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Endocrine Effects of Anorexia Nervosa

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EPIDEMIOLOGY

In 1874, Sir William Gull, one of Queen Victoria's physicians, coined the term anorexia nervosa to name a syndrome he had described in 1868 in an address to the Annual Meeting of the British Medical Association in Oxford, United Kingdom.¹ He reported having treated several girls and women between the ages of 16 and 23 years with severe emaciation for which he could discern no organic cause (including tuberculosis, a common cause of weight loss at the time). He noted the cardinal features of the disease to be bradycardia, hypothermia, and an endocrine complication, amenorrhea, that tended to reverse with refeeding. He also noted that the disease could on occasion be fatal. Although he reported that anorexia nervosa occurred primarily in women, he noted that it also occurred in men. He concluded that the syndrome was of psychiatric origin and although, in retrospect, the disease had likely existed for centuries (for example, Mary Queen of Scots' teenage illness has been attributed by some to anorexia nervosa), Gull's disease construct forms the basis of the current conception of the disease. The definition and understanding of anorexia nervosa have evolved, and continue to do so, with the most recent changes to the diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders V [DSM V]) due to be published in May of 2013. The DSM V criteria are widely expected to no longer include amenorrhea as a necessary condition of the diagnosis, recognizing that vulnerability to neuroendocrine dysregulation is highly variable, and many women with all of the psychiatric features of anorexia nervosa and very low weight continue to have regular menstrual cycles. The other diagnostic criteria expected to be included in the DSM V are similar to those of the previous DSM diagnostic criteria, but broader, and are expected to require low body weight, restrictive eating behavior, and body image disturbance. Anorexia nervosa is further subclassified into 2 types: restricting and binge-purge, the latter characterized by purging episodes. There is significant crossover between the two types,² and the anorexia nervosa binge-purge type differs from bulimia nervosa in that the former requires low weight for the diagnostic criteria to be met.

Anorexia nervosa is the third most common chronic disorder in adolescent girls³ and has a reported prevalence of 0.3% to 3% in women.⁴⁻⁶ The syndrome rarely affects boys and men, and less is known about the effects of anorexia nervosa in men, though they seem to suffer

from many of the same neuroendocrine complications as in girls and women. This article focuses on endocrine effects of anorexia nervosa in women.

Anorexia nervosa is commonly a chronic disease, particularly in adults. Between 20% and 30% of women with anorexia nervosa are afflicted chronically; 30% achieve partial recovery and 50% sustain a full recovery.⁷ Anorexia nervosa carries a high risk of death, with a standardized mortality ratio of 11 to 12 times that expected,^{8,9} and a particularly high risk of suicide of 56 times that expected for age and sex.⁹ Alcoholism, advanced age, history of suicide attempt, severity and length of time of disease, and diuretic use all increase the risk of death from the disease.⁹ Medical and endocrine complications of the disease include electrolyte disturbances, primarily hyponatremia, and hypokalemia, both of which occur in 20% of patients, and hypokalemia is observed in patients with binge-purge type anorexia nervosa.¹⁰ Hyponatremia can be severe enough to cause seizures, and may be caused by syndrome of inappropriate anti-diuretic hormone or primary polydipsia. Hypernatremia from diabetes insipidus has been reported but is rarely observed. Decreased T4 to T3 conversion is common.¹¹ Mild transaminitis (in 12%), anemia of chronic disease (in 39%), and leukocytopenia (in 34%) are commonly seen. With severely low weight, pancytopenia can occur.¹² Congestive heart failure secondary to ipecac, used to self-induce vomiting, is usually reversible with discontinuation of the offending agent. The endocrine complications about which most is known include hypothalamic amenorrhea, growth hormone (GH) resistance, hypercortisolemia, appetite hormone dysregulation, and bone loss (Table 1), and these are discussed in detail later.

