

# Impaired bone health in anorexia nervosa

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Anorexia nervosa (AN), a condition of malnutrition, has a multitude of effects, including low bone mineral density (BMD). Much has been discovered over the last couple of decades regarding the extent and pathophysiology of low BMD in AN, including the role of gonadal steroids, neuroendocrine hormones and appetite-regulating peptides. The effects of AN on bone are particularly concerning in adolescents, who are in the process of accruing peak bone mass, and decreased rates of bone-mass accrual in these critical years are predictive of poor bone health in later life. Although dual-energy x-ray absorptiometry continues to be the standard technique for monitoring BMD, newer techniques such as quantitative computed tomography and calcaneal ultrasound are being explored. Weight and menses recovery continue to be the most effective treatment for improving BMD in AN. Further research is needed to translate the pathophysiology being unraveled into clinical applications for improving BMD in AN.

Anorexia nervosa (AN) is a burgeoning condition affecting adolescents and adults of both genders all over the world, and its prevalence has increased over the last few decades, particularly in the industrialized world [1–3]. The lifetime prevalence of AN, as defined by DSM-IV criteria [4], is reported to be as high as 2.2% in all women [5]. It occurs in 0.2–1.0% of adolescent girls and 1.0–4.0% of college-aged young women [3]. This condition of severe malnutrition has a multitude of effects on the body and the mind. In this review, we will focus on the impact of AN on bone-mass accrual as well as bone mineral density (BMD).

Low BMD is characteristic of AN, and is associated with an increased risk for fractures [6–8], which persists for more than 10 years after diagnosis [8]. Osteoporosis (bone density T score:  $\leq -2.5$  SD in adults) can persist despite restoration of weight [9] and has been reported in up to 38% of adult AN patients [10]. Osteopenia (T score:  $-2.5$  SD– $-1.0$  SD) is even more common, and has been reported in up to 92% of adult AN patients [10–14]. Given data in postmenopausal women that indicate a doubling of fracture risk with each 1 SD decrease in BMD [15], these numbers are of some concern, even with the understanding that data from postmenopausal women may not strictly apply to younger populations, and fracture risk is lower in younger women with low BMD [16]. This is particularly so given recent indication of altered bone microarchitecture in adults with AN [17]. Also very concerning are emerging data regarding BMD in adolescent girls with AN. We have

demonstrated that 41% of teenagers with AN have BMD more than 1 SD below the mean for their age and gender at any site, and an additional 11% have BMD more than 2 SD below the mean. Moreover, a third of these girls report a recent history of low-impact fractures [18]. Given that the adolescent years are critical for increasing bone mass towards achievement of peak bone mass, these data are concerning as an inability to optimize peak bone mass when AN occurs in the adolescent years may have implications for bone health in later life.

Most of the current knowledge of the effect of AN on bone stems from research in adult women and, increasingly, in adolescents with AN. Importantly, there is a paucity of information in males with AN, who constitute 5–15% of patients with this condition [19]. In addition, the key outcome variable for both clinicians and researchers is bone fragility, which depends not only on BMD but also on factors such as bone microarchitecture and strength. Measurement of BMD is only one measurement of fracture risk. Whereas many studies have examined BMD in AN populations using dual-energy x-ray absorptiometry (DXA), there are few data regarding measures of bone microarchitecture and bone strength in AN.

## Adolescence: a critical time for optimizing bone health

Adolescence is characterized by marked increases in bone-mass accrual [20–22], with maximal increases in bone mass occurring between 11 and 14 years in girls and 13 and 16 years in boys [23].

**Keywords:** anorexia nervosa, bone mineral density, cortisol, estrogen, fracture, growth hormone, hypogonadism, IGF-1, leptin, osteoporosis

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Almost 25% of peak bone mass is formed in the 2 years surrounding peak height velocity, and 90% is achieved by the time an individual is 18 years old [22]. Low bone density occurring at this time of life is of immense concern given the narrow time window within which these increases in bone mass occur, and because complete 'catch up' with weight recovery may not be possible within this 'window', resulting in residual deficits in bone mass that persist into adult life [9]. AN, which often begins in adolescence, can therefore have a profound impact on bone health, leading to permanent deficits.

#### Effects of AN on bone metabolism

##### *Extent of low BMD in AN*

Low BMD occurs in AN irrespective of age, increasing the lifelong risk of morbidity from fractures. Varying degrees of reduction in bone mass have been consistently reported in adolescent girls [18,24–26] and adult women [10,12–14,27] with this disorder. Bachrach *et al.* demonstrated that 12 out of 18 girls with AN had BMD more than 2 SD below that of controls at the lumbar spine, and, importantly, more than half of these 12 girls had been diagnosed with AN for less than 1 year, implying that BMD can be severely affected early on in the course of this disease [28]. We have reported, in a more recent study from our group, that 41% of 60 adolescent girls with AN had BMD Z scores of less than -1 at one or more sites, and 11% had Z scores of less than -2 [18]. Several other studies have reiterated this negative impact of AN on BMD during the adolescent years [24,29–33]. Boys with AN also have low BMD, and Castro *et al.* reported Z scores of

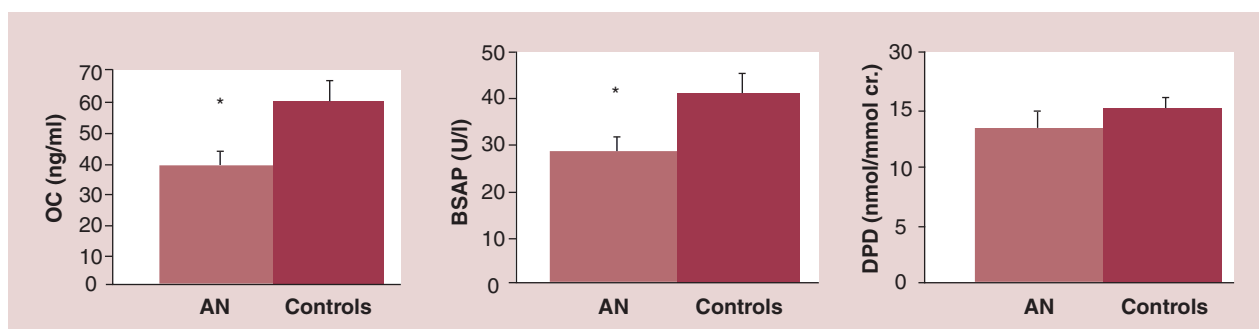
less than -1 in 35% of male adolescents with AN of more than 12 months' duration [34]. BMD in AN is negatively correlated with the duration of illness [18], and consequently, the impact of AN on bone is even more apparent in an adult population, presumably owing to longer duration of illness. Osteoporosis at one or more skeletal sites has been reported in up to 38% of adult AN patients and osteopenia has been reported in up to 92% [10–14,27]. Grinspoon *et al.* reported that the prevalence of osteopenia and osteoporosis was 50 and 13% for the anterior–posterior spine, 57 and 24% for the lateral spine, and 47 and 16% for the total hip, respectively [10]. Importantly, BMD is related to the timing of onset of AN, and women with onset of disease in adolescence have lower BMD than those with adult-onset AN, despite comparable duration of amenorrhea [35]. This finding emphasizes the importance of optimizing bone-mass accrual during the teenage years.

