Endocrine Consequences of Anorexia Nervosa

Madhusmita Misra, MD, MPH and Anne Klibanski, MD
Neuroendocrine Unit and Pediatric Endocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114

Summary

Anorexia nervosa (AN) is prevalent in adolescents and young adults, and endocrine changes include hypothalamic amenorrhea, a nutritionally acquired growth hormone resistance with low insulin like growth factor-1 (IGF-1), relative hypercortisolemia, decreases in leptin, insulin, amylin and incretins, and increases in ghrelin, PYY and adiponectin. These changes in turn have deleterious effects on bone, and may affect neurocognition, anxiety, depression and eating disorder psychopathology. Low bone density is particularly concerning; clinical fractures occur and changes in both bone microarchitecture and strength estimates have been reported. Recovery causes improvement of many, but not all, hormonal changes, and deficits in bone accrual may persist despite recovery. Physiologic, primarily transdermal, estrogen replacement increases bone density in adolescents, although catch-up is incomplete. In adults, oral estrogen co-administered with rhIGF-1 in one study, and bisphosphonates in another increased bone density, though not to normal. More studies are necessary to determine the optimal therapeutic approach in AN.

Keywords

estrogen; testosterone; cortisol; growth hormone; IGF-1; ghrelin; leptin; PYY; adiponectin; bone microarchitecture; bone strength; bone density

Introduction

Anorexia nervosa (AN) is a condition of severe undernutrition that is prevalent in adolescent girls and young women, and reported in 0.2–1% of this population. It is characterized by an altered body image, very low weight associated with an inability to gain or maintain weight, and in females, Diagnostic and Statistical Manual-IV (DSM-IV) included amenorrhea for at least three cycles in the diagnostic criteria. The revised DSM-V criteria for AN differ in that weight criteria are less stringent and amenorrhea is no longer required for this diagnosis. The condition occurs predominantly in women, and adolescence is a
common time for the onset of AN. AN is also reported in males, who comprise 10% of all diagnosed AN patients, although recent papers suggest a higher prevalence. In response to the severe energy restriction, alterations occur in many endocrine axes, most of which are adaptive to stimulate food intake, help maintain euglycemia, and divert available energy for essential body functions. Hypothalamic oligo-amenorrhea in AN causes infertility which typically reverses with stable weight restoration. Hormonal alterations contribute to low bone density and increased risk for fractures, a major co-morbidity associated with AN. Furthermore, neuropsychiatric co-morbidities such as anxiety and depressive symptoms may be associated with hormonal changes seen in AN.

Although 50% of adults with AN recover following behavioral, psychiatric and medical therapy, about 30% demonstrate only partial recovery, and the remainder are characterized by remissions and relapse or chronic disease. A major concern is a high risk for suicide, a common cause of death in AN. Among adolescents with AN, relapses occur following inpatient hospital admissions in 30% before medical recovery, however, about 70–75% completely recover over 5–10 years, with a low later risk of relapse. About 30% of restrictors will develop binge eating behaviors in the long term.

**Nutrient Intake and Resting Energy Expenditure in AN**

**Macronutrient Intake and Resting Energy Expenditure**

Adolescents and adults with AN have lower total caloric intake compared with normal-weight controls, and the reduced caloric intake is primarily from marked reductions in fat intake, although decreases are also observed in absolute protein and carbohydrate intake. Lower fat intake in AN is associated with lower fat mass. Individuals with AN have lower resting energy expenditure than normal-weight controls, likely an adaptive mechanism to preserve energy for vital functions. Consistent with findings of lower resting energy expenditure, cold activated brown (or metabolically active) adipose tissue is lower in AN compared with controls. One study reports that compared with constitutionally thin individuals and normal-weight controls, individuals with AN have similar total energy expenditure (assessed using doubly labeled water studies), but lower energy intake.

