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# Eating Disorders and Bone Metabolism in Women

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## Abstract

**Purpose of this Review—**Eating Disorders are psychiatric disorders associated with high risk for low bone mineral density (BMD) and fractures. Low BMD is likely to be a consequence of undernutrition, changes in body composition, and hormonal alterations. This review summarizes recent findings regarding: novel strategies for assessing bone outcomes in patients with eating disorders, factors contributing to altered bone metabolism, and possible therapeutic strategies.

**Recent Findings—**Emerging research in this field suggests that not only anorexia nervosa (AN), but also bulimia nervosa (BN) results in lower BMD compared to controls. To date studies of bone structure, and all randomized controlled trials (RCTs) examining the impact of various therapies on bone outcomes in AN, have focused on adolescent girls and women. We discuss the impact of AN on bone structure, and associations of resting energy expenditure, marrow adipose tissue (including the ratio of saturated to unsaturated fat), and cold activated brown adipose tissue (BAT) with BMD and bone structure. Promising strategies for treatment include physiological estrogen replacement (rather than oral contraceptives), in adolescent girls with AN, and bisphosphonates, as well as teriparatide, in adult women with AN.

**Summary—**Recent data on: (i) BMD and bone structure in adolescent girls and women with eating disorders, (ii) factors that contribute to altered bone metabolism, and (iii) RCTs reporting positive effects of physiologic estrogen replacement, bisphosphonates and teriparatide on bone health provide us with a greater understanding of the impact of eating disorders on bone and novel management strategies.

### Keywords

Osteoporosis; Bone; Bone Metabolism; Eating Disorders; Anorexia Nervosa

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## INTRODUCTION

Eating Disorders (ED) have the highest mortality among psychiatric disorders, with the most studied ED being Anorexia Nervosa (AN) and Bulimia Nervosa (BN) [1]. ED, specifically AN, are also associated with multiple neuroendocrine disruptions and low bone mineral density (BMD) [2]. Excessive food restriction, particularly during adolescence, can disrupt attainment of peak bone mass, resulting in long term skeletal complications [3]. The DSM-5 criteria for AN and BN diagnosis is summarized in Table 1 [4].

In a community sample of adult women with AN, 93% had BMD 1 standard deviation (SD) below the population mean and approximately 40% had BMD 2.5 SD below the population mean at one or more sites, meeting criteria for secondary osteoporosis [5, 6]. Adolescents with AN are also at risk for low BMD, with approximately 50% reported to have BMD 1 SD below the mean at one or more skeletal sites [7]. Approximately 30% of adolescent girls, as well as adult women with AN, report sustaining a fracture [6, 8]. Of note, both subtypes of AN, the restricting sub-type (AN-R) and the binge-purge subtype (AN-BP), are associated with reductions in spine BMD and increased fracture risk compared to controls [9]. AN-R and AN-BP are also associated with lower total body, hip and limb BMD, even in population-based samples, as shown in a longitudinal study from the UK [10*]. Furthermore, in addition to AN, normal weight BN patients have lower spine BMD than controls, suggesting that weight loss alone may not explain the deleterious effects of ED on bone [11].

The importance of developing efficacious treatments to increase BMD and reduce fracture risk in ED is highlighted by the persistence of long-term deficits in BMD despite recovery from the ED. Femoral neck BMD was reported to be lower in women with a past history of AN than controls, despite being in recovery for a mean of 21 years [12]. Maximal voluntary ground reaction force has been used as a measure of bone strength in women who had recovered from AN for approximately 27 years. Recovered women had lower volumetric BMD (vBMD) and maximal strength than healthy controls, suggesting that BMD deficits in AN persist despite recovery [13]. A previous population-based retrospective study found the cumulative incidence of fracture to be 57% in women with a history of AN, highlighting the significant pain and disability endured by this group [14].

