in lumbar spine or femoral neck BMD between the two groups. Despite treatment, reduction in BMD was persistent and, in some cases, progressive.¹⁵ Finally, in a multicenter, randomized, double-blind, placebo-controlled trial conducted on adolescent girls between 11 and 17 years of age with AN, treatment with a triphasic oral contraceptive containing norgestimate and 35 µg of ethinyl estradiol did not increase lumbar spine or hip BMD after 1 year of treatment.⁹⁵ Finally, a systematic review and meta-analyses examining the effects of oral estrogen preparations on bone health in women with AN concluded that there was insufficient evidence to support its efficacy and that most women with AN should avoid using estrogen.⁹⁶ This lack of treatment effect of oral estrogen preparations has been attributed to its suppression of the hepatic synthesis of insulin-like growth factor I (IGF-1), a key bone anabolic agent. As such, an 18-month RCT showed that physiological estrogen replacement as transdermal 17β-E2 with cyclic progesterone compared to placebo, increased bone accrual rates at the spine and hip in adolescents with AN.²⁶ However, physiological estrogen replacement does not result in complete 'catch-up' of BMD, likely because other hormonal abnormalities persist.

Recombinant Human IGF-1—IGF-1 is important for promoting bone growth in puberty and for maintaining healthy adult bones. It is thought the deficiency of IGF-1 may contribute to the decreased rate of bone formation and low bone density seen in AN. Therefore, IGF-I may be a useful therapy to address the low bone density in AN. One RCT showed that subjects who were randomized to either placebo or supraphysiologic doses of recombinant human GH (rhGH) treatment for 12 weeks⁶² did not differ for changes in levels of IGF-1 or bone turnover markers, likely because of the state of GH resistance in AN. However, rhIGF1 replacement in doses that normalize IGF-1 levels led to an increase in bone formation markers in adults and adolescents with AN.^{93,97} Grinspoon et al. randomized 60 adult women with AN to one of four treatment groups: rhIGF-1 alone, an oral contraceptive alone, the combination of rhIGF-1 and oral contraceptive, or neither treatment. Bone density was measured at baseline and again at 9 months. The investigators found that bone density increased the most (1.8%) in women taking both rhIGF-1 and oral contraceptive as compared to the untreated group.⁹³

Testosterone—Women with AN have been shown to be deficient in testosterone and testosterone promotes bone formation in AN. Soyka et al. showed that increases in testosterone levels with weight gain were predictive of increases in BMD.¹⁴ Despite this, administration of a low-dose patch of testosterone was not effective in increasing bone density over a 1-year period in adults with AN, despite increases in lean body mass and increased levels of ICTP.⁹⁸ Low testosterone levels are an important determinant of low bone density in young men and boys with AN.²⁵ In older men with testosterone deficiency who have osteoporosis, testosterone replacement improves bone density at the lumbar spine, although data for the femoral neck are not consistent.⁹⁹ The effect of testosterone replacement on bone mass accrual and bone microarchitecture in adolescent boys and adult men with AN is unknown.

Dehydroepiandrosterone (DHEA)—Young women with AN have reduced secretion of DHEA (compared to a reference database) that may also contribute to skeletal deficits.¹⁰⁰ Gordon et al. found that adolescents with AN have increased serum markers of bone formation and decreased urinary markers of bone resorption after administering DHEA for 3 months.¹⁰⁰ In a follow-up study, Gordon et al. randomly assigned 61 adolescent women with AN to receive either 50 mg/day of DHEA or a combination estrogen–progestin pill (20 µg ethinyl estradiol/0.1 mg levonorgestrel) for one year.¹⁰¹ There was no treatment effect on bone density with either DHEA or OCP after controlling for weight gain. Subsequently, DiVasta et al. conducted a 18-month randomized, placebo-controlled trial, investigating the effects of oral DHEA and combined oral contraceptive versus placebo on changes in bone geometry in young women with AN.¹⁰² DHEA and the combined oral contraceptive led to stabilization of femoral shaft BMD and improvement in femoral cross-sectional area, section modulus, and cortical thickness.

