Anorexia Nervosa and Its Associated Endocrinopathy in Young People

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Key Words

Bone · Cortisol · Eating disorders · Estrogen · Cortisol · Growth hormone · Insulin-like growth factor 1

Abstract

Anorexia nervosa (AN) is a condition of severe undernutrition associated with adaptive changes in many endocrine axes. These changes include hypogonadotropic hypogonadism, acquired growth hormone resistance with low insulin-like growth factor 1 (IGF-1) levels, hypercortisolemia, altered secretion of adipokines and appetite-regulating hormones, and low bone mineral density (BMD). Bone health is impaired subsequent to a low body mass index, decreased lean mass, and the endocrine changes described above. In addition to low areal BMD, AN is characterized by a decrease in volumetric BMD, changes in bone geometry, and reductions in strength estimates, leading to an increased risk for fracture. Weight restoration is essential for restoration of normal endocrine function; however, hypercortisolemia, high peptide YY levels, and ghrelin dynamics may not completely normalize. In some patients, hypogonadotropic hypogonadism persists despite weight restoration. Weight gain and menstrual recovery are critical for improving bone health in AN; however, residual deficits may persist. Physio-

logic estrogen replacement using transdermal, but not oral, estrogen increases bone accrual in adolescents with AN, while bisphosphonates improve BMD in adults. Recombinant human IGF-1 and teriparatide have been used in a few studies as bone anabolic therapies. More data are necessary to determine the optimal therapeutic strategies for low BMD in AN.

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Introduction

Anorexia nervosa (AN) is a condition of severe undernutrition associated with an impaired body image that occurs in 0.2–4% of adolescents and young adults [1]. Some, though not all, studies suggest an increasing prevalence of AN, particularly in adolescents [2–4]. AN is associated with many endocrine changes, most of which are adaptive and an attempt to mobilize energy reserves or conserve energy for vital body functions. Unfortunately, these endocrine changes also contribute to impaired bone metabolism leading to low bone mineral density (BMD), impaired bone geometry, and reduced strength estimates, which in turn increase the risk for fracture. A higher prevalence of fractures has been reported in both adults and

adolescents with AN [5–7]. This review will discuss the endocrine and bone changes that occur in AN and possible therapeutic approaches to low BMD, and it is based on a literature review of PubMed using combinations of search terms such as ‘anorexia nervosa’, ‘endocrine changes’, ‘bone density’, and ‘bone health’.

Growth Hormone/Insulin-Like Growth Factor 1 Axis

Adolescents and adults with AN have a nutritionally acquired resistance to growth hormone (GH) characterized by lower levels of insulin-like growth factor 1 (IGF-1) compared to normal-weight controls despite higher concentrations of GH [8–11]. Following an oral glucose load, nadir GH concentrations are higher than in controls, and a larger proportion of girls with AN fail to suppress their GH levels below 1 ng/ml [12]. Higher GH concentrations are a consequence of increases in basal secretion and secretory pulse amplitude and/or pulse frequency [8–11]. Disorderliness of GH secretion, quantified by approximate entropy, is also increased in AN [9]. Low IGF-1 levels despite increased GH concentrations are a result of decreased hepatic GH receptor expression, indicated by decreased systemic concentrations of GH-binding protein [11, 13], the cleaved extracellular component of the GH receptor. Increases in GH concentrations in AN are likely driven by decreased negative feedback from low hepatic IGF-1 secretion and increased secretion of the GH secretagogue, ghrelin [14]. Furthermore, low leptin levels in AN may contribute to increased GH secretion, as may higher fibroblast growth factor 21 concentrations [15, 16].

Hepatic GH resistance in AN is confirmed by the absence of an increase in IGF-1 levels following administration of supraphysiologic doses of recombinant human (rh) GH [17]. In one study, compared to placebo, rhGH given 5–6 times in physiologic replacement doses for a period of 3 months did not increase markers of bone formation and resorption (despite the known bone anabolic effects of GH) [17], and in observational studies, higher concentrations of GH in normal-weight controls, but not in girls with AN, are positively associated with concentrations of bone turnover markers [9]. In contrast, replacement doses of rhIGF-1 do increase markers of bone formation [18] and spine and hip BMD in AN in an estrogen-replete state [19]. These data support a resistance in AN to GH effects that are IGF-1 mediated. However, direct effects of GH appear to be preserved such that supraphysiologic doses of rhGH cause reductions in fat mass

and increases in lean mass in women with AN [17], and higher endogenous GH concentrations are associated with lower trunk fat in adolescents with AN [20].

The impact of GH resistance on longitudinal growth is evident in young boys with AN, who tend to be shorter than their peers [21]. However, data are conflicting in young women with AN with studies variably reporting shorter, comparable, or taller stature compared to peers [22–24]. This dichotomy between the sexes may relate to the fact that much of statural growth is complete at the time of AN onset in girls, given the earlier growth spurt and cessation of statural growth in girls compared with boys.

The state of GH resistance in AN is likely adaptive to the state of undernutrition to help provide energy (as glucose) for vital functions. GH is a potent stimulator of gluconeogenesis, and a potentially beneficial effect of higher GH concentrations (and lower IGF-1) in AN is maintenance of euglycemia. Consistent with this, lower glucose levels in AN predict higher concentrations of ghrelin, a GH secretagogue, suggesting that lower glucose availability may stimulate increased ghrelin and hence GH secretion [14].

Hypothalamic-Pituitary-Adrenal Axis

Adults and adolescents with AN have an upregulation of the hypothalamic-pituitary-adrenal axis [25, 26] with an increase in integrated cortisol concentrations and suboptimal cortisol suppression following administration of dexamethasone or a glucose load [26, 27]. Increased cortisol is subsequent to increased basal cortisol secretion, increased pulse frequency, and reduced cortisol clearance. Increased cortisol concentrations are associated inversely with BMD measures and markers of bone turnover in AN, in contrast to normal-weight controls [26, 27]. In addition, higher cortisol concentrations in AN predict lower extremity lean mass, consistent with the deleterious effects of excess cortisol on muscle [20].

