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TREATING BONE LOSS IN CHALLENGING SITUATIONS

Low Bone Mineral Density in Anorexia Nervosa: Treatments and Challenges

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Abstract

Anorexia nervosa, a psychiatric disease predominantly affecting women, is characterized by self-induced starvation and a resultant low-weight state. During starvation, a number of hormonal adaptations—including hypothalamic amenorrhea and growth hormone resistance—allow for decreased energy expenditure during periods of decreased nutrient intake, but these very same adaptations also contribute to the medical complications associated with chronic starvation, including low bone mass. Almost 90% of women with anorexia nervosa have bone mineral density (BMD) values more than one-standard deviation below the mean of healthy women at peak bone mineral density, and this disease is associated with a significantly increased risk of fracture. Although multiple therapies have been studied for the treatment of low bone mass in anorexia nervosa, there are currently no approved therapies and few promising long-term therapeutic options. This review will outline the mediators of low bone mass in anorexia nervosa, discuss therapies that have been studied for the treatment of low BMD in this disorder, and highlight the important challenges that remain, including the differences in bone modeling in adolescents with anorexia nervosa as compared to adults, necessitating that potential therapies be tested in these two populations separately, and the paucity of long-term therapeutic strategies for treating bone loss in this disorder.

Keywords Anorexia nervosa · Bone mineral density · Estrogen

Introduction

Anorexia nervosa, a psychiatric disorder predominantly affecting women, is characterized by low body-weight due to self-induced starvation. The disease, which typically presents during adolescence [1], has a lifetime prevalence of approximately 2.2% [2]. Importantly, this is a chronic disorder in that only 50–60% of women with anorexia nervosa recover even 20 years after diagnosis [3, 4]; therefore, this disease is also prevalent in older women.

The most common medical complication associated with anorexia nervosa is low bone mass [5]. More than 50% of women with anorexia nervosa meet the definition of osteopenia, defined as a T-score between − 1 and − 2.5 compared to healthy women at peak bone mineral density (BMD), and an additional 34–38% meet the definition of osteoporosis (T-score ≤ − 2.5) [5, 6]. This loss of bone mass is predominantly due to hormonal adaptations critical for reducing energy expenditure during periods of low caloric intake, including functional hypothalamic amenorrhea and growth hormone resistance. Although these adaptations advantageously divert energy away from reproduction and growth during periods of low nutrient intake, the long-term consequences of these adaptations include loss of bone mass and importantly, a significantly increased risk of fracture [7–10]. Approximately 30% of adolescent girls and women report a prior history of fracture [5, 9] and prospective data similarly demonstrate a sevenfold increased risk of fracture in young women with anorexia nervosa [7].

Given the chronic nature of this disorder and the fact that anorexia nervosa typically develops during adolescence, which is a critical time for bone accrual, the increased risk of fracture may persist even many years after initial diagnosis; a population-based study demonstrated a 57% cumulative incidence of fracture 40 years after the diagnosis of anorexia nervosa [11]. Therefore, finding effective, long-term treatment strategies for the prevention of bone loss in anorexia nervosa is critical. In this review, we will discuss possible determinants of the low bone mass and increased fracture risk in anorexia

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nervosa and we will review the efficacy of treatments that have been studied in this population. We will also discuss challenges that remain in the field, including the current lack of long-term therapeutic options for the treatment of bone loss in adult women with anorexia nervosa and the persistently heightened fracture risk in individuals who have recovered from this disorder.

Body Composition and Possible Nutritional Mediators of Low Bone Mass

Lean Body Mass and Peripheral Fat Stores

Individuals with anorexia nervosa have less lean body mass [12] and lower subcutaneous and visceral fat stores [13] as compared to normal weight controls. In most studies, lean body mass has been found to be a strong positive predictor of BMD in both girls and women with anorexia nervosa [14–16] and lean mass, but not fat mass, has been shown to be positively associated with parameters of bone geometry, as assessed by hip structural analysis [17]. Similarly, in longitudinal studies, change in lean body mass, but not change in fat mass, is positively associated with change in BMD [18, 19], likely due to the increased mechanical loading on bone with increased muscle mass.