HYPOTHALAMIC AMENORRHEA

The most widely recognized endocrine complication of anorexia nervosa is amenorrhea, which occurs in many, but not all, girls and women with anorexia nervosa. The early seminal characterization of minimum weight for height necessary for menarche and normal reproductive function, as described by Frisch and McArthur¹³ in the 1970s, is a concept that formed the basis for understanding the cause of amenorrhea that has evolved over the subsequent decades. It is now understood that many, but not all, women with anorexia nervosa develop hypothalamic amenorrhea, which may, in part, be regulated by adipocyte adipokine secretion. The physiology underlying hypothalamic amenorrhea was first described in a detailed manner in an article by Boyar and colleagues,¹⁴ published in the *New England Journal of Medicine* in 1974. In that paper and subsequent work, Boyar and colleagues¹⁴ carefully delineated several patterns of dysregulated luteinizing hormone (LH) pulsatility in amenorrheic women with anorexia nervosa. LH pulses reflect gonadotrophin-releasing hormone (GnRH) pulsatility and are readily measurable in the periphery by frequent blood sampling, in contrast with GnRH. Boyar and colleagues¹⁴ described altered LH, and therefore GnRH pulsatility, in women with anorexia nervosa, including an absence of pulsations and pubertal patterns in which pulsatility occurs only during the night. They also showed a reversal to normal of LH pulsatility abnormalities in women who regained weight and recovered menses. They also showed that the degree of immaturity of LH pattern did not correlate reliably with duration of illness, degree of fatness, or extent of deficit from ideal weight, and that regaining of menses did not show a simple relationship to weight.¹⁵ These observations reflect 2 important concepts observed in clinical practice that are still not well understood, namely: (1) that although many women with very low weight develop hypothalamic amenorrhea, others of comparable low weight remain eumenorrheic; and (2) although many women with anorexia nervosa recover normal reproductive function with weight restoration, approximately 15% remain amenorrheic.¹⁶ A partial understanding of the mechanisms underlying these phenomena has occurred with an evolution of concepts and the recognition of adipose tissue as an endocrine organ that secretes peptides that regulate energy balance, appetite, and other functions, including reproduction. Most of this work has

focused on leptin, a 16-kDa peptide, primarily expressed in adipocytes and secreted in response to short-term caloric intake. It is thought that leptin's primary role is to signal inadequate energy stores, and leptin has been shown in both humans and animals to directly regulate reproductive function. Leptin receptors are present in the hypothalamus, and congenital leptin deficiency is characterized by hypogonadotropic hypogonadism in addition to obesity.¹⁷ Particularly relevant to identifying the cause of hypothalamic amenorrhea in anorexia nervosa, leptin has been shown to play an important causal role in starvation-associated hypothalamic amenorrhea. In an important study by Ahima and colleagues,¹⁸ leptin replacement prevented the delay in estrous in mice caused by 48 hours of fasting, suggesting that the acute decrease in leptin observed with fasting is responsible for the impairment in reproduction function observed with starvation. Mean serum leptin levels are similarly lower in association with lower body fat mass in women with anorexia nervosa who experience amenorrhea than in women with anorexia nervosa of comparable mean low weight but without amenorrhea.¹⁹ However, in the study in which this was shown, there was considerable overlap between leptin levels in the two groups, and there was no threshold below which amenorrhea was a certainty or above which eumenorrhea could be predicted to resume.¹⁹ The implications of these findings include that leptin levels cannot be used clinically to set recovery goals and that hypoleptinemia is only one factor of likely many that are implicated in the pathophysiology of the hypothalamic amenorrhea in women with anorexia nervosa. Other endocrine and nonendocrine factors that may be involved include kisspeptin, cortisol, and/or appetite-regulating peptides, but none has been specifically implicated as a factor in the pathophysiology of hypothalamic amenorrhea in anorexia nervosa. Kisspeptin, the endogenous ligand for the hypothalamic kisspeptin receptor, inactivating mutations of which result in pubertal failure,^{20,21} is one candidate. Acute, but not chronic, administration of kiss-peptin has been shown to result in gonadotropin release in a group of women with hypothalamic amenorrhea,²² but women with anorexia nervosa specifically have not been studied. Leptin administration to 8 healthy-weight women with functional hypothalamic amenorrhea (body mass index [BMI] 18.8–24.4 kg/m²) resulted in ovulatory cycles in 3 but also resulted in weight loss.²³ Therefore, leptin administration, should it become more widely available, is not an appropriate therapeutic option for women with anorexia nervosa.

