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Bone Metabolism in Adolescents with Anorexia Nervosa

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Abstract

Adolescents with anorexia nervosa (AN) are at risk for low bone mass at multiple sites, associated with decreased bone turnover. Bone microarchitecture is also affected, with a decrease in bone trabecular volume and trabecular thickness, and an increase in trabecular separation. The adolescent years are typically the time when marked increases occur in bone mass accrual towards the attainment of peak bone mass, an important determinant of bone health and fracture risk in later life. AN often begins in the adolescent years, and decreased rates of bone mass accrual at this critical time are therefore also concerning for deficits in peak bone mass. Factors contributing to low bone density and decreased rates of bone accrual include alterations in body composition such as low BMI and lean body mass, and hormonal alterations such as hypogonadism, a nutritionally acquired resistance to growth hormone and low levels of IGF-1, relative hypercortisolemia, low levels of leptin, and increased adiponectin (for fat mass) and peptide YY. Therapeutic strategies include optimizing weight and menstrual recovery, and adequate calcium and vitamin D replacement. Oral estrogen-progesterone combination pills are not effective in increasing bone density in adolescents with AN. RhIGF-1 increases levels of bone formation markers in the short-term, while long-term effects remain to be determined. Bisphosphonates act by decreasing bone resorption, and are not optimal for use in adolescents with AN, in whom the primary defect is low bone formation.

Keywords

Anorexia nervosa; adolescents; bone density; bone turnover; bone microarchitecture; growth hormone; cortisol; estrogen; testosterone; leptin; ghrelin; peptide YY

Introduction

The adolescent years are a common time for the onset of anorexia nervosa (AN), a condition characterized by low weight, an intense fear of gaining weight, body image impairment, and in post-menarchal girls, amenorrhea for at least three consecutive cycles. As many as 0.2–4% of teenage girls and college aged young women are reported to suffer from this devastating eating disorder (1). Of concern, the onset of AN is often during the adolescent years, when bone mass accrual is maximal and attainment of peak bone mass is normally occurring (2). The condition is associated with alterations in multiple endocrine axes, and many of these hormonal alterations have a deleterious impact on bone metabolism. In this

review, we will discuss bone metabolism in adolescents with AN, the pathophysiology underlying low bone mass in this condition, and potential therapeutic strategies.

Bone Density and Microarchitecture in Adolescents with AN

Low bone density is common in adolescent girls and boys with AN compared with healthy adolescents (3–5). In a series of 60 adolescent girls with AN and 58 normal-weight controls, we assessed bone density using dual energy x-ray absorptiometry (DXA), and reported Z-scores of <-1 at one or more sites in 41% of the girls with AN and Z-scores of <-2 in an additional 11% (3). Bone density is lower in AN than in controls at multiple skeletal sites. Both the spine (primarily trabecular bone) and the hip (primarily cortical bone) are affected in girls with AN, although trabecular bone overall seems to be affected more than cortical. Measurement of bone density by DXA can underestimate bone mass in children, especially short children. Importantly however, height adjusted measures of bone density, such as spine bone mineral apparent density (BMAD) and whole body (WB) bone mineral content/height (BMC/Ht) (and corresponding Z-scores) are lower in girls with AN than normal-weight controls, supporting the concept that low bone density measurements in AN are not an artifact of shorter stature (6). In fact, in this cohort, girls with AN did not differ from controls for height or height SDS.

In addition to these worrisome cross-sectional data, prospective data indicate that girls with AN have a reduced rate of bone mass accrual compared with normal-weight controls. Whereas healthy girls continue to accrue bone over time, girls with AN have little or no increase in bone mass, leading to a continuing decrease in bone density Z-scores compared to normal girls (5). The lack of bone accrual in these critical adolescent years can result in permanent deficits in peak bone mass, and adult women who develop AN in their adolescent years have lower bone density than women who develop this disorder in adult life, even after controlling for the duration of amenorrhea or duration of illness (7).

