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The endocrine manifestations of anorexia nervosa: mechanisms and management

Melanie Schorr[1,2] and **Karen K. Miller**[1,2]

[1]Neuroendocrine Unit, Massachusetts General Hospital, 55 Fruit Street, Bulfinch 457B, Boston, MA 02114 USA

[2]Harvard Medical School, 25 Shattuck Street, Boston, MA 02115 USA

Abstract

Anorexia nervosa is a psychiatric disorder characterized by altered body image, persistent food restriction and low body weight, and is associated with global endocrine dysregulation in both adolescent girls and women. Dysfunction of the hypothalamic-pituitary axis includes hypogonadotrophic hypogonadism with relative oestrogen and androgen deficiency, growth hormone resistance, hypercortisolaemia, non-thyroidal illness syndrome, hyponatraemia, and hypooxytocinaemia. Serum levels of leptin, an anorexigenic adipokine, are suppressed and levels of ghrelin, an orexigenic gut peptide, are elevated in women with anorexia nervosa; however, levels of peptide YY, an anorexigenic gut peptide, are paradoxically elevated. Although most, but not all, of these endocrine disturbances are adaptive to the low energy state of chronic starvation and reverse with treatment of the eating disorder, many contribute to impaired skeletal integrity, as well as neuropsychiatric comorbidities, in individuals with anorexia nervosa. Although 5–15% of those affected by anorexia nervosa are men, only limited data exists regarding the endocrine impact of the disease in adolescent boys and men. Further research is needed to understand the endocrine determinants of bone loss and neuropsychiatric comorbidities in anorexia nervosa in both women and men, as well as to formulate optimal treatment strategies.

TOC image

Patients with anorexia nervosa severely restrict their food consumption. In this Review, Schorr and Miller discuss the endocrine abnormalities that arise in these patients with their severely reduced calorie intake and potential therapies that can help restore endocrine function.

Review Criteria

A PubMed database was searched using the following search terms, “anorexia nervosa endocrine”, “anorexia nervosa bone”, “anorexia nervosa gonadal dysfunction, “anorexia nervosa growth hormone”, “anorexia nervosa thyroid”, “anorexia nervosa cortisol”, “anorexia nervosa hyponatremia”, “anorexia nervosa oxytocin”, “anorexia nervosa bone marrow fat”, “anorexia nervosa adipokines,” “anorexia nervosa gut peptides” and “anorexia nervosa adolescent boys.” Full-text, English language articles were selected that were published between October 1974 to May 2016. The reference lists of several papers were searched for additional relevant publications. Detailed focus was placed on articles published within the past 5 years.

Competing interests statement

The authors declare no competing interests

Subject terms

Health sciences / Endocrinology / Endocrine system and metabolic diseases [URI /692/163/2743]; Health sciences / Diseases / Psychiatric disorders [URI /692/699/476]; Health sciences / Anatomy / Musculoskeletal system / Bone [URI /692/698/1671/63]; Health sciences / Pathogenesis [URI /692/420]; Health sciences / Health care / Weight management [URI / 692/700/2817]; Health sciences / Health care / Therapeutics / Drug therapy [URI / 692/700/565/1436]

Introduction

Anorexia nervosa is a psychiatric disorder characterized by altered body image, persistent food restriction and low body weight[1]. In 2013, the American Psychiatric Association revised the diagnostic criteria for anorexia nervosa by making the weight criteria less stringent and removing the requirement for amenorrhea to be present[1]. The formal diagnosis of 'atypical anorexia nervosa' was created within Other Specified Feeding or Eating Disorder (OSFED) for those who are not low weight but meet anorexia nervosa psychological criteria. Amenorrhea was removed as a criterion due to a recognition that endocrine dysregulation in anorexia nervosa is variable, and that some women with low weight and all the psychiatric features of anorexia nervosa continue to have regular menses[2]. Before these revisions, the incidence of anorexia nervosa in Europe had been stable since the 1970s according to primary care-based records[3,4]. However, the incidence seemed to be increasing among adolescent and young women aged 10–24 years according to a primary care-based study in the Netherlands and a population-based study in Rochester, Minnesota, USA[4,5]. Since the advent of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (known as DSM-5) and broadening of the diagnostic criteria for anorexia nervosa, investigators have seen a substantial increase in the prevalence of anorexia nervosa[6,7]. Although the disease most commonly affects young women, a population-based study in Europe reported a 0.17% lifetime prevalence of anorexia nervosa in women >45 years of age[8]. Anorexia nervosa might also affect adolescent boys and men, although disease prevalence was 8.1 times higher in women than in men in a population-based study in the USA[9]. In women, anorexia nervosa is characterized by global endocrine dysregulation, including hypothalamic–pituitary axis dysfunction and alterations in adipokine and appetite-regulating hormone levels[10]. Although these endocrine disturbances are mostly an adaptation to the low energy state, they can exert deleterious effects on skeletal health and neuropsychiatric comorbidities. Understanding the mechanisms responsible for endocrine complications of anorexia nervosa is important given the increasing prevalence and chronic nature of the disease. Approximately 50% of women with anorexia nervosa recover after therapy[11], ~30% only partially recover, and the remainder experience recurrent patterns of remission and relapse or chronic disease[12,13].

In this Review we discuss the endocrine complications of anorexia nervosa, including dysregulation of hypothalamic–pituitary axis hormones, adipokines and appetite-regulating hormones. We elaborate on the evidence that most of these endocrine disturbances are adaptive to the low energy state of chronic starvation; consequently, appropriate treatment consists of addressing the underlying eating disorder. We also discuss how this endocrine

dysregulation contributes to common comorbidities in anorexia nervosa, that is, impaired skeletal integrity and neuropsychiatric disease. Finally, we discuss the current knowledge of endocrine dysregulation in adolescent boys and men with anorexia nervosa, and areas for future research.

Differential diagnosis of anorexia nervosa

Patients with anorexia nervosa usually present with low weight in conjunction with self-induced starvation and intense fear of gaining weight[1]. However, the diagnosis of anorexia nervosa can be difficult because patients with anorexia nervosa can be in denial of their disease and do not view their behaviour and issues with body image as abnormal. In addition, laboratory test results, including complete blood count and chemistry panel, can be entirely normal[14]. Other psychiatric disorders and medical illnesses that can present with weight loss should be considered when appropriate, including depression, malignancy, chronic infections such as tuberculosis, adrenal insufficiency, uncontrolled type 1 diabetes mellitus, hyperthyroidism and malabsorption syndromes[15]. When the patient presents with a history of one of these diagnoses, and/or one of these diagnoses is evident on physical exam, appropriate clinical assessment should be pursued. This assessment should include a comprehensive medical history, thorough physical exam and basic screening tests including complete blood count and differential, comprehensive metabolic panel, thyroid function tests, markers of inflammation, urinalysis, fecal occult blood testing and radiologic imaging when appropriate[15]. When anorexia nervosa is in the differential diagnosis, a mental health provider with expertise in eating disorders should then be consulted.

