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Endocrinology of anorexia nervosa in young people: recent insights

Vibha Singhal[a], **Madhusmita Misra**[a,b], and **Anne Klibanski**[b]

[a]Pediatric Endocrine Units of Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

[b]Neuroendocrine Units of Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Abstract

Purpose of review—Anorexia nervosa is among the most prevalent chronic medical conditions in young adults. It has acute as well as long-term consequences, some of which, such as low bone mineral density (BMD), are not completely reversible even after weight restoration. This review discusses our current understanding of endocrine consequences of anorexia nervosa.

Recent findings—Anorexia nervosa is characterized by changes in multiple neuroendocrine axes including acquired hypogonadotropic hypogonadism, growth hormone resistance with low insulin-like growth factor-1 (likely mediated by fibroblast growth factor-1), relative hypercortisolemia, alterations in adipokines such as leptin, adiponectin and resistin, and gut peptides including ghrelin, PYY and amylin. These changes in turn contribute to low BMD. Studies in anorexia nervosa have demonstrated abnormalities in bone microarchitecture and strength, and an association between increased marrow fat and decreased BMD. One study in adolescents reported an improvement in BMD following physiologic estrogen replacement, and another in adults demonstrated improved BMD following risedronate administration. Brown adipose tissue is reduced in anorexia nervosa, consistent with an adaptive response to the energy deficit state.

Summary—Anorexia nervosa is associated with widespread physiologic adaptations to the underlying state of undernutrition. Hormonal changes in anorexia nervosa affect BMD adversely. Further investigation is underway to optimize therapeutic strategies for low BMD.

Keywords

bone microarchitecture; bone strength; brown adipose tissue; eating disorders; marrow fat

INTRODUCTION

Anorexia nervosa is a condition of severe under-nutrition that occurs in 0.3% of adolescents in the USA and affects primarily girls but is reported increasingly in boys. The prevalence is likely to increase with liberalization of diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V), which excludes amenorrhea as a diagnostic

Correspondence to Madhusmita Misra, MD, MPH, BUL 457, Neuroendocrine Unit, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. Tel: +1 617 726 3870; fax: +1 617 726 5072; mmisra@partners.org.

Conflicts of interest
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criterion, and disregards ‘intentions’ such as ‘refusal to maintain weight’ that are difficult to assess. As of now, however, available endocrine and bone data are based on studies that used DSM-IV criteria for diagnosis of anorexia nervosa. The importance of this is that DSM-IV has strict weight criteria for diagnostic inclusion. Adolescence is a critical time of physiological development, particularly with respect to growth, maturation of the reproductive axis and bone accrual and is a common time for onset of anorexia nervosa. Detrimental effects of severe chronic undernutrition on bone development have long been recognized. When these changes begin during adolescence, they are often not completely reversible even after resolution of anorexia nervosa. This review discusses the impact of anorexia nervosa on endocrine axes and bone.

BODY COMPOSITION AND FAT DISTRIBUTION IN ANOREXIA NERVOSA

Lean and fat mass

Anorexia nervosa is characterized by low BMI, fat and lean mass. Adolescent and adult women with anorexia nervosa have lower trunk fat and trunk to extremity fat ratio compared with controls [1,2], with reductions in visceral and subcutaneous fat [1,3]. Anorexia nervosa is now being increasingly identified in males, who in contrast to females have increased trunk and lower extremity fat than controls, attributed to low testosterone levels [4]. Lower lean mass affects bone mineral density (BMD) adversely independent of other factors, attributable to the mechanical effect of muscle pull.

Marrow adipose tissue

Women with anorexia nervosa have increased marrow adipose tissue (MAT) compared with normal-weight controls, associated with lower BMD [5]. This is consistent with emerging knowledge regarding the bone–fat connection, and reports of inverse associations of MAT with BMD in other populations. Adipocytes and osteoblasts originate from a common marrow progenitor mesenchymal stem cell (MSC), and studies suggest that increased differentiation along the adipocyte lineage may affect differentiation along the osteoblast lineage [6,7]. Preadipocyte factor-1 (Pref-1) is a member of the epidermal-like growth factor family that reduces MSC differentiation along the osteoblast lineage. Pref-1 is higher in women with anorexia nervosa than controls, associated with lower areal BMD (aBMD) [8], and Pref-1 and MAT decrease with recovery from anorexia nervosa [9■]. Pref-1 also decreases following transdermal estrogen administration in adolescents with anorexia nervosa, associated with improvement in spine BMD [10■■]. These data indicate a favorable impact of Pref-1 reductions on bone.

Brown adipose tissue

Brown adipose tissue (BAT) is important for cold and diet-induced thermogenesis, facilitated by its unique uncoupling protein, uncoupling protein (UCP)-1. BAT activity is associated with energy expenditure, and women with anorexia nervosa have lower BAT activity than controls [11], likely an adaptive, energy-conserving measure. Lower BAT activity (‘beige adipose tissue’ as measured by FDG- PET scanning induced by cold) in anorexia nervosa is also associated with lower BMD and higher Pref-1. This suggests that BAT may influence regulation of MSC differentiation toward the osteoblast lineage.

ENDOCRINE CHANGES IN ANOREXIA NERVOSA

Anorexia nervosa is characterized by changes in multiple endocrine axes. These changes are mostly adaptive to the low energy state, but can have deleterious skeletal consequences.