Although AN occurs mainly in females, males also develop AN and studies have shown that bone mass is also reduced in boys with this disorder. We examined bone density in 17 adolescent boys with AN compared with 17 normal-weight controls, and reported lower bone density at multiple skeletal sites (spine, total hip, femoral neck and whole body) in boys with this eating disorder (4). However, in contrast to girls with AN, bone density appears to be more severely affected in cortical than in trabecular sites in boys with AN, with hip BMD being most affected. In this study, 59% and 65% of boys with AN had Z-scores of <-1 at the hip and the femoral neck respectively, compared with 24% and 18% of normal weight controls. In contrast, the proportion of boys with low bone density Z-scores at the spine did not differ between the groups. As in girls, height adjusted measures of bone density (spine BMAD and WB BMC/Ht) and their Z-scores are lower in boys with AN compared with controls. Castro *et al.* have similarly reported high rates of low bone density in adolescent boys with AN, with 35% of the boys having Z-scores of <-1 at the spine and the femoral neck (8).

An important new area of investigation in bone biology and fracture risk prediction has been assessment of bone microarchitectural parameters and bone strength. Studies in adult women with AN using high resolution (HR) peripheral quantitative tomography (pQCT) have reported decreased cortical thickness compared with normal-weight women, and decreased trabecular bone density, trabecular number as well as increased trabecular separation (9). We reported lower bone trabecular volume, lower trabecular thickness and number, and greater trabecular separation in adult women with AN compared with controls, using flat panel ultra high resolution volume CT (FpVCT) (10). We have also examined bone microarchitecture using FpVCT in adolescent girls with relatively mild AN, and have

reported that these girls have lower bone trabecular volume, lower trabecular thickness and greater trabecular separation than controls (11). The important point made in this study was that abnormalities in bone microarchitectural parameters were found in these girls even though their bone density was still normal. These data suggest that deleterious microarchitectural changes may occur even before bone density decreases can be detected by DXA. Finally, we have used finite element analysis to demonstrate decreased bone strength in women with AN, as indicated by lower failure load and stiffness (12). All these data indicate significant bone impairment in AN.

A few studies have used quantitative ultrasonography (QUS) to assess the impact of AN on bone. One study reported higher speed of sound (SOS) at the radius and tibia in adolescent girls with AN than in controls (13). However, in this study, SOS did not correlate with DXA measures of bone density, height adjusted measures of bone density (such as spine BMAD), or with anthropometric parameters, leading the authors to conclude that QUS was not an effective measure of bone density in AN. In contrast, a prospective study reported a significant decrease in amplitude dependent SOS Z-scores of the hand phalanges in girls with AN over a mean of 19 months of follow-up, concerning for a worsening of bone density over time, leading the authors to infer that QUS of the phalanges may be a good method to monitor bone density in AN (14).

Bone Turnover in Adolescents with AN

Normal adolescence is characterized by increased bone turnover with increases in levels of both bone formation and bone resorption markers, particularly in the early pubertal years (15). This increased bone turnover is believed to be consequent to rising levels of growth hormone (GH) and insulin like growth factor-1 (IGF-1) in puberty. Subsequently, in later puberty, as levels of gonadal steroids increase, bone turnover decreases and approaches adult levels. In contrast to healthy adolescents, teenage girls and boys with AN have lower levels of both bone formation and bone resorption markers than normal-weight controls (4, 5, 16), suggestive of a reduced state of bone turnover contributing to low bone density. This is also in contrast to adults with AN, who have an uncoupling of bone turnover markers, with a decrease in bone formation, and an increase in bone resorption markers (17).