The mechanisms underlying lack of recovery of hypothalamic amenorrhea in some women with anorexia nervosa despite weight recovery are incompletely understood. One study showed lower leptin levels compared with healthy women of similar mean BMI and persistence of disordered eating-related psychological symptoms in a group of such women, possibly reflecting incomplete recovery in terms of fat mass and psychological symptoms in some of the women.²⁴

Hypothalamic amenorrhea in women with anorexia nervosa results in hypoandrogenemia in addition to hypoestrogenemia, with a further reduction in free testosterone levels in women with anorexia nervosa receiving oral contraceptives. This finding has been shown in a group of 169 women with anorexia nervosa compared with 21 healthy controls²⁵ and follows logically because, in women of reproductive age, approximately 60% of serum testosterone is secreted from the ovaries, whereas 40% is of adrenal origin, as shown in bilateral oophorectomy studies.²⁶ Studies in adults have shown no decrement in the adrenally derived prohormone dehydroepiandrosterone sulfate (DHEAS) compared with lean controls,²⁵ and dehydroepiandrosterone (DHEA) levels stimulate normally with cosyntropin.²⁷ In contrast, a study in adolescent girls showed low DHEAS levels in relation to a laboratory-generated normal range.²⁸ The consequences, if any, of relative androgen deficiency in women with anorexia nervosa are not known, but may include a reduction in muscle mass or bone mass, and or negative effects on mood, as observed in hypogonadal men, although testosterone levels are 10 to 20 times greater than in healthy women and therefore the relevance of

relatively low androgen levels in women cannot be extrapolated from data in men. With regard to muscle mass, a small, 1-year, randomized, placebo-controlled study of low-dose transdermal testosterone (300 µg daily) showed increases in lean body mass,²⁹ suggesting a possible effect of hypogonadism to cause a relative reduction in muscle mass. In contrast, the same study showed no effect on bone mass, despite an acute increase in a marker of bone formation.²⁹ A cross-sectional study showed an inverse relationship between serum androgen levels and severity of depression and anxiety symptoms in women with anorexia nervosa such that, in general, women with the lowest androgen levels experienced the most severe depression and anxiety symptoms.³⁰ Whether relative androgen deficiency contributes to affective comorbidities and whether androgen replacement therapy would be effective therapeutically is unknown. In addition, although the data regarding androgen effects on libido and sexual function in postmenopausal women show effectiveness on these end points, whether low libido or sexual dysfunction are prevalent and affected by relative androgen deficiency in women with anorexia nervosa and/or responds to low-dose androgen therapy has not been studied.

GH RESISTANCE

Roth and colleagues³¹ reported an increase in GH with fasting in healthy subjects in 1963 in *Science*, and, in contrast with what was expected given the known effects of GH to stimulate insulinlike growth factor I (IGF-I) release from the liver, subsequent studies showed low IGF-I levels, a phenomenon termed GH resistance because the liver is resistant to the usual effects of GH. Studies in the 1990s established that both basal and pulsatile GH release are increased in women with anorexia nervosa, the former 4 times and the latter 20 times the levels observed in healthy-weight women of comparable age.³² GH secretion is also higher in adolescent girls with anorexia nervosa than in healthy adolescent girls, including during the time of their physiologic peak in GH.³³ However, despite the increase in GH secretion, IGF-I levels are low in anorexia nervosa, and this cannot be attributed to decreases in binding globulins. This finding was shown by Stoving and colleagues,³⁴ who reported reduced IGF-I bioactivity using a kinase receptor activation assay. The low serum IGF-I levels are thought to cause the increase in GH through a feedback mechanism. Even high doses of GH are ineffective in overcoming GH resistance in women with anorexia nervosa, as was shown by Fazeli and colleagues,³⁵ who administered GH at a mean maximum daily dose of 1.4 mg/d for 12 weeks to a group of women with anorexia nervosa and observed no significant resultant increase in serum IGF-I levels. These doses of GH resulted in a reduction in fat mass and leptin levels, likely from the IGF-I-independent effects of GH, with no benefit to lean body mass or bone, because GH effects are known to be mediated primarily by IGF-I.