Given the positive association between lean body mass and BMD in anorexia nervosa, an important question is whether exercise should be encouraged as a possible treatment for low bone mass. Whereas some studies in adolescents and adults demonstrate positive associations between physical activity and BMD [20–24], others have shown no association [14, 25–27]. Importantly, one study showed that women who exercised more than 6 h/week had lower BMD compared to women who exercised between 1 and 6 h/week, suggesting a possible negative effect of increased physical activity [28]. Physical activity has also been associated with amenorrhea [29] and will necessitate increasing caloric intake. Therefore, while moderate physical activity does not necessarily need to be discouraged, data to date do not support encouraging exercise for the treatment of low bone mass in anorexia nervosa.

Leptin

Although fat mass does not appear to be a significant determinant of BMD in anorexia nervosa, leptin—an anorexigenic hormone secreted by adipose tissue—may be a determinant, in part because it is likely a key hormonal mediator in the development of hypogonadotropic hypogonadism in states of undernutrition. Compared to normal-weight controls, levels of leptin are low in girls and women with anorexia nervosa [30, 31]. Treatment with recombinant human leptin in women with functional hypothalamic amenorrhea has been shown to lead to recovery of menses when compared to placebo-treated individuals [32] and an increase in markers of bone formation [33]. Although leptin levels are positively associated with BMD in anorexia nervosa [34, 35], suggesting that low levels may be a contributor to low bone mass in this disorder, weight loss is a side effect of recombinant human leptin treatment, possibly due to its anorexigenic effects [32, 33]. Therefore, given the possible risk of further weight loss, leptin is not currently a potential treatment option for bone loss in individuals with anorexia nervosa.

Marrow Adipose Tissue

In contrast to peripheral adipose tissue stores, marrow adipose tissue may be a determinant of BMD in anorexia nervosa. Marrow adipose tissue is a component of the bone marrow microenvironment and in cross-sectional studies, levels of marrow adipose tissue are higher in anorexia nervosa as compared to controls [36, 37] and inversely associated with BMD [36]. In women who have recovered from anorexia nervosa, marrow adipose tissue levels appear to normalize and are similar to those of normal-weight controls [38]. Why this fat depot increases in size when peripheral fat stores are actively being used during chronic starvation is not known but in a recent longitudinal study, we demonstrate that levels of marrow adipose tissue increase with short-term weight gain and are positively associated with changes in BMD [39], suggesting that this fat depot may serve a different function with dynamic changes in weight as compared to the steady-state. Marrow adipose tissue has been associated with impaired bone integrity [40] and in anorexia nervosa, marrow adipose tissue is negatively associated with estimates of bone strength in adolescent girls [41], suggesting that it could be a determinant of increased fracture risk in this population.

Calcium, Vitamin D, and Protein Intake

Although insufficient caloric intake is a defining characteristic of anorexia nervosa, inadequate intake of calcium, vitamin D, and/or protein does not appear to be an important contributing factor to loss of bone mass in this population. Compared to controls, adolescents with anorexia nervosa are less frequently vitamin D deficient and consume more calcium and vitamin D, primarily through supplement intake [42, 43]. Similarly, although isolated protein deficiency, independent of caloric intake, may be associated with decreased cortical bone thickness [44] and low BMD [45], adolescents with anorexia nervosa have similar protein intake compared to normal-weight controls [42, 46, 47]. Therefore, insufficient calcium, vitamin D, or protein intake are unlikely to be significant factors contributing to low bone mass in anorexia nervosa, but given the known positive association between low 25-OH vitamin D levels and low BMD [48], individuals with

anorexia nervosa should be screened and treated for low 25-OH vitamin D levels.

Hyponatremia

Seven to 17% of women with anorexia nervosa have low sodium levels [5, 49]. This is likely due to a decreased ability to excrete free water in the setting of low solute intake. In rodent studies, hyponatremia is associated with reductions in trabecular and cortical bone [50] and in humans, hyponatremia is independently associated with an increased risk of fracture [51, 52]. In anorexia nervosa, women with a plasma sodium level of < 135 mmol/L have lower BMD compared to those with a sodium level ≥ 135 mmol/L [53], suggesting that hyponatremia may be a determinant of low BMD in this population.