**Micronutrient Intake**

Intake of saturated and unsaturated fat is lower in AN than controls. In contrast, intake of soluble and insoluble fiber is higher in AN, as is intake of oxalates and phytates, all of which may potentially reduce absorption of other nutrients. Thus attention to diet composition is important in AN. Vitamin intake from diet and supplements, including of vitamin D, is typically higher in AN than controls, mostly from increased supplement use. In one study of teenagers with AN, 76% of the girls with AN compared with 50% of controls met the recommended dietary intake (RDI) for vitamin D. Another study found a low prevalence of vitamin D deficiency in adolescents with AN (2% in AN compared to 24% in controls). Similarly, intake of calcium, magnesium and zinc is higher in AN than controls, and about 59% of AN girls compared with 30% of controls meet the RDI for calcium.
Impact of AN on Body Composition and Liver Function

In addition to lower BMI, individuals with AN have lower fat and lean mass, with marked reductions in percent trunk fat, trunk to extremity fat ratio (TEFR) and percent extremity lean mass 29–31. Reductions in trunk fat are related to increased growth hormone (GH) concentrations 31, whereas reductions in percent extremity lean mass are related to higher cortisol 31. Girls with the highest GH and lowest cortisol have the lowest trunk fat. GH and cortisol are gluconeogenic hormones that increase in conditions of energy deprivation and mobilize energy for vital functions. Effects of GH are mediated primarily through increased lipolysis, thus providing required substrate for gluconeogenesis 32. This is consistent with inverse associations of GH with body fat, and particularly with trunk fat. Associations of relative hypercortisolemia in AN with lower extremity lean mass are consistent with the muscle wasting reported in conditions of hypercortisolemia 33, although other factors may contribute. The impact of weight recovery on body composition varies with age group. Both adolescents and adults have increases in fat and lean mass, percent body fat, percent trunk fat and TEFR with weight gain. However, whereas in adolescents, percent trunk fat and TEFR approach that in normal-weight controls 29, in adults with AN, these parameters may exceed that in controls 30.

Endocrine Consequences of AN

Changes occur in multiple endocrine axes, and the severity of changes is related to the degree of undernutrition.

a) Growth hormone (GH)- Insulin like growth factor-1 (IGF-1) axis

Adolescents 34, 35 and adults 36–39 with AN have higher GH levels than controls 35, 37 (Figure 1), and those with the lowest BMI and fat mass have the highest GH 35, 37. However, systemic IGF-1 levels are low in AN 35–39, indicative of a nutritionally acquired resistance to GH. This is likely from a down-regulation of GH receptor expression, corroborated by low levels of GH binding protein, the cleaved extracellular domain of the GH receptor 36, 38. This state of GH resistance in AN is further confirmed by a lack of increase in IGF-1 following administration of supraphysiological doses of recombinant human GH (rhGH) in women with AN 40, 41. Because IGF-1 is an important bone anabolic hormone, GH resistance in AN associated with low IGF-1 levels is an important determinant of impaired bone metabolism.

The increase in GH in AN is consistent with its gluconeogenic role (through increased lipolysis), to maintain euglycemia in a state of low energy availability, and is subsequent to (i) decreased negative feedback from low levels of IGF-1 35, 36, and (ii) increased levels of ghrelin (a GH secretagogue) 34, 42. Importantly, effects of GH on carbohydrate metabolism and lipolysis are not IGF-1 mediated, and these effects are preserved in AN. Hence, supraphysiologic GH administration in adult women with AN leads to a decrease in fat mass, even though IGF-1 levels do not change 40. Weight gain leads to a normalization of GH secretion 36 and GHBP levels 36, 38, consistent with these changes being adaptive to nutritional status.