Hypothalamic–pituitary dysfunction

Hypothalamic–pituitary–gonadal axis

The low energy availability in patients with anorexia nervosa commonly results in hypothalamic amenorrhea. In studies in the 1970s, a wide range of luteinizing hormone pulsatility patterns were found in young women with anorexia nervosa who were amenorrheic[16,17]. These findings ranged from frank apulsatility to patterns characteristic of early puberty, in which luteinizing hormone pulses occurred only during sleep[16,17]; return of mature luteinizing hormone pulsatility did not seem to have a simple relationship with weight gain[17]. Investigation into the mechanisms of reduced gonadotropin releasing hormone (GnRH) secretion from the hypothalamus, and consequently reduced gonadotropin secretion from the pituitary, have focused on the role of leptin. Leptin is required for normal reproductive function in starved rodents[18], and mean serum leptin levels are low in amenorrheic women with anorexia nervosa in association with low fat mass[19] (Figure 1). Although administration of exogenous leptin has not been studied in women with anorexia nervosa, exogenous leptin administration restored ovulatory cycles in three of eight women of normal weight who had hypothalamic amenorrhea[20]. However, recombinant human leptin also led to a 4.3% decrease in fat mass among the five individuals who completed the 3 month intervention, which limits the potential of leptin to be used as a therapy in women with anorexia nervosa. In addition, a substantial overlap exists in serum levels of leptin between women who are amenorrheic and those who are eumenorrheic with anorexia

nervosa of comparable low weight and psychopathology, such that an individual's serum leptin levels cannot be used for diagnostic purposes[2]. Leptin is a proposed regulator of kisspeptin neurons in the arcuate nucleus of the hypothalamus; kisspeptin signalling is thought to be a key component of the pulse generator that drives pulsatile GnRH secretion[21]. Since its discovery in 1996, mutations in kisspeptin and the kisspeptin receptor have been found to result in a subset of idiopathic hypogonadotrophic hypogonadism[22], and acute administration of exogeneous kisspeptin can lead to gonadotropin release in women with functional hypothalamic amenorrhea[23]. However, no investigators have specifically examined the role of kisspeptin in women with anorexia nervosa, including whether underlying genetic variability in kisspeptin signalling might contribute to individual predisposition to hypothalamic amenorrhea[24].

Hypothalamic amenorrhea results in low androgen levels, in addition to low oestrogen levels, in women with anorexia nervosa[25] (FIG. 1). Somedata suggest that secretion of adrenal androgen precursors is not compromised in women with anorexia nervosa[25], such that hypogonadotrophic hypogonadism seems to be responsible for the hypoandrogenaemia seen in women with anorexia nervosa. Although recovery of reproductive function occurs in a large percentage of women with anorexia nervosa who are able to achieve an increase in weight and fat mass, no set body weight or percentage of fat mass exists above which menses resume[16]. For example, in one study of 100 adolescent girls with anorexia nervosa, 86% of patients who were able to achieve 90% of ideal body weight had resumption of menses within 6 months[26]. Amenorrhea persists in up to 15% of women despite recovery of normal body weight[27]. However, whether this amenorrhea is because of persistent eating disorder psychopathology, less body fat despite a similar weight, atrophy of gonadotrophs or other factors is unclear.

Growth hormone–insulin-like growth factor 1

Anorexia nervosa in both adolescents and adults is a state of acquired growth hormone (GH) resistance secondary to chronic nutritional deprivation and is characterized by increased GH secretion but decreased systemic insulin-like growth factor 1 (IGF1)[28,29] (FIG. 1). Increased plasma GH levels with prolonged fasting was first reported in 1963, when the insulin tolerance test as a diagnostic test for GH deficiency was first proposed[30]. In 1999, investigators demonstrated a fourfold increase in daily pulsatile GH secretion and a 20-fold increase in basal GH secretion in women with anorexia nervosa[29]. In subsequent studies, total and bioactive IGF1 levels were in fact found to be reduced in women with anorexia nervosa despite elevated GH levels[31,32], which is consistent with a state of relative GH resistance at the level of the liver. Low levels of IGF1 might be an adaptive response to preserve energy by decreasing expenditures on growth in states of chronic starvation[33]. GH resistance negatively affects longitudinal bone growth in adolescent boys with anorexia nervosa[34], but data are conflicting in adolescent girls with anorexia nervosa[35,36]. Elevated GH levels might also have a protective role by maintaining euglycaemia via gluconeogenesis[37] and mobilizing fat stores via lipolysis[38] in states of chronic starvation.

Multiple mechanisms have been proposed to contribute to GH resistance at the level of the liver and the resultant low circulating levels of IGF1, such as elevated fibroblast growth

factor 21 (FGF21). FGF21, whose production by hepatocytes[39] and white adipocytes[40] is induced by fasting[41], is thought to inhibit STAT-5[42], a mediator of intracellular GH effects. Consequently, plasma FGF21 levels are negatively associated with plasma levels of IGF1[42,43]. Low levels of insulin, which are characteristic of states of undernutrition, might also have a role in GH resistance by downregulating hepatic GH receptor expression, as seen in human cell lines[44]. Elevated GH levels are thought to result from the hypothalamic and pituitary gland responses to low circulating IGF1 levels, via classic negative feedback mechanisms[45]; a smaller contributor might be stimulation of GH secretion by increased ghrelin levels, which is a known GH secreatagogue[46,47]. GH resistance in individuals with anorexia nervosa is at least partially reversed during refeeding and with weight recovery[31]. IGF1 levels acutely increase with refeeding[48], and weight gain leads to a normalization of GH secretion[49]. However, during the active disease state, administration of supraphysiologic doses of recombinant GH does not seem to increase levels of IGF1, and might even be detrimental to the patient by leading to a decrease in fat mass secondary to GH stimulation of lipolysis in a patient who is already cachetic[50].

Hypothalamic–pituitary–adrenal axis

The hypothalamic–pituitary–adrenal (HPA) axis is in a chronically stimulated state in at least one-third of women with anorexia nervosa[51–56] (Figure 1). In classic studies conducted in the late 1970s and early 1980s, 24-hour mean plasma cortisol concentration was elevated in up to 80% of women with anorexia nervosa[51,52]. In subsequent studies, elevations in 24-hour urine free cortisol levels, late night salivary cortisol levels, and morning serum cortisol levels on a 1 mg overnight dexamethasone suppression test were also identified[53–56]. Although the degree of hypercortisolaemia correlates inversely with BMI and fat mass[53], cortisol measures rarely exceed twice the assay upper limit of normal. This hypercortisolaemia might be due to the stress of chronic nutritional deprivation and also as a means of maintaining euglycaemia in patients with anorexia nervosa[57]. In addition, increased ghrelin levels in anorexia nervosa might stimulate corticotropin releasing hormone (CRH)[58,59]; decreased metabolic clearance of cortisol might also contribute to hypercortisolaemia[51].

Although anorexia nervosa and Cushing’s syndrome are two disparate diseases with distinct and very different phenotypes, similarities between the two diseases in the clinical manifestations of hypercortisolaemia are apparent on closer examination. Similar to Cushing’s syndrome, hypercortisolaemia in women with anorexia nervosa is inversely associated with bone mineral density (BMD)[55,56] and positively associated with the severity of depression and anxiety symptoms[56]. Hypercortisolaemia might also inhibit the hypothalamic–pituitary–gonadal axis, and excess cortisol exerts a deleterious effect on muscle; both Cushing’s syndrome and hypercortisolaemia in women with anorexia nervosa are associated with reduced extremity lean mass[60]. Although reduced caloric intake prevents accumulation of adipose tissue in very low-weight women with anorexia nervosa, during weight recovery, high baseline cortisol levels are associated with trunk fat accumulation, as in patients with Cushing’s syndrome[61].