Lucas *et al.* showed that there is an increased fracture risk in both women and men with AN [7]. In fact, the cumulative incidence of any fracture at 40 years after the diagnosis of AN was 57%. Fractures of the hip, spine and forearm were late complications, occurring on average 38, 25 and 24 years, respectively, after diagnosis.

##### *Bone turnover in AN*

Adolescents with AN are in a state of decreased bone turnover, with a reduction in bone formation and bone resorption markers (Figure 1) [9,24]. Normal adolescence is a state of increased bone turnover from active bone modeling and remodeling processes [20], which lead to increases in

**Figure 1. Comparison of bone turnover markers in mature subjects with anorexia nervosa (n = 11) and controls (n = 15).**



Results are the mean ± SEM.

\* $p = 0.02$ .

AN: Anorexia nervosa; BSAP: Bone-specific alkaline phosphatase; cr.: Creatinine; DPD: Deoxypyridinoline; OC: Osteocalcin. Adapted from [24]. © 1999. The Endocrine Society.

long-bone width and thickness, both of which are critical for optimizing bone strength. The state of decreased bone turnover in adolescents with AN is worrisome and suggests reduced rates of bone modeling and remodeling, and, consistent with this concern, we have recently demonstrated that low whole-body BMD in adolescents with AN is a consequence of ‘thin’ bones, with decreased bone area for height as compared with controls, which is suggestive of impaired bone modeling/remodeling rates [36]. By contrast, low BMD in adults with AN is associated with an uncoupling of bone turnover, such that markers of bone formation are significantly decreased and markers of bone resorption are increased in comparison to healthy adults [37,38].

#### *Longitudinal changes in BMD in AN*

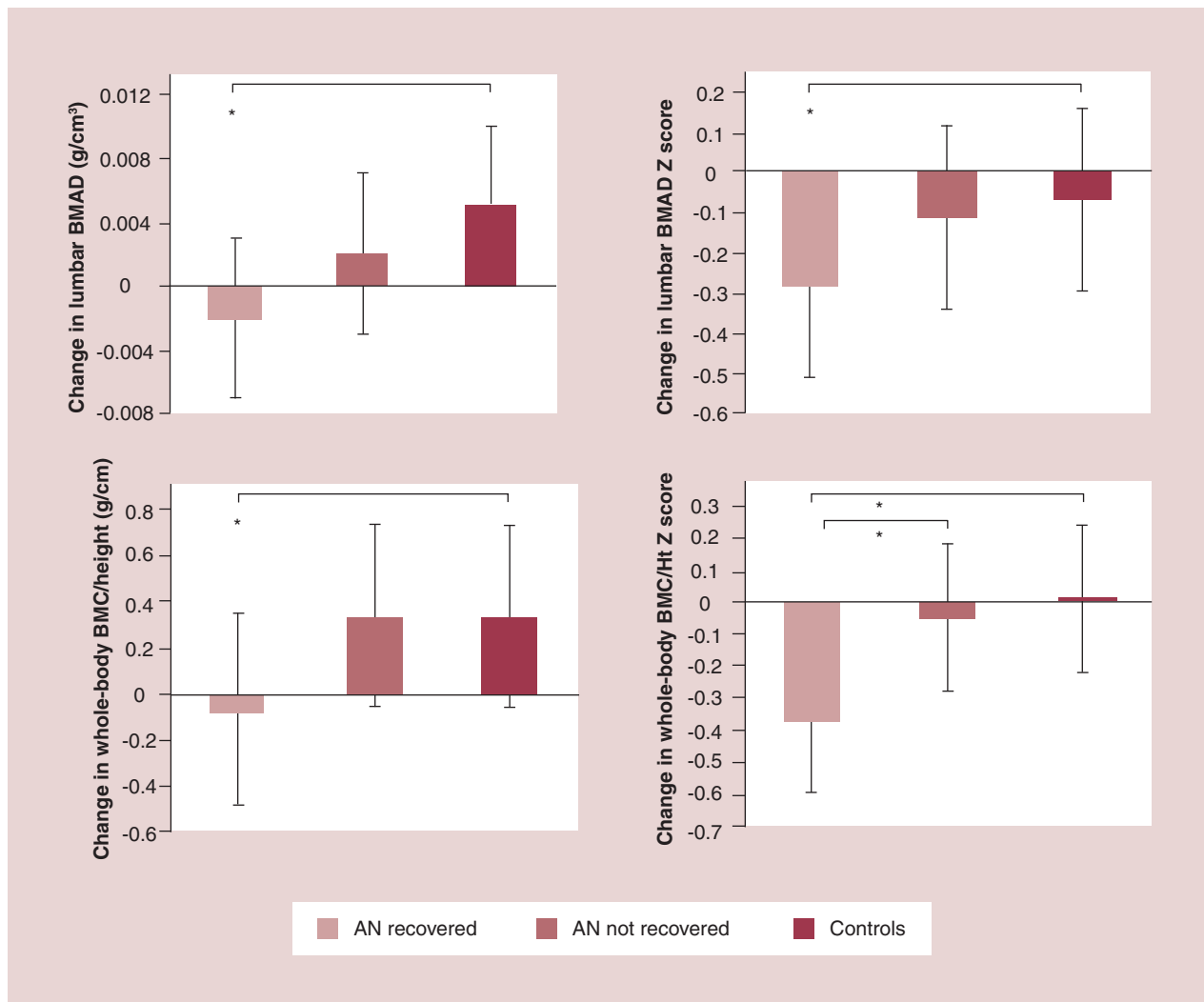
Many investigators have now examined the longitudinal impact of AN on bone. In a study of adolescents with AN, Bachrach *et al.* demonstrated that weight rehabilitation resulted in an increase in bone mineral even before the return of menses [39]. However, low BMD persisted after recovery, indicating that deficits in bone mineral acquired during adolescence may not be completely reversible. Consistent with these data, Soyka *et al.* demonstrated that despite recovery over 1 year, poor bone-mineral accrual persists in adolescent girls with AN, in contrast to the rapid bone-mass accrual observed in healthy girls [9]. Similar results were reported by Heer *et al.* [40], and in a longer follow-up study of the same patients over a period of 2 years, the authors reported that weight rehabilitation resulted in a restoration of bone-formation activity [30]. However, BMD did not increase. An ‘adolescent’ pattern of bone turnover markers was reported in patients at the end of the study, with high levels of both bone formation and resorption markers, similar to the pattern observed in healthy controls at study initiation. This suggests that eventually, and with sustained weight recovery, some ‘catch up’ in bone-mineral accrual may be possible. We have recently demonstrated that there is a stabilization of BMD measures in girls with AN with weight gain and menses recovery, even though BMD does not normalize, in contrast to continued decreases in these measures in nonrecovered girls (Figure 2) [36]. We have also previously reported an increase in bone turnover markers with weight recovery (Figure 3), and have shown that increases in bone formation markers precede increases in bone mass [9]. Similar data were reported in a