Bisphosphonates—Bisphosphonates have been shown to increase BMD in postmenopausal women, men with osteoporosis, adults with glucocorticoid-induced osteoporosis and children and adolescents with a number of conditions associated with low BMD and increased fracture risk. A 1-year RCT found a significant increase in BMD in adult women with AN treated with 5 mg of risedronate daily compared to placebo;⁹⁸ spine and hip BMDs increased by 3 and 2% in the treated group. An RCT in adolescents treated with alendronate vs. placebo for one year demonstrated improvement in spine BMD in the treated group (3.5%) but it did not differ significantly from the control group (2.2%).⁸³ Bisphosphonates are not generally recommended for women of childbearing age because of the concern of placental transfer of the medication and the potential for development of congenital abnormalities. There is the additional concern that bisphosphonates have a long half-life and can be released slowly from bone over a period of years.

Teriparatide—Teriparatide, recombinant human 1–34 parathyroid hormone, is a bone anabolic agent that is FDA approved for the treatment of osteoporosis in adults. One randomized controlled trial reported an increase in spine BMD following 6 months of teriparatide treatment compared to placebo in older adult women with AN.¹⁰³ Teriparatide has not yet been studied in children and adolescents with AN. Of concern, teriparatide has been shown to cause an increased incidence of osteosarcoma in rats. A black box warning

advises that this medication should not be prescribed for patients who are at increased baseline risk for osteosarcoma including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or in those who have received prior external beam or implant radiation therapy involving the skeleton.

Denosumab—Denosumab is a human monoclonal antibody that prevents RANKL-RANK interaction and thereby inhibits the differentiation and activation of osteoclasts. Denosumab has been shown to be effective in treating post-menopausal osteoporosis.¹⁰⁴ However, there are no data regarding the use of denosumab in AN.

Recommendations Based on Current Evidence

The first-line therapy for low BMD in AN is nutritional rehabilitation that results in sustainable weight restoration and resumption of spontaneous menses. In addition, calcium and vitamin D supplementation are reasonable recommendations, recognizing that there is no evidence supporting their ability to increase bone mass in AN. The potential benefits of physical activity must be considered against the deleterious effects of a delay in weight gain and resumption of menses. For instance, some patients with AN may exercise excessively resulting in lack of weight gain and persistent amenorrhea perpetuating subsequent bone loss. Oral estrogen preparations are not effective in increasing bone mass in adolescents or adults with AN. For older adolescents weight (bone age ≥ 15 years) who are unable to gain and sustain weight gain and have a BMD Z-score < -2.0 , one might consider the application of the 17- β estradiol patch (100 mcg twice weekly) with cyclic oral progesterone (for 10–12 days every month). Bisphosphonates may be considered in adults with osteoporosis, particularly when there is a history of fractures, but should be used cautiously in women of child bearing age. Further research is required to find safe therapeutic agents that increase bone formation and peak bone mass acquisition in young people with AN.

Conclusion and Key Bullet Points

Anorexia nervosa is associated with low bone density, impaired bone structure and strength, and an increased risk for fracture.

Key factors that contribute to impaired bone status in anorexia nervosa include low BMI and lean mass, hypogonadism, low IGF-1 levels, and alterations in other hormones such as cortisol adiponectin, leptin, PYY, insulin, amylin and oxytocin.

In the clinical setting, DXA is the most commonly used technique for measuring BMD; however, interpretation of results must be done cautiously in growing children and adolescents.

Weight gain and resumption of menses is associated with some improvement in BMD but residual deficits may persist.

Physiologic estrogen replacement as the transdermal estradiol patch is effective in prospectively halting BMD Z-score reductions in adolescents with AN, but does not result in complete-catch up. This treatment may be considered in adolescents with AN whose BMD

Z-scores are low and are decreasing over time despite all efforts at weight gain. In contrast, oral estrogen-progesterone containing contraceptive pills are not effective in adults or adolescents with AN.

rhIGF-1 combined with oral estrogen-progesterone increases BMD in adult women with AN. RhIGF-1 also increases bone formation in adolescents with AN and remains under investigation at this time as a therapeutic tool.

DHEA with oral estrogen-progesterone maintains hip BMD Z-scores in adolescent and young adult women with AN, but does not result in “catch-up”.

Bisphosphonates increase BMD in adults, and should be reserved for adults with repeated fractures in whom other therapeutic strategies are not effective. They should be used very cautiously in women of reproductive age given their long half-life.