Growth hormone–insulin-like growth factor-1 axis

Anorexia nervosa is a state of acquired nutritional growth hormone resistance. Girls and women with anorexia nervosa have increased growth hormone secretion [12,13] subsequent to increased ghrelin, a growth hormone secretagogue [14,15], and decreased systemic insulin-like growth factor-1 (IGF-1). Nadir growth hormone following an oral glucose load is higher in anorexia nervosa than controls [16]. Fibroblast growth factor-1 (FGF-21) levels in anorexia nervosa correlate positively with growth hormone levels and negatively with IGF-1 and may mediate growth hormone resistance [17,18]. FGF-21 is produced by hepatocytes via peroxisome proliferator-activated receptor (PPAR)a stimulation and white adipocytes via PPARg [19]. It is induced by fasting and reduces IGF-1 by inhibiting STAT-5, a mediator of intracellular growth hormone effects. Growth hormone favors gluconeogenesis, and increased growth hormone in anorexia nervosa may maintain euglycemia despite severe undernutrition. Changes in growth hormone and IGF-1 in anorexia nervosa are at least partially reversed during refeeding and with recovery. [20] Administration of supraphysiologic doses of recombinant human (rh) growth hormone to women with anorexia nervosa fails to increase IGF-1, although it does decrease fat mass, likely a direct growth hormone effect [21].

Hypothalamic-pituitary-adrenal axis

The hypothalmic-pituitary-adrenal axis is stimulated in anorexia nervosa [22–25], with increases in cortisol secretion that correlate inversely with BMI and fat mass [22]. Increases are reported in 24-h urinary free cortisol, overnight and 24-h serum cortisol, late night salivary cortisol, and abnormal overnight dexamethasone suppression [22–25]. Similar to growth hormone, cortisol is gluconeogenic, and increases in cortisol and growth hormone may together maintain euglycemia in anorexia nervosa. Greater trunk fat accumulation with recovery is attributed to higher baseline cortisol [1], which also predicts menstrual recovery in adolescents with anorexia nervosa [22]. There are conflicting reports of normal or decreased dehydroepiandrosterone/sulfate (DHEA/S) secretion in anorexia nervosa [26,27].

Hypothalamic-pituitary-thyroid axis

Severe weight loss in anorexia nervosa is characterized by the sick euthyroid syndrome. Total T3 is low and reverse T3 elevated from increased peripheral deiodination of T4 to reverse T3. Thyroid-stimulating hormone (TSH) is normal or slightly low, and the TSH response to exogenous thyrotropin releasing hormone (TRH) administration is blunted [28]. During recovery, total T3 rises with the rising metabolic rate [28]. Reductions in T3 are likely adaptive to the starved state to reduce metabolic rate.

Adipokines

Leptin is anorexigenic, and basal and pulsatile leptin secretion is reduced in anorexia nervosa [29] associated with reductions in subcutaneous fat [29], an appropriate adaptive response to starvation to reduce appetite suppressive effects. Leptin also stimulates GnRH secretion, and low leptin may contribute to hypogonadism in anorexia nervosa. Adiponectin increases insulin sensitivity by modulating PPARg, and adiponectin is increased in anorexia nervosa after controlling for fat mass [30,31], particularly the low-molecular-weight multimer [32■]. Levels are higher in women with the binge-purge subtype of anorexia nervosa compared with the restrictive subtype [33]. Irisin is a novel myokine and adipokine induced by exercise [34] and involved in the browning of white adipose tissue, making it metabolically active and capable of increasing thermogenesis. Irisin is lower in women with anorexia nervosa than controls, associated with lower BMI [35■]. Decreased irisin likely represents another adaptive mechanism to conserve energy by reducing browning of white fat.

Gut neuropeptides

Ghrelin is an appetite-stimulating peptide secreted by the stomach that is a growth hormone and adrenocorticotropic hormone (ACTH) secretatogue and an inhibitor of gonadotropin secretion. Acylated ghrelin stimulates appetite, whereas both acylated and deacylated forms inhibit gonadotropins [36,37]. Girls with anorexia nervosa have higher ghrelin than controls, associated with lower BMI and fat mass [15], another adaptive response to a starved state. In a pilot study in five women with restrictive anorexia nervosa who were motivated to gain weight but could not because of gastrointestinal discomfort, preprandial ghrelin infusion increased appetite and decreased postprandial bloating [38■]. Randomized controlled studies are necessary to confirm these findings. Peptide YY (PYY) is an anorexigenic hormone secreted by L-cells of the gut, whose levels correlate inversely with fat mass across the BMI spectrum [39]. Unlike other endocrine changes, higher PYY in anorexia nervosa compared with controls is not an adaptive response, and levels persist high despite weight gain. Amylin is secreted by pancreatic b cells in a 1:1 molar ratio with insulin, and levels are lower in anorexia nervosa than controls [30,31,40]. Glucagon like peptide (GLP)-1, which induces satiety, is decreased in anorexia nervosa [41].

Hypothalamic-pituitary-gonadal axis

Hypothalamic amenorrhea is common in anorexia nervosa, and can be primary or secondary. Earlier studies have shown immature luteinizing hormone (LH) pulses in anorexia nervosa [42], including a prepubertal pattern of low amplitude pulses or an early pubertal pattern of night-time entrainment of LH pulses, which reverse with weight gain. Estradiol and total and free testosterone levels are low [27,43].