cross-sectional study by Audi *et al.* in which BMD Z scores were progressively higher in adolescent and young adult women with AN who were weight recovered without resumption of menses followed by women who were weight recovered with resumption of menses [41]. Therefore, it is critical to emphasize the importance of recovery in AN, and to work towards increases in weight and resumption of menses.

In adults with AN, Viapiana *et al.* demonstrated significant increases in BMD at the spine and hip following weight gain [42]. Similarly, in a study involving 75 women aged 18–40 years with AN (mean age: 24 years), our group reported that bone loss occurred at a rate as high as 2.5% per year [43]. Women who did not gain weight or recover menses had a mean annual decline in BMD of 2.6% at the spine and 2.4% at the hip, and, by contrast, AN women who gained weight and recovered menses had a mean annual increase in BMD of 3.1 and 1.8%, respectively, at these sites. Menses recovery was associated with an increase in BMD at the spine but not the hip, independent of weight gain, whereas weight gain regardless of menstrual recovery was associated with a mean increase in BMD of the hip, but not the spine. An increase in fat-free mass (rather than an increase in weight or fat mass) was the most significant determinant of increases in BMD. Importantly, Hotta *et al.* demonstrated that even short-term improvement in nutritional status is associated with an increase in bone formation markers in adult women with AN [37]. This is likely to be even more marked, with sustained increases in weight and resumption of menses. In fact, Dominguez *et al.* have demonstrated that weight gain is associated with an increase in bone formation and bone resorption markers, whereas subsequent menses recovery is associated with a decrease in markers of bone resorption [44]. Therefore, improvements in weight and reproductive function are both necessary for skeletal recovery in women with AN, with spinal BMD recovery being positively influenced by menstrual recovery and hip BMD by weight gain.

Bass *et al.* reported near normalization of lumbar spine BMD in young women with osteopenia recovered from adolescent-onset AN after approximately 4 years of follow-up [45]. The improvement in BMD was noted after 2.7 years. However, the mean lumbar BMD Z score after 4 years was still only -0.4 (range: -0.9–0.1). Further research is required to determine the long-term effects of weight and menstrual recovery in AN.

**Figure 2. Change in lumbar spine bone mineral apparent density and whole-body bone mineral content/height measures in adolescent girls with anorexia nervosa who had not recovered menses or gained weight, those who had recovered menses and gained weight, and healthy adolescents.**



AN not recovered continued to lose bone mass over the 1-year follow-up period, and change in bone density measures was significantly different in this group compared with the increases in bone density in controls. AN recovered did not differ from controls (healthy adolescents) for change in bone density parameters, and differed significantly from AN not recovered for change in whole-body bone density Z scores.

\*p < 0.05.

AN not recovered: Girls with anorexia nervosa who had not recovered menses or gained weight; AN recovered: Girls with anorexia nervosa who had recovered menses and gained weight; BMAD: Bone mineral apparent density; BMC: Bone mineral content.

Adapted from [36]. © 2008. The Endocrine Society.

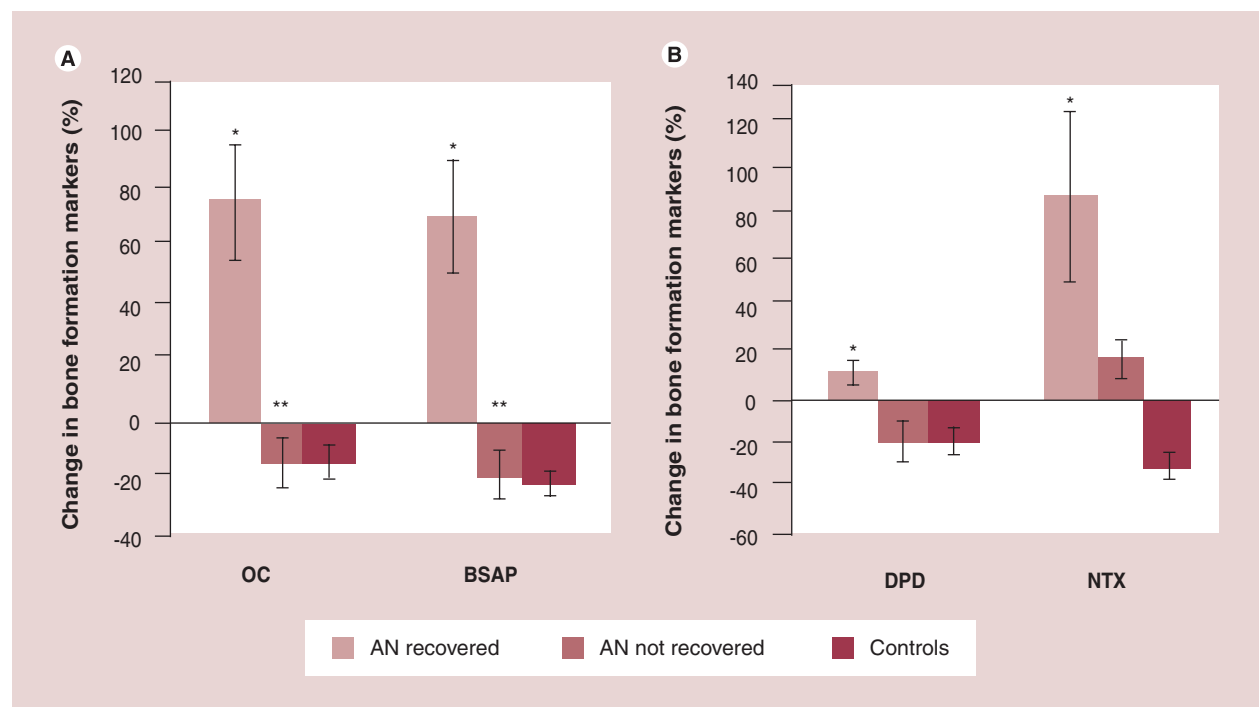
### Pathogenesis of low bone density in AN

An understanding of the mechanisms that result in low BMD in AN is essential in order to develop therapeutic strategies to optimize BMD. The etiology of low BMD in AN is multifactorial (Figure 4), and as research progresses, newer factors that contribute to this process are gradually coming to light.