Hormonal Adaptations to Undernutrition (Table 1)

Functional Hypothalamic Amenorrhea

Hypoestrogenemia

Although it is no longer a component of the diagnostic criteria in the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), amenorrhea is a common finding in the majority of women with anorexia nervosa [54]. Amenorrhea, or the absence of at least three consecutive menstrual periods, is due to disruption of gonadotropin-releasing hormone (GnRH) secretion [62–66] in this disorder. This shunting of energy away from the costly process of reproduction during periods of undernutrition is an adaptive, energy-preserving response, but the resultant hypoestrogenemia contributes to the loss of bone mass in states of chronic undernutrition such as anorexia nervosa. Low estrogen states are characterized by increased bone remodeling and subsequent bone loss [67–70] and in individuals with anorexia nervosa, longer duration of amenorrhea is associated with lower BMD [21, 25].

Despite the fact that duration of estrogen deficiency is significantly correlated with low BMD in anorexia nervosa, oral estrogen therapy has not been shown to improve BMD in this population. Whereas retrospective studies suggested beneficial effects of oral estrogen on BMD in anorexia nervosa [21], subsequent randomized and/or prospective studies demonstrated no overall benefit in BMD in individuals receiving oral estrogen versus placebo [71–73]. In contrast, physiologic doses of predominantly transdermal estrogen have been shown to be effective in increasing BMD in adolescent girls with anorexia nervosa [74]. BMD in the spine increased by 2.6% after 18 months of transdermal estrogen compared to < 0.5% in those not treated [74]. The reason for this difference in efficacy with low-dose transdermal estrogen as compared to oral estrogen may be due to suppression of insulin-like growth factor (IGF)-1—a bone-trophic hormone that is already low in individuals with anorexia nervosa [75]. Compared to transdermal estrogen, oral estrogen has been shown to have greater IGF-1 suppressive effects in a population of postmenopausal women [76, 77]. Similarly, higher doses of oral estrogen, such as the doses found in oral contraceptive pills, have greater IGF-1 suppressing effects compared to lower, more physiologic doses of oral estrogen [77]. Importantly, IGF-1 has been significantly correlated with BMD in anorexia nervosa [15] and therefore further suppression of this bone anabolic hormone may be the critical reason for the difference in efficacy between oral and transdermal estrogen in this population.

Although transdermal estrogen is a promising treatment for low bone mass in anorexia nervosa, it has only been studied in adolescents, and there are important differences in bone modeling/remodeling in adolescents as compared to adults

Table 1 Potential mediators of low bone mass in anorexia nervosa

	Association with bone in anorexia nervosa	References
Low IGF-1	Low IGF-I levels are associated with low BMD	[15]
Hypoestrogenemia	Duration of amenorrhea is associated with low BMD	[25]
Low testosterone	Low testosterone levels are associated with low BMD and impaired bone microarchitecture	[55, 56]
Elevated cortisol	High cortisol levels are associated with low BMD	[57]
Low DHEAS	Low DHEAS levels are associated with low BMD	[55]
FGF21	FGF-21 levels are associated with impaired bone microarchitecture	[58]
Low leptin	Low leptin levels are associated with low BMD and impaired bone microarchitecture	[34, 35, 56]
Elevated ghrelin	Baseline ghrelin levels are inversely associated with change in BMD in adolescent girls	[59]
Elevated PYY	Elevated PYY levels are associated with low BMD	[60]
Low oxytocin	Low oxytocin levels are associated with low BMD	[61]
Elevated preadipocyte factor 1 (Pref-1)	Elevated Pref-1 levels are associated with low BMD	[34]
Elevated levels of marrow adipose tissue	Elevated marrow adipose tissue stores are associated with low BMD	[36]