Cortisol stimulates gluconeogenesis, and levels in AN are associated inversely with fasting glucose [26], suggesting that increased cortisol secretion, similar to increased GH secretion, in AN is an adaptive mechanism to maintain euglycemia. Another potential driver is increased ghrelin secretion, which in addition to being a GH secretagogue also stimulates adrenocorticotrophic hormone secretion [14].

Interestingly, weight gain in AN results in a reduction in cortisol pulse frequency; however, cortisol concentra-

tions remain high for a variable period of time [26]. During weight recovery in adult women with AN, a higher baseline cortisol concentration predicts greater increases in trunk fat [28]. Further, in a study of adolescents with AN, those with higher baseline cortisol were more likely to gain weight and fat mass over time and resume menses [29].

Adipokines and Appetite-Regulating Hormones

Adipokines, such as adiponectin and leptin (an anorexigenic hormone), and other appetite-regulating hormones, such as ghrelin (orexigenic) and peptide YY (PYY; anorexigenic), are altered in AN. Adolescents and adults with AN have low levels of *leptin* compared with controls [15, 30] due to a decrease in basal leptin secretion and pulse amplitude [15]. Decreased leptin secretion in AN reflects decreased fat mass and is an appropriate adaptation to reduce a potential anorexigenic stimulus. In addition, normal leptin concentrations are permissive for normal functioning of the hypothalamic-pituitary-gonadal (HPG) axis, and lower leptin levels in AN may contribute to impaired gonadotropin secretion [15]. Women with AN who have higher fat mass and leptin levels than women with AN and comparable weight are more likely to have menses despite low weight [31]. Systemic leptin is bone anabolic, particularly for appendicular and cortical bone [32], whereas central leptin is deleterious to axial trabecular bone through its effects on the sympathetic nervous system [33]. In healthy populations [34] and in AN [35], lower leptin levels have been associated with lower levels of bone formation markers and lower BMD.

Adiponectin is reported to be increased, unchanged, or decreased in AN compared to a normal-weight population [35–39]. These differences may relate to assays detecting different circulating adiponectin isoforms [40], such that in AN, the percent of lower-molecular-weight to total levels is higher than in controls. In vitro studies suggest that higher adiponectin levels result in impaired gonadotropin secretion [41]. Further, in older men and postmenopausal women, higher adiponectin levels are associated with lower BMD [34] commensurate with a stimulatory effect of adiponectin on the secretion of RANKL (ligand of RANK) and a decrease in the secretion of osteoprotegerin, both of which increase osteoclastic activity [42].

Ghrelin is an orexigenic hormone secreted by the gastric oxyntic cells. Ghrelin increases secretion of GH and adrenocorticotrophic hormone and suppresses secretion

of luteinizing hormone (LH) and follicle-stimulating hormone. Ghrelin levels are increased in adults and adolescents with AN [14, 43–45] from increased basal secretion and secretory pulse amplitude [14]. Higher ghrelin concentrations are an appropriate adaptation to stimulate food intake in starvation, to cause increased secretion of GH and cortisol, and to potentially suppress gonadotropin secretion [14]. Ghrelin may also have bone anabolic effects. In healthy adolescents, but not in AN, higher ghrelin levels predict higher BMD [46], suggesting a possible resistance to ghrelin in AN.

PYY, an anorexigenic hormone, is increased in adults and adolescents with AN compared with controls [44, 47], although some studies in adults report unchanged [48] or lower [49] levels. Lower fat mass correlates with higher PYY levels [47]. PYY can impact gonadotropin secretion [50] and is deleterious to osteoblast function [51]. Consistent with this, higher PYY levels are associated with lower levels of bone turnover markers in adolescents with AN [47] and with lower BMD in adults [52].

HPG Axis

Although amenorrhea is no longer required for the diagnosis of AN based on DSM-5 criteria, menstrual dysfunction remains common in this condition. LH pulsatility patterns have been shown to revert in women with AN to an early pubertal pattern of sleep-entrained LH pulsatility or a prepubertal pattern of low-amplitude LH pulses [53] and return to normal with recovery. Serum levels of estradiol and testosterone are lower in adults and adolescents with AN compared with controls [54, 55], and hypoestrogenism manifests as functional hypothalamic oligo-amenorrhea. However, a spectrum of menstrual dysfunctions occurs in AN with more subtle forms such as a short luteal phase or anovulatory cycles, in addition to frank hypothalamic oligo-amenorrhea. Altered patterns of LH pulsatility and functional hypothalamic amenorrhea stem from the underlying state of low energy availability and low fat mass, and many hormones that are altered in this energy deficit state may also impact gonadotropin secretion. For example, hormones such as IGF-1 and leptin that typically have a stimulatory effect on the HPG axis are decreased in AN, whereas hormones that are inhibitory to the axis, such as cortisol and ghrelin, are increased in AN.

Menstrual resumption (associated with weight gain) is often considered a sign of improvement and/or recovery in females with AN. Compared to adolescents who remain

amenorrheic, those who regain menses tend to gain more fat mass over a given duration [29]. However, there is a significant overlap across groups, and there is no set body weight or percent fat mass above which menses resume. Menses recovery often occurs at a body weight that is about 2 kg above that at which menses stopped, and a large proportion of women with AN resume menses when they get to >90% of ideal body weight [56]. Ideal body weight can be difficult to quantify and is impacted by body size, parental height, and maturity, but is generally considered to correspond to the weight obtained by multiplying the 50th percentile of body mass index for age by the square of the individual's height in meters. Of note, it may take 6–12 months of being at this body weight before menses resume [56]. In one study of adolescent girls with AN, those with higher baseline integrated cortisol concentrations were more likely to resume menses [29].

In females with AN, lower estradiol levels, later menarchal age, and a longer duration of amenorrhea are important determinants of low BMD [29, 57–60]. Estrogen is antiresorptive and acts to reduce osteoclastic activity by decreasing secretion of RANKL and inflammatory cytokines and increasing secretion of osteoprotegerin [61]. It may also increase osteoblastic activity by reducing secretion of sclerostin, an inhibitor of osteoblast differentiation [62]. Testosterone also impacts bone, both directly and through its aromatization to estradiol [61]. Low testosterone levels have deleterious effects on bone, and an increase in testosterone following weight gain is an important predictor of increases in BMD in girls with AN [55]. Similarly, in boys with AN, lower testosterone levels predict lower BMD [54]. Lower testosterone in boys with AN is also associated with greater truncal adiposity [63]. Some studies have related estrogen deficiency in AN to alterations in cognitive measures and to greater anxiety and body dysmorphic symptoms with weight gain [64, 65].