Teriparatide and denosumab have not been investigated in adolescents with AN and should not be used in this young population at this time. Teriparatide was shown to increase BMD in older adult women with AN in one study.

Future research should focus on discovering safe therapies that are effective in promoting bone formation and optimizing peak bone mass acquisition in adolescents with AN.

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FIGURE 1.

Factors contributing to impaired bone metabolism in anorexia nervosa. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 1

Methods of assessing bone health in anorexia nervosa

$\mu\text{Sv} = \text{microSievert}$	DXA	QCT	pQCT	HR – pQCT
Site Measured	Lumbar Spine	Lumbar Spine	Distal Radius	Distal Radius
	Hip	Hip	Distal Tibia	Distal Tibia
	Total Body	Distal Radius		
Radiation Dose	5–6 μSv	30–7,000 μSv	<3 μSv	<3 μSv
BMD	Areal BMD	Volumetric BMD	Volumetric BMD	Volumetric BMD
Differentiates Cortical from Trabecular Bone	No	Yes	Yes	Yes
Bone Geometry	No	Yes	Yes	Yes
Bone Microstructure	No	No	No	Yes

Adapted with permission from Golden NH “Assessment of Bone Health in the Young Athlete” In “The Female Athlete Triad: A Clinical Guide” Gordon CM and Leboff MS, Editors, Springer Press, 2015.¹⁰⁴

Summary of effects of weight restoration and interventional studies on bone health in adults and adolescents with anorexia nervosa

TABLE 2

Author (year)	Study Design	Characteristics of Patients with AN Sex, N, Age	Intervention (s)	Control	Assessment	Duration of Follow-Up	Outcome
Weight Gain and Restoration of Menses							
Bachrach et al. (1991) ⁸²	Prospective observational	Females, $N = 15$ Mean age 16.7 ± 2.4 years (Range not provided)	Weight gain and restoration of menses	None	DXA, BMD (lumbar spine and whole body)	12–16 mos.	Whole body BMD increased. No change in spine BMD. Weight, height and BMI were predictors of change in BMD.
Soyka et al. (2002) ¹⁴	Prospective observational	Females $N = 19$ Mean age 15.4 ± 0.4 years (range, 12–18 years)	Weight gain	19 age-matched controls	DXA, BMD (lumbar spine and whole body), bone markers	12 mos.	Spine BMD did not increase in girls with AN while it did increase in healthy controls. Markers of bone turnover increased significantly in girls with AN compared to controls.
Stone et al. (2006) ¹⁷	Retrospective cohort	Females $N = 30$ Mean age 14.6 years (range not provided)	Weight gain	None	DXA, BMD and BMC (lumbar spine, femoral neck, whole body)	12 mos.	Significant decrease in age- and height adjusted BMD of the spine, femoral neck and whole body.
Compston et al. (2006) ⁸⁵	Prospective observational	Females $N = 26$ Mean age 16.5 ± 1.7 years (range, 13–20 years)	Weight gain	None	DXA, BMD (lumbar spine, femoral neck, whole body), bone markers	12 mos.	No Increase in BMD. Serum osteocalcin and BSAP increased significantly and remained higher than at baseline; urinary NTX excretion was lower at 12 mo than at baseline.
Miller et al. (2006) ¹²	Prospective observational	Females $N = 75$ Mean age 24.4 ± 0.6 years (range, 18–40 years)	Weight gain and/or restoration of menses	None	DXA, BMD (lumbar spine, total hip)	13.5 mos. (6–69 mos.)	Weight gain and menstrual recovery led to an annual mean increase in BMD of 3.1% at the spine and 1.8% at the hip compared to an annual decrease in those who did not gain weight or recover menses of 2.6% at the spine and 2.4% at the hip. Weight gain regardless of menstrual resumption led to an increase in BMD at the hip, but not the spine. Independent of weight gain, recovery of menses led to an increase in BMD at the spine but not the hip.