## ASSESSMENT OF BONE OUTCOMES, INCLUDING USE OF NOVEL TECHNIQUES

### Biochemical markers of bone turnover

Surrogate (or biochemical) bone turnover markers provide evidence of the rate of bone formation and resorption in women with AN compared to healthy women. Commonly reported bone formation markers include osteocalcin, bone specific alkaline phosphatase and the N-terminal propeptide of type 1 procollagen (P1NP). Commonly reported bone resorption markers include deoxypyridinoline, C-telopeptide, and N-telopeptide. Adolescents have decreases in biochemical markers of both bone formation and resorption, indicative of reduced bone turnover [15], whereas adults with AN have decreased bone

formation and increased resorption markers, indicative of an uncoupling of bone turnover, both of which lead to reductions in BMD [2]. Osteoclasts and osteoblasts facilitate bone modelling and remodelling in adolescents, and bone remodelling in adults, and extreme weight loss may disrupt this process in AN.

Osteoprotegerin (OPG) and soluble RANK ligand (sRANKL) levels and their ratio provide evidence of the ongoing drive for bone resorption [16]. RANKL is secreted by stromal precursor cells and osteoblasts, and these cells also secrete OPG, the soluble decoy receptor for RANKL. When RANKL binds to RANK (expressed on osteoclast precursors and osteoclasts), it activates osteoclast activation and function and reduces osteoclast apoptosis, thus increasing bone resorption. OPG, in contrast, by binding to RANKL prevents it from binding to RANK, and thus reduces osteoclast activation and function and increases osteoclast apoptosis, leading to decreased resorption. Therefore, the lower the ratio of OPG to sRANKL, the greater is the drive for bone resorption. Transforming growth factor β (TGF-β), a multifactorial cytokine, correlates positively with the OPG/sRANKL ratio. In AN, OPG and sRANKL levels are elevated, but the ratio of OPG to sRANKL is reduced. TGF- β secretion is reduced in AN, which may compromise the mechanism compensating for bone remodelling [17]. Omentin-1, secreted by visceral adipose tissue, is increased in AN, and has recently been suggested to exert a negative effect on bone remodelling [18], independent of menstrual status. This effect is greater in younger, pre- menarcheal girls [19].

## Assessment of areal bone density and hip structural analysis

Dual x-ray absorptiometry (DXA) is a well-recognized instrument to evaluate fracture risk in postmenopausal women, although the predictive capability for fracture risk in premenopausal women with AN is not fully established [20]. Areal BMD (aBMD) is a two-dimensional measurement, and its assessment is affected by changes in bone size, maturation, and body composition. Adolescent and adult women with AN have low aBMD at multiple sites, however, this does not always correlate with fracture prevalence [21].

In addition to BMD measured by DXA, bone geometry and microarchitecture and its mechanical load distribution are important determinants of bone strength. DXA allows reporting of hip structural analysis (HSA), which reveals the structural geometry of the proximal femur at the narrow neck, intertrochanteric and femoral shaft, with one study reporting that the majority of HSA-derived parameters were impaired in AN, and superior in obese/overweight women in comparison to healthy controls [22].

## Assessment of volumetric BMD, bone size and structure

AN has negative effects on vBMD, and bone size and structure, and these alterations may explain fracture risk independent of aBMD [21]. The primary tools for assessing vBMD and bone structure are quantitative computed tomography (QCT) and more recently, high-resolution peripheral QCT (HR-pQCT). QCT allows assessment of both bone geometry and vBMD, which have been reported to account for differences in bone strength in post-menopausal women, even without significant differences in aBMD [23]. Further, HR-pQCT allows assessment of bone microarchitecture. Finite element models of bone can be created

from in vivo three-dimensional QCT images, and more recently from HR-pQCT images [24–26], and allow bone strength estimation.

At the distal radius, girls with AN have lower total and trabecular vBMD, lower cortical area and thickness, and increased cortical porosity and trabecular separation compared with controls, as assessed using HR-pQCT [7]. Failure load and stiffness, estimated by microfinite element analysis (FEA), are 15% and 16% lower at the distal radius in girls with AN, indicative of reduced strength. This effect remained after controlling for bone age, height and adjusting for radial aBMD [7]. Deficits in cortical thickness and trabecular number have been reported in adults with AN at the distal radius, with cortical deficits being related to age of onset of the ED [27]. Furthermore, flat-panel volume CT is effective in evaluating trabecular structure, including apparent bone volume fraction, apparent trabecular thickness, and apparent trabecular number, all of which are reduced in adult women with AN compared to controls at the distal radius [28]. Fewer data are available for the distal tibia. However, one study assessed the distal tibia using pQCT, and reported lower trabecular, but higher cortical vBMD, in young women with AN compared with controls. AN girls in this study had a mean percent ideal body weight of 91%, and thus were not as low weight as in other studies [29*].