Leptin stimulates, whereas ghrelin inhibits gonadotropin secretion. Decreased leptin and increased ghrelin levels in anorexia nervosa may thus contribute to the hypogonadal state [29]. Weight gain is associated with increases in leptin; however, this does not always predict menstrual recovery [22,44]. Administration of metreleptin causes resumption of menses in up to 70% of women with hypothalamic amenorrhea and induces ovulatory cycles in about 40%. However, metreleptin causes reductions in fat mass [45], even when the dose is carefully titrated to prevent weight loss observed in an earlier study [46]. Hypercortisolemia, known to suppress GnRH secretion, may also contribute to hypogonadism in anorexia nervosa. Menstrual recovery in girls with anorexia nervosa depends on many factors, including changes in fat mass, leptin and cortisol [22,47,48].

BONE CONSEQUENCES IN ANOREXIA NERVOSA

Low BMD is characteristic of anorexia nervosa. This is especially critical in adolescence, a time when bone accrual peaks. Higher rates of fractures are reported in anorexia nervosa compared with controls [49]. Low BMD in girls with anorexia nervosa is associated with decreased bone turnover [43,50], unlike adult women with anorexia nervosa who have an uncoupling of bone turnover with an increase in bone resorption but a decrease in bone formation [50].

Both cortical and trabecular bone are affected in anorexia nervosa, although trabecular bone is more severely affected than cortical, which may reflect the dramatic impact of estrogen deficiency [51]. Evaluation of bone microarchitecture using ultra-high-resolution peripheral quantitative computed tomography (QCT) corroborates dual energy x-ray absorptiometry (DXA) reports of impaired bone status. In girls, bone trabecular volume and trabecular thickness are decreased, whereas trabecular separation is increased [52]. Adolescents with anorexia nervosa have lower cortical area and thickness, and increased cortical porosity [53■■], and finite element analysis estimates of bone strength, such as stiffness and failure

load, are lower than in controls [53■■]. Abnormalities in bone microarchitecture may precede changes in aBMD in anorexia nervosa [52].

Hip structural analysis (using DXA) in boys demonstrates lower cross-sectional area and cross-sectional moment of inertia at the narrow neck, trochanteric region and femoral shaft in anorexia nervosa than controls, after controlling for age and height [54■]. They also have lower cortical thickness and greater buckling ratio at the trochanteric region. These changes suggest reduced strength at a predominantly cortical site.

Hypogonadism and later menarchal age are important contributors to low BMD in anorexia nervosa. Estrogen decreases osteoclastic bone resorption by inhibiting secretion of proinflamma-tory cytokines, and reducing receptor activator of nuclear factor κ-B ligand (RANKL) activity by increasing osteoprotegerin (OPG) [55]. In anorexia nervosa, levels of proinflammatory cytokines are high [56,57] and may increase bone resorption. Despite low estrogen, OPG levels are high in anorexia nervosa associated inversely with BMD [58]. Effects of estrogen on bone are also attributed to reductions in sclerostin, a product of the *SOST* gene and a glycoprotein secreted by osteocytes. The *SOST* gene has estrogen response elements in its promoter region [59]. Sclerostin inhibits osteoblast activity by inhibiting Wnt signaling, and stimulates osteoclasts by increasing receptor activator of nuclear factor κ-B (RANK) activation by RANKL [60]. Whereas higher sclerostin is associated with increased levels of bone turnover markers in controls, this relationship is disrupted in anorexia nervosa [61■]. Of note, physiologic estrogen replacement in anorexia nervosa girls causes an improvement in BMD without changes in sclerostin [61■].

Another important hormonal determinant of low BMD in anorexia nervosa is growth hormone resistance with low IGF-1. Although growth hormone is bone anabolic, girls with anorexia nervosa have low BMD in the setting of high growth hormone, consistent with skeletal growth hormone resistance [12]. This is further supported by a lack of increase in bone turnover markers in anorexia nervosa following supraphysiologic doses of rhGH [21]. Small studies have shown an increase in bone formation markers following recombinant human insulin like growth factor-1 (rhIGF-1) administration in girls with anorexia nervosa [62], and an improvement in BMD when administered with estrogen in adults [63]. Larger trials are necessary to conclusively determine the impact of IGF-1 replacement on bone.

Other hormonal determinants of low BMD in anorexia nervosa include relative hypercortisolemia [25,64], low leptin, insulin, amylin and oxytocin [30,40,65], and high PYY and adiponectin [30,64–66]. Leptin affects BMD independent of weight in anorexia nervosa [67]. Rodent studies suggest variable paracrine and endocrine effects of adiponectin on bone [68], and adiponectin is inversely associated with BMD in anorexia nervosa [30]. Ghrelin receptors are present on osteoblasts and ghrelin may inhibit osteoclastogenesis [64]. The positive association between ghrelin and BMD in healthy girls is not observed in anorexia nervosa, suggestive of ghrelin resistance [15]. PYY acts through the Y2 receptor, and Y2 receptor knockout mice [69,70] and PYY null mice [71] have increased trabecular bone mass, whereas PYY transgenic mice have decreased bone mass [71]. Consistent with this, elevated PYY in anorexia nervosa is associated with lower levels of bone turnover markers in adolescents [64,66], and lower BMD in adults [66]. Furthermore, oxytocin is bone anabolic and nocturnal oxytocin is decreased in anorexia nervosa compared with controls associated with decreased BMD [65].