Weight gain and menstrual recovery are associated with a stabilization of BMD; however, complete catch-up does not occur, and residual deficits often persist [66–71] (fig. 1). Because gains in BMD are less than seen in a normal-weight population over the same duration, BMD Z-scores may continue to decrease over time. As will be discussed in the section Calcium and Bone Metabolism, physiologic estrogen replacement results in bone accrual rates comparable to rates in normal-weight controls [72]. Physiologic estrogen replacement also reduces trait anxiety and prevents the increase in state anxiety and body dysmorphic behavior observed in those not on replacement therapy [65].

Hypothalamic-Pituitary-Thyroid Axis

Thyroid-stimulating hormone and thyroid hormone levels in AN are reminiscent of a sick euthyroid state with normal or low levels of thyroid-stimulating hormone, low total triiodothyronine, and low normal or low free thyroxine [73]. Slight reductions in thyroid hormone levels are a normal adaptation to a low energy availability state and should help lower resting energy expenditure and conserve energy for vital functions. In fact, resting energy expenditure is lower in individuals with AN compared with controls [73]. Thyroid hormone status is an important determinant of the amount of brown adipose tissue, and women with AN have lower brown adipose tissue than controls [74], which should preserve energy by reducing nonshivering thermogenesis.

Other Hormones

Other hormones that are altered in AN include insulin, amylin, and oxytocin [35, 75, 76]. Insulin and amylin are secreted in equimolar concentrations from the pancreas, and levels of both hormones are lower in AN than in controls [35, 76]. Reductions in insulin are appropriate in AN and should help preserve euglycemia. Furthermore, peripheral levels of oxytocin (which is anorexigenic) are also appropriately lower in AN [75]. Insulin, amylin, and oxytocin are bone anabolic, and reductions in these hormones in AN are associated with low bone density [24, 64, 65].

Calcium and Bone Metabolism

One of the most important consequences of AN is low BMD. Adolescents and adults with AN have lower areal BMD (assessed using dual-energy X-ray absorptiometry; DXA) at multiple sites compared with controls [55, 57, 58, 66, 69, 77–84]. Adolescent girls and women with AN tend to have greater involvement of sites of predominantly trabecular bone, such as the spine, although the hip and whole body are also affected [55, 58]. Adolescent boys with AN tend to have greater involvement of the femoral neck and total hip than the spine, although the spine is also affected [54]. Adults with AN have a decrease in bone formation and an increase in bone resorption markers, indicating an uncoupling of bone turnover [85], whereas adolescents have a coupled decrease in bone turnover [86], likely reflecting differences in normal bone physiology in

Fig. 1. Change in lumbar bone mineral apparent density (BMAD) and whole-body BMC/height (Ht) measures in girls with AN who did not recover menses (AN-Not Recovered), girls with AN who recovered menses and gained weight (AN-Recovered), and healthy adolescents (Controls). AN-Not Recovered continued to lose bone mass over the 1-year follow-up period, and the change in bone

density measures was significantly lower in this group compared with controls. AN-Recovered did not differ from controls for change in bone density parameters and differed significantly from AN-Not Recovered for change in whole-body BMC/Ht Z-scores. * $p < 0.05$. From Misra et al. [66], Copyright 2008 by the Endocrine Society.

adolescents compared to adults, in whom peak bone mass is established. The effect of AN on bone is of particular concern during adolescence. The adolescent years are typically a time of increased bone accrual towards attainment of peak bone mass, an important predictor of future bone health and fracture risk. Bone accrual rates are markedly impaired in adolescents with AN, leading to a decrease in bone density Z-scores over time [55, 66].

In addition to areal BMD, measures of volumetric BMD, bone geometry and microarchitecture, and surrogate measures of bone strength are impaired in AN. Adult

and adolescent women with AN have a decrease in total and trabecular volumetric BMD, an increase in the trabecular cross-sectional area at the cost of the cortical cross-sectional area (likely from estrogen deficiency leading to increased endosteal bone resorption), and a decrease in trabecular number with an increase in trabecular separation [85, 87–90]. Adults also have reductions in cortical and trabecular thickness [89, 90]. These changes result in a decrease in strength estimates, such as stiffness and failure load, and predict an increased risk for fracture [85].

Fig. 2. Prevalence of fractures in 310 adolescent and young adult women with AN 12–22 years old compared with 108 normal-weight controls. Young women with AN had a higher incidence and prevalence of fractures than controls. However, the proportion of upper extremity (UE), lower extremity (LE), and non-extremity fractures did not differ across groups. * $p < 0.05$. Adapted from Faje et al. [5], Copyright 2014 by Wiley Periodicals, Inc.

Fracture incidence and prevalence are higher in adolescents and young adults with AN compared to controls [85], and overall, young women with AN have a 60% increase in fracture risk, although the distribution of fractures does not differ from controls (fig. 2). Similarly, a higher prevalence of fractures has been reported in adults with a past history of AN [3, 7]. Given the morbidity and economic costs of fracture, it is critical to identify appropriate therapies for impaired bone health in AN.

Factors contributing to low bone density and impaired bone geometry and strength in AN include reductions in lean mass and body mass index, low levels of gonadal steroids, IGF-1 and leptin, and high concentrations of cortisol and PYY. Increases in lean mass with recovery are associated with increases in BMD in girls with AN [55]. Weight gain and menses resumption cause some improvement in BMD, though not quite to the extent seen in controls, and residual deficits persist [66–71]. In adults with AN, weight gain results in increases in total hip BMD, whereas menstrual recovery leads to an increase in spine BMD, consistent with estrogen-mediated effects [84]. Overall, BMD increases by 2–3% annually in those who gain weight and recover menstrual function [84].