Pathophysiology Underlying Low Bone Density in AN

Alterations in Body Composition

Body composition is a known important determinant of bone density. In both boys and girls with AN, BMI, fat mass and lean mass are lower compared with healthy controls (3, 4). We have reported that BMI is an important predictor of spine bone density, whereas lean mass is a very strong predictor of bone density at multiple sites, including the spine, hip, femoral neck and whole body in adolescent girls with AN and controls (3). Similarly, in boys with AN and controls, BMI and lean mass are important predictors of bone density at the spine, hip and whole body (4). Lean mass is a particularly strong predictor of bone density in both boys and girls at multiple sites, likely because the pull of muscle on bone has bone anabolic effects, and increases in lean mass over time predict increases in bone density over the same period of time (5).

Hormonal Alterations

Hypothalamic-Pituitary-Gonadal (H-P-G) Axis

Gonadal steroids have important effects on bone metabolism. Estrogen inhibits osteoclastic bone resorption, and may have bone anabolic effects (18, 19). Testosterone is aromatized to estrogen and thus inhibits bone resorption, and may have independent bone anabolic effects

(19). AN is associated with hypogonadotropic hypogonadism, and LH pulsatility patterns in females with AN revert to an early pubertal pattern of night-time entrained pulses, or a prepubertal pattern of low amplitude pulses (20). Girls with AN have lower estradiol levels than similar age controls, even when the latter are assessed in the early follicular phase of their menstrual cycles, when their gonadal steroid levels are at a nadir (3). Levels of free testosterone are lower in mature girls with AN than controls (5), and lower levels of both total and free testosterone have been reported in adult women with AN compared with controls (21). Similarly, boys with AN have lower levels of testosterone and estradiol and a lower free androgen index than boys of similar age (4).

In girls, duration of amenorrhea is an inverse predictor of bone density measures (3), and estradiol is inversely associated with bone resorption markers (22). Free testosterone is an important determinant of DXA measures of bone density in both girls (5) and women with AN (21), and changes in serum testosterone levels over a one-year period are positively associated with changes in spine bone density over the same period (5). In adult women with AN, free testosterone levels were reported to be a positive predictor of bone trabecular volume and trabecular thickness (10). In boys with AN, testosterone levels are strongly and positively associated with bone density at various sites independent of body composition measures including BMI and lean mass (4). Some studies have also reported low levels of the adrenal androgen, DHEAS, in girls and young women with AN compared with controls, and have reported inverse associations of DHEAS with bone resorption markers (23). Other studies, however, did not find any difference in levels of DHEAS in girls with AN compared with controls (5).

Growth Hormone (GH)-Insulin Like Growth Factor-1 (IGF-1) Axis

GH is bone anabolic through both direct and IGF-1 mediated effects (24). Girls with AN have lower circulating IGF-1 levels compared with normal-weight girls of comparable age, despite higher GH levels, suggestive of a nutritionally acquired hepatic resistance to GH effects (25). Higher GH concentrations in girls with AN are consequent to increased basal GH secretion and also an increased frequency of GH secretory bursts. Approximate entropy, a measure of the disorderliness of GH secretion, is also higher in girls with AN compared with controls (25). Whereas GH concentrations strongly predict levels of bone turnover markers in normal-weight girls, this association is completely lost in girls with AN, suggestive of a resistance to GH effects also at the level of bone (25). These data are further corroborated by a randomized controlled study in which we found that changes in levels of IGF-1 or bone turnover marker did not differ in adult women with AN who were randomized to supraphysiological doses of rhGH compared with those randomized to placebo (26). These data demonstrated that in severe undernutrition there is a fixed block in IGF-1 production by the liver that cannot be overcome by increasing GH levels.

IGF-1 is a positive predictor of bone density and bone turnover markers in girls with AN, and changes in IGF-1 levels over a one-year period are positively associated with changes in levels of bone turnover markers over the same period (5). In adult women with AN, IGF-1 levels are independently associated with bone microarchitectural parameters such as trabecular volume, trabecular thickness and number, and inversely associated with trabecular separation, even after controlling for BMI. Additionally, short-term administration of recombinant human (rh) IGF-1 in doses of 30–40 mcg/kg/dose twice a day is successful in significantly increasing levels of bone formation markers over this period in both girls (27) and adult women (17) with AN.