Current therapeutic strategies for low body mineral density in anorexia nervosa

In girls, increases in weight and lean mass predict improvements in aBMD, emphasizing the importance of recovery [43]. In adults, menstrual recovery increases spine aBMD whereas weight recovery causes preferential increases in hip aBMD [72].

Despite the important role of hypogonadism in causing low BMD, oral estrogen is not effective in increasing aBMD in anorexia nervosa [73–75]. This may be because oral estrogen decreases IGF-1 production by the liver, an important bone trophic hormone already low in anorexia nervosa. However, physiologic estrogen replacement as the 100-μg transdermal estradiol patch (with cyclic progesterone) increases spine and hip aBMD and allows maintenance of BMD z scores [76]. Although physiologic estrogen replacement prevents ongoing bone loss in anorexia nervosa, it does not result in complete catch-up, likely because other hormonal deficiencies persist. Administration of DHEA with oral estrogen also maintains aBMD in women with anorexia nervosa [77]. Preliminary data indicate that IGF-1 replacement may improve BMD in an estrogen replete state [62,78], and long-term studies are underway to evaluate the efficacy of transdermal estradiol with rhIGF-1 on bone accrual in girls with anorexia nervosa.

Bisphosphonates do not increase spine aBMD in girls with anorexia nervosa after controlling for weight changes [79], likely because bisphosphonates act by decreasing bone turnover, already reduced in adolescents with anorexia nervosa. A recent trial in adults with anorexia nervosa reported that risedronate decreased bone resorption and increased aBMD [80]. Owing to their long half life and potential teratogenicity, bisphosphonates should not be used in reproductive age women until their efficacy and safety are established.

CONSEQUENCES OF ENDOCRINE CHANGES IN ANOREXIA NERVOSA ON NEUROCOGNITION, ANXIETY AND MOOD

Adults with adolescent-onset anorexia nervosa and menstrual dysfunction have cognitive impairment across a wide range of domains, and menstrual recovery (spontaneous or estrogen induced) results in improvement in certain domains, suggestive of an impact of estrogen on cognition [81]. Also, physiologic estrogen replacement in adolescents with anorexia nervosa improves trait anxiety without influencing eating attitudes and body shape perception, and prevents increases in body dissatisfaction scores with weight gain observed with placebo [82■■]. In addition, decreased testosterone levels are related to anxiety, depression and disordered eating behavior in anorexia nervosa [83], and very low-dose testosterone therapy improves depression scores in treatment resistant adult women [84]. The degree of cortisol elevation is also related to anxiety scores in anorexia nervosa [25]. Finally, oxytocin has anxiolytic and antidepressant effects. Although nocturnal oxytocin is lower in anorexia nervosa than controls, postprandial levels are higher [85,86■], associated with higher anxiety and depression [86■]. Because food intake can be stress-provoking in anorexia nervosa, higher post-prandial oxytocin may be adaptive to cope with the stress of food intake.

CONCLUSION

Anorexia nervosa is a state of chronic undernutrition with multiple adaptive endocrine changes that affect bone adversely. The most effective strategy to increase BMD is weight gain and menstrual recovery. However, this can be difficult to attain and maintain; relapses are common. Physiologic estrogen replacement, primarily transdermal, improves BMD in adolescent anorexia nervosa, and studies are underway to evaluate the impact of IGF-1 replacement on bone density and structure. Further investigation is necessary to clarify the bone–fat connection in anorexia nervosa, and develop additional therapeutic options.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1. Grinspoon S, Thomas L, Miller K, et al. Changes in regional fat redistribution and the effects of estrogen during spontaneous weight gain in women with anorexia nervosa. Am J Clin Nutr. 2001; 73:865–869. [PubMed: 11333838]
2. Misra M, Soyka L, Miller K, et al. Regional body composition in adolescents with anorexia nervosa and changes with weight recovery. Am J Clin Nutr. 2003; 77:1361–1367. [PubMed: 12791610]
3. Bredella MA, Ghomi RH, Thomas BJ, et al. Comparison of DXA and CT in the assessment of body composition in premenopausal women with obesity and anorexia nervosa. Obesity (Silver Spring). 2010; 18:2227–2233. [PubMed: 20111013]
4. Misra M, Katzman DK, Cord J, et al. Percentage extremity fat, but not percentage trunk fat, is lower in adolescent boys with anorexia nervosa than in healthy adolescents. Am J Clin Nutr. 2008; 88:1478–1484. [PubMed: 19064506]
5. Bredella MA, Fazeli PK, Miller KK, et al. Increased bone marrow fat in anorexia nervosa. J Clin Endocrinol Metab. 2009; 94:2129–2136. [PubMed: 19318450]
6. Rosen CJ, Ackert-Bicknell C, Rodriguez JP, Pino AM. Marrow fat and the bone microenvironment: developmental, functional, and pathological implications. Crit Rev Eukaryot Gene Expr. 2009; 19:109–124. [PubMed: 19392647]
7. Fazeli PK, Horowitz MC, MacDougald OA, et al. Marrow fat and bone–new perspectives. J Clin Endocrinol Metab. 2013; 98:935–945. [PubMed: 23393168]
8. Fazeli PK, Bredella MA, Misra M, et al. Preadipocyte factor-1 is associated with marrow adiposity and bone mineral density in women with anorexia nervosa. J Clin Endocrinol Metab. 2010; 95:407–413. [PubMed: 19850693]
9■. Fazeli PK, Bredella MA, Freedman L, et al. Marrow fat and preadipocyte factor-1 levels decrease with recovery in women with anorexia nervosa. J Bone Miner Res. 2012; 27:1864–1871. [PubMed: 22508185] [This article shows that marrow fat and Pref-1 levels decrease with recovery in women with anorexia nervosa, and that Pref-1 could play a role in regulating marrow adipose tissue.]
10■■. Faje AT, Fazeli PK, Katzman D, et al. Inhibition of Pref-1 (preadipocyte factor 1) by oestradiol in adolescent girls with anorexia nervosa is associated with improvement in lumbar bone mineral density. Clin Endocrinol (Oxf). 2013; 79:326–332. [PubMed: 23331192] [This study reported for the first time a reduction in Pref-1 levels in girls with anorexia nervosa following administation of transdermal estradiol, associated with an increase in BMD.]
11. Bredella MA, Fazeli PK, Freedman LM, et al. Young women with cold-activated brown adipose tissue have higher bone mineral density and lower Pref-1 than women without brown adipose tissue: a study in women with anorexia nervosa, women recovered from anorexia nervosa, and normal-weight women. J Clin Endocrinol Metab. 2012; 97:E584–E590. [PubMed: 22259053]
12. Misra M, Miller K, Bjornson J, et al. Alterations in growth hormone secretory dynamics in adolescent girls with anorexia nervosa and effects on bone metabolism. J Clin Endocrinol Metab. 2003; 88:5615–5623. [PubMed: 14671143]
13. Stoving R, Veldhuis J, Flyvbjerg A, et al. Jointly amplified basal and pulsatile growth hormone secretion and increased process irregularity in women with anorexia nervosa: indirect eveidence for disruption of feedback regulatin within the growth hormone-insulin like growth factor-I axis. J Clin Endocrinol Metab. 1999; 84:2056–2063. [PubMed: 10372710]
14. Kojima M, Hosoda H, Date Y, et al. Ghrelin is a growth-hormone releasing acylated peptide from stomach. Nature. 1999; 402:656–660. [PubMed: 10604470]