Studies suggest that GH resistance reverses with weight gain in women with anorexia nervosa. IGF-I levels seem to increase in a stepwise fashion with weight gain, resulting in a reduction of GH levels to normal through intact feedback mechanisms.^{32,34,36}

HYPERCORTISOLEMIA

In 1977, Boyar and colleagues¹¹ were also the first to establish that anorexia nervosa can be accompanied by hypercortisolemia. They reported that 24-hour mean plasma cortisol concentrations were nearly double in women with anorexia nervosa compared with healthy controls because of an increased half-life and decreased clearance rate rather than an increased cortisol production rate. In addition, 24-hour urinary cortisol was increased in 2 of 5 patients in whom the data were available. A subsequent study by Doerr and colleagues³⁷ in 1980 established lack of dexamethasone suppressibility of cortisol and the reversibility of the hypercortisolemia with a modest level of weight gain, although subsequent studies have

identified a subgroup of patients with anorexia nervosa in whom hypercortisolemia persists despite weight recovery.³⁸⁻⁴⁰ Subsequent studies have also established an increased serum cortisol response to cortrosyn²⁷ and increased midnight salivary cortisol levels⁴¹ in anorexia nervosa. Although women with hypercortisolemia secondary to anorexia nervosa are underweight in contrast with the characteristic central adiposity of Cushing syndrome, there are consequences of hypercortisolemia in anorexia nervosa that mirror those observed in Cushing syndrome. For example, women with anorexia nervosa and higher urine free cortisol levels tend to accumulate proportionally more trunk, than extremity, fat during recovery.⁴² Higher serum cortisol levels similarly predict future weight gain and return of menses in adolescent girls with anorexia nervosa,⁴³ the latter likely being a consequence, at least partially, of the former. Another impactful consequence of hypercortisolemia that mirrors that observed in Cushing syndrome is bone loss, which is discussed later. In addition, degree of hypercortisolemia is associated with severity of depression, anxiety, and reduced bone mineral density in anorexia nervosa.⁴⁴

APPETITE HORMONE DYSREGULATION

A recent area of investigation has been appetite regulation in anorexia nervosa, which is characterized by restrictive eating behavior despite low weight, leading to speculation about the presence of appetite hormone dysregulation in this syndrome. Although increased serum levels of anorexigenic hormones and suppressed serum levels of orexigenic hormones would be predicted in this state of chronic starvation, this has proved only partially to be the case. Serum levels of the anorexigenic hormone leptin are suppressed, as predicted based on lower fat mass, the source of leptin secretion.^{45,46} However, the anorexigenic hormone PYY, which is secreted by intestinal L cells in response to food intake, is increased in both girls and women with anorexia nervosa compared with normal controls,^{47,48} leading to speculation that dysregulation of the NPY-PYY appetite regulatory system may play a causal role in the development of anorexia nervosa in some patients. However, this hypothesis is difficult to test, and it is unclear whether it is the case. PYY levels are positively associated with degree of eating disorder thinking and behavior as determined by self-administered questionnaires, independently of weight,⁴⁹ suggesting a possible relationship between the psychological features of anorexia nervosa and PYY. Mean serum levels of the orexigenic hormone ghrelin, which is released by oxyntic cells of the stomach, seems to be higher in girls and women with anorexia nervosa than controls,⁵⁰⁻⁵² as would be predicted in a nutritionally deprived population. However, one study reported low ghrelin levels in women with anorexia nervosa and binge-purge type⁵³ and another showed an amplified reduction in ghrelin levels during a euglycemic hyperinsulinemic clamp,⁵⁴ raising the question of whether the normal ghrelin suppressive secretory response to food is exaggerated in anorexia nervosa and might lead to an increased sensation of satiety in such patients.

NEUROENDOCRINE DYSREGULATION AND BONE LOSS

Hypogonadism, GH resistance, hypercortisolemia, and appetite hormone dysregulation contribute to the severe bone loss observed in girls and women with anorexia nervosa. Despite a mean age in the mid-20s in most studies, more than 90% of women with anorexia nervosa have osteopenia and 40% have osteoporosis,⁵⁵ with fewer than 15% of such women having normal bone density at all skeletal sites.¹⁰ Bone mineral density decreases at a mean rate of 2.5% per year in women with anorexia nervosa,⁵⁶ and adolescent girls with anorexia nervosa do not experience the sharp increase in bone mineral density that normally occurs during puberty,⁵⁷ which results in lower bone mineral density in girls with anorexia nervosa compared with appropriate controls at a critical time for accrual of bone toward peak bone mass.⁵⁸ The consequence is an increased fracture risk in adolescent girls as well as women