Hypothalamic-Pituitary-Adrenal Axis

High levels of endogenous cortisol and high doses of exogenous glucocorticoids are deleterious to bone through multiple mechanisms (28–32). Hypercortisolemia is associated with impairment of vitamin D metabolism, including decreased calcium absorption from the gut and impaired renal handling of calcium, inhibitory effects on GH and IGF-1 secretion, inhibitory effects on osteoblasts and stimulatory effects on osteoclasts. Girls with AN have higher serum and urinary cortisol levels than normal-weight controls, and higher cortisol concentrations are a consequence of increased frequency of secretory bursts and shorter half-life (33). Higher cortisol levels in girls with AN are associated with lower levels of bone turnover markers and lower bone density (33). In adults with AN, higher cortisol levels are similarly associated with lower bone density (34).

Alterations in Appetite Regulating Hormones and Other Hormones Affected by Energy Availability

Several hormones that are affected by the state of energy availability such as leptin, ghrelin, peptide YY (PYY), adiponectin and insulin are altered in AN, a condition of very low energy availability, where energy intake is often insufficient to keep pace with energy expenditure. Many of these hormones have an effect on bone metabolism.

Leptin—Leptin is an anorexigenic adipokine with differential effects on cortical versus trabecular bone. Data from the leptin knock-out mouse suggest that leptin has a positive effect on cortical bone (35, 36) and a negative effect on trabecular bone (37). Levels of leptin are lower in girls with AN compared with normal-weight controls, and are positively associated with low fat mass and BMI (38). Low leptin levels are likely an adaptive mechanism to reduce anorexigenic inputs in AN, and are consequent to lower basal secretion and decreased burst mass (38). Weight recovery is associated with increases in leptin levels (39). Leptin levels are an independent and inverse predictor of GH and cortisol secretion in AN and are positively associated with estradiol (38), and also with bone density measures at multiple sites (16). In adults with AN, leptin levels positively predict bone trabecular volume, trabecular thickness and number, and inversely predicts trabecular separation, even after controlling for BMI (10). In a study in normal-weight adult women with hypothalamic amenorrhea, leptin administration for a three-month period led to resumption of ovulatory menstrual cycles in three out of eight women, and was associated with increases in levels of bone formation markers, but also led to a decrease in weight and appetite (40), consistent with its anorexigenic effects.

Ghrelin—Ghrelin is an orexigenic hormone that increases in conditions of energy deficit such as AN, and correlates inversely with BMI and fat mass. Ghrelin receptors are present on osteoblasts, and ghrelin administration increases the activity of these cells (41, 42), suggesting that ghrelin is bone anabolic. Because ghrelin is a GH and ACTH secretagogue, some effects of ghrelin on bone may also be mediated by GH, IGF-1 and cortisol. In our studies, ghrelin levels were significantly higher in girls with AN compared with controls subsequent to increases in basal secretion and in the frequency of secretory bursts (43). Ghrelin was a positive predictor of bone density in normal-weight girls even after controlling for body composition, GH and cortisol levels, consistent with a bone anabolic role (44). However, in girls with AN, we found no association of ghrelin with bone density, or with levels of bone turnover markers, suggestive of a resistance to ghrelin effects. It is also possible that the increase in ghrelin in AN is an adaptive mechanism to try and increase not only food intake, but also bone formation. There are no studies of ghrelin administration in AN at this time that may clarify the impact of ghrelin on bone. Studies, however, have examined the impact of ghrelin administration on GH secretion in adult women with AN. Broglio *et al.* and Miljic *et al.* reported a blunting of the GH response to ghrelin in AN

despite a hyper-responsiveness to GHRH (45, 46), suggestive again of a resistance to ghrelin in AN.