### Nutritional factors

Currently recognized nutritional factors that predict BMD include BMI [25,46–50], lean mass [9,18,24,51,52] and fat mass [18,51,52]. Grinspoon *et al.* [47] showed that lean body mass, independent of the duration and severity of estrogen deficiency, is an important predictor of bone loss among women with AN. This was

**Figure 3. Percentage change in markers of bone formation and bone resorption over 1 year in adolescent girls with anorexia nervosa and healthy adolescents.**



**(A)** Bone formation markers; **(B)** bone resorption markers. Percentage changes in levels of OC and BSAP were significantly higher in AN recovered than in AN not recovered ( $p = 0.03$  for OC;  $p = 0.0007$  for BSAP) and controls ( $p = 0.0003$  for OC;  $p < 0.0001$  for BSAP). Percentage changes in levels of markers of bone resorption (DPD and NTX) were significantly higher in AN recovered than in controls ( $p = 0.02$  for DPD;  $p = 0.002$  for NTX).

\*Significantly different from healthy controls.

\*\*Significantly different from AN recovered.

AN not recovered: Girls with anorexia nervosa who were not weight recovered; AN recovered: Girls with anorexia nervosa who were weight recovered; BSAP: Bone-specific alkaline phosphatase; DPD: Deoxypyridinoline; NTX: *N*-telopeptide of type 1 collagen; OC: Osteocalcin.

Adapted from [9]. © 2002. The Endocrine Society.

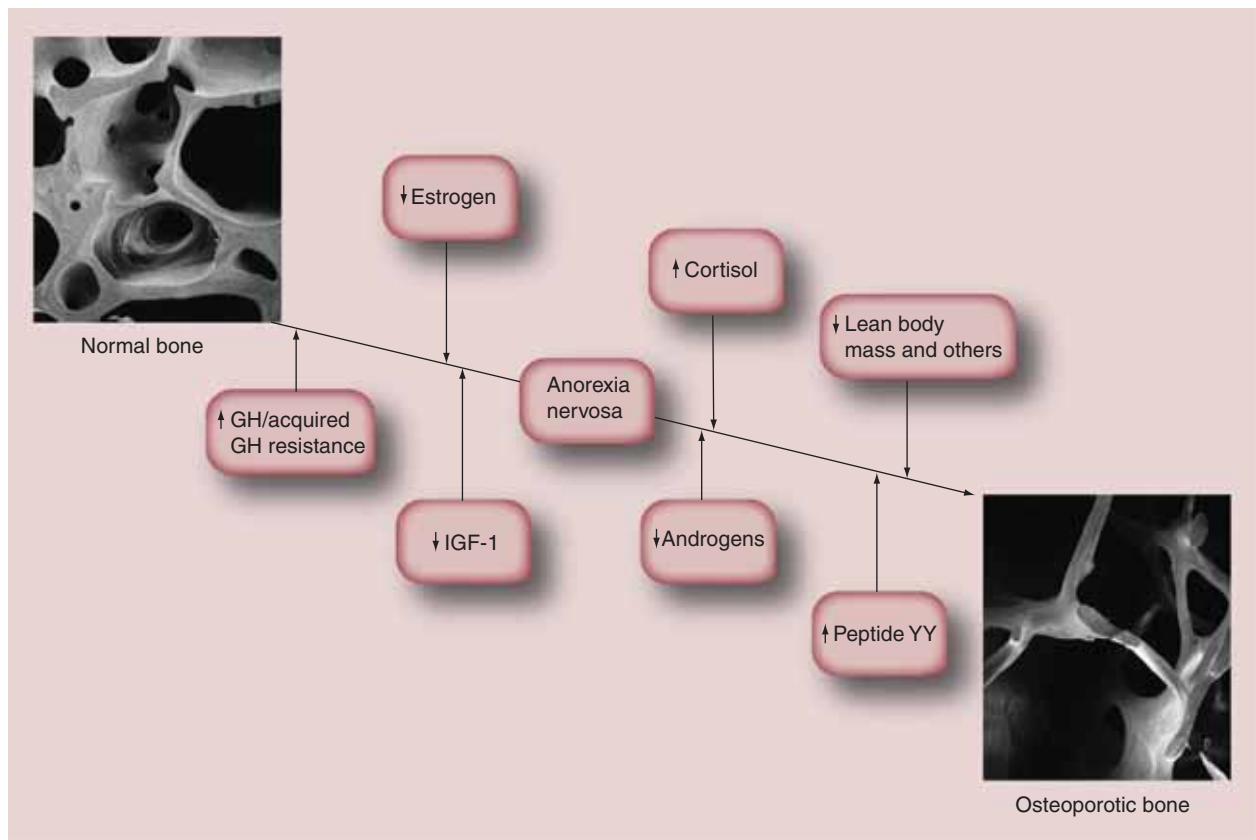
further corroborated by Soyka *et al.* [9], who showed that change in lean body mass, specifically, was a major determinant of change in total and lumbar BMD in girls with AN, as well as in healthy controls (Figure 5) [9]. The impact of lean body mass on BMD has been attributed to the pull of muscle on bone exerting an effect on osteocytes, which function as a 'mechanostat' and stimulate remodeling.

#### *Nutritionally acquired resistance to growth hormone & low IGF-1 levels*

Early puberty is characterized by rising levels of growth hormone (GH) and IGF-1, bone trophic factors that peak at mid-puberty. GH has direct stimulatory effects on the differentiation and proliferation of osteoblast precursors, and also acts indirectly through IGF-1 to stimulate the

differentiation of these precursors [50,53]. In AN, levels of IGF-1 are low and are associated with high concentrations of GH, indicating a state of GH 'resistance' [54], such that GH is unable to stimulate IGF-1 secretion by the liver. In addition, Misra *et al.* demonstrated that GH concentrations predict markers of bone turnover in healthy controls but not in AN, suggesting resistance to the effects of GH not only at the level of the liver, but also at the level of bone [54]. Levels of IGF-1 are very low in girls with AN [18], another possible cause of the low bone density. Soyka *et al.* reported a positive correlation of IGF-1 levels with bone formation markers in mature adolescents with AN [24]. Thus, functional resistance to the effects of GH and low levels of IGF-1, both crucial bone anabolic hormones, are important contributors to low BMD in AN.