Although estrogen deficiency is an important cause of low BMD, oral estrogen is not effective in increasing BMD in AN (except in a post hoc analysis of very-low-

weight women), likely because of its IGF-1-suppressive effects [19, 91–94]. In contrast, in one 18-month randomized placebo-controlled trial in adolescents with AN 12–18 years old, physiologic estrogen replacement as the 100- μ g transdermal 17- β -estradiol patch (with cyclic oral medroxyprogesterone acetate 2.5 mg daily for 10 days of every month) was effective in increasing bone accrual rates to those seen in a healthy control population [72] (fig. 3). However, bone density remained lower than in controls because accrual rates need to exceed those in controls for catch-up to occur. This was not observed with estrogen replacement alone, likely because other hormonal alterations were not simultaneously addressed. Physiologic estrogen replacement did prevent a further reduction of BMD Z-scores in girls with AN. Maintenance of BMD Z-scores was also reported in an 18-month randomized controlled trial (RCT) in young women with AN using 5 mg daily oral dehydroepiandrosterone and an oral estrogen-progesterone combination pill (with 20 μ g ethinyl estradiol) [95]. In contrast, testosterone replacement using the low-dose testosterone patch was not effective in increasing BMD in adult women with AN [96].

Low IGF-1 levels are an important determinant of low BMD in AN. A 9-month RCT in adult women with AN of (1) replacement doses of rhIGF-1 with oral estrogen-progesterone versus (2) rhIGF-1 alone, or (3) oral estrogen-progesterone alone, or (4) neither led to a 1.8% increase in spine BMD in the group that received combination therapy compared to a 1% decrease in those who received neither [19]. Similarly, a 7- to 10-day study of rhIGF-1 versus no therapy in adolescents with AN led to a significant increase in bone formation markers in girls who received rhIGF-1 [18]. The effect of transdermal estrogen replacement in adults on BMD is unknown.

Leptin is also bone anabolic, and leptin levels are low in AN. One 3-month study of metreleptin versus placebo in adult women with hypothalamic amenorrhea reported an increase in bone formation markers following leptin administration and resumption of menses in 70% [97]. However, leptin administration led to a reduction in appetite and body weight. Therefore, therapeutic leptin administration would not be advisable in women with amenorrhea due to AN. A subsequent 9-month RCT of metreleptin versus placebo showed an increase in lumbar bone mineral content (BMC), but not BMD, in these women, but fat mass decreased despite careful dose titration to prevent weight loss [98].

Pharmacological approaches to treat low BMD in AN include antiresorptive therapies such as bisphosphonates or denosumab, and bone anabolic therapies such as teri-

Fig. 3. Percent change in lumbar spine BMD in adolescent girls with AN randomized to placebo (AN E-), girls with AN randomized to physiologic estrogen replacement (AN E+), and normal-weight controls (C). AN E+ had significant increases in lumbar spine BMD at 6, 12, and 18 months compared with AN E-. When compared with C, AN E- had significant decreases in lumbar spine BMD at 6, 12, and 18 months, whereas AN E+ did not differ from C for changes in BMD over time. An analysis was performed for differences between means for pairs, * $p < 0.05$. From Misra et al. [72], Copyright 2011 by the American Society for Bone and Mineral Research.

paratide or the anti-sclerostin antibody. One 12-month study of alendronate (35 mg weekly) versus placebo in adolescents with AN 12–18 years old reported an improvement in BMD at the hip, but not of the spine [71]. Conversely, a 12-month study in adult women with AN of 35 mg weekly of risedronate versus placebo reported increases in spine and hip BMD (2–4%) in women who received the active drug [96]. One 6-month RCT of 20 μ g daily teriparatide versus placebo in older adult women with AN reported significant increases in spine BMD in those who received teriparatide [99]. In that study, posteroanterior spine increased $6.0 \pm 1.4\%$ versus placebo, $0.2 \pm 0.7\%$ being the highest increase in spine BMD seen in any intervention study in this disorder. There are no studies thus far of denosumab or the anti-sclerostin antibody in AN.

Summary and Conclusion

Impaired bone health in AN is a consequence of changes in body composition and various endocrine axes, including the HPG, GH/IGF-1, hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes, and in various adipokines and appetite-regulating peptides. In addition to reductions in areal BMD, AN leads to impaired bone structure and strength estimates, associated with an increased risk for fracture. It is thus important to assess BMD in all individuals with a diagnosis of AN, particularly when the condition persists for longer than 6–12 months [73]. Clinically, BMD is assessed using DXA. In children who are still growing, recommended sites for assessment include the lumbar spine and whole body (pref-

erably whole body less head), whereas in older adolescents who have completed growth and in adults, preferred sites include the lumbar spine and hip [100, 101]. In adolescents with AN, bone accrual rates are severely impaired, leading to further reductions in BMD Z-scores over time. Therefore, serial BMD assessment becomes important. In growing children and adolescents, repeat assessment may be performed every 6–12 months, whereas in older adolescents and adults, DXA scans are repeated every 1–2 years [100, 101].

All individuals with AN should have a treatment team in place [73], and the most important therapeutic goal is weight gain aiming for >90% of ideal body weight, followed by weight maintenance. Most females who attain >90% ideal body weight and are able to maintain this over 6–12 months will resume menstrual function [56]. When weight gain is difficult to achieve or if weight gain does not result in menstrual resumption, and particularly if bone density Z-scores are continuing to decrease or if the patient has a history of fractures or develops new fractures, it may be worthwhile considering physiologic estrogen replacement as the transdermal 17- β -estradiol patch with cyclic oral progesterone to stabilize or improve BMD Z-scores [72]. Of note, oral estrogen-progesterone therapy or testosterone replacement are not effective in increasing bone density in women with AN [92, 93, 96]. Testosterone replacement may be a reasonable option for hypogonadal men with AN and osteoporosis; however, data assessing the efficacy of testosterone replacement in men with AN are not available at this time. In adults with AN who have osteoporosis, bisphosphonates are an additional therapeutic option [96]. Although the use of bisphosphonates in premenopausal women

with osteoporosis is problematic because of potential effects on subsequent pregnancies, its use in postmenopausal women with osteoporosis is indicated provided no contraindications exist. In some cases where there is a history of osteoporosis and clinical fractures in premenopausal women, clinical judgment should be used in assessing risks versus benefits of treatment.