15. Misra M, Miller KK, Kuo K, et al. Secretory dynamics of ghrelin in adolescent girls with anorexia nervosa and healthy adolescents. Am J Physiol Endocrinol Metab. 2005; 289:E347–E356. [PubMed: 15755766]
16. Misra M, Miller KK, Herzog DB, et al. Growth hormone and ghrelin responses to an oral glucose load in adolescent girls with anorexia nervosa and controls. J Clin Endocrinol Metab. 2004; 89:1605–1612. [PubMed: 15070919]
17. Fazeli PK, Misra M, Goldstein M, et al. Fibroblast growth factor-21 may mediate growth hormone resistance in anorexia nervosa. J Clin Endocrinol Metab. 2010; 95:369–374. [PubMed: 19926712]
18. Inagaki T, Lin VY, Goetz R, et al. Inhibition of growth hormone signaling by the fasting-induced hormone FGF21. Cell Metab. 2008; 8:77–83. [PubMed: 18585098]
19. Wei W, Dutchak PA, Wang X, et al. Fibroblast growth factor 21 promotes bone loss by potentiating the effects of peroxisome proliferator-activated receptor gamma. Proc Natl Acad Sci U S A. 2012; 109:3143–3148. [PubMed: 22315431]
20. Counts D, Gwirtsman H, Carlsson L, et al. The effect of anorexia nervosa and refeeding on growth hormone-binding protein, the insulin-like growth factors (IGFs), and the IGF-binding proteins. J Clin Endocrinol Metab. 1992; 75:762–767. [PubMed: 1381372]
21. Fazeli P, Lawson E, Prabhakaran R, et al. Effects of recombinant human growth hormone in anorexia nervosa: a randomized placebo-controlled study. J Clin Endocrinol Metab. 2010; 95:4889–4897. [PubMed: 20668047]
22. Misra M, Prabhakaran R, Miller KK, et al. Role of cortisol in menstrual recovery in adolescent girls with anorexia nervosa. Pediatr Res. 2006; 59:598–603. [PubMed: 16549537]
23. Biller B, Federoff H, Koenig J, Klibanski A. Abnormal cortisol secretion and responses to corticotropin-releasing hormone in women with hypothalamic amenorrhea. J Clin Endocrinol Metab. 1990; 70:311–317. [PubMed: 2153693]
24. Misra M, Miller KK, Almazan C, et al. Alterations in cortisol secretory dynamics in adolescent girls with anorexia nervosa and effects on bone metabolism. J Clin Endocrinol Metab. 2004; 89:4972–4980. [PubMed: 15472193]
25. Lawson EA, Donoho D, Miller KK, et al. Hypercortisolemia is associated with severity of bone loss and depression in hypothalamic amenorrhea and anorexia nervosa. J Clin Endocrinol Metab. 2009; 94:4710–4716. [PubMed: 19837921]
26. Lawson EA, Misra M, Meenaghan E, et al. Adrenal glucocorticoid and androgen precursor dissociation in anorexia nervosa. J Clin Endocrinol Metab. 2009; 94:1367–1371. [PubMed: 19158192]
27. Miller KK, Lawson EA, Mathur V, et al. Androgens in women with anorexia nervosa and normal-weight women with hypothalamic amenorrhea. J Clin Endocrinol Metab. 2007; 92:1334–1339. [PubMed: 17284620]
28. Leslie RD, Isaacs AJ, Gomez J, et al. Hypothalamo-pituitary-thyroid function in anorexia nervosa: influence of weight gain. Br Med J. 1978; 2:526–528. [PubMed: 698555]
29. Misra M, Miller KK, Kuo K, et al. Secretory dynamics of leptin in adolescent girls with anorexia nervosa and healthy adolescents. Am J Physiol Endocrinol Metab. 2005; 289:E373–E381. [PubMed: 15811876]
30. Misra M, Miller KK, Cord J, et al. Relationships between serum adipokines, insulin levels, and bone density in girls with anorexia nervosa. J Clin Endocrinol Metab. 2007; 92:2046–2052. [PubMed: 17356044]
31. Pannacciulli N, Vettor R, Milan G, et al. Anorexia nervosa is characterized by increased adiponectin plasma levels and reduced nonoxidative glucose metabolism. J Clin Endocrinol Metab. 2003; 88:1748–1752. [PubMed: 12679468]
32■. Amitani H, Asakawa A, Ogiso K, et al. The role of adiponectin multimers in anorexia nervosa. Nutrition. 2013; 29:203–206. [PubMed: 23237649] [This study reported an increased proportion of low molecular weight adiponectin and a decreased proportion of high-molecular-weight adiponectin in women with anorexia nervosa compared with controls.]
33. Nogueira JP, Maraninchi M, Lorec AM, et al. Specific adipocytokines profiles in patients with hyperactive and/or binge/purge form of anorexia nervosa. Eur J Clin Nutr. 2010; 64:840–844. [PubMed: 20485307]