Lancet Diabetes Endocrinol. Author manuscript; available in PMC 2015 July 01.
b) Hypothalamic-pituitary-adrenal (HPA) axis

AN is associated with a state of relative hypercortisolemia in adults and adolescents \(^{15, 39, 43-50}\) (Figure 2). However, levels rarely exceed twice the upper limit of normal and are not associated with Cushingoid features. In addition to CRH stimulating increased secretion of ACTH and thus cortisol, increased ghrelin secretion in AN \(^{42}\) may stimulate increased secretion of CRH, ACTH and cortisol \(^{45, 50}\). In fact, positive associations are reported between ghrelin and cortisol secretory parameters in AN \(^{42}\). Those with the lowest BMI, fat mass and fasting glucose and insulin levels have the highest cortisol, consistent with the increase in cortisol being an adaptive mechanism to maintain euglycemia in a state of low energy availability \(^{43}\).

Higher cortisol levels predict lower percent extremity lean mass \(^{31}\) and lower bone density in AN\(^{15, 43}\). One study has reported that higher baseline cortisol in girls with AN is predictive of subsequent increases in fat mass, which in turn predicts resumption of menses \(^{51}\). In contrast, another study suggests that increased secretion of CRH in AN may contribute to the severity of weight loss in AN from the strong anorexigenic drive of CRH \(^{52}\), and higher cortisol secretion has been demonstrated to predict greater eating disorder psychopathology, independent of BMI \(^{16}\). No pharmacological approaches are currently recommended to address the relative hypercortisolemia in AN given that these are adaptive changes and do not contribute to a Cushingoid state (in contrast to pathological hypercortisolemia).

c) Hypothalamic-pituitary-thyroid (HPT) axis

Changes observed in the HPT axis in AN are consistent with starvation and those seen with the sick euthyroid syndrome, and do not need to be treated. Levels of total T3 are low, likely an adaptive mechanism to lower resting energy expenditure and conserve energy for vital functions. T3 levels are associated with lower BMI and leptin levels and higher ghrelin and cortisol \(^{42, 43}\). Free T4 varies from normal to low normal or low, depending on the severity of AN, while TSH levels are typically normal or low normal \(^{39, 42, 43}\). In adults with AN, the response of TSH to exogenous TRH administration is blunted \(^{53}\).

d) Insulin, gut peptides and adipokines

Low weight and BMI, and lower glucose levels in AN are associated with lower fasting insulin levels than in controls \(^{54}\). Lower levels of insulin enable counter-regulatory mechanisms to come into play, including glycogenolysis, lipolysis and gluconeogenesis. Amylin is a hormone secreted by pancreatic beta cells with insulin in a 1:1 ratio, and levels of amylin are low in AN \(^{55}\), associated with low BMI and percent body fat, as are levels of the incretins, glucagon like peptide-1 \(^{56}\) and glucose-dependent insulinotropic peptide (GIP) \(^{55, 57}\). Lower insulin and amylin levels help preserve euglycemia, but contribute to lower BMD in AN.

Changes also occur in other gut peptides in AN. It is unknown whether all changes in these peptides are adaptive to starvation and return to normal with sustained weight recovery, or whether some may play a role in the pathogenesis of AN. Levels of ghrelin and peptide YY (PYY) are higher in AN compared with normal-weight controls \(^{34, 42, 58}\), although studies
have also reported unchanged or lower PYY. Ghrelin is an orexigenic hormone (in addition to being a GH secretagogue), and is secreted by the oxyntic cells of the stomach. In healthy individuals, ghrelin levels increase immediately before meals, and nadir about 30 minutes after food intake. Higher fasting and overnight ghrelin levels have been reported in AN, associated inversely with BMI, fat mass, and insulin. Studies have reported differences in ghrelin levels in restrictive vs. binge-purge forms of AN (AN-R vs. AN-BP) vs. bulimia nervosa (BN), with ghrelin levels (compared to controls) being higher in AN-R, unchanged in BN, and lower in AN-BP. Obestatin, a ghrelin gene product that inhibits appetite and gastric motility, is also increased in adults with AN, and positively associated with ghrelin.