In addition to antiresorptive therapies such as estrogen and bisphosphonates, bone anabolic therapies such as rhGH, rhIGF-1, and teriparatide could be particularly useful in AN given that bone formation is decreased markedly in this condition. However, rhGH administration in supraphysiologic doses did not increase bone formation markers in adult women with AN, consistent with the state of GH resistance in this condition [17]. rhIGF-1 was effective in increasing bone formation markers in adults and adolescents with AN [18, 19] and in increasing bone density when given with oral estrogen in adults with AN [19]. rhIGF-1 with physiologic estrogen replacement is currently under investigation in adolescents with AN and may be even more efficacious in increasing bone density in this younger population given that IGF-1 levels typically peak during adolescence. Teriparatide was effective in increasing bone density in older women with AN

in one pilot study [99]. However, more studies are necessary to confirm this effect, and for now, teriparatide use should be reserved for older women with osteoporosis in whom other therapeutic strategies are ineffective or contraindicated. Teriparatide should not be used for younger patients with open epiphysis. At this time, the best strategy for treating low BMD in AN remains weight recovery.

Of note, physiologic estrogen replacement was also effective in reducing trait anxiety and in preventing increases in state anxiety and body dysmorphism observed with weight gain in adolescent girls with AN who received placebo [65]. The impact of hormone replacement on quality of life in AN is an important question that remains to be explored.

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The authors have no conflicts of interest to disclose.

References

- Smink FR, van Hoeken D, Hoek HW: Epidemiology, course, and outcome of eating disorders. *Curr Opin Psychiatry* 2013;26:543–548.
- Hay P, Girosi F, Mond J: Prevalence and sociodemographic correlates of DSM-5 eating disorders in the Australian population. *J Eat Disord* 2015;3:19.
- Lucas AR, Beard CM, O'Fallon WM, Kurland LT: 50-year trends in the incidence of anorexia nervosa in Rochester, Minn: a population-based study. *Am J Psychiatry* 1991;148:917–922.
- Lucas AR, Crowson CS, O'Fallon WM, Melton LJ 3rd: The ups and downs of anorexia nervosa. *Int J Eat Disord* 1999;26:397–405.
- Faje AT, Fazeli PK, Miller KK, Katzman DK, Ebrahimi S, Lee H, et al: Fracture risk and areal bone mineral density in adolescent females with anorexia nervosa. *Int J Eat Disord* 2014;47:458–466.
- Lucas AR, Melton LJ 3rd, Crowson CS, O'Fallon WM: Long-term fracture risk among women with anorexia nervosa: a population-based cohort study. *Mayo Clin Proc* 1999;74:972–977.
- Vestergaard P, Emborg C, Stoving RK, Hagen C, Mosekilde L, Brixen K: Fractures in patients with anorexia nervosa, bulimia nervosa, and other eating disorders – a nationwide register study. *Int J Eat Disord* 2002;32:301–308.
- Argente J, Caballo N, Barrios V, Munoz MT, Pozo J, Chowen JA, et al: Multiple endocrine abnormalities of the growth hormone and insulin-like growth factor axis in patients with anorexia nervosa: effect of short- and long-term weight recuperation. *J Clin Endocrinol Metab* 1997;82:2084–2092.
- Misra M, Miller K, Bjornson J, Hackman A, Aggarwal A, Chung 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.
- Scacchi M, Pincelli AI, Caumo A, Tomasi P, Delitala G, Baldi G, et al: Spontaneous nocturnal growth hormone secretion in anorexia nervosa. *J Clin Endocrinol Metab* 1997;82:3225–3229.
- Stoving RK, Veldhuis JD, Flyvbjerg A, Vinten J, Hangaard J, Koldkjaer OG, et al: Jointly amplified basal and pulsatile growth hormone (GH) secretion and increased process irregularity in women with anorexia nervosa: indirect evidence for disruption of feedback regulation within the GH-insulin-like growth factor I axis. *J Clin Endocrinol Metab* 1999;84:2056–2063.
- Misra M, Miller KK, Herzog DB, Ramaswamy K, Aggarwal A, Almazan C, 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.
- Counts DR, Gwirtsman H, Carlsson LM, Lessem M, Cutler GB Jr: 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.
- Misra M, Miller KK, Kuo K, Griffin K, Stewart V, Hunter E, et al: Secretory dynamics of ghrelin in adolescent girls with anorexia nervosa and healthy adolescents. *Am J Physiol Endocrinol Metab* 2005;289:E347–E356.
- Misra M, Miller KK, Kuo K, Griffin K, Stewart V, Hunter E, et al: Secretory dynamics of leptin in adolescent girls with anorexia nervosa and healthy adolescents. *Am J Physiol Endocrinol Metab* 2005;289:E373–E381.
- Fazeli PK, Misra M, Goldstein M, Miller KK, Klibanski A: Fibroblast growth factor-21 may mediate growth hormone resistance in anorexia nervosa. *J Clin Endocrinol Metab* 2010;95:369–374.

