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REVIEW

Restrictive Eating Disorders and Skeletal Health in Adolescent Girls and Young Women

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Abstract This article reviews the effects of restrictive eating disorders on bone health. The relationship between eating disorders and amenorrhea is discussed in detail. The pathologic impact of malnutrition on bone is explored by examining the results of studies using various available imaging techniques. The multiple hormonal alterations seen in adolescents and young women with anorexia nervosa are reviewed, as well as how these alterations may influence bone turnover, density, structure, and strength. The diagnostic clinical evaluation for adolescents and young women with these disorders is also outlined. Available treatment options, including those that hold promise for efficacy, as well as those we deemed to be ineffective, are considered from both the clinical and mechanistic standpoints. Finally, future research opportunities are offered, including intriguing work in the area of fat and bone interactions.

Keywords Anorexia nervosa · Eating disorder · Osteoporosis · Low bone mineral density · Amenorrhea

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Introduction

Anorexia nervosa (AN) is a psychological illness with serious medical complications, one of the most notable being the threat to bone health [1]. This article reviews the skeletal complications of restrictive eating disorders and potential treatment options. The clinical criteria used to diagnose eating disorders have recently changed, which we review, including the potential impact on our thinking about bone health [2]. We also aim to identify gaps in knowledge and areas worthy of future investigation.

Adolescent women with anorexia nervosa are at higher risk of fracture than those without this disease [3]. One study comparing adolescent females with and without AN found a higher prevalence of stress and nonstress fractures in subjects with AN. Adolescent girls with AN had an almost 60 % higher prevalence of fracture than healthy controls [4]. This elevated risk of fracture highlights the importance of prioritizing bone health as part of the treatment plan in AN.

Amenorrhea has traditionally been included among the criteria used to diagnose eating disorder [5]. Amenorrhea is associated with low bone mineral density (BMD) in both adolescents and women with this disease [6–8]. However, both amenorrhea and inadequate caloric intake appear to contribute to skeletal losses in restrictive eating disorders, and patients do not necessarily have to have a low body weight to be at risk [9, 10]. This is an important consideration with the transition from the Diagnostic and Statistical Manual (DSM)-4–(DSM)-5, and associated changes in the criteria used to diagnose eating disorders [2]. The DSM-5 has removed amenorrhea from the diagnostic criteria for AN (Table 1). However, excluding amenorrhea should not impact the management of these patients or

Table 1 Diagnostic criteria for anorexia nervosa and atypical anorexia nervosa [2]

Diagnosis	Diagnostic criteria
Anorexia nervosa	Restriction of energy intake relative to requirements, leading to a significantly low body weight
	Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight
	Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight
Atypical anorexia nervosa	All the criteria for anorexia nervosa are met, except that despite significant weight loss, the individual's weight is within or above the normal range

concerns about bone health. Roberto et al. performed a retrospective chart review of patients who met the criteria for AN, with or without amenorrhea, and found the only between-group differences to be admission body mass index (BMI) and lowest lifetime BMI [11]. Duration of illness, number of hospitalizations, and depression and anxiety assessments were similar between the groups. Eating Disorder Examination scores were also similar except in the Eating domain. These data suggest that there may be no association between illness severity and amenorrhea. Therefore, clinicians should not be reassured by a patient with a "normal" body weight in the context of amenorrhea, as these young women are still at risk concerning eating-disordered behaviors and the accompanied development of a low BMD.

A Look Inside: Imaging Modalities for Bone Assessments in Anorexia Nervosa

To understand whether skeletal deficits exist in patients with AN, it is helpful to consider the density and structure of bone, and ideally, on both macroscopic and microscopic levels. Several imaging modalities are available to evaluate bone health, including dual-energy x-ray absorptiometry (DXA), quantitative computed tomography (axial and peripheral), high-resolution quantitative computed tomography (HRpQCT), and magnetic resonance imaging (MRI). Each modality possesses both advantages and disadvantages.