Estimated vertebral strength, derived from integral vBMD values from QCT scanning is lower in low-weight AN compared to controls, and intermediate in atypical AN [30*]. Both measures were associated positively with BMI and inversely with the duration of amenorrhea. Another study assessed vertebral bone texture using a low-dose single-section quantitative CT of the L4 vertebral body with use of a calibration phantom, and reported altered bone texture in women with AN, which was associated with lowest lifetime body weight and duration of amenorrhea [31].

## FACTORS MEDIATING REDUCTIONS IN BONE MASS IN PATIENTS WITH EATING DISORDERS

### Energy status and body composition

Resting energy expenditure (REE) has been linked to bone remodeling, glucose homeostasis and adipokines, highlighting the importance of preventing energy deficiency in order to limit hormonal alterations and disruptions in bone mineralization in AN [32**]. Numerous studies demonstrate that lower body weight and particularly lower lean body mass are important determinants of deleterious bone outcomes in ED. Subtypes of AN include a restricting sub-type (AN-R) and a binge-purge subtype (AN-BP), both of which are associated with reductions in spine BMD and increased fracture risk compared to controls [10]. AN-R and AN-BP are also associated with lower total body, hip and limb BMD, even in population-based samples, as shown in a recent longitudinal study from the UK [10*]. Furthermore, normal weight BN patients have lower spine BMD than their healthy counterparts, suggesting that weight loss alone may not explain the deleterious effects of an ED on bone [11].

Lower fat mass (particularly subcutaneous fat) may also play a role, given that this is a source of leptin secretion, a hormone with bone anabolic effects. Recent studies have moved to assessing non-traditional fat stores in AN, including marrow adipose tissue (MAT) and cold activated brown adipose tissue (BAT). A common stromal progenitor stem cell in marrow differentiates into either an osteoblast or adipocyte depending on the marrow energetic and hormonal milieau, and MAT is higher in women with AN compared with controls, associated with lower BMD measures [33]. The degree of bone marrow fatty acid saturation correlates inversely with BMD, suggesting that saturated lipids may have negative effects on BMD in AN [34]. This inverse relationship was also observed in healthy individuals [35]. Women with AN have low cold-activated BAT, which may be due to impaired BAT thermogenesis and an adaptive mechanism to reduce energy expenditure in this state of energy deficit. Young women with BAT have higher BMD and lower preadipocyte factor-1 (Pref-1) (a negative regulator of osteoblastogenesis in the marrow) compared with women without BAT [36]. Given that women with AN have higher Pref-1 levels than controls, which correlate inversely with bone density [36], BAT may be involved in regulation of stem cell differentiation towards the bone lineage at the expense of adipogenesis [37].

## Nutrient intake

A recent study found that just 4 in 30 AN participants take multivitamin supplements, and 1 in 30 take calcium supplements [38]. Low calcium levels have been associated with hypogonadal states known to affect bone metabolism, and vitamin D receptors are closely linked to osteoblast function [39]. In a recent cross-sectional study, serum 25-hydroxy-vitamin D below 50 nmol/l was positively associated with spine BMD Z-scores in women with AN, and also with increased alkaline phosphatase levels, suggesting an adaptive osteoblastic reserve [40]. To date, there is no evidence to suggest that calcium or vitamin D supplementation increases BMD in AN, and no correlation between calcium or vitamin D intake and BMD in adolescents with AN [40]. However, a treatment goal is to optimize intake of these nutrients in adolescent and adult women with ED.

