Anorexia nervosa (AN) is a psychiatric disorder characterized by self-induced starvation with a lifetime prevalence of 2.2% in women. The most common medical co-morbidity in women with AN is bone loss, with over 85% of women having bone mineral density values more than one standard deviation below an age comparable mean. The low bone mass in AN is due to multiple hormonal adaptations to under nutrition, including hypothalamic amenorrhea and growth hormone resistance. Importantly, this low bone mass is also associated with a seven-fold increased risk of fracture. Therefore, strategies to effectively prevent bone loss and increase low bone mass are critical. We will review hormonal adaptations that contribute to bone loss in this population as well as promising new therapies that may increase bone mass and reduce fracture risk in AN.

Keywords
Anorexia nervosa; bone mineral density

Introduction
Anorexia nervosa (AN) is a psychiatric disease characterized by energy restriction, low body weight and an intense fear of gaining weight [1]. AN is recognized as the third most common chronic illness in adolescents and the teenage years are the most common time of onset of the disease [2, 3]. The lifetime prevalence of AN in women is 2.2% [4] but because only 50% of women with AN recover even many years after their initial diagnosis [5], this is a chronic disease for many women. In fact, the number of women over 35 years of age entering treatment facilities for AN has dramatically increased in recent years [6]. Although primarily recognized in females, males are also affected by this disease. Although it is reported that 10% of individuals affected by AN are male, the incidence may be much higher [7].

AN is associated with a number of medical complications, the most common of which is decreased bone mass [8]. Approximately 85% of women with AN have bone mineral...
density (BMD) values more than one-standard deviation below an age-comparable mean [8, 9] and this decrease in bone mass is associated with an increased fracture risk. Approximately thirty percent of women with AN report a prior history of sustaining a fracture [8] and a prospective study demonstrated a seven-fold increased risk of fracture in young women with AN compared to age-comparable, normal-weight controls [10]. Importantly, a population-based retrospective study found the cumulative incidence of fracture to be 57% in this population. Therefore, the elevated fracture risk persists many years after the diagnosis of AN [11].

Hormonal alterations occurring in AN serve to decrease energy expenditure in this state of negative energy balance and contribute to bone loss in this disorder. In adult women with AN, the hormonal alterations result in a profound increase in bone resorption coupled with a decrease in bone formation [12]. Only 50% of women with AN recover even many years after their initial diagnosis [5] and in those who remain low weight and amenorrheic, the annual rate of decline in BMD is −2.4% at the hip and −2.6% at the spine [13]. Therefore understanding the pathophysiology of this disease and finding potential treatments are critical. In this review, we will discuss the mechanisms of bone loss in AN and treatments that have been investigated in this population.

Mechanisms of Bone Loss

**Nutrient intake**—Women with AN have insufficient caloric and nutrient intake. Therefore, one potential mechanism contributing to bone loss in this disease could be decreased calcium and/or vitamin D intake. Yet both girls and women with AN consume more calcium and vitamin D -- predominantly through supplements -- compared to normal-weight controls [14, 15]. Therefore decreased intake of calcium and vitamin D does not appear to be an important mediator of bone loss in AN.