Peptide YY (PYY)—PYY is an anorexigenic hormone secreted by the L-cells in the distal gut in response to food intake, which acts through the Y2 receptor to inhibit NPY secretion and food intake. The Y2 receptor knock out mouse (which would be PYY resistant), has a high bone mass phenotype (47), suggesting that high PYY levels with an intact receptor should be deleterious to bone. PYY levels are high in AN (22) and low in obesity (48), and levels of PYY correlate inversely with BMI and fat mass. High PYY levels in AN are associated with low levels of bone turnover markers in adolescent girls (even after controlling for other hormones and body composition) (22), and with low bone density in adolescent boys (4) and adult women (49), consistent with animal data. Therefore, it is possible that elevated levels of PYY in AN contribute further to reduced bone mass.

Adiponectin—Adiponectin is secreted by fat cells, and levels of adiponectin are low in obesity, whereas conflicting data have been reported in adolescents and adults AN (16, 50–52). This adipokine also has an impact of bone metabolism, and high adiponectin levels have been shown to increase both osteoclastic and osteoblastic activity (53, 54). Additionally, inverse associations of adiponectin with bone density are reported in adults (55, 56). We have reported that after controlling for fat mass, adiponectin levels are higher in girls with AN than in controls, and adiponectin is inversely associated with bone density measures (16). However, overall, the role of adiponectin in low bone mass in AN is unknown at this time.

Other Hormones—Insulin is a bone anabolic hormone (57), and levels of insulin are low in girls with AN compared with normal-weight controls. In our studies, insulin was positively associated with levels of bone turnover markers (16). Similarly, amylin, which is low in AN, is positively associated with bone density measures in adult women with AN (58).

Vitamin D and Calcium Status

Adequate calcium and vitamin D intake is essential for optimizing bone health, and this raises concerns regarding the impact of calcium and vitamin D status on bone in AN, a condition associated with reduced food intake. However, most studies indicate a low prevalence of vitamin D deficiency in girls with AN compared with controls, mainly because of an increased use of supplements. One study reported that the prevalence of vitamin D deficiency was 2% in girls with AN, compared with 24% in controls (59). In this study, 86% of girls with AN compared with only 14% of controls reported supplementation with vitamin D. Another study indicated, however, that the prevalence of vitamin D deficiency in AN may be as high as 25% (60). We have reported that 77% of girls with AN compared with 50% of controls meet the Dietary Reference Index (DRI) for vitamin D intake, and 59% of the girls with AN compared with 30% of controls meet the DRI for calcium intake, and again, the greater intake of calcium and vitamin D in AN girls is primarily through use of supplements (61). One study did indicate that low calcium intake may be associated with low bone density in boys with AN (8). However, in another study, similar to data in girls with AN, boys with AN had higher calcium and vitamin D intake from food and supplements than did controls (4).

Genetic Factors

Genetic factors account for almost 60% of the variability in bone density in the population at large, and thus, a strong family history of low bone density likely predisposes to low bone

density in girls with AN. In active female adolescents overall, a family history of low bone density and fractures has been reported to be predictive of a higher risk of stress fractures (62).

Therapeutic Strategies

Table 1 summarizes representative studies that have examined the impact of various therapeutic strategies on bone turnover markers and bone density in AN.

Weight Gain and Resumption of Menstrual Function

Weight gain and recovery of gonadal function are to be strongly encouraged in girls and boys with AN based on existing data. Improvement in weight and menstrual function in girls with AN is associated with some increases in bone mass (albeit often not to the level seen in normal-weight controls), while girls not recovering weight and menstrual function continue to have lower bone mass over time (6, 60). Coincident with weight and menstrual recovery is a significant increase in levels of bone turnover markers over a one-year period, and increases in levels of bone turnover markers are strongly predictive of subsequent increases in bone mineral content (5). It is concerning, however, that increases in bone mass with recovery are not sufficient for complete catch-up, and that residual deficits persist at an age when optimizing bone mass is of critical importance. This is despite the fact that recovery of weight and menses is associated with an improvement in many hormones that impact bone metabolism in AN. Therefore, while weight gain and restoration of menstrual function are to be strongly encouraged, it appears that additional therapies may be necessary in AN to allow for catch-up of bone mass to levels seen in normal-weight controls.