Dysregulation of the HPA axis might persist in women with anorexia nervosa after weight gain, which suggests that recovery from anorexia nervosa is not complete despite weight gain or that the HPA axis might be involved in disease pathogenesis[61–63]. CRH is anorexigenic, and it is hypothesized that increased secretion of CRH in anorexia nervosa might contribute to the severity of weight loss[64]. No pharmacological approaches are currently recommended to address the relative hypercortisolaemia in anorexia nervosa, especially considering that therapies that lower cortisol might result in adrenal insufficiency and/or weight loss.

Whether anorexia nervosa is associated with alterations in the production of adrenal androgen precursors is unclear (FIG. 1). In one study, levels of dihydroepiandrosterone sulphate (DHEAS) were only lower in women with anorexia nervosa receiving oral contraceptives compared to normal-weight controls, presumably because oral contraceptives reduce albumin levels, DHEAS's primary binding globulin[25]. In a further study, basal and adrenocorticotropic hormone 1-24-stimulated dehydroepiandrosterone (DHEA) levels were normal in women with anorexia nervosa[65]. However, other investigators have reported a decrease in DHEAS levels in women with anorexia nervosa compared to a commercial laboratory's normal reference range[66] or a decreased ratio of DHEA to cortisol in women with anorexia nervosa compared with normal-weight controls[67].

Hypothalamic–pituitary–thyroid axis

Severe weight loss in anorexia nervosa is characterized by the nonthyroidal illness syndrome[68], a syndrome of abnormalities in thyroid function tests seen in patients with systemic illness, including chronic starvation[69]. In women with very low-weight anorexia nervosa, levels of total T_3 are low, reverse T_3 is elevated due to increased peripheral deiodination of T_4 to reverse T_3, free T_4 varies from normal to low-normal, and TSH varies from normal to low-normal[47,55,68] (FIG. 1). These changes are an adaptive response to decrease metabolic rate and energy expenditure and, therefore, nonthyroidal illness syndrome does not require treatment. In fact treatment might be harmful to the patient, as thyroid hormone use can itself lead to weight loss and has the potential for abuse[70]. During weight recovery, total T_3 levels normalize[71].

Posterior pituitary hormones and renal function

Arginine vasopressin, also known as antidiuretic hormone (ADH), is synthesized by the hypothalamus and stored in the posterior pituitary. ADH is an ACTH secretagogue that is upregulated in response to chronic stress in rat models[72]. In humans, depression is associated with elevated levels of ADH in cerebrospinal fluid and enhanced pituitary sensitivity to ADH[73]. Although some investigators have reported that anorexia nervosa is also associated with elevated ADH levels in cerebrospinal fluid, reduced pituitary sensitivity to ADH was also seen, which suggests a greater contribution of anorexigenic CRH than ADH to hyperactivity in the HPA axis seen in anorexia nervosa[64]. Whether this difference between depression and anorexia nervosa is part of the disease pathogenesis or is adaptive is unclear.

Abnormalities in electrolyte concentrations might occur in patients with anorexia nervosa. In one study, 7% of women with anorexia nervosa had hyponatremia[14], which is frequently due to inappropriate secretion of vasopressin (that is, the syndrome of inappropriate anti-diuresis (SIAD))[74] (Figure 1). Other causes of low serum sodium levels in women with anorexia nervosa include excessive water consumption, hypovolaemia due to inadequate nutrition and purging, impaired renal sodium reabsorption in the setting of malnutrition and the use of psychotropic medications that also might lead to SIAD[75–77]. Although hyponatremia is generally not severe in women with anorexia nervosa, one cross-sectional study reported serum sodium was as low as 122 mmol/l (normal range 135–145 mmol/l), and one patient reported a history of seizures secondary to hyponatremia[14]. As severe, and especially acute, hyponatremia can result in seizures in the absence of any warning[78], measuring levels of serum sodium is important in these patients. In addition, hypernatremia has been reported to occur in women with anorexia nervosa due to dehydration or diabetes insipidus, but these cases have been rare[79].

Patients with anorexia nervosa who develop hyponatremia often have hypovolaemia, SIAD and/or water loading as a cause[75–77]. However, hyponatremia should prompt a consideration of adrenal insufficiency in patients with weight loss but in whom psychiatric symptoms are not prominent[78]. Water loading as a cause of hyponatraemia is usually clear from a history of excessive water drinking and observation of the same, but if in doubt, a 24-hour urine volume can be helpful to ascertain that the patient has consumed large amounts of water. Assessment of urine sodium levels can be helpful to differentiate hypovolemia (urine sodium usually <10 mmol/l) from SIAD (urine sodium usually >25 mmol/l) except in women who use diuretics[78].

Other electrolyte abnormalities that might occur in anorexia nervosa include hypokalaemia, hypomagnesaemia and hypophosphataemia. Hypokalaemia is present in ~20% of women with anorexia nervosa, and is nearly exclusively limited to those women who purge (that is by vomiting, laxative use or diuretic consumption)[14]. Severe hypokalaemia, defined as a serum potassium concentration <2.5 mmol/l, of any cause is associated with a risk of cardiac arrhythmia[80]. In rare cases, hyperkalaemia might occur in women with anorexia nervosa, such as in those who abuse the diuretic spironolactone. Refeeding syndrome, which might occur as a result of fluid and electrolyte shifts during nutritional rehabilitation, is associated with hypokalaemia, hypophosphataemia, and hypomagnaesemia[81]. During nutritional rehabilitation, carbohydrate intake induces insulin release, which leads to cellular uptake of potassium, magnesium, and phosphate[82]. Consequently, electrolyte levels must be closely monitored during the refeeding process, and rapid increases in daily caloric intake should be avoided to try and prevent refeeding syndrome. If refeeding syndrome does occur, nutritional support should be decreased and electrolyte abnormalities aggressively corrected[83].

Anorexia nervosa is also associated with dysregulation of oxytocin secretion, which is an anorexigenic hypothalamic hormone[84] (FIG. 1). Although nocturnal levels of serum oxytocin are lower in women with anorexia nervosa than in normal-weight individuals[84], postprandial serum oxytocin levels are higher in women with active and weight-recovered anorexia nervosa than in normal-weight women[85]. One potential explanation for this

apparent contradiction is an inverse association between central and peripheral oxytocin levels[86], such that increased postprandial levels of serum oxytocin indicate an adaptive response to decreased postprandial central oxytocinergic satiety signalling[85].