34. Lecker SH, Zavin A, Cao P, et al. Expression of the irisin precursor FNDC5 in skeletal muscle correlates with aerobic exercise performance in patients with heart failure. Circ Heart Fail. 2012; 5:812–818. [PubMed: 23001918]

35■. Stengel A, Hofmann T, Goebel-Stengel M, et al. Circulating levels of irisin in patients with anorexia nervosa and different stages of obesity–correlation with body mass index. Peptides. 2013; 39:125–130. [PubMed: 23219488] [This is the first study to relate blood irisin levels positively to BMI, with lowest levels in women with anorexia nervosa and highest levels in those with severe obesity.]

36. Kluge M, Schussler P, Uhr M, et al. Ghrelin suppresses secretion of luteinizing hormone in humans. J Clin Endocrinol Metab. 2007; 92:3202–3205. [PubMed: 17550958]

37. Vulliemoz NR, Xiao E, Xia-Zhang L, et al. Decrease in luteinizing hormone pulse frequency during a five-hour peripheral ghrelin infusion in the ovariectomized rhesus monkey. J Clin Endocrinol Metab. 2004; 89:5718–5723. [PubMed: 15531534]

38■. Hotta M, Ohwada R, Akamizu T, et al. Therapeutic potential of ghrelin in restricting-type anorexia nervosa. Methods Enzymol. 2012; 514:381–398. [PubMed: 22975066] [In this pilot study of five women with restrictive anorexia nervosa, preprandial ghrelin infusion increased appetite and decreased postprandial bloating.]

39. Misra M, Miller KK, Tsai P, et al. Elevated peptide YY levels in adolescent girls with anorexia nervosa. J Clin Endocrinol Metab. 2006; 91:1027–1033. [PubMed: 16278259]

40. Wojcik MH, Meenaghan E, Lawson EA, et al. Reduced amylin levels are associated with low bone mineral density in women with anorexia nervosa. Bone. 2010; 46:796–800. [PubMed: 19931436]

41. Tomasik PJ, Sztefko K, Malek A. GLP-1 as a satiety factor in children with eating disorders. Horm Metab Res. 2002; 34:77–80. [PubMed: 11972291]

42. Boyar RM, Katz J, Finkelstein JW, et al. Anorexia nervosa. Immaturity of the 24-h luteinizing hormone secretory pattern. N Engl J Med. 1974; 291:861–865. [PubMed: 4412035]

43. Soyka L, Misra M, Frenchman A, et al. Abnormal bone mineral accrual in adolescent girls with anroexia nervosa. J Clin Endocrinol Metab. 2002; 87:4177–4185. [PubMed: 12213868]

44. Misra M, Miller KK, Almazan C, et al. Hormonal and body composition predictors of soluble leptin receptor, leptin, and free leptin index in adolescent girls with anorexia nervosa and controls and relation to insulin sensitivity. J Clin Endocrinol Metab. 2004; 89:3486–3495. [PubMed: 15240636]

45. Sienkiewicz E, Magkos F, Aronis KN, et al. Long-term metreleptin treatment increases bone mineral density and content at the lumbar spine of lean hypoleptinemic women. Metabolism. 2011; 60:1211–1221. [PubMed: 21741057]

46. Welt CK, Chan JL, Bullen J, et al. Recombinant human leptin in women with hypothalamic amenorrhea. N Engl J Med. 2004; 351:987–997. [PubMed: 15342807]

47. Dei M, Seravalli V, Bruni V, et al. Predictors of recovery of ovarian function after weight gain in subjects with amenorrhea related to restrictive eating disorders. Gynecol Endocrinol. 2008; 24:459–464. [PubMed: 18850384]