with this disease that may influence efficacy of treatment. Compared to normal-weight controls, adolescents with anorexia nervosa have lower levels of bone formation markers and similar levels of bone resorption markers [27, 78, 79], suggesting an overall low bone remodeling state. In contrast, adult women with anorexia nervosa have similarly low levels of bone formation markers but *elevated* levels of bone resorption markers compared to controls [80–83]. This difference in bone modeling/remodeling in adolescents versus adults may be due in part to the fact that adult women with anorexia nervosa are estrogen deficient in comparison to healthy adult women and as detailed above, estrogen deficiency is associated with increased bone remodeling [68–70, 84]. Therefore, bone loss in adult women with anorexia nervosa may be due to decreased bone formation in the setting of accelerated bone remodeling, whereas in adolescents with anorexia nervosa, there is an overall state of decreased remodeling. These differences may help explain differences observed in adolescents versus adults with anorexia nervosa in response to treatments for low bone mass. For example, 12 months of treatment with a bisphosphonate significantly improved BMD in adult women with anorexia nervosa compared to subjects treated with placebo [85], whereas 12 months of treatment with a bisphosphonate in adolescent girls did not result in a significant difference in change in BMD compared to placebo-treated subjects [86]. Given differences in bone modeling/remodeling in adolescents versus adults, bisphosphonates, which decrease rates of bone remodeling [87], may be more effective in adults with anorexia nervosa with their accelerated rate of bone remodeling as compared to adolescents with their overall low remodeling state. Therefore, potential therapies for bone loss must be studied separately in adults and adolescents with anorexia nervosa and it is not yet known if transdermal estrogen is an effective treatment for bone loss in adult women with this disease.

Low Testosterone Levels

Low testosterone levels, an androgen produced in part by the ovary, are also a characteristic finding in women with anorexia nervosa [55, 88]. Low levels of testosterone are associated with decreased BMD and impaired bone microarchitecture in this population [55, 56]. Despite these associations, transdermal testosterone treatment was not effective in increasing BMD in a randomized, placebo-controlled study in women with anorexia nervosa [85]. Therefore, decreased levels of testosterone may not be an important determinant of bone mass in this population.

Growth Hormone Resistance

Growth hormone (GH) is secreted by the pituitary gland and stimulates the liver to produce IGF-1—a hormone which mediates the majority of the growth-promoting effects of GH. GH has additional functions, including fat mobilization [89], and the counter-regulatory effects of GH may be critical for sustaining eugylycemia during periods of starvation [90]. Therefore, acquired GH resistance, which is signified by normal or elevated GH levels in the setting of low IGF-1 levels, allows for the counter-regulatory effects of GH to be maintained while energy is diverted away from the costly process of growth in states of starvation such as anorexia nervosa [91–94]. Yet similar to functional hypothalamic amenorrhea, this energy-preserving adaptation is also a likely contributor to the loss of bone mass.

Low IGF-1 Levels

IGF-1—a bone anabolic hormone—is produced and secreted by the liver in response to GH, but this hormone is extremely responsive to nutritional cues as well. During an acute fast, IGF-1 levels decrease significantly after 4 days and this drop in IGF-1 levels is coupled with a decrease in bone formation markers [95]. In a more chronic state of starvation, such as anorexia nervosa, levels of IGF-1 are also significantly lower as compared to controls [75]. Importantly, in anorexia nervosa, levels of GH are normal or elevated in the setting of low IGF-1 levels [91–94], demonstrating the primary importance of nutritional status in the regulation of IGF-1. In fact, even supraphysiologic doses of recombinant human GH do not raise IGF-1 levels in women with anorexia nervosa [96].

These decreased IGF-1 levels are likely a significant contributor to the loss of bone mass in anorexia nervosa. IGF-1 has been shown to be positively associated with BMD in women with anorexia nervosa [15] and in prospective studies, treatment with recombinant human IGF-1 increases bone formation markers in both girls and women with anorexia nervosa [97, 98]. Treatment with recombinant human IGF-1 has also been shown to increase lumbar spine BMD in women with anorexia nervosa when combined with oral estrogen [73]. Importantly, given the differences in bone remodeling in adolescents versus adults, the effects of IGF-1 on BMD in adolescent girls with anorexia nervosa are not yet known but this is an active area of investigation.