Figure 4. Contributing factors to low bone density in anorexia nervosa.



GH: Growth hormone.

Adapted from [124] with permission from the American Society for Bone and Mineral Research.

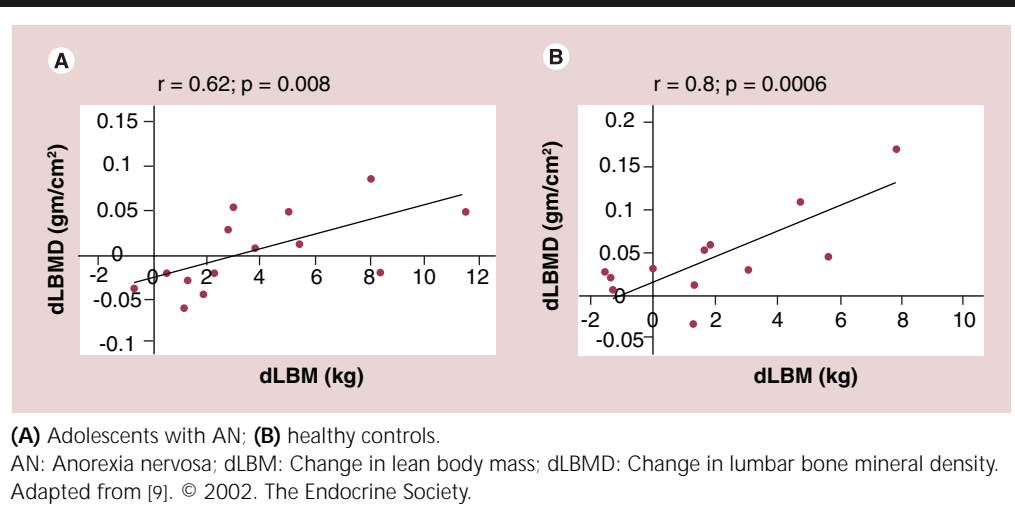
### Hypogonadism

Estrogen impacts bone-mass accrual in two important ways in adolescence. Gradually rising levels of estrogen in early adolescence stimulate increases in levels of GH and IGF-1 and increases in bone formation, and higher levels of estrogen in late adolescence result in a decrease in bone resorption. In adults, normal estradiol levels are important for maintenance of bone mass. AN is characterized by hypogonadism and low levels of estrogen [9,18] and androgens [9,55]. Estradiol levels in AN are predicted by nutritional status [18], and an improvement in nutritional status should therefore result in an increase in estradiol levels and in BMD. Importantly, administration of oral estrogen did not improve BMD in adult women or in adolescents with AN [56,57], suggesting that hypogonadism does not completely account for the extent of low BMD in AN. Of importance, we have demonstrated, in a recent study, the significance of menstrual recovery in addition to weight gain in stabilizing BMD measures [36].

The antiresorptive effects of estrogen on bone are mediated by the osteoprotegerin (OPG) RANK–RANKL system and by various pro-inflammatory cytokines. Estrogen increases OPG secretion by osteoblasts, which acts as a decoy receptor for RANKL, preventing its binding to RANK, thus inhibiting osteoclast differentiation and activation and stimulating osteoclast apoptosis. Estrogen also decreases the secretion of pro-inflammatory cytokines by macrophages and monocytes, leading to similar effects on osteoclasts. Hypogonadism in AN would thus be expected to be associated with low OPG levels and high levels of pro-inflammatory cytokines, such as IL-1, IL-6 and TNF- $\alpha$ . However, we have reported higher serum OPG levels in adolescent girls with AN compared with controls, and that OPG values inversely predict lumbar BMD Z scores as well as markers of nutritional status, suggesting a possible compensatory response to the bone loss seen in AN [58]. By contrast, high IL-6 levels in girls with AN [59] may be a consequence of hypogonadism, and may contribute to low BMD.



**Figure 5. Correlation between change in lean body mass and change in lumbar bone mineral density over 1 year in adolescents with anorexia nervosa and healthy controls.**



Levels of androgens are also reduced in AN [9,55,60–62], and may contribute to low BMD. Gordon *et al.* reported that dehydroepiandrosterone sulfate (DHEAS) levels were reduced in young women with AN and correlated inversely with markers of bone resorption [63]. By contrast, other studies have reported no differences in DHEAS levels in adult women [55] and adolescents [9] with AN compared with controls. Studies in adolescents [9] and adults [55] with AN have demonstrated that low testosterone levels predict BMD and fat-free mass.

#### Cortisol in AN

Hypercortisolemia is detrimental to bone, through both direct effects and effects on other bone anabolic hormones such as GH and IGF-1. Cortisol suppresses bone formation by inhibiting the replication, differentiation and function of osteoblasts and inducing the apoptosis of mature osteoblasts and osteocytes. An early phase of increased bone resorption, probably a result of the increased expression of RANKL and decreased expression of OPG, both promoting osteoclastogenesis [64,65], is usually followed by a more chronic state of decreased bone resorption resulting from a loss of cell signaling to osteoclast progenitors [66]. In addition, cortisol inhibits renal tubular calcium reabsorption and calcium absorption from the GI tract [67]. Glucocorticoids also decrease the secretion of GH [68]. Excess cortisol has been consistently linked with low BMD, irrespective of the source of cortisol, be it exogenous (such as in nephrotic syndrome [69,70] and inflammatory bowel disease [71]) or endogenous (as in Cushing's syndrome [72–74]).

Elevated urinary and serum cortisol levels have been described in adult women [35,75–81] and girls with AN [73,82,83] and may also contribute to low BMD in this condition. Hypercortisolemia in AN is a consequence of increased cortisol secretory burst frequency [82] and decreased clearance [75,82]. Biller *et al.* reported inverse correlations between cortisol and bone mass in adults with AN [35], and Vergely *et al.* also reported an association between low osteocalcin levels, a marker of bone formation, and high cortisol in AN [84]. This is further corroborated by our group, which has shown that high cortisol levels in adolescent girls with AN predict a decrease in bone formation markers, suggesting that hypercortisolemia may contribute to decreased bone formation rates and low BMD [82].

#### Appetite-regulating peptides & adipocytokines

Several peptide hormones have recently been linked to bone health in AN. These include neuroendocrine gastrointestinal-derived peptides regulating food intake and certain adipocytokines [85,86].