One study has implicated a genetic variation of the ghrelin activator gene ghrelin O-acyltransferase (GOAT) in the etiology of AN, and another suggests that the 3056 T-->C single nucleotide polymorphism of the ghrelin gene is related to recovery from AN-R. However, another study did not find a higher occurrence of three ghrelin gene polymorphisms in patients with eating disorders. It is unclear if and how these polymorphisms contribute to AN.

Higher ghrelin levels are consistent with an adaptive mechanism to increase food intake, and two-weeks of twice daily ghrelin infusion in a small group of five women with AN led to reduced gastrointestinal symptoms, and increased hunger and caloric intake. More studies are necessary to confirm these promising findings. In addition, ghrelin stimulates GH and ACTH secretion (thus contributing to the counter-regulatory response to maintain euglycemia), and inhibits gonadotropins. In girls with AN, higher ghrelin concentrations predict higher GH and cortisol secretion, and lower LH and estradiol.

Weight gain is associated with a reduction in ghrelin, consistent with an adaptive response to starvation, although levels may remain higher than in normal-weight controls. Circulating ghrelin is present in acylated (active) and des-acylated (inactive) forms, and following short-term weight gain, acylated ghrelin and the ratio of acylated/total ghrelin increase, whereas desacylated ghrelin levels decrease.

PYY is an anorexigenic hormone secreted by the L (endocrine) cells of the distal gut, whose levels rise 15–30 minutes after food intake and induce postprandial satiety. PYY levels are variably reported to be higher, unchanged, or lower in AN than in normal-weight controls, and correlate inversely with BMI and fat mass. Unlike other hormonal changes that are likely adaptive in AN and work to maintain a state of energy balance, an increase in PYY, an anorexigenic hormone, would not be adaptive and has been hypothesized that it may play an as yet undetermined role in the pathogenesis of this disorder.

Changes occur in adipokines in AN, including levels of leptin, adiponectin and inflammatory cytokines such as IL-6. Leptin levels are markedly lower in AN than controls, and correlate positively with fat mass, and weight gain is associated with an increase in leptin. In contrast, adiponectin levels are variably reported to be unchanged, higher, or lower in AN compared with controls and may depend on measurement of adiponectin isoforms. Lower adiponectin in very severe AN may be
a consequence of marked reductions in fat mass. All these hormone changes contribute to hypogonadism and low bone density. However, at this time, there are no data to indicate that these changes need to be addressed pharmacologically.

e) Hypothalamic-pituitary-gonadal (HPG) axis

Decreased energy availability in AN is believed to cause hypothalamic amenorrhea ⁷⁹. Women with AN often have patterns of LH pulsatility that resemble those in prepubertal or early pubertal girls, with very low amplitude LH pulses or a sleep entrained pattern of LH pulsatility ⁸⁰. Altered gonadotropin secretion in AN has been associated with decreases in fat mass, a reflection of energy stores, and alterations in hormones that are secreted by adipocytes (leptin and adiponectin) or regulated by fat/energy stores (ghrelin, PYY and cortisol) ⁶⁹, ⁷⁰, ⁸¹–⁸⁴. Normal leptin levels are permissive for puberty and facilitate normal gonadotropin secretion ⁸⁵.

Altered LH pulsatility manifests as hypothalamic amenorrhea. Some women with AN present with irregular periods rather than complete amenorrhea, and this may reflect changing energy status over time. With weight gain and an increase in fat mass, menstrual function resumes in a large proportion of women with AN, and data suggest that the most important determinant of resumption of menstrual function is an increase in fat mass ⁵¹ (Figure 3). Although there is significant overlap of fat content amongst those who do or do not recover weight and menses, one study in adolescents with AN reported that all girls with body fat greater than 24% resumed menses, whereas none of those with body fat less than 18% had menstrual recovery ⁵¹. There may be a lag period between increase in body weight and menstrual recovery in AN, and it is prudent to wait a period of at least 6 months following attainment of target weight before considering further investigations. A few studies have suggested that persistent amenorrhea following weight recovery in women with AN may indicate an underlying predisposition for polycystic ovarian syndrome (PCOS) ⁸⁶, ⁸⁷.