Fibroblast Growth Factor 21

Fibroblast growth factor (FGF)21 is a hormone induced during fasting in both mice [99, 100] and humans [101]. Although the mechanism underlying GH resistance in humans is not known, in murine models, FGF21 has been shown to be a mediator of GH resistance through a reduction in STAT5—a transcription factor critical for GH signaling and induction of IGF-1 [102]. In a cross-sectional study, FGF21 was inversely associated with IGF-1 and positively associated with GH-area-under-the-curve in adolescents with anorexia nervosa,

suggesting that FGF21 may also be a mediator of GH resistance in humans [103]. In murine models, FGF21 transgenic mice weigh less than wild-type littermates, have decreased bone mass, and an increase in the number and area of bone marrow adipocytes—a potential determinant of BMD [104, 105], and therefore FGF21 transgenic mice are phenotypically similar to individuals with anorexia nervosa. In a cross-sectional study in women with anorexia nervosa, FGF21 levels were inversely associated with bone microarchitecture parameters and estimates of bone strength [58], suggesting a possible role for FGF21 in the impaired bone phenotype of women with anorexia nervosa.

Adrenal Steroids

Hypercortisolemia

Elevated cortisol levels may also be an important mediator of low bone mass in anorexia nervosa. The negative effects of cortisol on bone are the result of a number of mechanisms including decreased calcium availability via a decrease in calcium absorption in the intestine and an increase in urinary calcium excretion [106–108], an impairment of bone formation via reduced osteoblast proliferation [109], and an increase in bone resorption due in part to inhibition of gonadotropin secretion [110]. Levels of cortisol are higher in individuals with anorexia nervosa, a physiologically stressful state, as compared to normal-weight controls [57, 111–113] and cortisol is inversely correlated with bone formation markers and BMD in adolescent girls and women with anorexia nervosa [25, 57, 113]. Therefore, cortisol may be an important mediator of bone loss in this disorder.

Dehydroepiandrosterone

Levels of the adrenal androgen precursor dehydroepiandrosterone (DHEA) and its sulfated form, DHEA-S [114, 115] are lower in individuals with anorexia nervosa compared to controls, and these low levels are associated with both increased levels of bone resorption markers and decreased BMD [22, 55]. Studies investigating the effects of DHEA replacement in individuals with anorexia nervosa demonstrate that treatment with DHEA in combination with oral estrogen for 18 months leads to improvement in parameters of bone geometry, as assessed by hip structural analysis, and stabilization of BMD as compared to placebo [116, 117]. In contrast, treatment with DHEA for 6 months or 1 year without oral estrogen does not lead to improvements in BMD when compared to placebo-treated individuals or those treated with oral estrogen [118, 119]. Therefore, low DHEA levels may also contribute to the low bone mass in individuals with anorexia nervosa.

Other Potential Hormonal Determinants

PYY

Similar to leptin, peptide YY (PYY), a hormone secreted by the intestine, is also an anorexigenic hormone. In contrast to leptin, PYY levels are elevated in girls and women with anorexia nervosa [47, 60], although whether these increased levels contribute to the decreased hunger reported in this disease is not known [120]. In murine models, compared to wild-type littermates, overexpression of PYY in female mice results in lower BMD and trabecular bone volume [121] and in anorexia nervosa, elevated PYY levels are associated with low BMD [60]. Therefore, elevated PYY levels may also be a mediator of low bone mass in anorexia nervosa.

Ghrelin

Ghrelin is an orexigenic hormone secreted by the stomach's fundal cells. Compared to healthy controls, individuals with anorexia nervosa have higher levels of ghrelin [122] but appear resistant to its appetite-stimulating effects, as women with anorexia nervosa report decreased hunger compared to controls [120]. Ghrelin administration has been shown to increase BMD in a rodent model [123] and in normal-weight adolescent girls, ghrelin is positively correlated with BMD [124], suggesting that ghrelin has beneficial effects on bone. Yet in a longitudinal study in girls with anorexia nervosa, there was a negative association between baseline ghrelin levels and changes in BMD [59], suggesting that individuals with anorexia nervosa may also be resistant to ghrelin's positive bone effects. It is possible that this resistance to the effects of ghrelin are due to differences in the ratio of acylated ghrelin—the active form of ghrelin which binds to the growth hormone secretagogue receptor 1a (GHSR1a)—to desacylated ghrelin, as levels of desacylated ghrelin are significantly higher in individuals with anorexia nervosa as compared to controls [125]. In a double-blind, randomized, placebo-controlled study, we have recently shown that treatment with a GHSR1a-agonist was able to overcome resistance to the gastric motility effects of ghrelin in women with anorexia nervosa [126] and we also found a trend toward a decrease in marrow adipose tissue—elevated levels of which are a potential determinant of low BMD in anorexia nervosa—with treatment [127]. Further studies will be necessary to determine whether treatment with a GHSR1a-agonist can also overcome the resistance to the bone anabolic effects of ghrelin in individuals with anorexia nervosa.

