Endocrine Dysregulation in Anorexia Nervosa Update

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Context: Anorexia nervosa is a primary psychiatric disorder with serious endocrine consequences, including dysregulation of the gonadal, adrenal, and GH axes, and severe bone loss. This Update reviews recent advances in the understanding of the endocrine dysregulation observed in this state of chronic starvation, as well as the mechanisms underlying the disease itself.

Evidence Acquisition: Findings of this update are based on a PubMed search and the author’s knowledge of this field.

Evidence Synthesis: Recent studies have provided insights into the mechanisms underlying endocrine dysregulation in states of chronic starvation as well as the etiology of anorexia nervosa itself. This includes a more complex understanding of the pathophysiologic bases of hypogonadism, hypercortisolemia, GH resistance, appetite regulation, and bone loss. Nevertheless, the etiology of the disease remains largely unknown, and effective therapies for the endocrine complications and for the disease itself are lacking.

Conclusions: Despite significant progress in the field, further research is needed to elucidate the mechanisms underlying the development of anorexia nervosa and its endocrine complications. Such investigations promise to yield important advances in the therapeutic approach to this disease as well as to the understanding of the regulation of endocrine function, skeletal biology, and appetite regulation. (J Clin Endocrinol Metab 96: 2939–2949, 2011)

Anorexia nervosa is a common psychiatric disorder in women and adolescent girls and is characterized by body image distortion and chronic severe undernutrition. Although psychiatric in origin, serious endocrine complications, including bone loss, are a prevalent feature of this disease. This Update reviews published research into the pathophysiology and treatment of endocrine complications of this disorder as well as recent insights into the etiopathology of the eating disorder itself. Although significant progress has been made in the understanding of the disorder and the endocrine physiology of chronic starvation, the fundamental basis of this disease remains unknown. Further research is needed to elucidate the etiology of the disorder and to identify effective treatments for anorexia nervosa and its complications.

Definition and Epidemiology

Sir William Withey Gull, one of Queen Victoria’s personal physicians, coined the term “anorexia nervosa” in 1868, providing a name for a syndrome of wasting for which no organic etiology, such as tuberculosis, could be identified (1). The disorder has since been recognized as psychiatric in origin and is currently diagnosed using standard psychiatric criteria as delineated in the Diagnostic and Statistical Manual IV. These include failure to maintain weight above 85% of ideal, a distorted body image or denial of the seriousness of one’s low body weight, fear of gaining weight, and amenorrhea (2). However, the amenorrhea criterion is under debate and may be excluded from the upcoming psychiatric diagnostic criteria revision (Diagnostic and Statistical Manual V) based on data that demonstrate few psychiatric differences between women with anorexia nervosa who do and do not have amenorrhea (3, 4). In addition, it has been recognized that individual susceptibility of the gonadal axis to undernutrition is highly variable, resulting in a subset of extremely low-weight women with all of the psychiatric features of anorexia nervosa.
Anorexia nervosa who maintain regular menses (5). There are two subtypes of anorexia nervosa: restricting and binge/purge. The latter is characterized by frequent episodes of purging and is distinguished from bulimia nervosa in that establishment of a diagnosis of anorexia nervosa, bulimic subtype requires low weight. In addition, a significant percentage of patients with a restricting subtype develop purging and/or binge-eating symptoms, with more than 50% developing bulimic behaviors over the course of the disease (6).

Anorexia nervosa affects 0.3 to 3.0% of women (7–9) and is the third most prevalent chronic disease afflicting adolescent girls (10) in Western societies. It is primarily a disease of young women, but men and older women are affected at lower rates (8, 10). The risk of death is relatively high for a young population, with an overall standardized mortality ratio of 11 to 12 (11, 12), a substantial portion of which is attributable to a suicide rate 56 times that expected for age and sex (12). Alcoholism is an independent risk factor for mortality (12), and other factors associated with an increased risk of death include older age, longer duration since eating disorder onset, history of suicide attempt, diuretic use, patient desire for low body mass index (BMI), and severity of disordered eating symptomology (11). Although approximately 50% of patients with anorexia nervosa recover fully, 30% sustain only partial recovery, and 20–30% suffer from chronic disease (13). Therefore, complications of the disease may be chronic and may exert long-lasting and serious health effects. In addition, some sequelae, such as low bone mass, may persist even with weight recovery.

**Endocrine Complications of Eating Disorders**

Anorexia nervosa is complicated by hypothalamic-pituitary dysregulation, including hypothalamic amenorrhea, hypothalamic-pituitary-adrenal axis dysregulation resulting in hypercortisolemia, and GH resistance (Table 1), all of which contribute to the high prevalence of severe bone loss in adults and adolescents with this disorder. Electrolyte disorders are also common, with hypokalemia in 20% (a consequence of purging), and hyponatremia in 20%, as is a mild transaminitis (12%), anemia (39%), and leukocytopenia (34%) (14).