Calcium and Vitamin D Replacement—It is important to optimize calcium and vitamin D in all adolescents with AN given their known beneficial effects. We recommend 1200 mg of calcium and 800 IU of vitamin D daily for all AN patients. However, a higher proportion of girls with AN than normal-weight controls actually meets the recommended daily intake of these micronutrients (59, 61, 63), and, of importance, calcium and vitamin D supplementation is not sufficient to prevent bone loss or low bone density in adolescents or adults with AN (5, 64).

Replacement of Gonadal Steroids—Hypogonadism is an important contributor to low bone density in adolescents with AN, and this would suggest that replacement with estrogen in girls and testosterone in boys would be a good strategy to improve bone density in AN. However, multiple studies now indicate that oral estrogen (given as an estrogen-progesterone combination pill) does not improve bone density in girls with AN (65, 66), likely attributable (at least in part) to the IGF-1 suppressive effects of oral estrogen, and possibly to a decrease in free testosterone levels with oral estrogen (21), from increases in sex hormone binding globulin. The impact of transdermal estrogen in increasing bone density in girls with AN is currently under investigation. Another study indicates that administration of DHEA, an anabolic adrenal androgen, does not increase bone density in girls and young women with AN after controlling for effects of weight gain (67). The impact of testosterone replacement in adolescent boys with AN remains to be studied.

Replacement of IGF-1—A state of GH resistance and low levels of IGF-1 also contribute to low bone density in AN. This would suggest that possible therapeutic strategies would include (i) administration of supraphysiological doses of rhGH to overcome the nutritionally acquired GH resistance in AN, or (ii) administration of rhIGF-1 to normalize IGF-1 levels. Although there are no studies that have examined the impact of supraphysiological doses of rhGH in adolescents with AN, a study in adults indicated no increases in IGF-1 or in levels

of bone formation markers in women who received rhGH compared with placebo for a three-month period (26).

RhIGF-1 is effective in increasing levels of bone formation markers in adolescents and young adults with AN in the short-term (17, 27). In adults with AN, rhIGF-1 has been shown to increase bone density significantly (compared with placebo) when given with oral estrogen over a nine-month period (68).

Bisphosphonates—One study by Golden *et al.* examined the effect of oral alendronate versus placebo on bone density in adolescent girls with AN over a one-year period, and reported no increases in bone density at the spine and minimal increases in bone density at the femoral neck after controlling for weight changes (69). The mechanism of action of bisphosphonates is to suppress osteoclastic activity and bone turnover, and given that girls with AN are in a state of reduced bone turnover, the utility of bisphosphonates in this population is problematic. In addition, concerns persist regarding the long-term effects of bisphosphonates when administered to a young population, given the very long half-life of these drugs.

Others—Although leptin has beneficial effects on cortical bone, and rhleptin has been demonstrated to increase levels of bone turnover markers in adult women with hypothalamic amenorrhea, it also causes weight loss and a decrease in appetite (40). Therefore, leptin is not conceptually an optimal therapy for adolescents with AN. The role of ghrelin or antagonists of PYY remains to be explored in future studies.

Conclusion

Adolescent girls with AN are at risk for low bone density and reduced rates of bone mass accrual, with attendant concerns regarding attainment of peak bone mass and impaired fracture risk in later life. Changes in body composition and several hormonal alterations contribute to impaired bone metabolism in AN. Studies are consistent in reporting that lower BMI and lean mass, lower levels of gonadal steroids and higher levels of PYY are predictive of low bone density in both boys and girls with AN, while a longer duration of amenorrhea, and low IGF-1 and higher cortisol and adiponectin levels are also predictive of low bone density in girls with AN. Cortisol levels have not been assessed in boys with AN, and data are mixed regarding levels of adrenal androgens in AN, with some studies reporting low, and others reporting normal levels. Many current studies are limited by their associative nature, and although some prospective data are now available in girls with AN, there are few such data in boys with this condition.