**Hormonal mediators of decreased bone mass in AN (Table 1)**

**Abnormalities in reproductive hormone levels**

**Estradiol:** Hypogonadotropic hypogonadism is a characteristic finding in women with AN. The hypogonadism is due to an abnormal GnRH secretory pattern, which results in a luteinizing hormone (LH) secretory pattern similar to that seen in pre-pubertal girls – one of low amplitude LH pulsatility [16–20]. Importantly, with weight recovery, this abnormal secretory pattern normalizes [20]. States of estrogen deficiency, such as menopause, result in increased bone resorption and subsequent loss of bone mass [21] and therefore, amenorrhea is likely a significant contributor to bone loss in AN. This is supported by the fact that duration of amenorrhea is inversely associated with BMD in AN [22]. Whether estrogen replacement can improve BMD in women with AN is an important question that has been extensively investigated. Two randomized, placebo-controlled trials investigated the effects of oral estrogen on BMD in women with AN and both studies found no difference in BMD in the women treated with estrogen as compared to those treated with placebo [23, 24]. A recent study investigated the effects of physiologic estrogen replacement -- predominantly in the form of a transdermal patch -- in adolescent girls with AN. Treatment with transdermal, physiologic estrogen resulted in a 2.6% increase in spine BMD after 18 months [25]. Taken together, these studies suggest that physiologic doses, particularly when given
transdermally, but not the supraphysiologic doses of estrogen found in oral contraceptive pills, may be beneficial in AN. However, transdermal estrogen has only been studied in adolescents with AN. Adolescence, a time of maximal bone accrual is associated with a high turnover state with formation exceeding bone resorption. In adolescents with AN, a low turnover state has been found, in contrast to adults with AN [26]. Therefore, it is unknown whether transdermal estrogen would have a similarly beneficial effect in adults with this disorder. It has been hypothesized that the lack of efficacy of oral estrogen may be due to suppression of insulin-like growth factor I (IGF-I) – a protein which has important bone anabolic effects -- by oral estrogen [25].

**Testosterone:** Women with AN have low testosterone levels [27, 28] and importantly, the low levels of testosterone have been shown to predict low BMD in AN [28]. Although one might hypothesize that testosterone replacement could lead to improvements in BMD in women with AN, a randomized, placebo-controlled study evaluated the effects of 12 months of transdermal testosterone replacement in AN and found no difference in change in BMD in the testosterone treated group as compared to the placebo treated group [29]. Therefore, factors other than testosterone may play a more significant role in AN-associated bone loss.

**Leptin:** Although leptin is an anorexigenic hormone secreted by adipose tissue, it is an important mediator of hypogonadotropic hypogonadism in states of negative energy expenditure and therefore a key reproductive hormone. Individuals with AN have low levels of adipose tissue, including subcutaneous fat and consequently have low levels of leptin [30, 31]. The hypothalamic amenorrhea characteristic of AN is likely mediated by the low leptin levels, as women with AN who are amenorrheic have significantly lower levels of leptin compared with women with AN who are not amenorrheic despite comparable weights [32]. Importantly, in AN, decreased levels of leptin have been associated with decreased BMD, independent of duration of amenorrhea [33], and with worsened microarchitectural parameters [34]. Administration of recombinant human leptin to women with hypothalamic amenorrhea resulted in increased levels of osteocalcin and bone-specific alkaline phosphatase – two markers of bone formation, although a major effect of treatment was weight loss [35]. Therefore, although leptin may be a mediator of the low bone mass in AN and treatment with recombinant human leptin may stimulate bone formation, this is not a potential treatment for individuals with AN, given the associated weight loss.

**Growth hormone resistance**—Growth hormone (GH) resistance is a characteristic finding in states of under-nutrition and is an adaptive response to the state of nutritional deprivation. Girls and women with AN have elevated levels of GH coupled with low levels of IGF-I – a hormone produced in the liver in response to GH and a key mediator of many of the growth-promoting actions of GH [36–39]. Low IGF-I levels help minimize energy expenditure on growth -- including expenditures on the growth and maintenance of bone – during periods of under-nutrition. Importantly, IGF-I levels are exquisitely sensitive to nutritional cues. Both acute and chronic nutritional deprivation lead to dramatic decreases in IGF-I levels; a four-day fast results in a 50% decrease in IGF-I levels [40] and women with AN have levels of IGF-I that are 50% lower than healthy-weight controls [41]. In AN, IGF-I
levels also quickly increase in response to re-feeding, with levels increasing by 50% after three days of hyper-alimentation therapy [42].

The elevated GH levels characteristic of GH resistance are the consequence of both positive feedback on the GHRH/GH axis from the low IGF-I levels [43] and ghrelin-stimulated GH secretion. Ghrelin is an orexigenic hormone secreted by cells in the fundus of the stomach and levels are elevated in girls and women with AN [44–46]. Ghrelin -- via its receptor, the growth hormone secretagogue receptor 1a -- stimulates GH secretion and the elevated levels of ghrelin and GH are likely an important means of maintaining euglycemia [47] and mobilizing fat stores [48] in states of under-nutrition. Therefore, the GH resistance state is likely an adaptive response to chronic nutritional deprivation.