DXA

DXA is currently the gold standard for measuring bone mineral density (BMD) in the clinical setting and is also the imaging modality used most commonly for research [12]. DXA allows for the measurement of BMD by means of x-ray beams of two different (dual) photon energies to separate bone from soft-tissue densities. This technique allows for isolated BMD measurements by subtracting the contribution of soft-tissue x-ray beam attenuation [13]. DXA measurements are quick, with some scanners able to capture images in as little as 10 s. The speed of DXA is noteworthy as rapid measurement can be advantageous for anxious patients; young women with eating disorders often have co-morbid anxiety. Another advantage is the limited radiation exposure, especially important when considering the examination of pediatric patients, and restrictive eating disorders are common among adolescents. However, there are also significant disadvantages of DXA. This technique affords only a two-dimensional measurement of BMD and does not represent true volumetric (or three-dimensional) density. This point is important since bone size will alter the measurement in an underweight patient with anorexia nervosa, and scans of small bones may represent an underestimate of true BMD [14]. Another limitation of DXA among adolescents is that the technique does not take into consideration pubertal stage, height, and changes in body composition with age [15–17]. This limitation is particularly problematic when measuring BMD in adolescents with an eating disorder since they may not only have smaller bones, but may also have delayed puberty and short stature. The International Society for Clinical Densitometry recommends adjusting BMD results by the height-for-age *Z*-score or calculation of bone mineral apparent density, depending on skeletal site. There are no official adjustments for BMD with regard to pubertal status at present. In general, adjustment for height-for-age *Z*-scores is felt to provide the most accurate information, but use of other adjustments is under study [18].

In addition to bone mineral density measurements, DXA also has the capability to measure body composition. This information may be useful when assessing the females with AN. For example, a higher percent body fat, as measured by DXA, is associated with resumption of menses in females with AN and amenorrhea [19]. While there is no identified target for either fat of lean muscle mass compartments so far, using DXA to track body composition over time can be helpful as another measure of musculoskeletal health.

Quantitative Computed Tomography

Quantitative computed tomography (QCT) is uniquely different from DXA in that it allows for a volumetric

measurement of BMD [20, 21]. Both standard pQCT and HRpQCT are able to measure volumetric BMD of the peripheral skeleton (i.e., forearm and tibia) , thus limiting the amount of radiation exposure. Both pQCT and HRpQCT are able to separate the densities of trabecular and cortical bones, which can be valuable in understanding the etiology of bone loss in a pathological condition and to evaluate the response to interventions. Trabecular bone is more active metabolically, and the ability to assess skeletal structure can be helpful in the evaluation of changes that occur with age or treatment. HR-QCT provides a "virtual bone biopsy" and affords information on bone microarchitectures.

MRI

In addition to information on BMD, MRI has the ability to examine bone marrow composition [22, 23]. Furthermore, ^{1}H magnetic resonance (MR) spectroscopy can further characterize bone marrow content, including differentiating saturated and unsaturated fatty acid content [24, 25]. A benefit of an MRI assessment of bone is the absence of radiation. At present, MRI is not routinely used for clinical bone evaluations and is limited primarily for research purposes.

A Deeper Look: The Microarchitecture of Bone

When considering the pathological findings of bone disease in AN, it can be helpful to examine and consider cortical bone, trabecular bone, and bone marrow, separately.

Cortical Bone

Dense cortical bone makes up the majority of the human skeleton and is less metabolically active than trabecular bone. Pathological cortical bone findings seen in AN include decreased cortical thickness and increased porosity. Faje et al. evaluated cortical porosity and thickness in patients with AN versus. Controls using HRpQCT measurements of the radius. Cortical porosity was significantly increased, and cortical thickness decreased in patients with AN compared to normal weighted controls [26]. This same study did not demonstrate a difference in cortical vBMD. Milos et al. used three-dimensional pQCT measurements of the radius in patients with AN and controls to evaluate differences in BMD and other bone microarchitectural parameters [21]. Cortical thickness was significantly lower in the group with AN [21]. Another study compared cortical thickness in women with AN to both postmenopausal women and healthy control subjects using pQCT measures of the radius. Although cortical thickness was higher in patients with AN compared to the older women, it was significantly lower than that seen in the healthy controls [27]. Another study of women with AN demonstrated similar findings at both the radius and tibia [28].