Hypothalamic oligo-amenorrhea leads to hypoestrogenism and decreased gonadal secretion of testosterone ⁸⁸, ⁸⁹. Decreased gonadal steroid secretion has a deleterious effect on bone metabolism, and hypogonadotropic hypogonadism causes infertility that is reversible with recovery from AN ¹².

One longitudinal study of the HPG axis in three males with AN reported low morning levels of leptin, gonadotropins and testosterone at the onset of the study, with an increase in these levels with weight gain ⁹⁰. Another study also demonstrated lower LH, FSH and testosterone, but normal inhibin levels in males with AN than in controls ⁹¹. Low testosterone secretion in young men with AN has detrimental effects on bone and body composition ⁷¹, ⁹².

Fertility in Anorexia Nervosa—Women with AN and hypothalamic oligo-amenorrhea are typically infertile until their HPG axis recovers with stable weight restoration ¹¹, ¹². The occurrence of AN with bulimia nervosa is associated with a longer time to conceive on treatment, and negative feelings during pregnancy ⁹³. In women with persistent infertility, fertility is inducible with ovulation induction techniques ¹², ⁹⁴. Also, unplanned pregnancies
are reported to be more common in AN compared to the general population. There are reports of an increased risk for miscarriages, cesarean deliveries, premature births and perinatal lethality in women with a history of AN, indicating the need for careful monitoring of these women during pregnancy and their offspring following birth. One study reported that whereas 50 of 140 women gave birth to a total of 86 children, none of 11 males with AN had children. While these are small numbers, it is possible that perturbations in the male reproductive axis may have a greater impact on fertility than those in women.

f) Posterior Pituitary Hormones (Including Renal Function)

Some studies have reported altered osmoregulation in AN, attributed to abnormalities in osmoregulation of vasopressin, intrinsic renal defects and the effects of antidepressants. Women with AN have lower plasma sodium and osmolality, higher levels of antidiuretic hormone (ADH) and more concentrated urine than controls. Following water deprivation, however, ADH secretion is suboptimal with decreased urine concentrating ability. Older case reports indicate a risk for nephrocalcinosis, renal calculi, rhabdomyolysis and renal failure in AN; however, there are only a few recent reports of these renal complications, likely because of earlier diagnosis and improved medical care. Rhabdomyolysis has been associated with both hypokalemia and hypophosphatemia. Hypokalemia can also occur from purging behaviors, particularly in bulimia nervosa, and from laxative and diuretic abuse. Hypophosphatemia may occur during refeeding. Thus, it is important to monitor electrolytes in individuals with AN.

Pooled nocturnal oxytocin is lower in adult women with AN than in controls and is associated with lower fat mass. Oxytocin has anorexigenic effects and is also bone anabolic through effects on osteoblasts. Recent studies have also shown that estrogen increases oxytocin secretion on osteoblasts, which then acts on its own receptor to exert an anabolic effect on bone. Thus, lower oxytocin levels in AN may contribute to impaired bone metabolism. Importantly, food induced oxytocin secretion in AN-R (and in recovered AN patients) predicts eating disorder psychopathology and hypo-activation of food motivation circuitry.

g) Bone mineral metabolism

One of the most concerning consequences of AN that may persist even with weight recovery is low bone mineral density (BMD), associated with altered bone microarchitecture and reduced strength estimates. Importantly, women with AN have a higher prevalence of fractures than reported in the general population.

Bone mineral density in AN—Adults and adolescents with AN have low areal bone mineral density (aBMD) at the spine and the hip compared with controls, indicating that both trabecular and cortical sites are affected in this disease. One study reported that 92% and 38% of adult women with AN have T-scores of <-1 and <-2.5 respectively at one or more skeletal sites. In the absence of weight and menstrual recovery, women with AN lose bone mass at an annual rate of 2.6% at the spine and 2.4% at the hip (Figure 4). With weight gain, preferential increases occur in bone density at the
total hip, whereas with menstrual recovery, preferential gains are noted at the spine \(^{110}\) (Figure 4).