Vitamin K supplements may reduce loss of BMD in women with AN, with adequate vitamin K intake being required to achieve gamma-carboxylation of osteocalcin. Serum undercarboxylated osteocalcin levels are negatively correlated with vitamin K intake in AN [41]. Furthermore, vitamin K deficiency was more pronounced in AN binge-purge subtype than AN restricting subtype, suggesting that further study into Vitamin K deficiency in other ED diagnoses is necessary [42].

## Alterations in endocrine axes

In addition to weight loss, bone is affected by the various neuroendocrine alterations observed in women with ED.

**Hypothalamic-pituitary gonadal axis—**Amenorrhea has now been removed from the revised DSM-5 criteria for the diagnosis of AN, however, hypothalamic amenorrhea is still common in AN. Suppression of the hypothalamic-pituitary-gonadal axis preserves energy in a state of semi-starvation by preventing energy being diverted towards reproduction and

maintenance of a growing fetus [43]. Estrogen typically inhibits osteoclastic bone resorption [44], and may increase bone formation as well by inhibiting sclerostin and Pref-1 [45, 46]. Estrogen deficiency is closely linked to amenorrhea in AN, although bone resorption is higher in adult amenorrheic women with AN than post-menopausal women [47], suggesting that other factors also contribute to increased bone resorption in AN. Testosterone is another gonadal hormone believed to have a positive effect on bone through its aromatization to estradiol (E2), and also through its direct bone anabolic effects [48]. Females with AN have lower testosterone levels than controls, associated with lower BMD measures.

**Hypothalamic-pituitary-adrenal axis—**Adolescents and young women with AN have higher cortisol levels than controls, which is also deleterious to bone. High cortisol levels have an inhibitory effect on the HPG and GH-IGF-1 axes, impair calcium absorption from the gut, and inhibit OPG and increase RANKL secretion. They may also have a direct inhibitory effect on osteoblasts.

**Growth hormone–insulin-like growth factor-1 axis—**AN is associated with a nutritionally acquired growth hormone (GH) resistance with lower IGF-1 and higher concentrations of GH than observed in controls. Reductions in IGF-1 correlate with a reduction in bone formation markers and lower spine BMD [49] and endogenous IGF-I levels predict bone microarchitecture independent of BMI in women with AN [35]. In AN, higher GH levels are associated with lower levels of IGF-1 and FGF-21 (fibroblast growth factor 21), a hormone produced in the liver which may play a role in the mechanism of GH resistance in AN. FGF-21 levels are inversely associated with estimates of radial bone strength (stiffness and failure load) in AN [50].

**Appetite regulating hormones—**Appetite regulating hormones such as leptin (an anorexigenic hormone), ghrelin (orexigenic), and peptide YY (PYY; anorexigenic), are altered in AN. Leptin and ghrelin are bone anabolic, whereas PYY inhibits osteoblast differentiation. Compared to controls, adults and adolescents with AN have lower leptin levels, a potential resistance to ghrelin with higher ghrelin levels [51] and an increase in PYY [52]. In healthy adolescents, higher ghrelin concentrations predict higher BMD. However, this association is not observed in AN, suggesting a resistance to ghrelin [53]. Lower leptin and higher PYY levels are associated with lower levels of bone turnover markers and lower BMD [43].

**Other hormones and neurotransmitters—**Oxytocin has anorexigenic and bone anabolic effects [54] and oxytocin levels are lower in women with AN than controls (likely an adaptive response), associated with lower BMD [55].

Serotonin (5-HT) receptors are found on osteoblasts, osteoclasts and osteocytes [56], and an inverse relationship exists between serum serotonin levels and femoral neck, total and trabecular vBMD in healthy women [57]. However, in a cross-sectional analysis of serum serotonin, BMD and bone metabolism markers, a negative relationship was noted between serum serotonin and bone turnover markers [58*], suggesting that this warrants further study. At least one study has demonstrated that a longer duration of use of selective

serotonin reuptake inhibitors is associated with lower BMD in young women with AN even after controlling for the duration since diagnosis and duration of amenorrhea [59].