Trabecular Bone

Trabecular bone is a lattice of struts and plates that surrounds the bone marrow and is a key consideration in the determination of bone strength. Its primary function is the handling of mechanical load on the skeleton [29]. With aging, trabecular bone volume, number, and strength decline [30]. In AN, trabecular bone suffers similar changes in function and structure. Using HRpQCT, Fazeli et al. observed a significant decrease in trabecular number and thickness, and increased trabecular separation at the radius and tibia in patients with AN versus healthy controls [28]. The findings of decreased trabecular number, decreased trabecular thickness, and increased trabecular separation have been demonstrated by multiple investigators in this patient group [21, 31, 32]. These derangements in trabecular microarchitecture are contributors to poor bone quality in these patients.

Bone Marrow

Healthy bone marrow consists of both red and yellow marrow [33]. Red marrow is the site of hematopoiesis and yellow marrow is rich in adipose tissue. At birth, the medullary cavities of long bones are filled primarily with red marrow. With aging, the red marrow is gradually replaced by yellow marrow and by adulthood, most of an individual's red marrow is confined to flat bones (vertebrae, sternum, pelvic bones, etc.) and proximal end of long bones. Adipocytes in marrow are not sequestered in lobules as in other tissues and are instead, scattered in the hematopoietic milieu [34]. A bone marrow biopsy provides the most accurate assessment of bone marrow microanatomy. However, the invasiveness of this procedure is not practical for most clinical situations, especially among the pediatric and adolescent age groups. There are a few studies of bone marrow biopsies in patients with AN [35–37]. However, MRI is the preferred method to evaluate bone marrow composition.

The function of bone marrow fat is not completely understood and is an area of active research. Once thought to be of little physiologic significance, bone marrow fat is now understood to be an active tissue that is under the influence of various factors that are nutrition dependent. Examples of nutritional mediators of marrow fat include hormones (e.g., estrogen and growth hormone), the adipokine, leptin, and metabolic effects, including fatty acid metabolism that occurs during starvation [38, 39].

AN exemplifies the complex relationship between nutrition and bone marrow fat. In most patients with this disease, both histopathologic and imaging studies suggest an increase in bone marrow fat in many patients, despite an overall decrease in total body fat (including striking deficits in subcutaneous fat). Abella et al. obtained bone marrow aspirates and biopsies from 44 patients (40 female) with AN who were admitted to a psychiatric inpatient unit. Bone marrow specimens were classified as normal, hypoplastic, aplastic, partial gelatinous degeneration of bone marrow (GDBM) , and complete GDBM [35]. Note that hypoplasia and aplasia samples were characterized by an increased proportion of adipocytes, while the GDBM samples had "scanty degenerated adipocytes". The aspirate and biopsy specimens revealed overall decreases in cellularity and increased proportions of adipocytes. The histological results revealed 11 % of the samples to be normal, while 39 % showed hypoplasia or aplasia, 30 % partial GDBM, and 20 % complete GDBM.

Two case reports have been particularly informative regarding the bone marrow consequences of extreme emaciation. Hiramatsu et al. described the bone marrow biopsy results of a severely malnourished woman (body mass index, BMI, of 11 kg/m^2). There was almost complete replacement of bone marrow with adipose tissue. Additional findings included increased cortical bone porosity, decreased trabecular connections, and decreased trabecular thickness [37]. Another report replicated those findings and showed the virtual absence of marrow fat in an extremely emaciated 19-year-old young woman (BMI 10.5 kg/m^2 and 49 % of median BMI) with longstanding orthorexia nervosa (an extreme preoccupation with avoidance of foods perceived to be unhealthy) [36].

Since marrow sampling is often impractical, MRI is the preferred method to evaluate the composition of bone marrow. Bredella et al. used ^{1}H MR spectroscopy of the femoral diaphysis to demonstrate that women with AN had significantly higher total marrow fat in the axial skeletal compared to controls [24]. Using MRI images of the knee, Ecklund et al. showed adolescent females with AN to have increased marrow fat in the peripheral skeletal, with premature conversion of red marrow to yellow marrow [40].