Adipokines and appetite-regulating hormones

In 1994, leptin was identified as a satiety factor whose deficiency resulted in profound obesity in *ob/ob* mice[87]. Since that time, our understanding of leptin as an anorexigenic adipokine has increased substantially. In anorexia nervosa, basal and pulsatile secretion of leptin is reduced in association with reductions in fat mass[88]. In one study, mean overnight serum leptin levels were 71% lower in adolescent girls with anorexia nervosa than in healthy adolescents[88]. Leptin stimulates secretion of GnRH and hypoleptinaemia might contribute to hypothalamic amenorrhea in anorexia nervosa[18]. Hypoleptinaemia might also contribute to elevated levels of physical activity in women with anorexia nervosa for whom compulsive exercise is a component of the psychiatric syndrome[89]. The hypothesis that hypoleptinaemia might contribute to hyperactivity in the state of starvation is supported by preclinical data, in which semi-starvation-induced hyperactivity in rats can be prevented and suppressed by leptin administration[89]. With refeeding and weight recovery, endogeneous levels of serum leptin increase[90]. However, in one study, 17 out of 18 adolescent girls with anorexia nervosa who achieved their target weight actually had higher serum leptin levels than predicted for their BMI based on a control group of 18 normal-weight age-matched adolescent girls[91]. Whether this relative hyperleptinaemia of weight recovery contributes to resistance to weight gain or recurrent weight loss is unknown.

Adiponectin levels have been variably reported to be unchanged[92], higher[93,94], or lower[95] in women with anorexia nervosa than in normal-weight controls (FIG 1). In one study, adiponectin levels were higher in women with anorexia nervosa after controlling for fat mass[92,93]. These differences might relate to assays detecting different circulating adiponectin isoforms[96]. Further research is needed in this area.

Although one would expect increased levels of anorexigenic hormones and suppressed levels of orexigenic hormones in women with anorexia nervosa, this finding has proven to only partially be the case. Ghrelin is an appetite-stimulating hormone that is also a GH and adrenocorticotropic hormone secretagogue[58], both of which help to maintain euglycaemia during starvation, and is also an inhibitor of gonadotropin secretion[97,98]. In one study, mean overnight serum ghrelin levels were 46% higher in 22 adolescent girls with anorexia nervosa than in 18 healthy adolescent girls, and ghrelin levels were inversely associated with BMI[47]. Elevated ghrelin levels seem to be an adaptive response to chronic nutritional deprivation, and decrease with weight gain[99]. However, ghrelin levels might remain higher in women with weight-recovered anorexia nervosa than normal-weight controls[47]. This effect might occur because weight and/or body composition parameters are not normalized for a particular patient and/or because appetite regulation abnormalities may be involved in the pathogenesis of the disease. Whether resistance to ghrelin contributes to the development of anorexia nervosa, or if the elevation in ghrelin levels is simply an appropriate response to chronic starvation, is unknown. In a pilot study of five women with anorexia nervosa, preprandial ghrelin administration was associated with an increase in appetite, suggesting

that women with anorexia nervosa are capable of responding to the orexigenic effects of supraphysiologic ghrelin[100]. However, this study was small and not placebo-controlled; therefore, further investigation of the potential role of ghrelin in anorexia nervosa is needed. Amplified reduction in ghrelin levels has also been seen during a euglycaemic hyperinsulinaemic clamp in 19 women with anorexia nervosa compared with 26 normal-weight women[101]. This finding raises the question of whether the suppression of ghrelin in response to food intake is exaggerated in anorexia nervosa and might lead to an increased sensation of satiety in such patients.

Peptide YY (PYY), which is secreted by intestinal L cells, is an anorexigenic hormone and serum levels of this hormone are inversely correlated with BMI in adolescent girls with anorexia nervosa[102] (FIG. 1). Unlike ghrelin, increased serum levels of PYY in adolescent girls and women with anorexia nervosa compared to normal-weight controls is not considered an adaptive response because one would expect PYY levels to be low in anorexia nervosa as PYY suppresses appetite. Elevated levels of PYY in women with anorexia nervosa might contribute to decreased nutrient intake and disordered eating psychopathology[103], and might also remain elevated despite weight gain[104].

Skeletal integrity

BMD and bone microarchitecture

Global endocrine dysregulation in anorexia nervosa has deleterious consequences on skeletal health and reduced BMD is a common comorbidity. In one study of 214 women with anorexia nervosa and a mean age of 25 years, 52% of women had osteopenia (BMD T-score less than –1.0 at one or more sites) and 34% had osteoporosis (BMD T-score below –2.5 at one or more sites)—only 13.8% had normal BMD at all skeletal sites[14]. Similarly, in a study of 60 adolescent girls with anorexia nervosa and a mean age of 15.8 years, 52% had BMD Z-scores less than –1.0 at one or more sites[105]. In addition, alterations in both cortical and trabecular bone microarchitecture and bone strength have been identified in adolescent girls and young women with anorexia nervosa using high resolution peripheral quantitative computed tomography[106–108]. Despite the young age of individuals with anorexia nervosa, this decrement in BMD does indeed translate into an increase in fracture risk. For example, the nonspinal fracture rate was found to be seven times higher in women with anorexia nervosa compared to normal-weight age-matched women[109], and in a meta-analysis, the disease was found to be associated with an increased likelihood of both osteoporosis (OR 12.59, 95% CI, 3.30–47.9, P <0.001, I^2 = 0%, from four studies) and fractures (OR 1.84, 95% CI 1.17–2.89, P = 0.008, I^2 = 56, from six studies) in women[110]. The prevalence of fractures is also 59.8% higher in adolescent girls with anorexia nervosa than in healthy controls (31.0% versus 19.4%, P = 0.02), even in the absence of reductions in BMD[111]. This finding might be the result of alterations in bone microarchitecture—that is the 3D organization and distribution of bone, which is an important determinant of bone strength that cannot be measured by dual-energy x-ray absorptiometry[112].

Adolescence is normally a period of high bone turnover, with bone formation exceeding bone resorption as peak bone mass accrues[113]. In contrast to healthy adolescents, in whom continued bone accrual occurs to attain peak bone mass, adolescents with anorexia nervosa

have decreased bone formation and bone resorption compared with Tanner stage-matched normal-weight controls[114]. Accrual of bone, therefore, plateaus[114] and optimum peak bone mass is not achieved, which impairs future bone health and increases fracture risk. By contrast, bone loss in women with anorexia nervosa reflects a decrease in bone formation and an increase in bone resorption. For both adolescents and adults, decreased BMD can occur relatively rapidly in anorexia nervosa, with changes often apparent after just 1 year of disease[115]. Moreover, the duration of illness is associated with a lower BMD[116], suggesting that bone loss might continue throughout the course of the illness.

Determinants of impaired BMD—Factors that contribute to low BMD in anorexia nervosa include low weight and abnormalities in body composition, anterior and posterior pituitary hormone dysregulation, and abnormalities in adipokine and gut peptide secretion. Reduced BMI is associated with low BMD in adolescent girls and women with anorexia nervosa[105,117]; the resultant aberrations in body composition as weight loss occurs might further contribute to bone loss. For example, muscle has an anabolic effect on bone through mechanical loading and hormonal cross-talk, and low lean body mass is associated with impaired BMD and bone microarchitecture in both adolescent girls and women with anorexia nervosa[105,118].