with anorexia nervosa.¹⁰ Two different studies have reported a 30% prevalence of history of fracture in women with anorexia nervosa¹⁰ and a fracture rate 7 times that expected for sex and age.⁵⁹ Newer imaging modalities have shown abnormalities in bone microarchitecture, both the trabecular and cortical components, in both women⁶⁰ and girls^{61,62} with anorexia nervosa. Moreover, bone strength, as determined by finite element analysis modeling, is reduced in anorexia nervosa.⁶³ Bredella and colleagues⁶² showed abnormalities in bone microarchitecture in girls with recent-onset anorexia nervosa, before decrements in bone mineral density are evident. This finding suggests that anorexia nervosa exerts deleterious effects on bone early in the disease, and, that early intervention may be necessary to prevent bone loss. Although bone mass generally increases with weight recovery, residual bone loss is common,⁶⁴ and weight recovery may take years to achieve. Therefore, early intervention with the goal of weight and neuroendocrine function restoration is important, and research into therapeutic strategies aimed at treating low bone mineral density is important.

The pathophysiology of bone loss is complex, and several neuroendocrine systems have been implicated (see Table 1). Bone formation is reduced, and bone resorption is increased in women with anorexia nervosa,⁶⁵ resulting in particularly severe bone loss in this disease. In contrast, both bone formation and resorption are suppressed in adolescent girls with anorexia nervosa,⁶⁶ reflecting important differences in skeletal physiology during adolescence versus adulthood. Adolescence is a period of heightened bone turnover (reflected by an increase in markers of bone metabolism, both formation and resorption) leading to rapid accrual of bone mass in the attainment of peak bone mass. Bone metabolism overall is suppressed in adolescent girls with anorexia nervosa, preventing the normal rapid bone mass accrual seen in this age group. Because of these differences in underlying skeletal physiology between these two age groups, caution is advised in extrapolating research results from one age group to the other. Studies in both adults and adolescents implicate hypogonadism, hypercortisolemia, relative IGF-I deficiency, and appetite hormone dysregulation in the pathogenesis of bone loss; however, significant differences in response to therapies in the two groups of women have been observed.

The importance of hypogonadism as a contributing factor has been highlighted in several studies. The regaining of menses has been shown as critical to skeletal recovery, independently of weight gain.⁵⁶ In 1 study, weight gain without reproductive function recovery did not result in skeletal recovery.⁵⁶ In another study, bone mineral density in 74 women with anorexia nervosa and amenorrhea was compared with that of 42 women with anorexia nervosa and eumenorrhea.¹⁹ Both groups showed low mean bone mineral density, particularly at the spine. However, although the mean posteroanterior spine T score in the amenorrheic group was -1.9 (1.9 standard deviations less than the mean for a healthy young woman), that of the eumenorrheic group was -0.9 . Bone mineral density is similarly lower in women with anorexia nervosa than in normal-weight women with hypothalamic amenorrhea.⁶⁷ These studies suggest that gonadal steroid deficiency is a significant contributor to bone loss in women with anorexia nervosa; roughly as important a factor as nutritional state (ie, weight).

However, amenorrhea may simply be a marker of degree of undernutrition and/or degree of neuroendocrine dysregulation. Undernutrition, as reflected in body mass index, is an important determinant of weight, with lean body mass the most predictive body composition component.⁵⁷ The only fat depot that studies have shown to be strongly associated with bone mineral density in anorexia nervosa is bone marrow fat, which is increased in anorexia nervosa and negatively correlates with bone mineral density.⁶⁸ Whether this observation holds clues to the pathogenesis of bone loss in anorexia nervosa is unknown. Because osteoblasts and adipocytes share a common mesenchymal stem cell precursor, the increased bone marrow fat in anorexia nervosa may provide a key to understanding the mechanisms

underlying reduced bone formation or simply reflect a default into the fat lineage caused by impaired osteoblastogenesis. No specific macronutrient or micronutrient component of the diet has been identified as an important determinant of bone mineral density. The cause and development of bone loss in this population does not seem to involve calcium and vitamin D deficiency, because both women and girls with anorexia nervosa ingest comparable amounts with those of healthy counterparts (largely in the form of supplements^{69,70}) but have lower bone mineral density.