Oxytocin

Oxytocin, a hormone secreted by the posterior pituitary and known primarily for promoting uterine contractions during childbirth and milk ejection during lactation, has also been shown to

have bone anabolic effects [128]. In an ovariectomized-osteoporotic mouse model, treatment with oxytocin led to improved trabecular bone volume fraction and a decrease in marrow adipocyte number [129]. Compared to controls, levels of oxytocin are lower in women with anorexia nervosa and positively associated with BMD [61]; therefore, low oxytocin levels may also contribute to the low bone mass phenotype in this population.

Preadipocyte Factor 1

Preadipocyte factor (Pref)-1 is a member of the epidermal growth factor family of proteins and an inhibitor of osteoblast and adipocyte differentiation [130]. In anorexia nervosa, circulating levels of Pref-1 are elevated compared to controls and Pref-1 is inversely associated with BMD and positively associated with marrow adipose tissue [34]. Further studies are necessary to better understand the role of circulating Pref-1 and its association with bone mass and marrow adipose tissue in anorexia nervosa.

Sclerostin

Sclerostin is secreted by osteocytes and negatively affects bone formation via inhibition of Wnt signaling. In postmenopausal women, treatment with a sclerostin monoclonal antibody increases BMD [131] and reduces risk of fracture [132]. Sclerostin levels are higher in anorexia nervosa compared to controls [133], suggesting that it may be a determinant of low bone mass in this population, but elevated levels are not associated with low spine or hip BMD in anorexia nervosa [133] and changes in circulating sclerostin levels do not appear to mediate increases in BMD in response to 6 months of teriparatide in women with anorexia nervosa [134] or in response to 12 months of transdermal estrogen in adolescents [135]. Therefore, further study is necessary to better understand the potential role of sclerostin in the low bone mass phenotype of anorexia nervosa.

Challenges in the Treatment of Low BMD in Anorexia Nervosa

The most significant challenges in the treatment of loss of bone mass in anorexia nervosa are (1) the chronicity of the disease, (2) a lack of long-term therapeutic options, and (3) the persistence of low bone mass and increased fracture risk even after recovery [11, 136]. Because only 50–60% of women recover from anorexia nervosa decades after their initial diagnosis [3, 4], long-term therapeutic strategies for low bone mass are critical but currently lacking. We will review various pharmacologic therapies that have been studied for the treatment of bone loss in anorexia nervosa below (Table 2), but to date, the most effective long-term treatment for bone loss in anorexia nervosa is recovery from the disorder, inclusive of both weight recovery and a resumption of menses. Weight recovery accompanied by a resumption of menses results in an annual rate of increase in BMD of 3.1% in the spine and 1.8% in the hip [19], which is in sharp contrast to an annual rate of bone loss of 2.6% in the spine and 2.4% in the hip in women who remain amenorrheic and low-weight [19]. Yet even in patients who recover from anorexia nervosa, there may be a persistence of low BMD and increased fracture risk [11, 136], and there are currently no prospective studies investigating how to best treat this post-recovery population.

Given the association between hormonal adaptations to starvation, including functional hypothalamic amenorrhea and growth hormone resistance, and low bone mass, a number of hormonal treatment strategies have been studied in girls and women with persistent anorexia nervosa; these hormonal treatments include estrogen, DHEA, IGF-1, and testosterone. Physiologic doses of predominantly transdermal estrogen increase spine BMD by 2.6% in adolescent girls after 18 months of treatment [74] and therefore transdermal estrogen is a promising long-term treatment option for low bone mass in adolescents with anorexia nervosa. In contrast, oral estrogen, predominantly in the form of oral contraceptives, when used alone, does not improve BMD in women or adolescents with anorexia