It is unclear at this time whether increased bone marrow fat in AN is a type of compensatory mechanism or whether it represents a pathological process [41]. Although the purpose of bone marrow fat is unclear, there are hormonal alterations in AN, many induced by malnutrition, that predispose to premature and increased development of marrow fat among these adolescent girls. The relationship of marrow adipose tissue to fat depots in other regions of the body is complex and may play a role in the integration of metabolic homeostasis, hematopoiesis, and osteogenesis. The increasing recognition of bone–fat interactions has led to the identification of novel molecules that may emerge as targets for the enhancement of bone formation and possibly the prevention of osteoporosis and fractures.

Hormones and Bone

Multiple hormonal pathways may be altered in an adolescent or woman with AN, which ultimately impact bone health. These include estrogens, androgens, growth hormone, insulin-like growth factor- I (IGF-I), cortisol, leptin, insulin, and thyroid hormones. Understanding the interplay between hormones and bone has influenced the development of treatment options.

Estrogens

Under normal circumstances, the presence of estrogen stimulates osteoclast apoptosis and thus protects trabecular bone from resorption [42]. An association between protein intake and estrogen receptors (ER α) on the liver supports a link between nutrition and estrogen status [43]. Low estradiol concentrations have been demonstrated in multiple studies of women and adolescents with AN, amenorrhea, and low BMD (vs healthy controls) [44–48].

Growth Hormone and Insulin-Like Growth Factor-I

Growth hormone (GH) is known to be an important participant in bone growth and skeletal maintenance throughout the lifespan. GH stimulates the proliferation of osteoblasts and hence supports bone formation [49]. GH may also regulate osteoclast activity. IGF-I is important in the determination of peak bone mass. Patients with AN demonstrate GH resistance manifesting as elevated GH levels and low IGF-1 levels [9, 47, 50].

In addition to GH resistance, low IGF-I levels in AN may also be a result of estrogen level derangements, since activation of estrogen receptors on liver cells signals an increase in IGF-I levels [51]. An association between low levels of IGF-I and disruption of the menstrual cycle has been demonstrated in animal models [43, 52]. Likewise, in adolescents and young women with AN, amenorrhea, and low BMD have been associated with low serum concentrations of IGF-I [46–48]. The relationship between IGF-I and menstrual regulation was seen in a study by Miller et al. that showed IGF-I levels to be higher in women with AN who reported menses compared to amenorrheic women with AN [45].

Cortisol

Elevated cortisol levels result in decreased bone turnover, increased number of osteoclasts, and decreased osteoclast apoptosis, all leading to an increase in bone resorption

[53, 54]. Bone formation is also impaired as a result of a decreased number of osteoblasts, a shift of progenitor cells from osteoblasts to adipocytes, and increased osteoblast apoptosis [53].

Cortisol measurements are higher in females with AN versus controls [9, 47, 55]. An increase in corticotropin hormone and adrenocorticotropin hormone levels likely mediates this increase [7, 8]. The elevation of cortisol is also exaggerated by the hypercortisolemia that is associated with depression, as many anorexic patients have psychiatric co-morbidities [1].

Androgens

Androgens (dehydroepiandrosterine, DHEA sulfate, and testosterone) may stimulate osteoblast proliferation and decrease osteoblast apoptosis, resulting in an increased bone formation [56, 57]. Androgens may also upregulate IGF-I which may support normal menstrual function and have implications for lean body mass and skeletal support in adolescents and young women [54, 55]. The adrenal androgen, DHEA, appears to be a nutrition-dependent factor with potential for anabolic effects on bone by augmenting secretion of IGF-I [1]. DHEA sulfate has been shown to be low in some reports of adolescents and young women with AN [41, 82, 99], but Miller et al. found serum testosterone concentrations, but not DHEA sulfate to be low in women with this disease [58].

Adipokines

Leptin

Leptin plays an active role in bone metabolism. Leptin receptors on bone marrow mesenchymal stromal cells may be a determinant of cell differentiation [59]. Zheng et al. were able to stimulate osteogenesis by overexpressing leptin in osteoporotic cells [60]. Bone marrow adipocytes also secrete leptin [34, 61]. Furthermore, leptin has a positive association with BMD [62]. Leptin affects menstrual function by stimulating gonadotropin, releasing hormone from the hypothalamus [10]. Malnutrition lowers leptin levels in animal models, which is expected since leptin is derived from adipocytes [63].