Fat depots also have important roles in regulating bone mass in anorexia nervosa. A new area of investigation is bone marrow adipose tissue mass, which is paradoxically elevated in women with anorexia nervosa despite reduced total body fat[119,120]. One of the mechanisms underlying the increase in bone marrow adipose tissue in anorexia nervosa might be preadipocyte factor (Pref1), which is an important regulator of mesenchymal stem cell differentiation[121] (Figure 2). In one study, 20 women with anorexia nervosa had significantly higher mean levels of Pref1 than normal-weight controls (AN: 0.46 ± 0.03 versus 0.37 ± 0.02 ng/ml, $P = 0.01$), and Pref1 was associated with increased bone marrow adipose tissue mass in women with anorexia nervosa[121]. However, Pref1 is only one of many factors that contribute to the interplay between osteoblast and adipocyte differentiation. Bone marrow adipose tissue mass is inversely associated with BMD in patients with anorexia nervosa[120]; whether bone marrow adipose tissue has a causal role in low BMD or simply expands to fill the space in the absence of hematopoetic and bone producing cells is unclear. Further research is needed to determine the mechanisms underpinning and the implications of this fat depot, which is dynamic and has been demonstrated to decrease with weight recovery[122].

Anterior pituitary hormones are important determinants of BMD including GH resistance resulting in relative IGF1 deficiency, which is a major contributor to bone loss in women with anorexia nervosa[28,107]. GH and IGF1 both stimulate osteoblast differentiation while inhibiting osteoclast differentiation, and GH independently stimulates osteoblast proliferation[123] (FIG. 2). Accordingly, low serum levels of IGF1 in women with anorexia nervosa are associated with low markers of bone formation such as serum osteocalcin[48,114], low BMD[114], as well as impaired bone microarchitecture[107]. By contrast, cortisol decreases bone formation and increases bone resorption by inhibiting osteoprotegerin secretion, a factor that inhibits osteoclastogenesis and osteoclast activity, and increasing RANKL secretion, which increases osteoclastogenesis and osteoclastic activity[124] (FIG. 2).

Consequently, measures of cortisol levels are inversely associated with BMD in adolescent girls and women with anorexia nervosa[55,56]. Oestrogen inhibits bone resorption by inhibiting the secretion of inflammatory cytokines and RANKL and increasing the secretion of osteoprotegerin[125], in addition to stimulating bone formation by inhibiting sclerostin secretion, a factor that inhibits osteoblast differentiation[126] (FIG. 2). Testosterone levels, which are reduced in amenorrheic women with anorexia nervosa, in addition to oestradiol, also exerts both anabolic and antiresorptive effects on bone[127] (FIG. 2). Consequently, the duration of amenorrhea, as a proxy for gonadal steroid deficiency, is negatively associated with BMD in women with anorexia nervosa[128].

Anti-diuretic hormone and oxytocin, hypothalamic hormones that are stored in the posterior pituitary, are also important for normal bone metabolism[84,129]. Hyponatraemia is associated with reduced BMD in a rodent model of SIAD[130], and oxytocin deficiency is also associated with low BMD in oxytocin and oxytocin receptor null mice[131]. Similar to preclinical studies, hyponatraemia[129] is associated with decreased BMD in women with anorexia nervosa independent of BMI; low nocturnal serum oxytocin levels[84] are also associated with decreased BMD.

In addition, alterations in adipokines and appetite-regulating hormones might contribute to low bone mass in anorexia nervosa. Preclinical data regarding the action of leptin on the bone microenvironment are complex, and suggest a central inhibitory effect via the sympathetic nervous system[132], but also a peripheral stimulatory effect of leptin on bone metabolism[133] (FIG. 2). Moreover, the effects of leptin on bone might not be uniform throughout the skeleton, as leptin-deficient *ob/ob* mice have decreased femoral BMD but increased spine BMD[134]. In women with anorexia nervosa, hypoleptinaemia is independently associated with low BMD at both the femoral neck and spine, as well as abnormalities in bone microarchitectural parameters, independently of BMI[107]. Adiponectin, which might or might not be elevated in women with anorexia nervosa (these data are conflicting), can affect osteoblastogenesis either positively[135] or negatively[136] while suppressing osteoclastogenesis[135] (FIG. 2). PYY might inhibit osteoblastic activity while increasing osteoclastic activity[137] (FIG. 2). Consistent with these data, mean overnight PYY levels are strongly inversely associated with BMD in women with anorexia nervosa independently of BMI[138]. The relative contributions on these factors on impaired BMD and bone microarchitecture in anorexia nervosa is not well understood and is a focus of current research.

Management of impaired BMD

The effects of hormone replacement on BMD in adolescent girls and women with anorexia nervosa are complex. Oral oestrogen is not effective in increasing BMD in adolescent girls and women with anorexia nervosa, as shown in randomized controlled trials[139–141]. One contributing factor might be that oral oestrogen decreases IGF-1 production by the liver[142]. By contrast, in adolescent girls, physiological transdermal oestrogen replacement with cyclic progesterone increases spine and hip BMD and prevents the decline in BMD Z-scores observed in untreated girls with anorexia nervosa[143]. However, such therapy is not sufficient to normalize BMD[143], possibly because it does not correct other hormonal abnormalities

that are important for skeletal health as described earlier in the text. In addition, replacement of androgens, in the form of testosterone or DHEA, does not improve BMD as compared to placebo in small randomized controlled trials[144,145], although, when combined with an oral contraceptive, DHEA can maintain BMD in adolescent girls and young women with anorexia nervosa[146].

Preliminary data suggest that in women with anorexia nervosa, IGF1 replacement might prevent bone loss when administered alone and improve BMD at the spine by mean 1.8% in combination with oral contraceptives, but does not normalize BMD[147]. A small study of 20 adolescent girls with anorexia nervosa has also shown an increase in bone formation markers such as procollagen type 1 N-terminal propeptide (P1NP) following recombinant human IGF1 (rhIGF1) administration[148]. The change in levels of P1NP over the study duration was significantly higher (29.4 ± 9.8 versus 2.5 ± 4.8%, $P = 0.02$) in adolescent girls with anorexia nervosa who received rhIGF1 than those who did not.

Bisphosphonates and teriparatide, which are approved for the treatment of postmenopausal osteoporosis, have also been studied in anorexia nervosa. In a trial investigating the use of risedronate in 77 women with anorexia nervosa, 1 year of treatment with risedronate decreased the bone resorption marker C-terminal telopeptide (CTX) by 41% (95% CI 17–65%, $P = 0.002$), postero-anterior spine BMD increased by 3.2% (95% CI 1.8–4.6%, $P < 0.0001$), and total hip BMD increased by 1.9% (95% CI 0.4–3.4%, $P = 0.013$) compared with placebo[144]. However, in a randomized controlled trial of bisphosphonate therapy in 32 adolescent girls with anorexia nervosa (mean age 16.9 ± 1.9 years), no increase in spine BMD was seen compared with placebo[149]. This lack of effect might be because bisphosphonates decrease bone turnover, which is already lowered in adolescents with anorexia nervosa, or because girls in both trial arms gained a substantial amount of weight (13.5 ± 9.9% for the intervention group versus 16.2 ± 16.4% for the control group; $P = 0.59$), which might have overwhelmed the detectable response to bisphosphonate therapy. Bisphosphonates are not FDA-approved for use in girls or women of childbearing age with anorexia nervosa because these drugs cross the placenta and some of them have a long half-life, meaning they can be released slowly from bone over a period of years[150]. Consequently, bisphosphonates should be used with caution in girls and in women of childbearing age and only after a thorough discussion of the risks and benefits, and should be avoided altogether in women who are seeking pregnancy in the near future.