- 17 Fazeli PK, Lawson EA, Prabhakaran R, Miller KK, Donoho DA, Clemmons DR, et al: Effects of recombinant human growth hormone in anorexia nervosa: a randomized, placebo-controlled study. *J Clin Endocrinol Metab* 2010;95:4889–4897.
- 18 Misra M, McGrane J, Miller KK, Goldstein MA, Ebrahimi S, Weigel T, et al: Effects of rhIGF-1 administration on surrogate markers of bone turnover in adolescents with anorexia nervosa. *Bone* 2009;45:493–498.
- 19 Grinspoon S, Thomas L, Miller K, Herzog D, Klibanski A: Effects of recombinant human IGF-I and oral contraceptive administration on bone density in anorexia nervosa. *J Clin Endocrinol Metab* 2002;87:2883–2891.
- 20 Misra M, Miller KK, Almazan C, Worley M, Herzog DB, Klibanski A: Hormonal determinants of regional body composition in adolescent girls with anorexia nervosa and controls. *J Clin Endocrinol Metab* 2005;90:2580–2587.
- 21 Modan-Moses D, Yaroslavsky A, Novikov I, Segev S, Toledano A, Miterany E, et al: Stunting of growth as a major feature of anorexia nervosa in male adolescents. *Pediatrics* 2003;111:270–276.
- 22 Modan-Moses D, Yaroslavsky A, Kochavi B, Toledano A, Segev S, Balawi F, et al: Linear growth and final height characteristics in adolescent females with anorexia nervosa. *PLoS One* 2012;7:e45504.
- 23 Prabhakaran R, Misra M, Miller KK, Kruczek K, Sundaralingam S, Herzog DB, et al: Determinants of height in adolescent girls with anorexia nervosa. *Pediatrics* 2008;121:e1517–e1523.
- 24 Roze C, Doyen C, Le Heuzey MF, Armoogum P, Mouren MC, Leger J: Predictors of late menarche and adult height in children with anorexia nervosa. *Clin Endocrinol (Oxf)* 2007;67:462–467.
- 25 Boyar RM, Hellman LD, Roffwarg H, Katz J, Zumoff B, O'Connor J, et al: Cortisol secretion and metabolism in anorexia nervosa. *N Engl J Med* 1977;296:190–193.
- 26 Misra M, Miller KK, Almazan C, Ramaswamy K, Lapcharoensap W, Worley M, 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.
- 27 Lawson EA, Donoho D, Miller KK, Misra M, Meenaghan E, Lydecker J, 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.
- 28 Grinspoon S, Thomas L, Miller K, Pitts S, Herzog D, Klibanski A: 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.
- 29 Misra M, Prabhakaran R, Miller KK, Tsai P, Lin A, Lee N, et al: Role of cortisol in menstrual recovery in adolescent girls with anorexia nervosa. *Pediatr Res* 2006;59:598–603.
- 30 Lawson EA, Miller KK, Blum JJ, Meenaghan E, Misra M, Eddy KT, et al: Leptin levels are associated with decreased depressive symptoms in women across the weight spectrum, independent of body fat. *Clin Endocrinol (Oxf)* 2012;76:520–525.
- 31 Miller KK, Parulekar MS, Schoenfeld E, Anderson E, Hubbard J, Klibanski A, et al: Decreased leptin levels in normal weight women with hypothalamic amenorrhea: the effects of body composition and nutritional intake. *J Clin Endocrinol Metab* 1998;83:2309–2312.
- 32 Hamrick MW, Pennington C, Newton D, Xie D, Isles C: Leptin deficiency produces contrasting phenotypes in bones of the limb and spine. *Bone* 2004;34:376–383.
- 33 Takeda S, Eleftheriou F, Levasseur R, Liu X, Zhao L, Parker KL, et al: Leptin regulates bone formation via the sympathetic nervous system. *Cell* 2002;111:305–317.
- 34 Biver E, Salliot C, Combescure C, Gossec L, Hardouin P, Legroux-Gerot I, et al: Influence of adipokines and ghrelin on bone mineral density and fracture risk: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011;96:2703–2713.
- 35 Misra M, Miller KK, Cord J, Prabhakaran R, Herzog DB, Goldstein M, et al: Relationships between serum adipokines, insulin levels, and bone density in girls with anorexia nervosa. *J Clin Endocrinol Metab* 2007;92:2046–2052.
- 36 Tagami T, Satoh N, Usui T, Yamada K, Shimatsu A, Kuzuya H: Adiponectin in anorexia nervosa and bulimia nervosa. *J Clin Endocrinol Metab* 2004;89:1833–1837.
- 37 Pannacciulli N, Vettor R, Milan G, Granzotto M, Catucci A, Federspil 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.
- 38 Housova J, Anderlova K, Krizova J, Haluzikova D, Kremen J, Kumstyrova T, et al: Serum adiponectin and resistin concentrations in patients with restrictive and binge/purge form of anorexia nervosa and bulimia nervosa. *J Clin Endocrinol Metab* 2005;90:1366–1370.
- 39 Modan-Moses D, Stein D, Pariente C, Yaroslavsky A, Ram A, Faigin M, et al: Modulation of adiponectin and leptin during refeeding of female anorexia nervosa patients. *J Clin Endocrinol Metab* 2007;92:1843–1847.
- 40 Amitani H, Asakawa A, Ogiso K, Nakahara T, Ushikai M, Haruta I, et al: The role of adiponectin multimers in anorexia nervosa. *Nutrition* 2013;29:203–206.
- 41 Lu M, Tang Q, Olefsky JM, Mellon PL, Webster NJ: Adiponectin activates adenosine monophosphate-activated protein kinase and decreases luteinizing hormone secretion in LbetaT2 gonadotropes. *Mol Endocrinol* 2008;22:760–771.
- 42 Luo XH, Guo LJ, Xie H, Yuan LQ, Wu XP, Zhou HD, et al: Adiponectin stimulates RANKL and inhibits OPG expression in human osteoblasts through the MAPK signaling pathway. *J Bone Miner Res* 2006;21:1648–1656.
- 43 Janas-Kozik M, Krupka-Matuszczyk I, Malinowska-Kolodziej I, Lewin-Kowalik J: Total ghrelin plasma level in patients with the restrictive type of anorexia nervosa. *Regul Pept* 2007;140:43–46.
- 44 Nakahara T, Kojima S, Tanaka M, Yasuhara D, Harada T, Sagiya K, et al: Incomplete restoration of the secretion of ghrelin and PYY compared to insulin after food ingestion following weight gain in anorexia nervosa. *J Psychiatr Res* 2007;41:814–820.
- 45 Monteleone P, Serritella C, Martiadis V, Scognamiglio P, Maj M: Plasma obestatin, ghrelin, and ghrelin/obestatin ratio are increased in underweight patients with anorexia nervosa but not in symptomatic patients with bulimia nervosa. *J Clin Endocrinol Metab* 2008;93:4418–4421.
- 46 Misra M, Miller KK, Stewart V, Hunter E, Kuo K, Herzog DB, et al: Ghrelin and bone metabolism in adolescent girls with anorexia nervosa and healthy adolescents. *J Clin Endocrinol Metab* 2005;90:5082–5087.
- 47 Misra M, Miller KK, Tsai P, Gallagher K, Lin A, Lee N, et al: Elevated peptide YY levels in adolescent girls with anorexia nervosa. *J Clin Endocrinol Metab* 2006;91:1027–1033.
- 48 Sedlackova D, Kopeckova J, Papezova H, Hainer V, Kvasnickova H, Hill M, et al: Comparison of a high-carbohydrate and high-protein breakfast effect on plasma ghrelin, obestatin, NPY and PYY levels in women with anorexia and bulimia nervosa. *Nutr Metab (Lond)* 2012;9:52.
- 49 Germain N, Galusca B, Le Roux CW, Bossu C, Ghatei MA, Lang F, et al: Constitutional thinness and lean anorexia nervosa display opposite concentrations of peptide YY, glucagon-like peptide 1, ghrelin, and leptin. *Am J Clin Nutr* 2007;85:967–971.
- 50 Pinilla L, Fernandez-Fernandez R, Vigo E, Navarro VM, Roa J, Castellano JM, et al: Stimulatory effect of PYY-(3–36) on gonadotropin secretion is potentiated in fasted rats. *Am J Physiol Endocrinol Metab* 2006;290:E1162–E1171.
- 51 Wong IP, Driessler F, Khor EC, Shi YC, Horner B, Nguyen AD, et al: Peptide YY regulates bone remodeling in mice: a link between gut and skeletal biology. *PLoS One* 2012;7:e40038.
- 52 Utz AL, Lawson EA, Misra M, Mickley D, Gleysteen S, Herzog DB, et al: Peptide YY (PYY) levels and bone mineral density (BMD) in women with anorexia nervosa. *Bone* 2008;43:135–139.
- 53 Boyar RM, Katz J, Finkelstein JW, Kapen S, Weiner H, Weitzman ED, et al: Anorexia nervosa. Immaturity of the 24-hour luteinizing hormone secretory pattern. *N Engl J Med* 1974;291:861–865.
- 54 Misra M, Katzman DK, Cord J, Manning SJ, Mendes N, Herzog DB, et al: Bone metabolism in adolescent boys with anorexia nervosa. *J Clin Endocrinol Metab* 2008;93:3029–3036.