Ghrelin is a gastric-derived orexigenic peptide and GH secretagogue, levels of which are increased in AN [87,88]. Ghrelin mRNA is expressed in cartilage [89] and ghrelin administration causes increased proliferation of osteoblasts in culture, suggesting a role for ghrelin in bone metabolism [90]. We have shown that high ghrelin levels in girls with AN predict GH and cortisol burst frequency [87,88], both of which can affect bone. In a follow-up study, we noted that

ghrelin secretion strongly predicted BMD in healthy girls, but not in girls with AN [91], possibly suggesting an inability to respond to ghrelin in AN.

Peptide YY (PYY) is an intestinally derived anorexigen that acts via the Y2 receptor of neuropeptide Y to decrease neuropeptide Y secretion and therefore inhibit food intake, and Y2 receptor deletion in rodents results in increased bone formation [92]. We have reported higher PYY levels in AN compared with healthy adolescents, a trend towards a decrease in these values with weight recovery, and inverse correlations of PYY with bone turnover markers, suggesting a possible role for high PYY in decreased bone turnover and BMD in AN [93].

Leptin is an anorexigenic adipocytokine that is low in AN [94,95]. Leptin-deficient and leptin-resistant mice are obese and hypogonadal but still have high BMD [96,97], and administration of leptin to leptin-deficient mice leads to a decrease in BMD, suggesting a negative impact of leptin on bone. Studies have shown that leptin inhibits bone formation through a hypothalamic relay [96,98], indicating a role for other neuromediators. Takeda *et al.* showed that leptin regulates bone formation via the sympathetic nervous system [98]. The group demonstrated that a  $\beta$ -adrenergic agonist decreases bone mass in leptin-deficient and wild-type mice, while a  $\beta$ -adrenergic antagonist increases bone mass in wild-type and ovariectomized mice without affecting body weight. In contrast to animal studies, a positive association between leptin and BMD has been reported in humans [99], and the relationship between leptin and bone remains under investigation. However, we have recently shown that another adipocytokine, adiponectin, contributes significantly to the variability of BMD, while insulin is an important contributor to the variability of levels of bone turnover markers in adolescents with AN [85].

#### Diagnosis of low bone density in AN

It is imperative to monitor BMD in individuals suffering from eating disorders, especially restrictive eating disorders, given the deleterious effect of AN on BMD. Several methods are available to monitor bone density, including DXA, ultrasound, quantitative computed tomography (+), metacarpal width or density from hand x-rays, and MRI. Importantly, studies are necessary that

assess bone microarchitecture and bone strength in AN given that bone fragility is a function not only of BMD, but also of these measures.

DXA is an accurate and readily available method of monitoring BMD, with the benefit of minimal radiation exposure and excellent reproducibility. Over the last decade, age- and race-specific databases for adolescent girls have been established [100,101]. One limitation is that DXA, being a 2D technique, reports areal density (bone mineral content [BMC] [gm]/cross-sectional area of bone [cm<sup>2</sup>]), rather than volumetric bone density (BMC [gm]/volume of bone [cm<sup>3</sup>]). DXA thus underestimates BMD in short people, and overestimates BMD in tall people. However, formulas are available to calculate bone mineral apparent density, a surrogate for volumetric bone density, which normalizes BMC to a derived bone reference volume [102]. As bone acquisition changes during periods of rapid skeletal growth, when bone age may differ from the chronological age in children, adjustments also have to be made based on skeletal maturity and bone age readings. In addition, DXA measurements of bone do not differentiate between low BMD from light versus thin bones. This shortcoming of DXA can be circumvented by using the Molgaard approach [103], which differentiates between reported low bone density resulting from 'short' bones (based on height Z scores) versus that resulting from 'thin' bones (based on measures of bone area for height) or 'light' bones (based on measures of BMC for bone area).

Importantly, fracture risk based on the WHO definition of osteoporosis was developed for DXA measurements at the lumbar spine, hip or forearm in postmenopausal women. These criteria for the identification of postmenopausal women at risk for osteoporosis and fractures can not be applied to other skeletal sites, to technologies other than DXA, or to adolescents and young adults with AN. A recent study did find associations between measures of BMD and fractures in children [104]. However, fracture risk predictors based on BMD measurements in children and young adults are yet to be developed.

Quantitative computed tomography provides a direct estimate of volumetric bone density, differentiates between cortical and trabecular bone, and also allows for derivation of measures of bone strength. However, because of lesser reproducibility and the risk of increased exposure to



ionizing radiation compared with DXA, use of QCT for longitudinal assessment of BMD remains largely a research tool. Peripheral QCT holds greater promise given lesser radiation exposure than axial QCT. Higher-resolution CT techniques have been used to delineate bone microarchitecture in adult women with AN, and one study reported decreased cortical thickness and trabecular number in women with AN compared with controls [17].

Calcaneal ultrasound is a new, non-invasive development in the field of bone density monitoring. Its portability, low cost and lack of exposure to ionizing radiation make it a feasible alternative to DXA and QCT. The calcaneus has a higher metabolic turnover rate than cortical bone and is more likely to show early signs reflecting altered bone metabolism. In addition, because it is made of cancellous bone similar to the spine, it could be a quick surrogate marker for lumbar spine BMD. In adults, heel ultrasound measurements have been demonstrated to correlate with DXA and predict fracture risk [105,106]. Resch *et al.* reported highly significant correlations between broadband ultrasound attenuation and BMD at the spine and the hip in adult women with AN [107]. Lum *et al.* reported moderate correlations between calcaneal ultrasound and DXA measurements of the spine, hip and total body in subjects aged 9–25 years [108]. However, studies in adolescents and young adults with AN are less promising [109]. Again, routine clinical use of this technique is contingent on development of databases and standards for children and adults.

Until age- and sex-specific databases have been established for the other methods of BMD measurement, DXA continues to be the gold standard for monitoring BMD. Because of the ongoing pathophysiology in eating disorders, serial monitoring of BMD is recommended. We recommend at least annual BMD assessment during the critical period of peak bone-mass accrual in adolescents with AN and also in adults.

#### Management of low bone density in AN

Apart from weight gain and menses recovery, no treatment thus far has been shown to effectively improve BMD in AN.