Weight and menstrual recovery, and calcium and vitamin D replacement are recommended to optimize bone health in adolescents with AN, however, residual bone deficits persist despite these measures. Oral estrogen-progesterone pills are not effective in increasing bone density in this population, and the role of transdermal estrogen is under investigation. Oral DHEA and alendronate were not effective in increasing bone density in adolescent girls with AN after controlling for effects of weight gain, although some minimal benefits were observed at the hip with alendronate. RhIGF-1 is effective in increasing bone formation in adolescent and adult women with AN, and with estrogen, is effective in increasing bone density in adults with AN. This remains an experimental strategy at this point, and further studies are necessary in adolescents to validate the impact of rhIGF-1 on bone. RhLeptin has been demonstrated to increase levels of bone formation markers in adult women with hypothalamic amenorrhea, however, this is also associated with weight loss, thus not an optimal outcome in AN. There are no therapeutic studies available to date in boys with AN.

Studies are ongoing regarding other potential therapeutic strategies for low bone density in teenagers with AN, and the results of these studies as well as future studies will be useful in determining the optimal strategy to normalize bone accrual in this population. At this time, it remains important to emphasize the importance of weight recovery and normalization of gonadal status in boys and girls with AN. Additionally, vitamin D replacement should be optimized in those with suboptimal levels of this vitamin.

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Table 1
Summary of some studies examining therapeutic strategies to increase bone density in AN

	Therapeutic strategy	Study design	Number of subjects	Study duration	Results	Limitations
Misra et al. <i>J Clin Endocrinol Metab</i> 2008 ⁽⁶⁾	Weight gain with menstrual recovery	Prospective observational	34 girls with AN 33 normal weight controls between 12–18 years old; 20 were non-recovered AN and 14 had recovered weight and menses	1 year	Change in bone density and corresponding Z-scores was significantly lower in non-recovered girls with AN vs. controls for the spine, whole body and height adjusted measures of both; recovered girls with AN had changes in bone density that were in between those seen in non-recovered AN and controls	Followed girls for only 1 year
Audi et al. <i>Pediatr Res</i> 2002 ⁽⁶⁰⁾	Active AN vs. weight gain vs. weight gain with menstrual recovery	Cross-sectional study	73 Tanner stage 5 women; 13.8–22.6 years old, 34 were non-recovered, 20 were weight recovered, 19 were weight and menses recovered	No follow-up	The groups did not differ for spine bone density or for corresponding Z-scores	Cross-sectional study; examined bone density only at the spine
Soyka et al. <i>J Clin Endocrinol Metab</i> 2002 ⁽⁵⁾	Calcium and vitamin D supplementation (1200 mg and 400 IU daily); all girls were advised supplementation	Prospective observational	19 girls with AN and 19 normal-weight controls 12–18 years old	1 year	Vitamin D supplementation was not associated with significant increases in bone density; no significant differences were observed in bone density amongst those who recovered vs. those that did not.	Not a randomized study; all girls were advised to take supplements
Klibanski et al. <i>J Clin Endocrinol Metab</i> 1995 ⁽⁶⁴⁾	Oral estrogen and progesterone with calcium and vitamin D supplements vs. calcium and vitamin D supplements alone.	Randomized, double blind, controlled study	Adult women with AN (mean age 23.7 years) randomized to an oral estrogen-progesterone combination with calcium and vitamin D supplements (n=22) vs. calcium and vitamin D supplements alone (n=26)	1 year	No significant increases in bone density occurred in either group; on post-hoc analysis, women with AN with the lowest weights did have a significant increase in bone density	Normal weight women were not followed over the same time; not placebo controlled
Golden et al. <i>J Pediatr Adolesc Gynecol</i> 2002 ⁽⁶⁵⁾	Oral estrogen and progesterone combination pill	Prospective observational study	22 girls with AN 13–21 years old received an oral estrogen-progesterone combination pill, while 28 received no medication. All received calcium supplementation	Mean duration of follow-up was 23.1+/- 11.4 months	No significant differences in absolute or net change in bone density at the spine and femoral neck were observed at one-year of follow-up between the groups	Not a randomized study; normal weight controls were not followed prospectively to assess how change in bone density in girls with AN compared with that in normal weight girls over the study period
Strokosch et al. <i>J Adol</i>	Oral estrogen and progesterone combination pill	Randomized, double blind, placebo controlled study	123 girls with AN or EDNOS 11–17 years old randomized to an oral estrogen-progesterone combination triphasic pill vs. placebo	1 year (13 cycles of pills)	No significant increases occurred in bone density at the spine or the hip after controlling for weight gain	Normal weight controls were not followed prospectively over the same period; included patients with EDNOS