IGF-I has important bone anabolic effects and therefore the low levels of IGF-I are a significant contributor to the low bone mass in AN. IGF-I acts as a chemotactic factor that induces osteoblast recruitment [49] and has been shown to stimulate DNA synthesis and increase bone collagen content in cultured rat calvaria [50]. In women with AN, IGF-I levels have also been positively associated with BMD [51]. Therefore, whether recombinant human (rh)IGF-I has effects on bone turnover and BMD in girls and women with AN is an important area of investigation. Two studies have shown that treatment with rhIGF-I results in increased levels of bone formation markers in both girls and women with AN [24, 52, 53]. Treatment with rhIGF-I in combination with an oral contraceptive pill also resulted in a 1.8% increase in lumbar spine BMD in women with AN [24], further supporting the hypothesis that decreased IGF-I levels contribute to the decreased bone mass in AN.

Potential mediators of GH resistance

**FGF-21:** FGF-21 is a hormone produced in the liver [54] and adipocytes [55] and may be a mediator of GH resistance in AN. Similar to women with AN, FGF-21 transgenic mice weigh less and have a lower core body temperature than wild-type littermates [56, 57]. FGF-21 transgenic mice also have elevated levels of GH coupled with low IGF-I levels and are therefore GH resistant [58]. FGF-21 is thought to induce GH resistance by reducing STAT5 levels – a transcription factor important in mediating GH signaling [58]. FGF-21 levels have been shown to be higher in adolescent girls with AN as compared to normal-weight girls after controlling for % body fat and insulin resistance -- two factors which may affect FGF-21 levels [59]. There was also a positive correlation between GH-area-under-the-curve and FGF-21 levels and an inverse association between IGF-I and FGF-21 in girls with elevated FGF-21 levels [59], suggesting that FGF-21 may play a role in mediating GH resistance in AN. Similar to individuals with AN, FGF-21 transgenic mice also have profound bone loss due to uncoupling of bone formation and bone resorption [60]. Histomorphometric studies demonstrate that FGF-21 transgenic mice, as well as mice treated with pharmacologic doses of FGF-21, have increased osteoclast number and surface, lower osteoblast number and surface and increased marrow adipocyte number and area [20]. The phenotype of bone loss coupled with increased marrow adipose tissue is one observed in women with AN as well [61]. Whether FGF-21, independent of its contribution to the GH resistance state, plays a role in the bone loss in AN is an area of active investigation.
**SIRT1:** Sirtuin 1 (SIRT1) may also play a role in mediating GH resistance in states of under-nutrition. SIRT1 is a histone deacetylase which promotes fatty acid oxidation and gluconeogenesis during states of nutrient deprivation [62]. SIRT1, like FGF-21, may mediate GH resistance by reducing STAT5 phosphorylation [63]. SIRT1 knockdown mice have higher GH-dependent increases in IGF-I compared to wild-type mice during a 48hr fast, suggesting that SIRT1 may be an important mediator of fasting-induced GH resistance [63].

**Ghrelin:** Ghrelin also contributes to the GH resistance state in AN. Ghrelin is an orexigenic hormone secreted by cells in the fundus of the stomach which decreases after food intake. Compared to normal-weight controls, ghrelin levels are higher in AN [44–46] and decrease after weight gain [44]. Because ghrelin induces GH secretion, the higher ghrelin levels in AN result in higher GH levels, thereby contributing to the state of GH resistance.

Ghrelin has been shown to stimulate bone formation in both *in vitro* and in animal models. The ghrelin receptor is found in rat osteoblast-like cells and a dose-dependent increase in osteoblast-like cells is observed after treatment with ghrelin [64]. In a rodent model, administration of ghrelin also results in increases in BMD [64]. In normal-weight adolescent girls, there is a positive association between ghrelin and BMD but this same relationship is not observed in adolescent girls with AN [65]. In adolescent girls with AN, the opposite relationship is observed -- ghrelin and BMD are inversely correlated [66]. Therefore, AN appears to be a state of ghrelin resistance, as the appetite-stimulating effects and the potential bone formation effects observed in normal-weight individuals are not observed in individuals with AN.