##### *Weight gain*

Soyka *et al.* showed that BMD remains low despite weight gain [9]. The group demonstrated that despite recovery over 1 year, poor bone-mineral accrual persists in adolescent girls with

AN in contrast to rapid bone-mass accrual in healthy girls. This was upheld by many subsequent studies [36,52]. However, Soyka *et al.* also showed that low levels of bone turnover markers present in girls with AN at baseline significantly increased in association with an improvement in nutritional status [9]. Specifically, increases in lean body mass and the nutritionally dependent bone growth factor IGF-1 were important predictors of increases in bone turnover markers (Figure 5). Moreover, increases in surrogate markers of bone turnover correlated with an improvement in lumbar and total BMC and BMD in the AN group. Similarly, Mika *et al.* demonstrated that weight rehabilitation leads to restoration of bone formation activity in adolescents with AN, despite no increase in BMD, in the 2 years following inpatient feeding [30]. Iketani *et al.* showed that BMD of the spine improves with weight gain, but not to the level of that in controls [26]. BMD further increased with resumption of menses. We have delineated this further in a recent study by examining the effects of weight gain and menstrual recovery on BMD in adolescent girls with AN [36]. We found that even short-term weight gain with menstrual recovery is associated with a stabilization of BMD measures (measured using the Molgaard approach [103] and adjusted for height). In the absence of menstrual recovery, whole-body parameters improved somewhat with weight gain, albeit to a lesser extent than that noted with weight gain and menstrual recovery. Importantly, there was no improvement in bone parameters at the spine solely with weight gain, reiterating the significance of gonadal steroids in optimizing trabecular BMD. These studies suggest that persistent and long-term recovery may be associated with an improvement in BMD measures, and consistent with this, Bass *et al.* reported near normalization of lumbar spine BMD in young women with osteopenia who recovered from adolescent-onset AN after a 4-year follow-up period [45].

##### *Replacement with gonadal steroids*

Given that hypogonadism is an important cause of low BMD in AN, reversal of hypogonadism should be a physiological method to improve BMD. However, use of oral contraceptives does not improve BMD in AN, as reported in multiple studies [56,57,110,111]. Of concern, in one study, there was no increase in BMD despite a mean 11.7% weight gain in women with AN receiving oral contraceptives, whereas women

not receiving these medications did have some increase in BMD [43]. This might perhaps be attributed to the IGF-1- [112,113] and androgen- [55] suppressive effects of oral estrogen administered in the relatively high doses present in birth-control pills. These data argue strongly against the prevalent practice of prescribing oral contraceptives to induce menses in AN. Transdermal estrogen has been shown to be less IGF-1 suppressive than oral estrogen [113,114], and studies are currently ongoing to explore the efficacy of transdermal estrogen in increasing BMD in adolescent girls with AN.

Subnormal levels of adrenal androgens have been reported in some [60–63], but not all [9,55], studies in AN. Gordon *et al.* demonstrated an increase in bone formation markers following 3 months of DHEA administration in young women with AN [115]. However, a subsequent randomized, controlled trial of DHEA versus hormone-replacement therapy over 1 year in young women with AN revealed no significant increase in BMD in AN after controlling for the effects of weight gain [116].

Miller *et al.* reported, in a pilot study in adult women with AN, that testosterone replacement for 3 weeks to approximate levels as those in healthy women is associated with an increase in the C-terminal propeptide of type 1 procollagen, a bone formation marker [117]. Further data are needed to determine whether testosterone administration increases bone formation and bone density in this population.

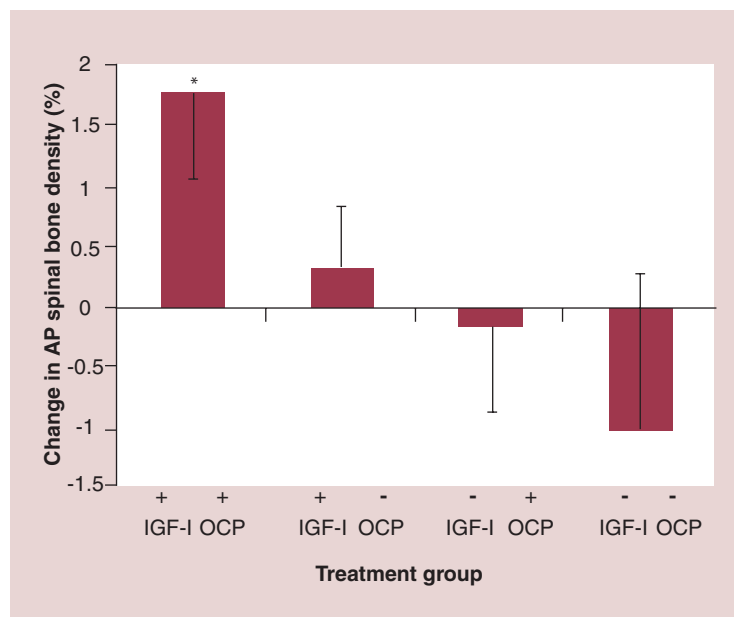
#### Recombinant human growth hormone & IGF-1

Considering the crucial role of GH and IGF-1 in bone anabolism, overcoming the body's resistance to GH in AN using supraphysiological doses of recombinant human (rh)GH, as has been performed in other conditions of GH resistance [118,119], would be expected to increase bone mass. In a recent study, Hashizume *et al.* reported that administration of high doses of rhGH to AN subjects caused increases in IGF-1 levels [120]. However, there was no report on the effect on bone turnover markers. Of importance, BMI increased in AN subjects, which could also cause increases in IGF-1, and it is unclear whether increases in IGF-1 were a consequence of increases in weight or of rhGH administration. Additional studies are needed to determine the efficacy of rhGH therapy in this population. rhIGF-1, when given with oral contraceptives, has been shown to increase BMD in adult women with AN (Figure 6) [111,121]. This is conceivably owing to a combination of the anabolic effects of IGF-1 and the antiresorptive effects of estrogen. As yet, there are no data on the use of rhIGF-1 in young girls and adolescents with AN, although pilot studies are currently underway. The restricted availability of rhIGF-1, until recently, limited research in the use of rhIGF-1 in AN.