Direct effects of hypogonadism on bone, if present, may be secondary to relative estrogen or androgen deficiency. Data in support of estrogen mediation are stronger than those for androgen mediation, mostly in the form of small, prospective controlled studies of gonadal hormone administration. Oral estrogens at doses used routinely to treat postmenopausal osteoporosis do not seem to increase bone mineral density in women with anorexia nervosa,⁷¹ although at the higher oral contraceptive doses they may help prevent further bone loss,⁷² but the data in this regard are not conclusive. The most important role of estrogen, and how treatment may be able to have a significant impact, is in older adolescents, in whom peak bone mass attainment is inhibited by the effects of starvation. Misra and colleagues⁷³ showed that estrogen administration in low doses designed to mimic estrogen levels observed in puberty (100 µg of 17-beta estradiol with cyclic progesterone transdermally in girls with a bone age 15 years and oral ethinyl estradiol 3.75 µg daily from 0 to 6 months, 7.5 µg from 6 to 12 months, and 11.25 µg from 12 to 18 months in girls with bone age <15 years) increased bone mineral density significantly, although these interventions were less than normal bone accrual rates during an 18-month period. Although low-dose estrogen is the most promising therapy for adolescent bone loss in anorexia nervosa so far investigated, further studies are needed to optimize therapy to achieve normalization of bone mineral density and attainment of optimal peak bone mass. Although low-dose testosterone administration stimulates bone formation over a period of weeks to months,^{29,74} it does not result in significant increases in bone mineral density in women with anorexia nervosa.²⁹ Neither DHEA nor ethinyl estradiol 20 µg/levonorgestrel 0.1 mg daily administered to a group of young adults and adolescents improved bone mineral density after controlling for increases in weight,²⁸ but a subsequent study combining the two hormonal strategies resulted in preservation of spine and total-body bone mineral density compared with placebo, which was associated with decreases in bone mineral density at these sites.⁷⁵ A small, randomized, controlled study of DHEA 100 mg daily (double the dose administered in the two previous studies) showed no effects on bone mass but did show an increase BMI.⁷⁶ These findings have not been replicated.

The importance of GH as a bone anabolic agent cannot be overstated, as shown by numerous studies establishing it as one of the primary factors responsible for linear growth in children and maintenance of normal bone mass in adults. The actions of GH are largely mediated through its stimulation of IGF-I secretion. IGF-I is anabolic to bone, stimulates osteoblast differentiation, and also exerts antiresorptive effects. Therefore, GH resistance, and the accompanying absence of normal IGF-I levels in women with anorexia nervosa, are of central importance in the development of bone loss in this population. Low serum IGF-I levels are associated with low markers of bone formation, suggesting that a lack of normal anabolic action accompanies relative IGF-I deficiency in anorexia nervosa.⁵⁷ Moreover, Lawson and colleagues⁶⁰ showed an association between serum IGF-I levels and bone microarchitectural parameters. Recombinant IGF-I (rhIGF-I) replacement therapy has been shown to increase bone mineral density in women with anorexia nervosa compared with placebo (2.8% when combined with oral contraceptives and 1.4% when administered alone) over 9 months.⁷² However, this increase is not large enough to result in normal bone mineral density, and rhIGF-I is not approved by the US Food and Drug Administration for this

indication. In addition, it is not known whether IGF-I replacement therapy is effective at increasing bone density in adolescents with anorexia nervosa.

Consistent with the deleterious effects of hypercortisolemia on the skeletal system observed in patients with Cushing syndrome, hypercortisolemia may be a factor contributing to bone loss in women with anorexia nervosa. Bone mineral density is inversely associated with pooled frequently sampled serum cortisol levels in both women and girls with anorexia nervosa.^{44,77} At this time, it is unknown how to translate the known relationship between hypercortisolemia and low bone mineral density into a clinical strategy, because lowering of cortisol levels is predicted to result in weight loss and may cause adrenal insufficiency.