As expected, women with AN have lower leptin levels [9, 17, 64, 65]. The link between malnutrition, low BMD, and menstrual dysfunction was demonstrated in a study comparing female runners. The study found lower leptin levels in runners with elevated bone turnover compared to those with normal turnover [7]. Legroux-Gérot et al. also demonstrated lower leptin levels and lower BMD in women with AN when compared to normal women [66].

Ghrelin

Ghrelin is a gastric peptide that increases secretion of GH by acting as an endogenous ligand for the growth hormone secretagogue receptor [67]. Ghrelin stimulates appetite and its levels increase in starvation [68]. Increased ghrelin levels have been described in females with AN, and may be an explanation for elevated GH levels and the GH resistance associated with AN [68–70]. Ghrelin may also promote secretion of ACTH and could be a factor mediating increased cortisol levels in women with AN [44, 71]. Luteinizing hormone (LH) may also be suppressed by ghrelin [69]. Ghrelin would be expected to have a negative effect on BMD, given its association with growth hormone and ACTH secretion in addition to LH suppression; however, ghrelin secretion was shown to have a positive correlation with BMD in healthy female adolescents and no correlation in females with AN [70]. Furthermore, ghrelin was shown to stimulate osteoblast proliferation and stimulation [72]. This apparent contradiction suggests that the skeletal losses seen in AN are independent of ghrelin secretion or possible ghrelin resistance [68].

Peptide YY

Peptide YY (PYY) is an anorexigenic peptide that is secreted from the distal small intestine and colon [73]. PYY contributes to bone metabolism; however, the mechanism is not entirely clear [74]. In females with AN, PYY levels are higher than in controls, and there is an inverse relationship between PYY and bone turnover markers [47, 75, 76].

Adiponectin

Adiponectin promotes osteoblast proliferation and inhibits osteoclastogenesis [77]. There are inconsistent findings regarding the relationship between adiponectin levels and bone density, with some studies showing an inverse relationship and others finding no relationship [78, 79]. In patients with AN, one study found no difference in serum adiponectin levels between patients with AN compared to controls, but an inverse correlation in lumbar spine BMD and this factor [47].

Clinical Evaluation

Amenorrhea (with clinical concern beginning after 3 months of no menstruation) is never a normal finding and warrants further evaluation. An anecdotal observation is the misconception that irregular periods are the norm in adolescent girls and especially among adolescent female

athletes. However, even athletes who develop amenorrhea, engaging in weight-bearing exercise, are at risk of low BMD [7]. Adolescent girls or women with amenorrhea, stress fracture, or fracture as a result of minimal trauma should have a thorough history performed that includes weight loss, menstrual status, dietary assessment, and typical exercise. Symptoms of eating disorders including caloric restriction, bingeing, or purging should be assessed. Other medical diagnoses to consider include polycystic ovary syndrome, thyroid dysfunction, pituitary disorders, or gastrointestinal disease (e.g., inflammatory bowel disease or celiac disease) that may be manifesting as amenorrhea. A psychiatric history should be carried out to evaluate for anxiety, depression, or psychosocial stressors. A review of medications is also important because some antiepileptic drugs (e.g., divalproex sodium), contraceptive agents, glucocorticoids, and antipsychotics may induce amenorrhea [10, 80].

Important findings to note on physical examination include signs of malnutrition such bradycardia, hypothermia, lanugo, and temporal wasting [81]. Pubertal stage should be assessed. Signs of hyperandrogenism should be noted, including hirsutism or clitoromegaly. Dental enamel erosions or parotid hypertrophy may suggest purging. Laboratory testing to consider is listed in Table 2.

Treatment Options

Many factors are responsible for bone loss and affect its manifestation in adolescents with AN. Examples include age of onset, pubertal status, trabecular versus cortical bone, mechanical factors, and presence or absence of various hormonal alterations. These patients can also be reluctant to try new therapies due to concerns about potential weight gain. Therefore, the identification of effective treatments for the bone loss associated with AN has proven challenging (Table 3).

What has not Worked?