#### Bisphosphonates

Bisphosphonates are very effective in increasing BMD in postmenopausal women by inhibiting osteoclastic bone resorption. Golden *et al.*, while reiterating that weight restoration is the most important determinant of BMD, showed a significant within-group increase in BMD of the spine and femoral neck in adolescents with AN receiving alendronate, but not in those receiving placebo [122]. However, these increases were not significant when compared with the placebo group. In an uncontrolled study in adults with AN who received risedronate, Miller *et al.* demonstrated a decrease in bone resorption and an

**Figure 6. Percent change from baseline in anterior–posterior spinal bone density in adult women with AN randomized to rhIGF-1 with OCPs, rhIGF-1 alone, OCPs alone or neither.**

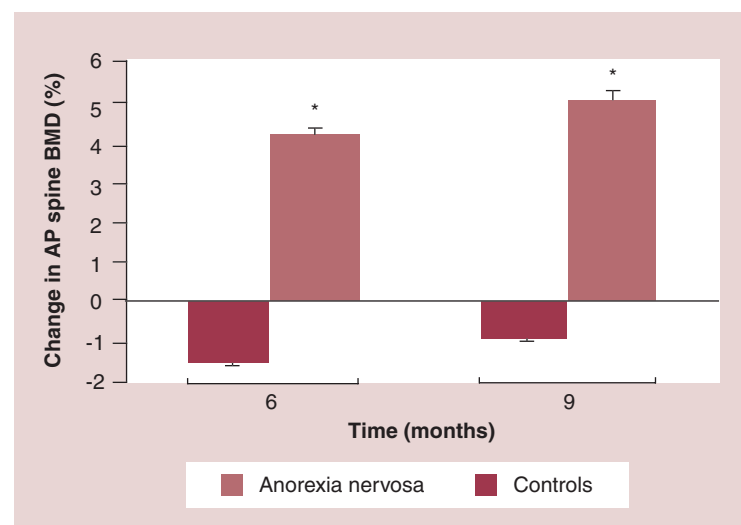


A significant increase in bone density was observed in the group randomized to rhIGF-1 with OCPs compared with the group that received neither medication. \*p < 0.05 versus control subjects.

AN: Anorexia nervosa; AP: Anterior–posterior; OCP: Oral contraceptive pill; rhIGF-1: Recombinant human IGF-1.

Adapted from [111]. © 2002. The Endocrine Society.

**Figure 7. Effects of risedronate on bone density in anorexia nervosa and controls at 6 and 9 months.**



A significant increase in bone density was observed with use of risedronate in women with anorexia nervosa.

AP: Anterior–posterior; BMD: Bone mineral density.

Adapted from [123]. © 2004. The Endocrine Society.

increase in BMD (Figure 7), despite a lack of significant weight gain [123]. Owing to the paucity of data regarding the safety of such medications in women of reproductive age, bisphosphonates currently remain in the realm of research treatments for osteoporosis in AN. Additional studies are needed to establish the efficacy and safety of bisphosphonate therapy in this population before clinical use. Particularly, the use of bisphosphonates needs to be very carefully considered in adolescents with AN, who are already in a state of reduced bone turnover, and in whom bisphosphonates would be expected to cause further reductions in bone turnover, with potential deleterious effects on pubertal bone modeling and remodeling.

Importantly, these drugs are not US FDA-approved for use in women of childbearing age as they are retained in the skeleton. Concerns exist that these drugs may affect fetal development as they are released from the mother's skeleton. As the effectiveness of these drugs is much less than weight gain and return of menses, they do not represent appropriate therapy until more data are available.

#### Calcium & vitamin D supplementation

Calcium and phosphorus are the building blocks of bone, and vitamin D is critical for calcium

absorption by the gut. Our group has demonstrated that calcium and vitamin D supplementation alone do not improve BMD in adults [56] or adolescents [24] with AN. However, it is important to maintain an adequate intake of calcium and vitamin D in this population, and we recommend 1300–1500 mg of elemental calcium and 400 IU of vitamin D for all adolescents and adults with AN.

#### Conclusion

Although there is no established treatment thus far for poor bone health in AN, prevention of significant effects on bone mass by early identification and treatment of AN and optimizing known positive predictors of BMD, such as weight restoration and menstrual recovery, are critical. Serial monitoring of BMD in this population is strongly recommended. As we better understand the pathophysiology of low BMD in AN, including the role of hitherto unknown peptides, exciting potential strategies may emerge to aid us in the prevention and/or treatment of low BMD in AN.

#### Future perspective

As more data are gathered, the effects of AN on bone will be better delineated in both sexes and at all ages. The pathophysiology of AN and its effects will be further deciphered following an improved understanding of neuroendocrine peptides altered in this condition. This will pave the way for therapeutic possibilities for improving bone health in AN, perhaps from:

- Physiological methods of replacing gonadal steroids;
- Modulating the response to hormones, such as growth hormone, that the body has become resistant to in AN;
- Targeting identifiable appetite-regulating peptides that contribute to the pathology of eating issues and bone loss.

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**Executive summary**

- Anorexia nervosa (AN) is a condition of malnutrition that affects the bone health of children and adults suffering from this disorder.

**Prevalence of the problem**

- Osteoporosis has been reported in up to 38% of adult AN patients. Osteopenia is even more common, and has been reported in up to 92% of adults with AN.
- More than half of all teenagers with AN have bone mineral density (BMD) below 1 SD of the mean for their age and gender.

**Increased fracture risk**

- AN is associated with increased fracture risk in both women and men.
- Cumulative incidence of any fracture at 40 years after the diagnosis of AN is 57%.
- Fractures of the hip, spine and forearm are late complications, noted occurring on average 38, 25 and 24 years, respectively, after diagnosis.

**Longitudinal changes in BMD in AN**

- Persistence of low weight is associated with impaired rates of bone-mass accrual in adolescents, and a worsening of BMD in adults.
- Weight rehabilitation results in an increase in bone-mass accrual rates and BMD, but low BMD can persist even after recovery.

**Pathogenesis of low BMD**

- Many nutritional and hormonal factors contribute to low BMD in AN.
- Nutritional factors predicting low BMD include low BMI and decreased lean and fat mass.
- Hormonal aberrations that contribute to low BMD in AN include:
  - Hypogonadism
  - A nutritionally acquired resistance to growth hormone
  - Low IGF-1 levels
  - Hypercortisolemia
  - Alterations in certain appetite-regulating peptides and adipocytokines, such as ghrelin, leptin, peptide YY and adiponectin

**Diagnosis**

- Dual-energy x-ray absorptiometry is currently the most widely used modality for BMD monitoring, with established standards available for comparison in adolescents and adults.
- Quantitative computed tomography has the additional advantage of being able to estimate volumetric bone density, unlike dual-energy x-ray absorptiometry, but is limited by less reproducibility and increased exposure to ionizing radiation.
- Studies with calcaneal ultrasound in AN have been less favorable than either of these modalities.
- Serial monitoring of BMD is recommended to assess decreased rates of bone-mass accrual in adolescents and ongoing bone losses in adults.

**Management strategies**

- Definite efficacy: weight gain and menses recovery. Weight gain alone without menses recovery is less effective in increasing BMD.
- No efficacy: calcium and vitamin D supplementation alone or oral estrogen–progesterone combination pills.
- Benefits evident in preliminary studies: recombinant human (rh)IGF-1 (particularly when given with estrogen), testosterone, bisphosphonates.
- Ongoing research: transdermal estrogen, rhGH, rhIGF-1, dehydroepiandrosterone.

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