**Insulin:** Low insulin levels are also a characteristic finding in AN and may contribute to the state of GH resistance. *In vitro*, there is up-regulation of the GH receptor by insulin [67] and *in vivo*, GH receptor expression is decreased in hypoinsulinemic states and increases with insulin treatment [68]. Therefore low insulin levels may be a mediator of the GH resistance characteristic of AN.

**Alterations in adrenal hormone levels**

**DHEA:** Levels of two adrenal hormones -- the adrenal androgen precursor, dehydroepiandrosterone (DHEA), and cortisol -- are altered in AN. DHEA levels are low in AN compared to healthy controls [69] and these low DHEA levels are a predictor of decreased BMD [28] and increased bone resorption [70]. Therefore, it has been hypothesized that DHEA replacement may have beneficial effects on bone mass in AN. Two randomized, placebo-controlled studies have investigated the effects of DHEA replacement in girls and women with AN. One year of DHEA replacement did not lead to improvements in BMD compared to placebo [71], whereas 18 months of DHEA coupled with oral contraceptives resulted in maintenance of BMD in girls and women with AN [72]. Therefore, these studies suggest that while low DHEA levels are associated with low BMD, other factors appear to play a more significant role in the low bone mass state of AN.
**Cortisol:** Cortisol levels are often high in girls and women with AN [73–75]. These increased levels are likely due to a number of factors including 1) decreased metabolic clearance of cortisol [73]; 2) the activation of a stress response pathway by chronic under-nutrition; and 3) the important role of cortisol in potentially maintaining euglycemia by activation of a counter-regulatory response pathway [76]. Importantly, cortisol levels may contribute to the low bone mass in AN; cortisol levels have been inversely associated with both markers of bone formation and bone mass in AN. In adolescent girls with AN, elevated cortisol levels are associated with lower levels of two markers of bone formation -- osteocalcin and C-terminal propeptide Type 1 procollagen [74]. In adult women with AN, both urinary cortisol and elevated overnight pooled cortisol levels are associated with decreased BMD [22, 75]. Elevated cortisol levels likely contribute to the decreased bone mass in AN through a number of mechanisms. First, cortisol decreases calcium absorption in the intestine [77]. Second, elevated cortisol levels may decrease bone formation both by decreasing osteoblast proliferation [78] and inhibiting GH secretion, thereby decreasing IGF-I synthesis at the level of the bone [79]. Lastly, cortisol may also increase bone resorption indirectly, both by decreasing gonadotropin secretion [80] and by increasing PTH receptor expression on osteoblasts [81].

**Non-thyroidal illness syndrome:** In AN, a state of chronic under-nutrition, there is a survival advantage to utilizing as little energy as possible and many of the hormonal alterations discussed thus far, including hypogonadotropic hypogonadism and GH resistance, minimize energy expenditure. Women with AN also have abnormal thyroid hormone levels and these abnormal levels are consistent with the drive to decrease energy utilization. Non-thyroidal illness syndrome, previously called the euthyroid-sick syndrome is a characteristic finding in AN. T4 and T3 levels are low or low-normal in AN coupled with normal thyroid stimulating hormone (TSH) levels and elevated reverse T3 levels [82–85] and the low T3 levels are due, in part, to decreased peripheral conversion of T4 to T3 [82, 83]. Importantly, T3 levels increase with weight recovery [86, 87] and are associated with increases in resting energy expenditure [88], suggesting that the low T3 levels help minimize energy expenditure in states of under-nutrition.

Although bone loss is typically associated with hyperthyroid states [89], it is possible that the low levels of T4 and T3 in AN also contribute to decreased bone mass. Thyroid hormone receptors have been found on osteoblasts [90] and like women with AN, thyroid hormone receptor knockout mice have decreased trabecular BMD and high levels of marrow fat [61, 91]. IGF-I levels also increase after treatment of hypothyroidism and IGF-I is an important potential stimulator of bone formation [92]. Despite this evidence suggesting that low levels of thyroid hormone may contribute to the low bone mass, whether this is actually the case in individuals with AN remains controversial and importantly, the low levels of T3 and T4 are an adaptive and protective response in a state of chronic under-nutrition and therefore should not be treated.