Given the various hormonal aberrations described, a focus on correction of individual hormone imbalances has provided potential treatment opportunities (Fig. 1). It would seem reasonable to correct estrogen deficiency with estrogen add-back therapy, or low IGF-I with supplemental

Table 2 Labs to consider in females with weight loss, eating disorders, and or amenorrhea

Hormonal variable	Clinical significance
β-human chorionic gonadotropin	Positive in pregnancy
Thyrotropin (TSH) and free thyroxine	TSH typically low in nutritional deficiency
Prolactin	May be elevated with atypical antipsychotic use; consider prolactinoma
Follicle stimulating hormone (FSH)	May be low in nutritional deficiency; evaluate for ovarian insufficiency (with accompanying FSH elevation)
Free testosterone, dehydroepiandrosterone sulfate	Evaluate for hyperandrogenism (polycystic ovary syndrome, among other causes)
Complete blood count	Leukopenia, anemia, and thrombocytopenia are all possible with nutritional deficiency; consider also underlying systemic illness
Renal panel	Hypokalemia and hypophosphatemia are seen in restrictive eating disorders; metabolic alkalosis may occur in patients with bulimia
25-hydroxyvitamin D	Evaluate for vitamin D deficiency

Table 3 Various hormonal therapies that did not improve bone health in AN

Hormonal target	Treatment
Low estradiol	Combined oral contraceptive pills as monotherapy [88, 104, 105]
Low androgens	DHEA monotherapy [106]
	Transdermal testosterone [95]
Low IGF-I	Growth hormone [107]
	IGF-I monotherapy [88]

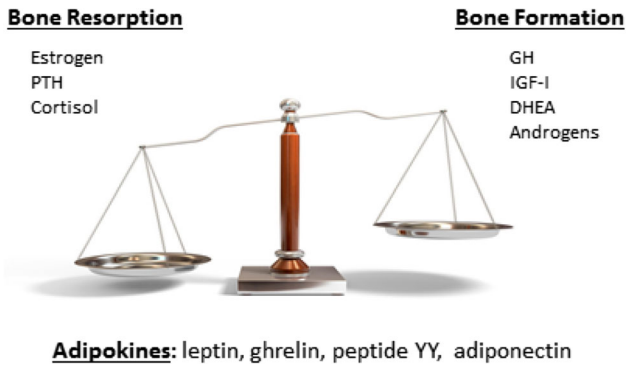

Fig. 1 Biochemical mediators of bone turnover, each which may be altered by a restrictive eating disorder

IGF-I. However, given the multiple interactions between various hormones, hormone receptors, cell types, etc., this simplistic approach has not been shown to have long-term efficacy. One example of a treatment with disappointing and even adverse effects was the use of recombinant leptin replacement therapy to restore ovulatory function and/or BMD. Unfortunately, small but significant decreases in weight and fat mass were noted in two reports of women who received subcutaneous leptin injections [82–84]. Table 3 lists some of the hormonal therapies that have not been shown to improve bone health consistently in AN.

Therapies Demonstrating Potential Efficacy

Dual Therapy with DHEA and Combined Oral Contraceptives

Although monotherapy with combined oral contraceptives (OCs) does not improve BMD in the setting of a restrictive eating disorder, a combination of DHEA and OCs has yielded promising results in older adolescents and young women. In a double-blind, placebo-controlled, randomized trial comparing DHEA 50 mg + 20 μg ethinyl estradiol/0.1 mg levonorgestrel to placebo, BMD and bone turnover markers were measured at baseline and 18 months in a young women ranging in age from 15 to 30 years. At the study's conclusion, there was stabilization of bone density seen at the lumbar spine, hip, and whole body, while those in the placebo group showed progressive skeletal losses [85]. This same combined therapy may also improve bone strength, as evidenced by improvements in hip bone geometry and strength variables [86].

Transdermal Physiologic Estrogen Replacement Therapy

The ethinyl estradiol dose in a combined OC does not represent a physiological estrogen dose for an adolescent or young woman which may explain why combined OC pills are not effective in treating low BMD in AN. To assess whether physiologic estrogen dosing could have a positive effect on BMD, a trial comparing physiological dosing of ethinyl estradiol delivered by transdermal patch vs. placebo was carried out in adolescent girls with AN. After 18 months, patients on physiologic estrogen dosing showed a significant increase in BMD over time, but the increase did quite approach that of healthy control subjects [87]. Transdermal delivery may also represent a safer and more effective treatment regimen for estrogen replacement, as hepatic "first pass" effects are avoided and the suppression of IGF-I seen after oral administration is avoided. However, an anabolic therapy may also be needed to allow for "catch up" skeletal gains to occur in adolescents with eating disorders.