- 55 Soyka LA, Misra M, Frenchman A, Miller KK, Grinspoon S, Schoenfeld DA, et al: Abnormal bone mineral accrual in adolescent girls with anorexia nervosa. *J Clin Endocrinol Metab* 2002;87:4177–4185.
- 56 Golden NH, Jacobson MS, Schebendach J, Solanto MV, Hertz SM, Shenker IR: Resumption of menses in anorexia nervosa. *Arch Pediatr Adolesc Med* 1997;151:16–21.
- 57 Castro J, Lazaro L, Pons F, Halperin I, Toro J: Predictors of bone mineral density reduction in adolescents with anorexia nervosa. *J Am Acad Child Adolesc Psychiatry* 2000;39:1365–1370.
- 58 Misra M, Aggarwal A, Miller KK, Almazan C, Worley M, Soyka LA, et al: Effects of anorexia nervosa on clinical, hematologic, biochemical, and bone density parameters in community-dwelling adolescent girls. *Pediatrics* 2004;114:1574–1583.
- 59 Audi L, Vargas DM, Gussinye M, Yeste D, Marti G, Carrascosa A: Clinical and biochemical determinants of bone metabolism and bone mass in adolescent female patients with anorexia nervosa. *Pediatr Res* 2002;51:497–504.
- 60 Schneider M, Fisher M, Weinerman S, Lesser M: Correlates of low bone density in females with anorexia nervosa. *Int J Adolesc Med Health* 2002;14:297–306.
- 61 Riggs B: The mechanisms of estrogen regulation of bone resorption. *J Clin Invest* 2000;106:1203–1204.
- 62 Modder UI, Clowes JA, Hoey K, Peterson JM, McCready L, Oursler MJ, et al: Regulation of circulating sclerostin levels by sex steroids in women and in men. *J Bone Miner Res* 2011;26:27–34.
- 63 Misra M, Katzman DK, Cord J, Manning SJ, Mickley D, Herzog DB, 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.
- 64 Chui HT, Christensen BK, Zipursky RB, Richards BA, Hanratty MK, Kabani NJ, et al: Cognitive function and brain structure in females with a history of adolescent-onset anorexia nervosa. *Pediatrics* 2008;122:e426–e437.
- 65 Misra M, Katzman DK, Estella NM, Eddy KT, Weigel T, Goldstein MA, 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.
- 66 Misra M, Prabhakaran R, Miller KK, Goldstein MA, Mickley D, Clauss L, et al: Weight gain and restoration of menses as predictors of bone mineral density change in adolescent girls with anorexia nervosa-1. *J Clin Endocrinol Metab* 2008;93:1231–1237.
- 67 Mika C, Holtkamp K, Heer M, Gunther RW, Herpertz-Dahlmann B: A 2-year prospective study of bone metabolism and bone mineral density in adolescents with anorexia nervosa. *J Neural Transm* 2007;114:1611–1618.
- 68 Compston JE, McConachie C, Stott C, Hannon RA, Kaptoge S, DeBiram I, et al: Changes in bone mineral density, body composition and biochemical markers of bone turnover during weight gain in adolescents with severe anorexia nervosa: a 1-year prospective study. *Osteoporos Int* 2006;17:77–84.
- 69 Bachrach LK, Guido D, Katzman D, Litt IF, Marcus R: Decreased bone density in adolescent girls with anorexia nervosa. *Pediatrics* 1990;86:440–447.
- 70 Bachrach LK, Katzman DK, Litt IF, Guido D, Marcus R: Recovery from osteopenia in adolescent girls with anorexia nervosa. *J Clin Endocrinol Metab* 1991;72:602–606.
- 71 Golden NH, Iglesias EA, Jacobson MS, Carey D, Meyer W, Schebendach J, 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.
- 72 Misra M, Katzman D, Miller KK, Mendes N, Snelgrove D, Russell M, et al: Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa. *J Bone Miner Res* 2011;26:2430–2438.
- 73 Misra M, Klibanski A: Endocrine consequences of anorexia nervosa. *Lancet Diabetes Endocrinol* 2014;2:581–592.
- 74 Bredella MA, Fazeli PK, Freedman LM, Calder G, Lee H, Rosen CJ, 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.
- 75 Lawson EA, Donoho DA, Blum JL, Meenaghan EM, Misra M, Herzog DB, 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.
- 76 Wojcik MH, Meenaghan E, Lawson EA, Misra M, Klibanski A, Miller KK: Reduced amylin levels are associated with low bone mineral density in women with anorexia nervosa. *Bone* 2010;46:796–800.
- 77 Golden NH, Lankowsky L, Schebendach J, Palestro CJ, Jacobson MS, Shenker IR: The effect of estrogen-progestin treatment on bone mineral density in anorexia nervosa. *J Pediatr Adolesc Gynecol* 2002;15:135–143.
- 78 Stone M, Briody J, Kohn MR, Clarke S, Madden S, Cowell CT: Bone changes in adolescent girls with anorexia nervosa. *J Adolesc Health* 2006;39:835–841.
- 79 Garcia-De Alvaro MT, Munoz-Calvo MT, Martinez G, Barrios V, Hawkins F, Argente J: Regional skeletal bone deficit in female adolescents with anorexia nervosa: influence of the degree of malnutrition and weight recovery in a two year longitudinal study. *J Pediatr Endocrinol Metab* 2007;20:1223–1231.
- 80 Oswiecimska J, Ziora K, Pluskiewicz W, Geisler G, Broll-Waska K, Karasek D, et al: Skeletal status and laboratory investigations in adolescent girls with anorexia nervosa. *Bone* 2007;41:103–110.
- 81 Jagielska G, Wolanczyk T, Komender J, Tomaszewicz-Libudziec C, Przedlacki J, Ostrowski K: Bone mineral density in adolescent girls with anorexia nervosa – a cross-sectional study. *Eur Child Adolesc Psychiatry* 2002;11:57–62.
- 82 Jagielska G, Wolanczyk T, Komender J, Tomaszewicz-Libudziec C, Przedlacki J, Ostrowski K: Bone mineral content and bone mineral density in adolescent girls with anorexia nervosa – a longitudinal study. *Acta Psychiatr Scand* 2001;104:131–137.
- 83 Grinspoon S, Thomas E, Pitts S, Gross E, Mickley D, Miller K, et al: Prevalence and predictive factors for regional osteopenia in women with anorexia nervosa. *Ann Intern Med* 2000;133:790–794.
- 84 Miller KK, Lee EE, Lawson EA, Misra M, Minihan J, Grinspoon SK, et al: Determinants of skeletal loss and recovery in anorexia nervosa. *J Clin Endocrinol Metab* 2006;91:2931–2937.
- 85 Faje AT, Karim L, Taylor A, Lee H, Miller KK, Mendes N, 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.
- 86 Misra M, Soyka LA, Miller KK, Herzog DB, Grinspoon S, De Chen D, et al: Serum osteoprotegerin in adolescent girls with anorexia nervosa. *J Clin Endocrinol Metab* 2003;88:3816–3822.
- 87 Bredella MA, Misra M, Miller KK, Madisch I, Sarwar A, Cheung A, 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.
- 88 Bredella MA, Fazeli PK, Miller KK, Misra M, Torriani M, Thomas BJ, et al: Increased bone marrow fat in anorexia nervosa. *J Clin Endocrinol Metab* 2009;94:2129–2136.
- 89 Milos G, Spindler A, Rueggsegger P, Seifert B, Muhlebach S, Uebelhart D, et al: Cortical and trabecular bone density and structure in anorexia nervosa. *Osteoporos Int* 2005;16:783–790.
- 90 Lawson EA, Miller KK, Bredella MA, Phan C, Misra M, Meenaghan E, et al: Hormone predictors of abnormal bone microarchitecture in women with anorexia nervosa. *Bone* 2010;46:458–463.