In one study, teriparatide, which is a potent bone anabolic agent, increased spine BMD substantially (6–10%) after only 6 months of therapy in older women (mean age 47 years) with anorexia nervosa[151], and might, therefore, be a promising therapy. However, further data, including with subsequent consolidation antiresportive therapy, are needed. Notably, teriparatide is associated with an increased incidence of osteosarcoma in rats in a dose and time-dependent manner[152], and an FDA warning advises that this medication should not be prescribed to patients who are at increased baseline risk for osteosarcoma, including paediatric and young adult patients with open epiphyses[153].

The most important strategy to improve BMD in anorexia nervosa is treatment of the underlying eating disorder with recovery of weight and menstrual function. For example, in

one study of 75 women with anorexia nervosa the mean annual increase in BMD was 1.8% at the hip and 3.1% at the spine for those who gained weight and resumed menses. In those who remained low weight and amenorrheic, the annual rate of decline was –2.4% at the hip and –2.6% at the spine in this study[118]. Despite a comparable amount of weight gained, those women who resumed menses had a mean annual increase in BMD of 3.1% at the spine, while those who did not recover menstrual function demonstrated a mean annual decline in BMD of –2.4% at the spine. This finding suggests that normalization of reproductive function in addition to weight gain is necessary for maximal skeletal recovery. However, despite the combination of weight gain and resumption of menses, BMD does not normalize in all women[154], especially for those who have not achieved their peak bone mass due to anorexia nervosa. In one small study of 19 women recovered from anorexia nervosa for a mean period of 21 years, mean BMD at the femoral neck was still significantly lower (0.922 versus 1.073 g/cm^2, $P = 0.004$) than healthy controls[155]. Investigators in another study reported that peripheral quantitative CT measurements at the tibia, including total volumetric BMD at 14% tibia length, were significantly lower (528 ± 70 versus 486 ± 84 mg/cm^{-3}; $P < 0.05$) in a group of 22 women in recovery from anorexia nervosa for a mean of 27 years compared with healthy controls[156]. Adolescent girls and women with active or recovered anorexia nervosa might assume that calcium and vitamin D supplementation alone is sufficient to normalize BMD, but this is not effective for two reasons. Firstly, calcium and vitamin D supplementation alone cannot overcome the short-term and long-term detrimental effects of anorexia nervosa on bone mass[14]. Secondly, as a group, adolescent girls and women with anorexia nervosa already have higher intakes of both calcium and vitamin D, predominantly through supplementation, than normal-weight controls[157,158]. As decreased BMD is often a long-term complication of anorexia nervosa, development of FDA-approved therapies to treat bone loss and reduce fracture risk in women with anorexia nervosa will have important positive public health implications. In the interim, dual-energy X-ray absorptiometry evaluations remain useful to demonstrate the detrimental effects of anorexia nervosa on bone, to counsel patients regarding fracture risk and to motivate patients to pursue eating disorder treatment.

Neuropsychiatric comorbidities

Anxiety and depression are common co-morbid conditions in women with anorexia nervosa, present in 50–75% of patients[159]. Anxiety and depression, as well as eating disorder psychopathology, are associated with dysregulation of hormones, including oestrogen, androgen, cortisol, leptin, PYY and oxytocin levels[56,85,103,160–162]. Oestrogen deficiency might negatively affect mood and anxiety[161,163]. For example, in rat models, ovariectomy resulting in hypoestrogenaemia is associated with increased anxiety[164]. In addition, fear extinction, or the gradual decrease of a conditioned fear response, was impaired in female rats during the metestrus phase (low estrogen/progesterone) compared to male rats[165]. Similarly, hypoandrogenaemia has been associated with increased severity of depression and anxiety scores in women with anorexia nervosa independent of weight[160], which is consistent with data demonstrating increased depression and anxiety scores in men with hypogonadism[166]. Depression and anxiety measures are also positively associated with levels of serum cortisol[56], and negatively associated with serum leptin levels[162]; the latter

association remained significant after controlling for body fat or weight[162]. Measures of eating disorder psychopathology have been positively associated with serum cortisol and PYY levels independent of BMI[103], and negatively associated with elevated levels of serum leptin[162], in women with anorexia nervosa. Postprandial oxytocin levels are also associated with higher eating disorder psychopathology, anxiety and depression scores in anorexia nervosa[85,167], possibly as an adaptive response to cope with the stress of food intake as oxytocin has known anxiolytic and antidepressant effects[167].

The effect of hormone replacement therapy on eating disorder psychopathology with comorbid depression and anxiety is less clear. In one study, gonadal steroid sufficiency, either through resumption of menses or oral contraceptive use, rather than weight recovery alone, was an important predictor of improved cognitive function (as assessed by a comprehensive neuropsychological evaluation using the Standard Battery of the Woodcock-Johnson III, the Hopkins Verbal Learning Test-Revised, and the visual reproduction subscale of the Wechsler Memory Scale-Revised) in 66 women with anorexia nervosa compared with 42 normal-weight controls[168]. In adolescent girls 13–18 years old with anorexia nervosa, an estradiol patch improved trait anxiety (that is, the tendency to experience anxiety) independently of weight changes, but did not affect attitudes toward eating, eating behaviours or body shape perception[169]. Pilot studies administering low-dose testosterone patches at a dose of 300 mcg/day to women without anorexia nervosa suggest that this treatment might have positive effects on mood[170–172]. However, whether low-dose testosterone would be beneficial for the treatment of comorbid mood disorders in women with anorexia nervosa is unclear.

Anorexia nervosa in men

Although 5–15% of those affected by anorexia nervosa are men, very limited data exists regarding the endocrine impact of the disease in this population. Adolescent boys with anorexia nervosa are known to have lower BMI, lean mass, fat mass, testosterone levels, and estradiol levels than normal-weight controls[173]. Men with anorexia nervosa have a higher percentage trunk fat and a higher trunk-to-extremity fat ratio than healthy men after controlling for weight[174]. This finding is attributed to hypogonadotrophic hypogonadism, as men with acquired hypogonadism have greater waist-to-hip circumferences and abdominal subcutaneous fat than eugonadal men, and testosterone replacement results in a decrease in these measures[175–177]. In a small longitudinal study of three men with anorexia nervosa, levels of serum testosterone increased into the normal range of the commercial lab assay with weight gain[178].

Adolescent boys and men with anorexia nervosa also have reduced BMD[173]. The proportion of adolescent boys age 12–19 years with anorexia nervosa who have BMD Z-scores below –1.0 at the femoral neck and spine are 65% and 50%, respectively, compared with 18% and 24% for normal-weight adolescent boys[173]. Compared with adolescent girls with anorexia nervosa, for whom BMD is most affected at the lumbar spine[105], low BMD Z-scores at the hip and femoral neck are more common in adolescent boys with anorexia nervosa (58.8% and 64.7%, respectively) compared with adolescent girls with anorexia nervosa (20% and 13.6%, respectively)[105,173]. The sex-specific effects of anorexia nervosa on BMD suggest

that not all data from women can be extrapolated to the male population. Data on the efficacy of testosterone replacement on BMD in adolescent boys or men with anorexia nervosa are not available. Fracture data in men with anorexia nervosa is largely unknown and limited to case reports[179,180]; studies have been limited by impediments in recruiting large numbers of patients given the lower prevalence of eating disorders in men than women, delays in diagnosis or even failure to recognize the disease in men.