Author (year)	Study Design	Characteristics of Patients with AN Sex, N, Age	Intervention (s)	Control	Assessment	Duration of Follow-Up	Outcome
Mika et al. (2007) ⁸⁴	Prospective observational	Females $N = 19$, Mean age 14.4 ± 1.6 years (range not provided)	Weight gain	19 healthy controls	DXA, BMD (lumbar spine, femoral neck)	24 mos.	BMD in girls with AN was significantly lower than in controls and did not change during the study. Bone turnover in girls with AN was similar to controls.
Misra et al. (2008) ²³	Prospective observational	Females $N = 34$ Mean age 15.9 ± 1.5 years (range, 12–18 years)	Weight gain and restoration of menses	33 healthy, sex and age-matched controls	DXA, BMD (lumbar spine BMAD and whole body BMC/height)	12 mos.	Menstrual recovery and weight gain in AN resulted in stabilization of BMD measures. Girls with AN who did not recover had a decrease in BMD measures over 12 mos. compared with normal-weight controls.
Estrogen Replacement Therapy							
Klibanski et al. (1995) ⁸⁹	RCT	Females $N = 48$ Mean age 24.9 ± 6.9 years (range, 16–42 years)	Estrogen: Conjugated equine estrogen 0.625 mg (days 1–25) with medroxy-progesterone acetate (days 16–25) OR ethinyl estradiol 35 mcg (as OC)	No medication	Dual energy computed tomography, Volumetric BMD (lumbar spine)	18 Mos.	Estrogen-progestin did not significantly increase BMD compared to no treatment (except in a subset of women whose initial body weight was <70% of ideal)
Golden et al. (2002) ¹⁵	Prospective observational	Females $N = 50$, Mean age 16.8 ± 2.3 (range, 13–21 years)	Ethinyl estradiol 20–35 mcg (as OC)	No medication	DXA, BMD (lumbar spine, femoral neck)	Mean 23.1 mos.	Estrogen-progestin did not significantly increase BMD compared to no treatment
Sirokosch et al. (2006) ⁹⁵	RCT	Females $N = 112$ Mean age 15.2 ± 1.3 (range, 11–17 years)	Triphasic OC containing norgestimate 180–250 mcg and ethinyl estradiol 35 mcg	Placebo	DXA, BMD (lumbar spine and femoral neck)	13 mos.	Triphasic OC did not significantly increase lumbar spine or femoral neck BMD compared with placebo.
Munoz-Calvo et al. (2007) ⁵⁷	Prospective observational	Females $N = 20$ Mean age 15.3 ± 1.5 years (range not provided)	10 received oral estrogen treatment plus nutrition and 10 received nutrition alone	19 age-matched controls with normal BMI and regular menses	DXA, BMD (lumbar spine)	12 mos.	BMD did not increase over the year. At 12 mos. the group receiving estrogen had lower BMD compared to those treated with nutrition only.
Misra et al. (2011) ²⁶	RCT	Females $N = 110$, Mean age 16.5 ± 0.2 years (range 12–18 years)	Mature AN (BA 15 years; $n = 96$) were randomized to transdermal 100 mcg 17 β -estradiol (with cyclic progesterone) or placebo. Immature AN (BA <15 years; $n = 14$) were randomized to	Placebo controlled Also followed 40 normal-weight controls (mean age 15.6 ± 0.2 years, range 12–18 years) without any intervention	DXA, BMD (lumbar spine and total hip)	18 mos.	Physiological estradiol replacement increased spine and hip BMD in girls with AN compared with placebo to approximate bone accrual rates in controls; catch-up in BMD did not occur.