Similar to adults, low aBMD is characteristic of adolescents with AN. Early studies indicated that as many as 50% of girls with AN may have aBMD Z-scores of <-2 at diagnosis \(^{117}\). However, recent studies are more encouraging, likely because of greater awareness of this condition and earlier diagnosis and treatment. We have reported that 52\% of adolescents with AN have aBMD Z-scores of <-1 at one or more sites, with the spine (a site of trabecular bone) being commonly affected \(^{111}\). In addition, in contrast to healthy adolescents who demonstrate the continued increase in bone accrual that is necessary for attainment of optimal peak bone mass, bone accrual plateaus in adolescents with AN \(^{89, 118}\). This raises concerns for attainment of peak bone mass, a critical determinant of future bone health and fracture risk. With weight and menses recovery, increases occur in bone accrual \(^{118}\). However, rates remain lower than in normal-weight controls, and catch-up does not occur. In fact, aBMD Z-scores often continue to decrease even following weight gain \(^{118}\). In addition, low bone density is observed in adolescent boys with AN \(^{71, 119}\). In contrast to girls, boys have greater involvement of sites of predominantly cortical bone (such as the hip), with 65\% and 50\% of boys with AN having Z-scores of <-1 at the femoral neck and spine compared with 18\% and 24\% of normal-weight boys \(^{71}\).

**Bone microarchitecture and strength estimates**—Adult women with AN have decreased cortical thickness and cortical volumetric bone mineral density (vBMD) at the distal radius, as assessed by high resolution peripheral quantitative computed tomography (HRpQCT) \(^{120}\). Trabecular parameters are also impacted, with reductions in trabecular number and thickness and increased trabecular separation \(^{113, 120}\). Strength estimates assessed using micro finite element analysis (μFEA) are lower in women with AN than controls \(^{121}\). Similarly, adolescents with AN have altered bone microarchitecture with lower cortical and trabecular thickness, lower cortical area, increased trabecular area, and lower total and trabecular vBMD compared to controls \(^{112}\). Cortical porosity is higher in AN, and stiffness and failure load (strength estimates) lower \(^{112}\).

**Determinants of impaired bone metabolism**—Important determinants of low bone density in AN include lower BMI and lean body mass \(^{110, 111, 116}\), consistent with known effects of mechanical loading on bone. Particularly, lower lean mass predicts lower bone density at the hip and whole body, and size parameters of bone microarchitecture, such as cortical thickness and total area.

A major contributor to low bone density and impaired bone microarchitecture is hypogonadism. Later age at menarche and a longer duration of amenorrhea are associated with lower bone density and impaired microarchitecture, and lower estradiol and testosterone predict lower bone density in AN \(^{71, 88, 111, 116}\). Many studies have demonstrated that oral estrogen administration as monotherapy is not effective in increasing bone density in adults and adolescents with AN \(^{122, 123}\), attributed to the IGF-1 lowering effects of oral estrogen \(^{124, 125}\). Importantly, physiologic estrogen replacement using transdermal estradiol with cyclic progesterone increases spine and hip aBMD Z-scores in adolescents with AN \(^{126}\) (Figure 5). However, complete catch-up does not occur, likely

*Lancet Diabetes Endocrinol*. Author manuscript; available in PMC 2015 July 01.
because residual alterations persist in other hormones that may impact bone. In a randomized placebo-controlled study, transdermal testosterone replacement did not improve bone density in adult women with AN. Data are not available regarding the impact of testosterone replacement on bone density in males with AN. Oral DHEA with ethinyl estradiol was demonstrated in one study to prevent further decreases in bone density. A key determinant of impaired bone metabolism in AN is GH resistance with low IGF-1. In AN, IGF-1 levels correlate positively with markers of bone turnover, aBMD, and bone structural parameters, and administration of rhIGF-1 in replacement doses of 30–40 mcg/kg twice daily increases levels of bone formation markers in both adolescents and adults with AN. One 9-month randomized controlled study of oral estrogen with rhIGF-1 in adults with AN demonstrated an increase in aBMD compared to no treatment, estrogen or rhIGF-1 alone, and studies of estrogen and rhIGF-1 administration in adolescents with AN are ongoing.