	Therapeutic strategy	Study design	Number of subjects	Study duration	Results	Limitations
Health 2006 (66)						
Gordon et al. J Clin Endocrinol Metab 2002 (67)	DHEA or an oral estrogen-progestosterone combination pill	Randomized, double blind study	61 young women with AN 14–28 years old; 31 were randomized to 50 mg oral DHEA daily, and 30 to an oral estrogen-progestosterone combination pill	1 year	No significant increases occurred in bone density at the spine or the hip after controlling for weight changes	No control group was included in the study; normal weight adolescents were not studied prospectively over the study duration; calcium and vitamin D supplements not provided to all subjects
Misra et al. Bone 2009 (27)	RhIGF-1 or no medication All received calcium and vitamin D supplements	Prospective study; 10 consecutive girls with AN and 10 matched historical controls	10 girls with AN 12–18 years old in each group	7–10 days	Significant increase in bone formation markers with rhIGF-1 replacement	Short-duration pilot study with few subjects; no information available or possible regarding the impact on bone density
Grinspoon et al. J Clin Endocrinol Metab 1996 (17)	RhIGF-1 or placebo	Randomized, double blind, placebo controlled study	23 women with AN 18–29 years old randomized to receive 30 mcg/kg of rhIGF-1 twice daily, or 100 mcg/kg of rhIGF-1 twice daily or placebo	6 days	Significant increase in bone formation and bone resorption markers with 100 mcg/kg of rhIGF-1 given twice daily; significant increase in only bone formation markers with 30 mcg/kg of rhIGF-1 given twice daily	Short-duration pilot study; no information available or possible regarding the impact on bone density
Grinspoon et al. J Clin Endocrinol Metab 2002 (68)	RhIGF-1 (30 mcg/kg twice daily) with oral estrogen and progesterone vs. rhIGF-1 alone or oral estrogen and progesterone alone, or neither; all subjects received 1500 mg of calcium and 400 IU of vitamin D	Randomized, double blind, placebo controlled (to rhIGF-1) study	60 osteopenic women with AN 18–38 years old were randomized to one of the four arms	9 months	Significant increase in spine bone density in women who received rhIGF-1 with estrogen versus neither medication	Small number of subjects
Welt et al. N Engl J Med 2004 (40)	RhLeptin (0.08 mg/kg/day) vs. no treatment	Prospective study	8 women with hypothalamic amenorrhea 19–33 years old received rhLeptin for 3 months; 6 women with hypothalamic amenorrhea 27–38 years old were followed without intervention for 3 months	3 months	Significant increase in levels of bone formation markers	Small number of subjects; additionally, rhLeptin use was associated with a decrease in weight
Golden et al. J Clin Endocrinol Metab 2005 (69)	Alendronate (10 mg daily) vs. placebo	Randomized, double blind, placebo controlled study	32 young women with AN 12–21 years old; 15 randomized to alendronate and 17 to placebo	1 year	No significant increases occurred in bone density at the spine after controlling for weight gain; did see a significant increase in femoral neck bone density	Bisphosphonates inhibit bone resorption and suppress bone modeling, which is already low in AN; long-terms effects are still not known; did not follow normal-weight controls over the study duration