48. Jacoangeli F, Masala S, Staar Mezzasalma F, et al. Amenorrhea after weight recovery in anorexia nervosa: role of body composition and endocrine abnormalities. Eat Weight Disord. 2006; 11:e20–e26. [PubMed: 16801735]

49. Lucas AR, Melton LJ 3rd, et al. Long-term fracture risk among women with anorexia nervosa: a population-based cohort study. Mayo Clin Proc. 1999; 74:972–977. [PubMed: 10918862]

50. Misra M, Klibanski A. Anorexia nervosa and osteoporosis. Rev Endocr Metab Disord. 2006; 7:91–99. [PubMed: 16972186]

51. Grinspoon S, Thomas E, Pitts S, et al. Prevalence and predictive factors for regional osteopenia in women with anorexia nervosa. Ann Intern Med. 2000; 133:790–794. [PubMed: 11085841]

52. Bredella MA, Misra M, Miller KK, et al. Distal radius in adolescent girls with anorexia nervosa: trabecular structure analysis with high-resolution flat-panel volume CT. Radiology. 2008; 249:938–946. [PubMed: 19011190]

53■■. Faje AT, Karim L, Taylor A, et al. Adolescent girls with anorexia nervosa have impaired cortical and trabecular microarchitecture and lower estimated bone strength at the distal radius. J Clin Endocrinol Metab. 2013; 98:1923–1929. [PubMed: 23509107] [This is the first study to use

high resolution peripheral quantitative computed tomography and finite element analysis to demonstrate impaired bone microarchitecture and lower bone strength estimates in adolescent girls with anorexia nervosa.]

54■. Misra M, Katzman DK, Clarke H, et al. Hip structural analysis in adolescent boys with anorexia nervosa and controls. J Clin Endocrinol Metab. 2013; 98:2952–2958. [PubMed: 23653430] [This is the first study to demonstrate impaired measures of bone structure at the hip in boys with anorexia nervosa using hip structural analysis.]

55. Riggs B. The mechanisms of estrogen regulation of bone resorption. J Clin Invest. 2000; 106:1203–1204. [PubMed: 11086020]

56. Misra M, Miller KK, Tsai P, et al. Uncoupling of cardiovascular risk markers in adolescent girls with anorexia nervosa. J Pediatr. 2006; 149:763–769. [PubMed: 17137889]

57. Kwan Tat S, Padrines M, Theoleyre S, et al. IL-6, RANKL, TNF-alpha/IL-1: interrelations in bone resorption pathophysiology. Cytokine Growth Factor Rev. 2004; 15:49–60. [PubMed: 14746813]

58. Misra M, Soyka LA, Miller KK, et al. Serum osteoprotegerin in adolescent girls with anorexia nervosa. J Clin Endocrinol Metab. 2003; 88:3816–3822. [PubMed: 12915674]

59. Rossini M, Gatti D, Adami S. Involvement of WNT/beta-catenin Signaling in the Treatment of Osteoporosis. Calcif Tissue Int. 2013; 93:121–132. [PubMed: 23748710]

60. Li X, Zhang Y, Kang H, et al. Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. J Biol Chem. 2005; 280:19883–19887. [PubMed: 15778503]

61■. Faje AT, Fazeli PK, Katzman DK, et al. Sclerostin levels and bone turnover markers in adolescents with anorexia nervosa and healthy adolescent girls. Bone. 2012; 51:474–479. [PubMed: 22728230] [This study reported no changes in sclerostin levels following physiologic estrogen replacement in adolescent girls with anorexia nervosa, indicating that beneficial effects of transdermal estradiol on bone density are likely not mediated by reductions in sclerostin.]

62. Misra M, McGrane J, Miller KK, et al. Effects of rhIGF-1 administration on surrogate markers of bone turnover in adolescents with anorexia nervosa. Bone. 2009; 45:493–498. [PubMed: 19523548]

63. Grinspoon S, Thomas L, Miller K, et al. Effects of recombinant human IGF-I and oral contraceptive administration on bone density in anorexia nervosa. J Clin Endocrinol Metab. 2002; 87:2883–2891. [PubMed: 12050268]

64. Misra M, Prabhakaran R, Miller KK, et al. Prognostic indicators of changes in bone density measures in adolescent girls with anorexia nervosa-II. J Clin Endocrinol Metab. 2008; 93:1292–1297. [PubMed: 18089697]

65. Lawson EA, Donoho DA, Blum JI, et al. Decreased nocturnal oxytocin levels in anorexia nervosa are associated with low bone mineral density and fat mass. J Clin Psychiatry. 2011; 72:1546–1551. [PubMed: 21903023]

66. Utz AL, Lawson EA, Misra M, et al. Peptide YY (PYY) levels and bone mineral density (BMD) in women with anorexia nervosa. Bone. 2008; 43:135–139. [PubMed: 18486583]

67. Lawson EA, Miller KK, Bredella MA, et al. Hormone predictors of abnormal bone microarchitecture in women with anorexia nervosa. Bone. 2010; 46:458–463. [PubMed: 19747572]

68. Shinoda Y, Yamaguchi M, Ogata N, et al. Regulation of bone formation by adiponectin through autocrine/paracrine and endocrine pathways. J Cell Biochem. 2006; 99:196–208. [PubMed: 16598753]