Combined Therapy With IGF-I and Oral Contraceptives (OC)

Grinspoon et al. randomized 60 women with AN to 4 treatment groups: IGF-I and OC, IGF-I monotherapy, OC as monotherapy, and placebo. Only the IGF-I/OC combo group had a significant increase in BMD compared to placebo. The greatest increase was at the AP spine with a 1.8 % increase in BMD. The treatment was well tolerated and provided proof of concept for the use of combined antiresorptive and anabolic therapy for women with AN [88].

Teriparatide

Teriparatide, a recombinant parathyroid hormone, stimulates bone formation and increases bone density. A trial comparing teriparatide to placebo in women with AN showed an increase in lumbar spine BMD in the treatment group at 6 months [89]. Although these findings are promising, further study of teriparatide use in AN patients, and especially adolescents, is necessary before its use can be endorsed. Unfortunately, there are safety concerns regarding administration of this agent among teenagers with open epiphyses, as its administration in young rats was associated with the development of osteosarcoma, although no such association has been observed in humans [90–93]. Further safety trials are needed to advance its use in the adolescent age group.

Bisphosphonates

Bisphosphonates decrease osteoclast activity which can lead to an ultimate decrease in bone resorption. These agents have been shown to increase BMD in adult women with AN, with

increases in lumbar spine BMD ranging from 3 to 5 % [94, 95]. Golden et al. administered oral alendronate to adolescent girls with AN in a randomized, double-blind, placebo trial [96]. Although there was an increase in bone density observed at both the hip and the spine, the difference was not significant when compared to placebo. Although bisphosphonates have been used safely in some pediatric populations, without a clear benefit evident in patients with AN, its use at this time cannot be recommended for this population. The long half-life of these agents and associated safety issues, and questions around potential teratogenicity are the primary concerns limiting their use among adolescent girls and young women.

Mechanical Stimulation

Theoretically, low magnitude mechanical stimulation (LMMS) could have therapeutic benefits for adolescent girls with AN. The standard of care when these patients become hemodynamically unstable is complete bed rest [1, 81]. One study showed a striking decline in level of bone-specific alkaline phosphate during the first 5 day of an inpatient hospitalization, reflecting an exacerbation of low bone formation [97]. Thus, LMMS may have application to avoid suppression of bone formation in the inpatient setting, and is under study.

Weight Gain

Return to and maintenance of a healthy weight represents the most important treatment for low BMD in patients with AN [9, 64, 98]. Unfortunately, there may be long-term consequences related to low BMD, in particular when it is noted in an adolescent [99]. Multiple authors have reported that women with AN have persistently lower bone density when compared to peers without AN, despite weight gain [100–103]. It is for this reason that the identification of treatments to prevent BMD loss and to improve bone health in those identified to have a low BMD is so critically important.

Conclusion

With advances in imaging techniques, it is now possible to examine bone microarchitecture without the invasiveness of a biopsy. The ability to examine bone in this way will hopefully reveal how hormones and other factors influence bone structure and function that influence fracture risk, and will allow novel treatments for low bone density to be discovered in patients with restrictive eating disorders. Considerations for future studies include examining bone density, in addition to bone quality determinants, in individuals with either classical or atypical anorexia nervosa. It will also be important in future protocols to monitor bone health in young women at a "healthy" weight, who may represent an individual who is actually malnourished. Examining bone health in males and minorities with restrictive eating disorders will be important to address, as only sparse information is currently available on these patient groups at this time. Another important area to explore is the use of HR-QCT and MRI to monitor therapy effects, since vBMD cannot be assessed as accurately with DXA. The long-term goal is to one day help patients with AN maintain bone health as they recover from the psychological symptoms of their illness.

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Conflict of interest Darcey Thornton and Catherine M. Gordon declare that they have no conflict of interest.

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