Other determinants of low BMD include high levels of cortisol and PYY and low levels of leptin, insulin and amylin. PYY inhibits osteoblastic activity, and PYY transgenic mice have decreased bone formation. In AN, high PYY levels correlate with lower BMD in adults, and with lower levels of bone turnover markers in adolescents. Leptin, insulin and amylin all have bone anabolic effects, and lower levels of these hormones in AN correlate with lower BMD. Finally, adiponectin is deleterious to bone, and inverse associations exist between adiponectin and spine bone mineral apparent density in AN.

Management of low bone density and impaired bone accrual—The most important strategy to improve bone density and bone accrual in adolescents with AN is recovery of weight and menstrual function. However, catch-up does not occur even with recovery, and because bone accrual rates remain lower than in controls, bone density Z-scores continue to decrease. This lack of catch-up may reflect persistent abnormalities in hormones such as cortisol, or frequent relapses. It is important to supplement vitamin D to maintain 25(OH) vitamin D levels above 30 ng/ml. Because the teenage years are such a narrow window of time during which to optimize bone accrual, one may consider physiologic transdermal estrogen replacement (with cyclic progesterone) in teenagers with AN who have completed growth and have a significant fracture history, or very low bone density Z-scores with deterioration over time. However, the impact of estrogen replacement on fracture risk in AN remains unclear. Testosterone replacement is not effective in increasing bone density in women with AN. Bisphosphonates increase bone density in adults, but do not increase spine bone density measures in adolescents with AN. If considered as a therapeutic strategy, these drugs should be given cautiously in women of reproductive age, given concerns regarding their long half-life.

Impact of Endocrine Changes on Eating Disorder Psychopathology, Anxiety and Depression in AN

Lower levels of gonadal hormones, oxytocin and leptin, and higher cortisol and PYY have been implicated in eating disorder psychopathology, and symptoms of anxiety and
depression in AN. Administration of transdermal estradiol reduces trait anxiety in girls with AN without affecting eating attitudes or body shape perception. In addition, estrogen replacement prevents the increase in aberrant eating attitudes and body dissatisfaction noted with weight gain in AN.

Conclusion

AN is thus associated with mostly adaptive changes in multiple endocrine axes to optimize energy intake and availability for vital functions (Figure 6). However, these changes contribute to low bone density and possibly to neurocognitive changes and psychopathology in AN. Studies are ongoing to assess the impact of various therapeutic strategies on bone accrual, density, and structure in AN, and to better understand the links between various hormonal changes and food motivation pathways that involve reward and satiety.

Acknowledgments

Funding Sources: NIH Grant Numbers 1 R01 HD060827, 1 K24 HD071843-01A, 5 UL1 RR025758 and 2 RO1 DK062249.

Bibliography

7. Association AP. Diagnostic and Statistical Manual of Mental Disorders. 5. 2013. DSM-5


Lancet Diabetes Endocrinol. Author manuscript; available in PMC 2015 July 01.


Lancet Diabetes Endocrinol. Author manuscript; available in PMC 2015 July 01.
Search Strategy