The interplay between appetite hormone dysregulation and bone mineral density has been investigated, with resultant data mostly suggesting indirect effects. The exception is that of PYY, levels of which are paradoxically high in women and girls with anorexia nervosa and strongly inversely correlated with bone mineral density, even after controlling for weight.⁷⁸ In contrast, no direct relationship between ghrelin or leptin and bone mineral density in anorexia nervosa has been shown. However, leptin may mediate bone loss through its effects on reproduction, and further studies on the effects of appetite hormones on skeletal physiology are warranted and ongoing.

Nonhormonal treatments for low bone density have also been investigated, particularly bisphosphonates. Risedronate has been shown to be effective at increasing bone mineral density in women with anorexia nervosa, although, as in other cited therapeutic studies, bone mineral density did not normalize with a 1-year course of therapy.²⁹ In contrast, Golden and colleagues⁷⁹ studied the effects of alendronate administration on bone mineral density in adolescent girls with anorexia nervosa, and showed no increase in bone mineral density at any skeletal site after accounting for increases caused by weight gain over time. Whether the differences in effects are attributable to specific age-based or endocrine-based differences between adults and adolescents, differences in recovery rates, or other factors is unknown. In addition, the effects of bisphosphonates on fetal development are unknown and therefore these medications should not be used in women or adolescent girls who are pregnant or at risk of becoming pregnant during or shortly after their use.

A question that is often raised is whether weight-bearing exercise is beneficial to skeletal health in patients with anorexia nervosa, as it has shown to be for postmenopausal women. Health care providers routinely restrict exercise in women with anorexia nervosa in order to aid in the restoration of energy balance and promote weight gain. A recent study confirmed that exercise exerts deleterious effects on bone mineral density in underweight women with anorexia nervosa.⁸⁰ However, a beneficial effect was shown in women who were weight-recovered from anorexia nervosa.⁸⁰ Further research is warranted to more fully understand the mechanisms responsible for bone loss in anorexia nervosa and to determine the most effective and safest therapies.

IMPLICATIONS

Neuroendocrine hormone dysregulation, including hypothalamic amenorrhea, GH resistance, and hypercortisolemia, has serious implications for the health of girls and women with anorexia nervosa. In most patients with anorexia nervosa, this results in severe bone loss, which increases the risk for fractures. The pathophysiology of bone loss in anorexia nervosa is incompletely understood, and further studies are warranted to determine an optimal treatment strategy that results in normalization of bone mass. It is important when evaluating research results and considering therapeutic options to bear in mind that, because adolescent skeletal physiology differs in fundamental ways from that of adult skeletal physiology, results from investigations in one age group cannot be extrapolated to the other.

Neuroendocrine dysfunction largely reverses with weight gain and psychiatric recovery, including reproductive dysfunction, which usually recovers with weight gain but can be permanent. In such cases, assisted-reproductive technologies may be successful. Bone loss tends to reverse also, especially in those who regain menses with weight gain, but residual deficits often persist. The mainstay of therapy for anorexia nervosa remains a treatment team approach, usually consisting of a psychologist and/or psychologist, nutritionist, and primary care physician, with the therapeutic goal of restoration of psychological health and weight restoration.

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KEY POINTS

- Anorexia nervosa is a disease of psychiatric origin and is characterized by chronic starvation, with resultant neuroendocrine dysregulation.
- Endocrine complications of anorexia nervosa include hypothalamic amenorrhea, growth hormone resistance, and hypercortisolemia.
- Appetite hormone dysregulation has also been shown in girls and women with anorexia nervosa.
- Bone loss is prevalent and severe and a consequence of neuroendocrine hormone dysregulation in anorexia nervosa.
- The standard-of-care treatment of anorexia nervosa is multidisciplinary care aimed at psychological and nutritional recovery.
- Most, but not all, endocrine abnormalities, improve with psychological and nutritional recovery of anorexia nervosa.

Table 1

Endocrine dysfunction in women and adolescent girls with anorexia nervosa

	Women and Adolescent Girls with Anorexia Nervosa	Implicated in Bone Loss
Hypothalamic amenorrhea	✓	✓
GH resistance	✓	✓
GH	✓	—
IGF-I	✓	✓
Hypercortisolemia	✓	✓
Appetite Hormone Dysregulation		
PYY	✓	✓
Leptin	✓	—
Ghrelin	✓	—

Abbreviation: IGF-I, insulinlike growth factor I.