69. Wortley KE, Garcia K, Okamoto H, et al. Peptide YY regulates bone turnover in rodents. Gastroenterology. 2007; 133:1534–1543. [PubMed: 17920065]

70. Baldock PA, Allison S, McDonald MM, et al. Hypothalamic regulation of cortical bone mass: opposing activity of Y2 receptor and leptin pathways. J Bone Miner Res. 2006; 21:1600–1607. [PubMed: 16995815]

71. Wong IP, Driessler F, Khor EC, et al. Peptide YY regulates bone remodeling in mice: a link between gut and skeletal biology. PLoS One. 2012; 7:e40038. [PubMed: 22792209]

72. Miller KK, Lee EE, Lawson EA, et al. Determinants of skeletal loss and recovery in anorexia nervosa. J Clin Endocrinol Metab. 2006; 91:2931–2937. [PubMed: 16735492]

73. Strokosch GR, Friedman AJ, Wu SC, Kamin M. Effects of an oral contraceptive (norgestimate/ethinyl estradiol) on bone mineral density in adolescent females with anorexia nervosa: a double-blind, placebo-controlled study. J Adolesc Health. 2006; 39:819–827. [PubMed: 17116511]

74. Golden NH, Lanzkowsky L, Schebendach J, et al. The effect of estrogenprogestin treatment on bone mineral density in anorexia nervosa. J Pediatr Adolesc Gynecol. 2002; 15:135–143. [PubMed: 12106749]

75. Klibanski A, Biller B, Schoenfeld D, et al. The effects of estrogen administration on trabecular bone loss in young women with anorexia nervosa. J Clin Endocrinol Metab. 1995; 80:898–904. [PubMed: 7883849]

76. Misra M, Katzman DK, Miller KK, et al. Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa. J Bone Miner Res. 2011; 26:2430–2438. [PubMed: 21698665]

77. Divasta AD, Feldman HA, Giancaterino C, et al. The effect of gonadal and adrenal steroid therapy on skeletal health in adolescents and young women with anorexia nervosa. Metabolism. 2012; 61:1010–1020. [PubMed: 22257645]

78. Grinspoon S, Miller K, Herzog D, et al. Effects of recombinant human insulin-like growth factor (IGF)-I and estrogen administration on IGF-I, IGF binding protein (IGFBP)-2, and IGFBP-3 in anorexia nervosa: a randomized-controlled study. J Clin Endocrinol Metab. 2003; 88:1142–1149. [PubMed: 12629097]

79. Golden NH, Iglesias EA, Jacobson MS, et al. Alendronate for the treatment of osteopenia in anorexia nervosa: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab. 2005; 90:3179–3185. [PubMed: 15784715]

80. Miller KK, Meenaghan E, Lawson EA, et al. Effects of risedronate and low-dose transdermal testosterone on bone mineral density in women with anorexia nervosa: a randomized, placebo-controlled study. J Clin Endocrinol Metab. 2011; 96:2081–2088. [PubMed: 21525157]

81. Chui HT, Christensen BK, Zipursky RB, et al. Cognitive function and brain structure in females with a history of adolescent-onset anorexia nervosa. Pediatrics. 2008; 122:e426–e437. [PubMed: 18676530]

82■■. Misra M, Katzman D, Estella NM, et al. Impact of physiologic estrogen replacement on anxiety symptoms, body shape perception, and eating attitudes in adolescent girls with anorexia nervosa: data from a randomized controlled trial. J Clin Psychiatry. 2013; 74:e765–e771. [PubMed: 24021517] [This randomized controlled trial showed that physiologic estrogen replacement improves trait anxiety in adolescent girls with anorexia nervosa. To our knowledge, this is the first study to document improvement in anxiety scores with estrogen replacement.]

83. Miller KK, Wexler TL, Zha AM, et al. Androgen deficiency: association with increased anxiety and depression symptom severity in anorexia nervosa. J Clin Psychiatry. 2007; 68:959–965. [PubMed: 17592924]

84. Miller KK, Perlis RH, Papakostas GI, et al. Low-dose transdermal testosterone augmentation therapy improves depression severity in women. CNS Spectr. 2009; 14:688–694. [PubMed: 20394176]

85. Lawson EA, Holsen LM, Santin M, et al. Oxytocin secretion is associated with severity of disordered eating psychopathology and insular cortex hypoactivation in anorexia nervosa. J Clin Endocrinol Metab. 2012; 97:E1898–E1908. [PubMed: 22872688]

86■. Lawson EA, Holsen LM, Santin M, et al. Postprandial oxytocin secretion is associated with severity of anxiety and depressive symptoms in anorexia nervosa. J Clin Psychiatry. 2013; 74:e451–e457. [PubMed: 23759466] [This study reported higher postprandial oxytocin levels in women than anorexia nervosa than controls associated with higher anxiety and depression scores.]

KEY POINTS

- Anorexia nervosa is associated with multiple endocrine changes, most of which are adaptive, but which impact bone adversely.
- Bone density, microarchitecture and strength are adversely affected in anorexia nervosa consequent to decreased BMI and lean mass, hypogonadism, low IGF-1 and leptin levels, and relatively elevated cortisol, adiponectin and PYY.
- Bone marrow fat and Pref-1 levels are increased in anorexia nervosa associated with lower BMD; marrow fat and Pref-1 decrease following recovery.
- Brown adipose tissue (metabolically active fat) is reduced in anorexia nervosa, likely an adaptation to decrease energy utilization.