We searched PUBMED (1990–2013) using the search terms “anorexia nervosa” or “eating disorders” in combination with the terms “hypogonadism”, “estrogen”, “testosterone”, “growth hormone”, “IGF-1”, “cortisol”, “thyroid”, “ghrelin”, “leptin”, “peptide YY”, “adiponectin”, “amylin”, “GLP-1”, “GIP”, “bone density”, “bone structure or microarchitecture”, “finite element analysis”, or “fractures”. We largely selected publications in the past 15 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. A few review articles and book chapters are cited to provide readers with more details and references than can be accommodated in this Review.”
Figure 1. Impact of anorexia nervosa (AN) on growth hormone (GH) and IGF-1
A. Representative overnight GH secretory characteristics in a teenage girl with AN (left) and a normal-weight control (right) showing increased GH secretion in the girl with AN.
B. Mean overnight GH concentrations (left) and fasting IGF-1 levels (right) in adolescent girls with AN and controls. Adolescent girls with AN have lower IGF-1 levels than controls despite higher GH concentrations, suggestive of a nutritionally acquired resistance to GH effects. Adapted from Misra et al. J Clin Endocrinol Metab 88: 5615–5623; 2003. Copyright © by The Endocrine Society 2003.
Figure 2. Impact of anorexia nervosa (AN) on cortisol secretion
A. Representative overnight cortisol secretory characteristics in a teenage girl with AN (left) and a normal-weight control (right), showing greater cortisol secretion in the girl with AN.
B. 24-h urinary free cortisol levels in adolescent girls with AN and controls. Adolescent girls with AN have higher 24-h urinary free cortisol compared with controls. Adapted from Misra et al. J Clin Endocrinol Metab 89: 4972–4980; 2004. Copyright © by The Endocrine Society 2004.
Figure 3. The proportion of body fat is an important determinant of menstrual function

A. Percent body fat in girls with anorexia nervosa (AN) who did or did not resume menses: Girls with AN who recovered menstrual function over a year of follow-up had greater percent body fat at the end of the follow-up period than those who did not. All girls with body fat greater than 24% resumed menses, whereas none of those with body fat less than 18% had menstrual recovery. From Misra et al. Pediatr Res 59: 598–603; 2006. Copyright © by International Pediatric Research Foundation, Inc., 2006.

B. Percent body fat in low weight adult women who were amenorrheic (mean BMI 16.8±0.2 kg/m²) vs. those who were eumenorrheic (mean BMI 17.1±0.2 kg/m²). Despite similarly low BMI status, eumenorrheic women had greater percent body fat than amenorrheic women. Adapted from Miller et al. J Clin Endocrinol Metab 89: 4434–38; 2004. Copyright © by The Endocrine Society 2004.
Figure 4. Impact of weight and/or menstrual recovery on bone density parameters in adult women with anorexia nervosa not receiving oral contraceptives

A. Women who both improved weight and resumed menses increased BMD at the PA spine and hip, compared with those who neither improved weight nor resumed menses.
B. Women who resumed menses increased PA spine BMD (but not hip BMD), compared with those who did not improve menstrual function.
C. Women who improved weight increased hip BMD (but not PA spine BMD), compared with those who did not improve weight.

Black bars, PA spine BMD; white bars, hip BMD. *, P < 0.05.

Figure 5. Impact of physiologic estrogen replacement on bone density in adolescent girls with anorexia nervosa (AN). Girls with AN randomized to physiologic estrogen administration (ANE+) had significant increases in bone density at the lumbar spine over 6, 12 and 18 months compared with those randomized to placebo (ANE−), to approximate bone accrual rates observed in controls (C) (adjusted for baseline age and weight).

Figure 6. Endocrine changes in anorexia nervosa that maintain euglycemia and preserve energy for vital functions, and also contribute to impaired bone metabolism

CRH: corticotrophin releasing hormone; ACTH: adrenocorticotropic hormone
GH-IGF-1 axis: growth hormone- insulin like growth factor-1 axis
GHBP: GH binding protein
GLP-1: glucagon like peptide-1; GIP: glucose-dependent insulinotropic peptide
HPG axis: hypothalamic-pituitary-gonadal axis
HPA axis: hypothalamic-pituitary-adrenal axis
HPT axis: hypothalamic-pituitary-thyroid axis
LH: luteinizing hormone
PYY: peptide YY
T3: tri-iodothyronine; T4: tetra-iodothyronine; TSH: thyroid stimulating hormone