- 91 Munoz MT, Morande G, Garcia-Centenera JA, Hervas F, Pozo J, Argente J: The effects of estrogen administration on bone mineral density in adolescents with anorexia nervosa. *Eur J Endocrinol* 2002;146:45–50.
- 92 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.
- 93 Klibanski A, Biller BM, Schoenfeld DA, Herzog DB, Saxe VC: The effects of estrogen administration on trabecular bone loss in young women with anorexia nervosa. *J Clin Endocrinol Metab* 1995;80:898–904.
- 94 Munoz-Calvo MT, Barrios V, Garcia de Alvaro MT, Lefort M, Mendez-Davila C, Argente J, et al: Maintained malnutrition produces a progressive decrease in (OPG)/RANKL ratio and leptin levels in patients with anorexia nervosa. *Scand J Clin Lab Invest* 2007;67:387–393.
- 95 Divasta AD, Feldman HA, Giancaterino C, Rosen CJ, Leboff MS, Gordon CM: The effect of gonadal and adrenal steroid therapy on skeletal health in adolescents and young women with anorexia nervosa. *Metabolism* 2012;61:1010–1020.
- 96 Miller KK, Meenaghan E, Lawson EA, Misra M, Gleysteen S, Schoenfeld D, 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.
- 97 Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM, et al: Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl J Med* 2004;351:987–997.
- 98 Sienkiewicz E, Magkos F, Aronis KN, Brinkoetter M, Chamberland JP, Chou S, 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.
- 99 Fazeli PK, Wang IS, Miller KK, Herzog DB, Misra M, Lee H, et al: Teriparatide increases bone formation and bone mineral density in adult women with anorexia nervosa. *J Clin Endocrinol Metab* 2014;99:1322–1329.
- 100 Bianchi ML, Leonard MB, Bechtold S, Hogler W, Mughal MZ, Schonau E, et al: Bone health in children and adolescents with chronic diseases that may affect the skeleton: the 2013 ISCD Pediatric Official Positions. *J Clin Densitom* 2014;17:281–294.
- 101 Crabtree NJ, Arabi A, Bachrach LK, Fewtrell M, El-Hajj Fuleihan G, Kecskemethy HH, et al: Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD Pediatric Official Positions. *J Clin Densitom* 2014;17:225–242.