## IMPACT OF DSM-IV VS. DSM-5 BASED DIAGNOSIS OF EATING DISORDERS ON BONE OUTCOMES

Schorr et al have reported that despite liberalizing diagnostic criteria, many women diagnosed with AN and atypical AN using DSM-5 criteria have low BMD [60**]. In this study, BMD Z-scores were <−1.0 in 78% of DSM-IV, 82% of DSM-5, and 69% of atypical AN. Mean Z-scores were comparably low in women meeting diagnostic criteria for AN per DSM-IV and DSM-5, intermediate in atypical AN, and highest in normal-weight controls. Lack of prior low weight or amenorrhea was not protective against bone loss. The authors concluded that the deleterious effect of EDs on BMD extends beyond those with current low weight and amenorrhea.

In another study, Kandemir et al evaluated the clinical utility of existing cut-offs for low weight in adolescents and young adults with ED, as well as severity criteria for low weight by determining which are most strongly associated with risk for low BMD [61**]. Among severity categories, BMI Z scores had the greatest utility in assessing the degree of malnutrition in adolescent girls that corresponded to lower BMD.

## TREATMENT STRATEGIES

The first line of management of low BMD in AN is weight gain and resumption of menses. In addition, a number of treatment strategies have been investigated in adolescent and adult women with AN, including oral contraceptives, physiologic estrogen replacement as the transdermal patch, testosterone replacement, DHEA and recombinant human (rh)IGF-1 (in combination with estrogen-progesterone combination pills), bisphosphonates and teriparatide. Potential therapeutic options and the rationale for these treatment strategies, are summarized in Table 2.

Estrogen-progesterone combination pills providing estrogen doses of 20–35 mcg ethinyl estradiol per day, do not improve BMD in this condition [45, 62], likely because of the IGF-1 lowering effect of oral estrogen. In contrast, physiologic estrogen replacement as the 100 mcg transdermal 17-beta estradiol patch, known to bypass first pass hepatic metabolism, increases spine and hip BMD in adolescent girls with AN. Girls with AN receiving physiologic estrogen replacement (with cyclic progesterone) for 18-months had greater increases in BMD than AN girls on placebo, with bone accrual rates approaching that observed in normal-weight controls ($p = 0.044$ and 0.040, respectively) [63]. This may reflect either the type of estrogen used (17 beta estradiol vs. ethinyl estradiol), or the administration method (transdermal vs. oral), or both. Data are lacking regarding the effect of oral 17-beta estradiol on bone outcomes in AN. Of note, although BMD increased significantly in the AN girls, catch-up did not occur, likely because other hormone deficiencies/excess were not addresssed.

A combination of oral estrogen–progesterone and DHEA (50 mg daily) for 18 months in young women with AN was reported to increase cortical thickness, improve femoral cross sectional area and selection modulus (measured by HSA) [44], with a maintenance of DXA measures of BMD Z-scores over the study duration [45, 64].

Weight gain in women with AN correlates with increases in testosterone levels, which in turn correlate with an increase in BMD [68]. However, low-dose transdermal testosterone administration over one year did not increase BMD in adult women with AN [48].

Short term rhIGF1 replacement increases bone formation markers in adults and adolescents with AN [69, 70], and when combined with an estrogen–progesterone combination pill in a placebo-controlled trial, was found to increase spine and hip BMD in adult women with AN compared with controls who received neither (1.8% ± 0.8% vs. −1.0% ± 1.3% at the spine, $P < 0.05$) [65]. An ongoing RCT at Massachusetts General Hospital aims to investigate if rhIGF1 combined with transdermal E2 replacement (vs. transdermal E2 alone) is effective in increasing BMD Z-scores in adolescents with AN, and if this enables the ‘catch-up’ effect to increase BMD to a level comparable to healthy controls.

Bisphosphonates are not recommended to women with ED of reproductive age due to limited knowledge of their long-term efficacy. Following one year of administration of alendronate (10 mg daily) to adolescents with AN, vBMD of the femoral neck was higher in those receiving alendronate compared to placebo controls [66]. However, no effect was observed at the spine. In adults with AN, risedronate (35 mg weekly) has been shown to increase spine BMD over one year [48].