**Elevated Peptide YY levels:** Peptide YY (PYY) is an anorexigenic hormone secreted by cells in the intestine, which is elevated in girls and women with AN [93, 94]. Because levels are elevated levels in AN, when a predictive adaptive response would be lower levels, it has
been hypothesized that PYY may be a pathophysiologic contributor to this disease. Elevated levels of PYY may also contribute to the low bone mass in AN. Animal models suggest that PYY may be a negative regulator of bone formation -- mice that are deficient in PYY’s receptor, the Y2 receptor, have increased trabecular bone parameters [95]. Similarly, PYY is negatively associated with BMD in girls and women with AN [66, 94] and therefore this hormone may contribute to both the decreased nutrient intake and loss of bone mass in AN.

**Adiponectin:** Adiponectin is a hormone secreted by adipocytes, but levels are lower in obese individuals as compared to normal-weight individuals. In AN, levels of adiponectin have been reported to be higher, lower and similar to normal-weight individuals [96–98] but importantly, adiponectin levels are higher in AN after controlling for fat-mass [96] and adiponectin isoform levels have also been shown to differ in AN as compared to healthy controls [99]. These relatively elevated levels of adiponectin may contribute to the loss of bone mass in AN. BMD has been shown to be inversely associated with adiponectin levels in adolescent girls with AN [96]. In animal models, eight-week old adiponectin transgenic mice have significantly lower bone mineral content at the femur and decreased measures of femoral strength [100]. Adiponectin both increases levels of RANK-ligand -- an osteoclast activator -- and decreases levels of osteoprotegrin – a RANK-ligand decoy receptor which inhibits RANK-ligand’s osteoclast-activating effects, thereby suggesting a mechanism by which adiponectin may contribute to the decreased bone mass in AN.

**Oxytocin:** Oxytocin is a hormone produced in the hypothalamus and stored and released by the posterior pituitary gland. Oxytocin’s primary role is to facilitate uterine contractions during childbirth and to promote milk ejection during lactation, but this hormone may also play a role in appetite regulation [101, 102] and bone mass [103]. In animal models, deletion of oxytocin or the oxytocin receptor results in decreased bone formation and osteoporosis [104], and in ovariectomized mice, treatment with subcutaneous oxytocin increases trabecular bone volume fraction and trabecular number [105]. In women with AN, pooled overnight serum levels of oxytocin are lower as compared to normal-weight controls and these lower levels of oxytocin are associated with decreased spine BMD [106]. Therefore, low levels of oxytocin may potentially contribute to the low bone mass in AN.

**Sclerostin:** Sclerostin is a protein secreted by osteocytes and a negative regulator of bone formation via Wnt signaling inhibition. In animal models, inhibition of sclerostin with a monoclonal antibody results in increased bone mass and bone strength [107] and recently, in a population of postmenopausal women, 12 months of treatment with a sclerostin monoclonal antibody significantly increased bone mineral density at the spine and hip [108]. Sclerostin levels have been shown to be significantly higher in young women with AN as compared to normal-weight controls [109], although serum sclerostin levels do not appear to mediate increases in BMD in girls and women with AN in response to treatment with transdermal, physiologic estrogen replacement [110] or teriparatide [111]. Whether sclerostin is an important contributor to the low bone mass in AN and whether treatment with a sclerostin monoclonal antibody will increase BMD in this population remains to be seen.
Other factors associated with decreased BMD in AN

**Marrow fat**—Despite having low levels of subcutaneous and visceral adipose tissue, women with AN have elevated levels of marrow adipose tissue [61]. Marrow adipose tissue has been associated with markers of decreased bone integrity [112] and in AN, as well as in healthy individuals, marrow adipose tissue is inversely associated with BMD [61, 113–116]. Importantly, there are a number of examples where marrow adiposity and BMD are not inversely associated. For example, during puberty both bone mass and marrow adipose tissue increase. Similarly, HIV is a disease state in which both BMD and marrow adipose tissue are decreased [117]. Whether increased levels of marrow adipose tissue directly contribute to the decreased BMD or bone strength in AN is currently an active area of investigation.