Table 2 Therapies that been investigated for the treatment of low bone mass in adults and/or adolescents with anorexia nervosa and have shown efficacy in at least one of these populations

Therapy	Effect on BMD in adults	Duration of treatment (adults)	Effect on BMD in adolescents	Duration of treatment (adolescents)
Physiologic estrogen replacement (transdermal)	Not known	–	2.6% increase in spine BMD [74]	18 months
IGF-1 + oral contraceptives	1.8% increase in spine BMD [73]	9 months	Not known	–
DHEA + oral contraceptives	Maintenance of BMD (mixed population of adolescents and adults) [116]	18 months	Maintenance of BMD (mixed population of adolescents and adults) [116]	18 months
Bisphosphonates	2–4% increase in spine/hip BMD compared to placebo [85]	12 months	No significant difference compared to placebo [86]	12 months
Teriparatide	6–10% increase in spine BMD [134]	6 months	Not known	–

nervosa [71–73]. Yet when added to other hormonal treatments, including IGF-1 or DHEA, oral estrogen shows modest efficacy; treatment with recombinant human IGF-1 combined with oral contraceptives increases spine BMD by 1.8% after 9 months in adult women with anorexia nervosa [73] and the combination of oral estrogen and DHEA is effective in preserving BMD in a mixed population of adolescent girls and adult women with anorexia nervosa [116]. Importantly, given the differences in bone remodeling in adults versus adolescents with anorexia nervosa, the effects on BMD of IGF-1 combined with estrogen in adolescents and the effects of transdermal estrogen in adults are not known but are currently being investigated. The effects of 12 months of transdermal testosterone have also been studied in women with anorexia nervosa, but testosterone did not improve BMD when compared to placebo [85].

Additional treatments, including bisphosphonates and teriparatide, have demonstrated benefit in short-term studies in women with anorexia nervosa, but long-term use of these medications is limited. Six months of teriparatide increases spine BMD by 6–10% in women with anorexia nervosa [134], but teriparatide is only approved for 24 months of use and also carries an FDA warning because of an increased risk of osteosarcoma observed in rat studies [137]. Therefore, teriparatide cannot be used long-term and should not be prescribed to individuals at increased risk of osteosarcoma, including individuals with open epiphyses. Similarly, compared with placebo, bisphosphonates increase spine and hip BMD by 2–4% after 12 months in adults [85], but in adolescents treated for 12 months, bisphosphonates do not increase BMD any more than placebo [86], emphasizing the need to separately test potential therapies for bone loss in both adolescent and adult populations. Importantly, long-term use of bisphosphonates has been associated with an increased risk of atypical femoral fractures in population-based studies [138], and in rodent studies, bisphosphonates cross the placenta and are associated with fetal abnormalities [139]. Given the long half-life of bisphosphonates in bone [140], caution must be taken when considering bisphosphonate therapy in premenopausal women, as the risks of bisphosphonates to the human fetus have not been well-established. Therefore, there are currently no promising BMD-improving therapies that can be used long-term in adults with anorexia nervosa.

Conclusions

Anorexia nervosa is a chronic psychiatric illness, predominantly affecting women and characterized by inadequate caloric intake [3, 4]. Low bone mass, due primarily to hormonal adaptations to the state of chronic undernutrition, is the most common medical complication associated with anorexia nervosa, and approximately 90% of women have BMD values more than one standard deviation below the mean of comparably-aged women [5, 6]. Importantly, this low bone mass is associated with a significantly increased risk of fracture [5, 7] and therefore therapeutic strategies for preventing this morbidity are critical. Although there are currently no approved treatments for low bone mass in anorexia nervosa, physiologic, transdermal estrogen is a promising therapy for adolescents. The treatments which have demonstrated the greatest benefit in adult women with anorexia nervosa, notably bisphosphonates and teriparatide, are not potential long-term treatment options and therefore there remains a significant need for therapies for the treatment of low BMD in the adult population. It is also important to note that we do not know whether any of the treatments that improve BMD in anorexia nervosa also reduce the fracture rate in this population. Therefore, future studies are critically needed to evaluate the long-term efficacy and safety of potential treatment strategies for bone loss in anorexia nervosa.

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