Teriparatide (TPT; human PTH) is a bone anabolic agent with proven anti-fracture efficacy in postmenopausal women and men with osteoporosis. Shibli-Rahhal et al. found a 21% increase in BMD and no re-occurrence of fractures following 2 years or teriparatide in a 52 year old AN patient [67]. Fazeli et al. confirmed these findings with a placebo-controlled RCT and found a 6–10% increase in spine BMD after 6 months of teriparatide treatment (20 mcg daily) in older women with AN [71]. However, safety concerns associated with the use of TPT derive from the increased risk of osteosarcoma in rodent studies, suggesting that TPT may be unsuitable for young women and adolescents.

## CONCLUSIONS

A better understanding of the neuroendocrine disturbances associated with ED, particularly in AN, and their impact on BMD and bone microarchitecture provides an opportunity to explore future interventions in this population. Recent advances in assessment techniques for aBMD, vBMD and bone microarchitecture have led to a better characterization of bone compromise in women with EDs. Physiologic estrogen replacement has been successful in increasing BMD in young women with AN, although complete ‘catch-up’ does not occur. Bisphosphonates, such as risedronate, increase BMD in adult women with AN but should be used with caution in women of reproductive age. The positive effects of teriparatide suggest a promising future bone anabolic treatment for low BMD in older women with AN, however, this is not currently an option in young women and adolescents. Trials of rh-IGF1

in combination with estradiol are ongoing in adolescents to determine whether this combination therapy allows for ‘catch-up’ to occur in AN. The significant, long-term, deleterious impact of ED on bone health highlights the importance of adequate and timely assessment and early intervention.

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**KEY POINTS**

- Not only anorexia nervosa (AN), but also bulimia nervosa (BN) results in lower BMD compared to controls.
- Promising treatment strategies include physiological estrogen replacement (rather than oral contraceptives) in adolescent girls with AN, and bisphosphonates, as well as teriparatide, in adult women with AN.
- The association between resting energy expenditure, marrow adipose tissue, and cold activated brown adipose tissue with BMD and bone structure in AN is discussed.

**Table 1**

DSM-5 Criteria for Anorexia Nervosa and Bulimia Nervosa

| **Anorexia Nervosa** | **Bulimia Nervosa** |
|---|---|
| Restriction of energy intake leading to significantly low body weigth in the context of age, gender and developmental age | Recurrent episodes of binge eating: eating an amount of food in a discrete period of time which is larger than most people would eat under similar circumstances with a sense of loss of control |
| Intense fear of gaining weight or fatness, or perstistent behaviors aimed at weight loss | Recurrent compensatory behaviours in order to prevent weight gain, including vomiting, laxative abuse, diuretics, enemas, excessive exercise and other medication misuse. |
| Self evaluation is unduly influenced by weight and shape | Self evaluation is unduly influenced by weight and shape |
| *Restricting sub-type*: There are no episodes of binge-eating or purging<br>*Binge-purging sub-type*: Episodes of binge-eating and/or purging accompany the above criteria. | Binge eating and compensatory behaviours occur on average at least once a week for three months, and in the absence of Anorexia Nervosa. |

Data from [4] Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub

**Table 2**

Possible Treatment Strategies to Increase BMD in Anorexia Nervosa (AN)