Author (year)	Study Design	Characteristics of Patients with AN Sex, N, Age	Intervention (s)	Control	Assessment	Duration of Follow-Up	Outcome
Recombinant Human Growth Hormone							
Fazeli et al. (2010) ⁶²	RCT	Females $N = 21$ Mean age 28.0 ± 2.1 years (active group) and 29.2 ± 2.6 years (placebo group) (range, 18–45 years)	RhGH: 15 mcg/k SC daily with dose increments to a maximum dose of 36.6 mcg/k per day	Placebo	IGF-1, PINP and CTX levels measured	3 Mos.	Supraphysiological rhGH administration decreased fat mass in AN without increasing IGF-1 or bone markers
Recombinant Human IGF-1							
Grinspoon et al. (2002) ⁹³	RCT	Females with BMD T -scores < -1 $N = 60$ Mean age 25.2 ± 0.7 years (range, 18–38 years)	RhIGF-1 (30 mcg/k sc twice daily) with OC (ethinyl estradiol 35 mcg) (Group 1) OR rhIGF-1 alone (Group 2) OR OC alone (Group 3)	No treatment (Group 4)	DXA, BMD (lumbar spine, total hip, whole body), Bone markers	9 Mos.	Factorial analysis: RhIGF-1 (but not OC) caused an increase in lumbar spine BMD. BMD increased to the greatest extent in the combined treatment group compared to no treatment
Misra et al. (2009) ⁹⁷	Prospective	Females $N = 20$ Mean age 16.2 ± 0.5 years (range, 12–18 years)	10 adolescents received RhIGF-1 (30–40 mcg/kg twice daily) for 7–9 days.	10, age-matched girls with AN were followed without rhIGF-1 for a similar period.	IGF-1, PINP and CTX levels measured	7–9 days	RhIGF-1 caused an increase in markers of bone formation compared with no therapy
DHEA							
Gordon et al. (2002) ¹⁰⁰	RCT	Females $N = 61$ Mean age 17.8 ± 2.9 years (range, 14–28 years)	Oral DHEA 50 mg/d	20 mcg ethinyl estradiol and 0.1 mg levonorgestrel	DXA, BMD (lumbar spine, hip). Bone markers	12 mos.	After controlling for weight gain, no treatment effect was observed with either DHEA or OC on BMD.
DiVasta et al. (2012) ¹⁰¹	RCT	Females $N = 94$ Mean age 18.1 ± 2.7 years (range, 13–27)	Oral DHEA 50 mg/d plus OC 20 mcg ethinyl estradiol and 0.1 mg levonorgestrel PO daily	Placebo	DXA, BMD (lumbar spine, hip). Bone markers	18 mos.	Combined DHEA and OC prevented bone loss whereas placebo led to decreases in areal BMD. Catch-up did not occur.
Bisphosphonates							
Golden et al. (2005) ⁸³	RCT	Females $N = 32$ Mean age 16.9 ± 1.9 years (range, 12–21 years)	Alendronate 10 mg PO daily	Placebo	DXA, BMD (lumbar spine, femoral neck)	12 mos.	Femoral neck and lumbar spine BMD increased $4.4 \pm 6.4\%$ and $3.5 \pm 4.6\%$ in the alendronate group compared to 2.3 ± 6.9 and 2.2 ± 6.1 in the control

Author (year)	Study Design	Characteristics of Patients with AN Sex, N, Age	Intervention (s)	Control	Assessment	Duration of Follow-Up	Outcome
Miller et al. (2011) ⁹⁸	RCT	Females with BMD Z-scores < -1 at one or more sites <i>N</i> = 77 Mean age 25.3 ± 6.3 years (Risidronate only group), 27.1 ± 7.3 years (Testosterone pill (Group 1) and placebo doses (Group 2)), 26.9 ± 7.2 years (double placebo group) range not provided)	Risidronate 35 mg weekly with placebo patch (Group 1), Testosterone 150 mcg patch (titrated to maintain testosterone levels in the upper half of the normal range for women) and placebo pill (Group 2), testosterone and Risidronate in above doses (Group 3)	Double placebo	DXA, BMD (lumbar spine, total hip, radius), Bone markers	12 mos.	group (not significant). BMD of the spine and hip group (not significant). BMD of the spine and hip group (not significant). BMD of the spine and hip group (not significant). BMD of the spine and hip group (not significant).
Teriparatide Fazeli et al. (2014) ¹⁰²	RCT	Females <i>N</i> = 21	Teriparatide 20 micrograms daily	Placebo	DXA, BMD (lumbar spine, hip), Bone markers	6 mos.	Postreroanterior spine BMD increased 6.0 ± 1.4% and lateral spine 10.5 ± 2.5% compared with placebo (posteroanterior spine, 0.2 ± 0.7%, p <.01; lateral spine, −0.6% ± 1.0%; p <.01).

DXA, dual energy X-ray absorptiometry; BMD, bone mineral density; BMAD, bone mineral apparent density; BA, bone age; OC, oral contraceptive (oral estrogen progesterone combination pills); BSAP, bone specific alkaline phosphatase; NTX, N-telopeptide; PINP, N-terminal propeptide of type 1 procollagen; CTX, C-telopeptide; mos, months; rhGH, recombinant human growth hormone; rhIGF-1, recombinant human insulin like growth factor-1.