Future research directions

Future research should include elucidating the mechanistic and genetic bases for individual predisposition to endocrine dysregulation in adolescents, women and men with anorexia nervosa, as well as to the aetiopathology of the disease itself. Further research is also needed to understand the interplay between appetite-regulating hormones and brain food motivation circuitry, specifically in anorexia nervosa. The pathophysiology of bone loss and psychiatric comorbidities in anorexia nervosa is also incompletely understood, and optimal treatment strategies still need to be developed. Much less is known about anorexia nervosa in adolescent boys and men than girls and women, and should be an active area of investigation. Endocrine dysregulation in other eating disorders, such as normal-weight women with bulimia nervosa, is also an area in need of active investigation. In some studies, investigators report that women with bulimia nervosa have BMD comparable to healthy controls[181], but others report that those women who have a history of low weight and/or amenorrhea are at risk of bone loss[182]. Another group of women, for whom a history of low weight and/or amenorrhea is associated with deleterious effects on BMD despite current normal weight, includes those with atypical anorexia nervosa[183]. Atypical anorexia nervosa is a new formal diagnosis within Other Specified Feeding or Eating Disorder (OSFED) for individuals who meet anorexia nervosa psychological criteria but are not low weight[183].

Conclusions

Anorexia nervosa is associated with global endocrine dysregulation, including dysfunction of the hypothalamic–pituitary axis and alterations in adipokines and appetite-regulating hormone levels. Most of these endocrine abnormalities are adaptive but nevertheless might contribute to impaired skeletal integrity as well as neuropsychiatric symptoms. Specifically, hypogonadism, hypercortisolaemia, GH resistance, hypooxytocinemia and hyponatraemia are all among the endocrinologic factors that might contribute to reduced BMD, which is a common and severe long-term complication in patients with anorexia nervosa. Weight restoration and gonadal axis recovery are crucial for the improvement of skeletal health, but low BMD might persist despite recovery of the eating disorder. Currently, no FDA-approved medications exist to treat low BMD in anorexia nervosa. The reported associations between hypothalamic–pituitary axis and appetite-regulating hormones with neuropsychiatric disease in anorexia nervosa might provide promising avenues for treatment. As most of the endocrine abnormalities observed in anorexia nervosa are adaptive to the state of chronic starvation, management consists of treatment of the underlying eating disorder via a team approach, which typically includes a psychologist and/or psychiatrist, primary care physician and nutritionist.

Biographies

Melanie Schorr received her BA in genetics, cell, and developmental biology from Dartmouth College, Hanover, New Hampshire, USA and her MD from The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. She completed her Internal Medicine Residency at the Brigham and Women's Hospital and her Endocrinology Fellowship at Massachusetts General Hospital, both Boston, Massachusetts, USA. She is currently an Assistant in Medicine at Massachusetts General Hospital, and an Instructor of Medicine at Harvard Medical School. Her research interests include skeletal health across the weight spectrum in young women and men, as well as its body composition and hypothalamic-pituitary axis hormonal determinants.

Karen K. Miller received her BA in philosophy from Yale College, New Haven, Connecticut, USA and her MD from The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. She completed her Internal Medicine Residency at the Brigham and Women's Hospital, and her Endocrinology Fellowship at Massachusetts General Hospital, both Boston, Massachusetts, USA. She is currently a Physician in Medicine at Massachusetts General Hospital, and a Professor of Medicine at Harvard Medical School. Her research focuses on the neuroendocrine regulation of body composition, skeletal integrity and brain function at the extremes of the weight spectrum.

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Key points

- Anorexia nervosa is associated with endocrine dysregulation, including dysfunction of the hypothalamic–pituitary axis and alterations in adipokines and appetite-regulating hormone levels
- Most endocrine abnormalities are adaptive to the state of chronic starvation, but nevertheless might contribute to impaired skeletal integrity, as well as neuropsychiatric symptoms
- Weight restoration and gonadal recovery are critical to improving skeletal health, but low bone density and increased fracture risk might remain a long-term complication for individuals in recovery from anorexia nervosa
- Further research on the reported associations between hypothalamic–pituitary axis and appetite-regulating hormones with neuropsychiatric symptoms and brain food motivation circuitry might help formulate new treatment modalities

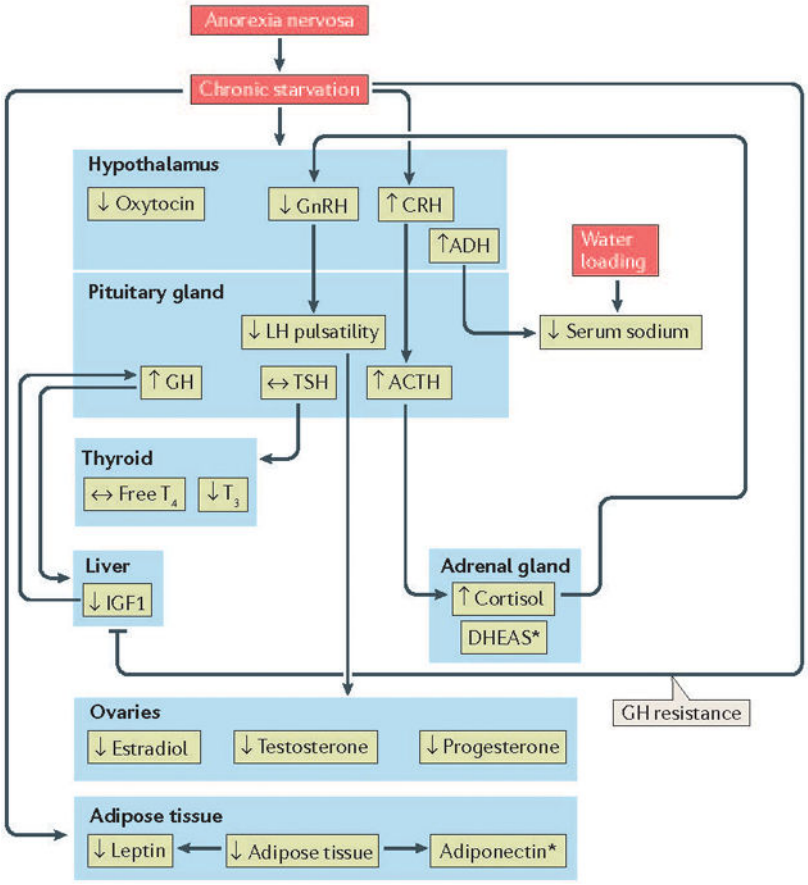

Figure 1. Endocrine dysregulation in anorexia nervosa

Endocrine abnormalities in anorexia nervosa are likely adaptive to the state of chronic starvation except for elevated levels of peptide YY (PYY). Anorexia nervosa commonly results in hypothalamic amenorrhea, with reduced gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) pulsatility and resultant low estradiol and testosterone levels. Anorexia nervosa is a state of acquired growth hormone (GH) resistance, characterized by increased GH secretion and decreased systemic insulin-like growth factor 1 (IGF1) levels. The hypothalamic-pituitary-adrenal axis may be in a chronically stimulated state, with elevated levels of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol. Nonthyroidal illness syndrome, characterized by low levels of T_3 levels, might be present. Anti-diuretic hormone (ADH) might be inappropriately secreted, resulting in free water retention in the kidneys and hyponatremia. The adipokine, leptin, is low in anorexia nervosa due to reduced fat mass, whereas adiponectin levels have been variably reported to be unchanged, increased or reduced. The orexigenic hormone, ghrelin, is elevated, but the anorexigenic hormone PYY is paradoxically also elevated. * factors whose levels are variably reported to be unchanged, elevated or reduced. DHEAS, dehydroepiandrosterone sulphate.