| Therapeutic Option | Rationale | Evidence for Efficacy or Lack Thereof |
|---|---|---|
| Weight Gain | Weight gain in AN to >90% of expected body weight is associated with resumption of menses, stabilization of hormones and an increase in BMD. | Weight restoration is central to all treatment of AN, although achievement and long-term maintenance of weight restoration can be challenging. |
| Calcium and vitamin D supplementation | Calcium and phosphorus are essential for bone mineralization; vitamin D is essential for increasing calcium and phosphorus absorption from the gut. | Calcium and vitamin D supplementation alone are not considered to be sufficient to increase bone density in AN, but should be optimized in all patients.<br>Dose: At least 1300 mg of elemental calcium and 600 IU of vitamin D daily (or as needed to maintain vitamin D levels between 30–50 ng/ml) |
| Estrogen replacement | Oligo-amenorrheic girls/women with AN are hypoestrogenic. Normal estrogen status is essential for pubertal bone accrual and to prevent bone loss in adult women with AN. This is because estrogen typically inhibits osteoclastic bone resorption and may increase bone formation, consequentially increasing BMD. | Oral contraceptives are not effective in increasing bone density measures in adolescents or adults with AN [45, 62], likely because of the IGF-1 lowering effects of ethinyl estradiol in oral contraceptives through hepatic first pass. In contrast, transdermal 17 beta estradiol administration has been demonstrated to significantly increase spine and hip bone density in adolescents with AN over 18-months to approximate bone accrual rates in controls [63].<br>Dose: 100 mcg 17-beta estradiol patch given continuously, with cyclic oral medroxyprogesterone acetate (MPA) (2.5 mg daily for 10 days every month). An alternative to MPA is micronized oral progesterone 100–200 mg given daily for 10–12 days. |
| Testosterone replacement | Testosterone levels are low in adolescent and adult women with AN compared with controls. Testosterone is known to inhibit bone resorption through its aromatization to estradiol (E2), and also has direct bone anabolic effects. | Initial trials investigating administration of testosterone (as the low dose testosterone patch) showed that this strategy was not effective in increasing bone density in adult women with AN over 12-months [48].<br>Dose used: 150 mcg testosterone patch; dose titrated to maintain testosterone levels in the upper half of the normal range for women |
| DHEA administration | One study has reported low DHEA levels in adolescent and young adult women with AN. DHEA is a precursor for both estrogens and androgens, and may inhibit osteoclastic bone resorption indirectly through mechanistic links to estrogen receptors. | Oral DHEA given with an oral estrogen-progesterone combination contraceptive pill has been reported to maintain BMD Z-scores in adolescents and young adult women with AN over 18-months, but is not recommended as a treatment option in isolation [45, 64].<br>Dose: 50 mg of oral micronized DHEA daily with an oral contraceptive pill containing 20 mcg of ethinyl estradiol and 0.1 mg levonorgestrel. |
| Recombinant human (rh) IGF-1 | Adolescents and adults with AN have low IGF-1 levels. Reductions in IGF-1 levels correlate with reductions in surrogate markers of bone formation and lower BMD in AN. | RhIGF-1 given twice daily as SC injections, with an oral estrogen-progesterone combination pill has been shown to increase spine and hip bone density in adult women with AN over 9-months (compared to a group that received neither) [65]. An ongoing RCT in adolescents with AN at Massachusetts General Hospital (MGH) aims to investigate if rhIGF1 combined with transdermal E2 replacement is effective in increasing bone density in this population more than transdermal E2 alone.<br>Dose: 30 mcg/kg of rhIGF-1 given SC twice daily with an oral contraceptive pill containing 35 mcg ethinyl estradiol and 0.4 mg norethindrone daily |
| Bisphosphonates | These are the most commonly prescribed drugs to treat osteoporosis. Bisphosphonates inhibit bone resorption by increasing osteoclast apoptosis. | Bisphosphonates have been shown to increase bone density at the spine and hip in adult women with AN over 12-months (study of 35 mg risedronate weekly vs. placebo), and to cause small increases in femoral neck bone density in adolescent girls with AN over 12-months (10 mg of alendronate daily vs. placebo) [48, 66]. These drugs are typically not recommended for women of reproductive age at this time due to their very long half-life, and potential adverse effects on the foetus.<br>Dose: 35 mg of oral risedronate weekly; 10 mg of oral alendronate daily |
| Teriparatide (TPT) | This is a bone anabolic agent that increases bone formation and is commonly prescribed in postmenopausal women and men with osteoporosis. | One small study in older women with AN demonstrated that TPT use (20 mcg daily SC) led to significant increases in spine (but not hip) bone density over 6-months [67]. The ‘black box’ warning for TPT in the context of an increased risk of osteosarcoma observed in rodent studies limits the use of this agent as a treatment option for adolescents with AN at this time, and also for young women with the condition.<br>Dose: 20 mcg of teriparatide SC daily |

AN = Anorexia Nervosa; rhIGF-1 = recombinant human insulin-like growth factor; sig. = statistically significant ($p<0.05$).