**Treating the low bone mass in AN (Table 2)**

Only approximately 50% of women with AN recover even many years after their initial diagnosis [5] and because the annual rate of bone loss is ~2.4% at the hip and -2.6% at the spine in those who remain low weight and amenorrheic [13], finding a treatment for the bone loss associated with this disease is critically important. In women who do recover from AN, bone mass has been shown to increase. Recovery from AN involves both weight gain and recovery of the hypothalamic-pituitary-ovarian axis, and in women who successfully regain weight and recover their menses, the mean annual rate of increase is 3.1% at the posterior-anterior spine and 1.8% at the hip [13]. Importantly, although recovery from the disease may lead to an increase in bone mass, because AN most commonly begins during adolescence, individuals with AN may still have BMD values below what they may have achieved had they not developed the disease during a period critical for skeletal acquisition. Fracture risk also remains elevated in this population, as demonstrated by a retrospective cohort study performed in Rochester, Minnesota [11]. The cumulative incidence of fracture was found to be 57% forty years after the diagnosis of AN, suggesting that even in individuals who do recover from AN, the failure to achieve peak bone mass is an important predictor of future fracture risk [11].

As previously discussed, a number of treatments have been found to be effective in maintaining or improving BMD in AN including physiologic transdermal estrogen replacement in adolescents, which increases spine BMD by approximately 2.6% after 18 months of treatment [25]; DHEA combined with oral contraceptives, which maintains BMD in girls and women with AN [72]; and in adult women, IGF-I in combination with oral contraceptives, which after 9 months increases spine BMD by 1.8% [24]; and treatment with a bisphosphonate, which increased spine and hip BMD by 2–4% after 12 months of treatment [29]. Recently, the effect of teriparatide -- an anabolic agent which is approved for the treatment of osteoporosis in postmenopausal women -- has been reported in women with AN. In a randomized, placebo-controlled trial of women with AN and osteoporosis, teriparatide increased lumbar spine BMD by 6% and lateral spine BMD by 10% after only 6 months of treatment [111]; this is the greatest reported increase in BMD to date in a treatment trial of women with AN. Importantly, it is not known what happens to the BMD gains in this population once teriparatide is stopped, effects of a longer duration of therapy...
and effects on bone microarchitecture and strength. Therefore, further studies will be necessary to further evaluate the effects of teriparatide and other treatments in AN.

Conclusions

AN is a psychiatric disorder characterized by chronic undernutrition. There are a number of hormonal alterations which occur in order to minimize energy expenditure in this state of nutritional deprivation. The hormonal alterations, which include GH resistance, hypogonadotropic hypogonadism, hypercortisolemia, and the non-thyroidal illness syndrome, not only decrease energy expenditure in AN but also contribute to loss of established bone mass. Importantly, AN is not only associated with a loss of bone mass but also a significant increased risk of fracture [10, 11]. As AN is a chronic disease from which only approximately 50% of women recover even many years after their initial diagnosis, it will be important to find effective treatments to increase bone mass and minimize fracture risk. There are currently no approved treatments for the bone loss associated with AN or the decreased bone mass accrual in adolescents with this disorder although a number of treatments have been investigated. The most effective treatment to date in adults has been teriparatide, an anabolic agent, which increased spine BMD by 6–10% after 6 months of treatment [111]. A number of other treatments have also been found to be beneficial including physiologic estrogen replacement in adolescents, bisphosphonates, which increase BMD by 4% and the combination of recombinant human IGF-I and oral contraceptives in adults which increase BMD by 1.8%. Importantly, we do not know the effect of these treatments on fracture risk and therefore further studies will be necessary to better understand the pathophysiology of low bone mass in AN and to further investigate potential treatment options for this major co-morbid condition.

Acknowledgments

Sources of support: K23 DK094820 (Fazeli) and R24 DK092759 (Klibanski)

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Highlights

• Anorexia nervosa is associated with significant bone loss and an increased risk of fracture

• The bone loss in anorexia nervosa is a result of hormonal adaptations to a state of chronic under-nutrition

• There are a number of therapeutic strategies, currently under investigation, that may be effective in reducing anorexia nervosa-associated bone loss
Table 1

Hormonal alterations in anorexia nervosa and their potential effect on bone mass

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Table 2
Treatments that have shown efficacy in the treatment of low bone mineral density in anorexia nervosa

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