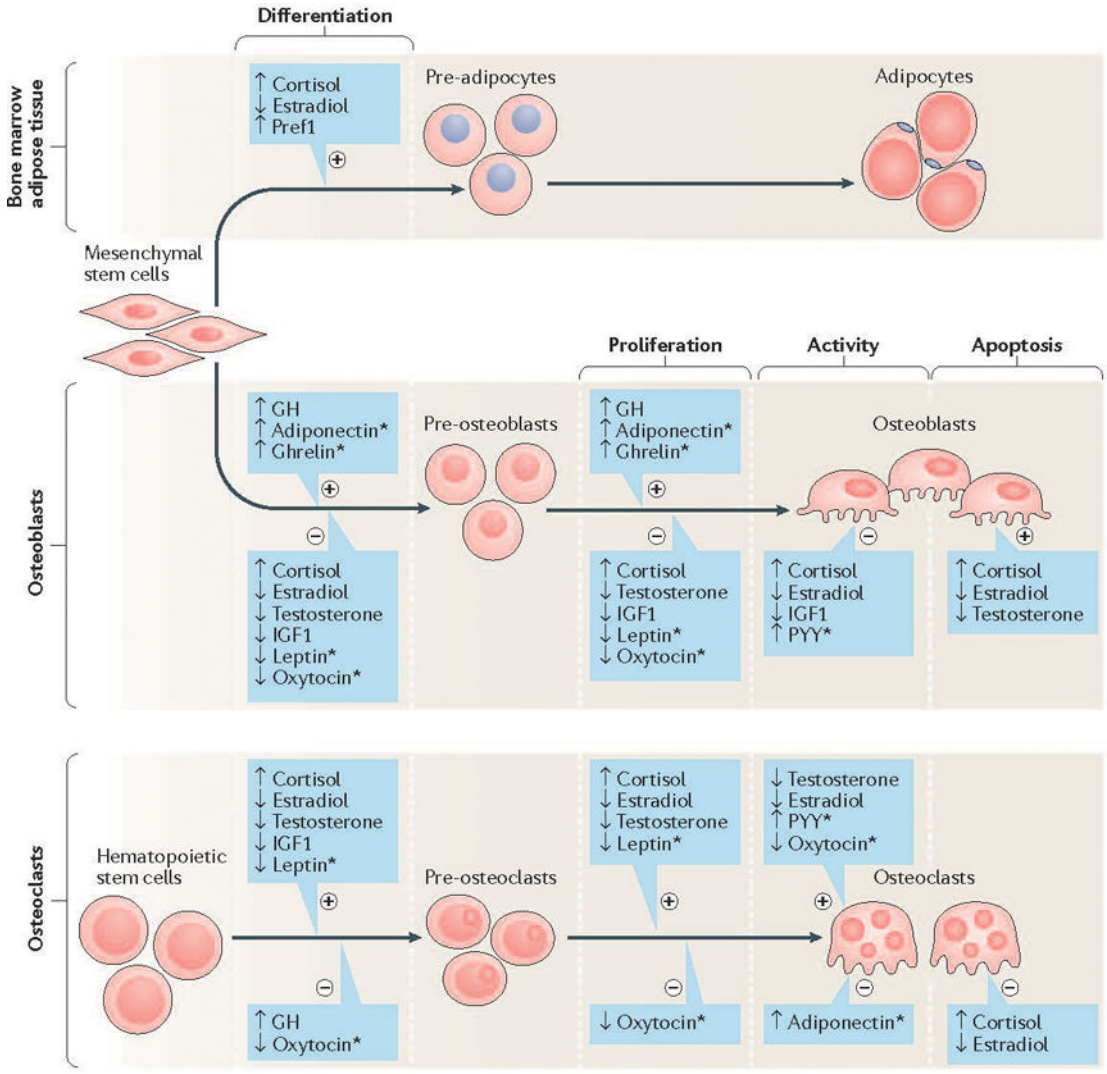

Figure 2. The effect of endocrine dysregulation on the bone microenvironment

Bone marrow adipose tissue is paradoxically elevated in anorexia nervosa despite reduced total body fat. Elevated levels of Pref1, which are an important regulator of mesenchymal stem cell differentiation, may be one of the mechanisms underlying the increase in bone marrow adipose tissue. Overall, a decrease in osteoblast differentiation, proliferation and activity with a concomitant increase in osteoblast apoptosis is seen, in addition to an increase in osteoclast differentiation, proliferation and activity with a concomitant decrease in osteoclast apoptosis. Growth hormone (GH) and insulin-like growth factor 1 (IGF1) stimulate osteoblast differentiation while inhibiting osteoclast differentiation, and GH independently stimulates osteoblast proliferation. In contrast, cortisol decreases bone formation and increases bone resorption. Both oestrogen and testosterone stimulate bone formation and inhibit bone resorption. Alterations in adipokines, such as leptin and adipokine, and appetite-regulating hormones, such as peptide YY (PYY), might also contribute to impaired bone microarchitecture in anorexia nervosa but are not well

understood. * Hormone effect for which there are limited data. +, positive effect; -, negative effect.

Table 1

Therapies to treat low BMD in adolescent girls and women with anorexia nervosa

Therapy	Age	*n*	Change in BMD	Treatment length (months)	Reference
Oral oestrogen/progestin	16–42	48	No change versus placebo	19 (mean)	139
	12–21	50	No change versus placebo	12	141
	18–38	60	No change versus placebo	9	147
	11–17	112	No change versus placebo	12	140
Physiologic oestrogen replacement	12–18	110	Increase in spine BMD versus placebo (2.6% vs 0.3%). Stable hip BMD versus decline in placebo (0.004% vs 1.2%)	18	143
Recombinant hIGF1	18–38	60	Increase in spine BMD versus placebo (1.1% vs −0.6%)	9	147
Recombinant hIGF1plus oral contraceptive	18–38	60	Increase in spine BMD versus placebo (1.8% vs −1.0%)	9	147
Testosterone	19–49	77	No change versus placebo	12	144
DHEA	14–28	61	No change to oral estrogen/progestin group. Similar increase in hip BMD (1.7%) in both DHEA and oral estrogen/progestin group, but change was not significant after controlling for weight gain.	12	145
DHEA plus oral contraceptive	13–27	94	Maintenance of spine and hip BMD versus decrease in placebo group	18	146
Oral bisphosphonates	12–21	32	No change versus placebo, although both groups gained weight and increased spine and hip BMD	12	149
	19–49	77	3-4% increase in spine BMD and 2% increase in hip BMD versus placebo	12	144
Teriparatide	32–58	32	Increase in spine BMD versus placebo (6% vs 0.6%). No change in hip BMD versus placebo	6	151
Weight gain and resumption of menses	18–40	75	1.8% increase in hip BMD, 3.1% increase in spine BMD compared with baseline	12	Miller 2006

DHEA, Dehydroepiandrosterone; hIGF1, human insulin-like growth factor-1.