**Gonadal axis dysregulation**

Dysregulation of GnRH pulsatility in anorexia nervosa was first characterized in detail by Boyar et al. in 1974 (15). Boyar’s group demonstrated a range of GnRH patterns in amenorrheic young women with anorexia nervosa, which included apulsatility, and reversion to pubertal pulsatility patterns (15, 16). Consistent with clinical observations, the degree of luteinizing hormone (LH) suppression did not correlate reliably with duration of illness or degree of thinness, and return of menses did not demonstrate a simple relationship to weight. Studies over the past few years have sought to identify the regulators of GnRH pulsatility responsible for amenorrhea in women with starvation. Such studies have focused primarily on the roles of leptin and kisspeptin. Low levels of leptin, a 16 kDa adipokine, appear to signal energy unavailability and inhibit normal reproductive function in rodent models. Consistent with this hypothesis, leptin replacement during a 48-h fast prevented the starvation-induced delay in estrous in female mice (17), and congenital leptin deficiency in humans is complicated by hypogonadatrophic hypogonadism (18). As would be expected given the low fat mass characteristic of women with anorexia nervosa, amenorrheic women with anorexia nervosa have, on average, lower leptin levels than normal-weight women, and leptin levels strongly correlate with fat mass (19). However, there is no leptin level cutoff that predicts amenorrhea. There is significant overlap in leptin levels between women with anorexia nervosa with amenorrhea and women of comparable low weight and psychologic characteristics of anorexia nervosa but preserved menstrual function (5). Although leptin administration in women with anorexia nervosa has not been studied, Welt et al. administered leptin to normal-weight (BMI of 18.8–24.4 kg/m²) women with hypothalamic amenorrhea, which resulted in ovulatory cycles in three of eight women studied (20), raising the possibility that leptin may play an important pathophysiologic role in the development of hypothalamic amenorrhea in women with hypothalamic amenorrhea. However, a decrease in weight, attributable to a reduction in fat mass, was observed in the leptin-treated women, consistent with an anorexigenic effect of leptin and limiting its therapeutic potential in anorexia nervosa. More recent research has focused on kisspeptin, an endogenous ligand for the kisspeptin receptor, as a putative important regulator of reproductive function in women.

**TABLE 1.** Endocrine dysregulation in anorexia nervosa

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<tr>
<th>Endocrine Axis</th>
<th>LH pulsatility</th>
<th>Androgens</th>
<th>Cortisol</th>
<th>DHEAS</th>
<th>GH resistance (GH/IGF-1)</th>
<th>Leptin</th>
<th>Ghrelin</th>
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↑, Increased in women with anorexia nervosa; ↓, decreased.
with functional hypothalamic amenorrhea, though no studies specifically examining its role in women with anorexia nervosa have been published. Acute, but not chronic, administration of kisspeptin has been shown to result in gonadotropin release in women with hypothalamic amenorrhea (21), and inactivating mutations cause pubertal failure (22, 23). Further studies are warranted to determine the pathophysiology of amenorrhea in anorexia nervosa.

Hypogonadotrophic hypogonadism results in relative hypoandrogenemia, in addition to hypooestrogenemia, in women with anorexia nervosa (24). Sixty percent of testosterone is derived from ovarian sources in healthy women of reproductive age, with the remaining 40% from adrenal precursors (23). Published data suggest that adrenal androgen precursor secretion is not compromised in women with anorexia nervosa. Therefore, hypogonadotropic hypogonadism appears to be responsible for the hypoandrogenemia observed in such women. In one study, cortrosyn stimulation after dexamethasone suppression stimulated an exuberant cortisol response in women with anorexia nervosa compared with normal-weight controls; however, stimulated dehydroepiandrosterone (DHEA) levels were comparable in the two groups (26). In a large cross-sectional study, DHEA sulfate (DHEAS) levels were not lower in women with anorexia nervosa compared with healthy, normal-weight controls, except in those receiving oral contraceptives (a binding globulin effect) (24), though, in contrast, another study reported decreased DHEAS levels in relation to an assay normal range (27). The effects of androgen deficiency in women with anorexia nervosa are largely unknown. A cross-sectional study showed inverse associations between androgen levels and severity of both depression and anxiety symptoms in women with anorexia nervosa, independent of weight (28), suggesting that relative androgen deficiency may be a factor contributing to the severity of mood-related symptoms in such patients. Pilot studies administering low-dose testosterone in replacement doses in other adult female populations suggest possible positive mood effects with few side effects (29–31), but it remains to be established whether low-dose androgen administration would be a useful clinical tool for the treatment of mood comorbidities alone or in combination with other agents in women with anorexia nervosa.

Hypothalamic-pituitary-adrenal axis dysregulation

Anorexia nervosa is characterized by hypercortisolemia in many adults (32) and adolescents (33). Elevated 24-h urine free cortisol levels (34), overnight mean serum cortisol levels (32, 35, 36), cortisol response to cortrosyn administration (26), dexamethasone suppressibility (37), and midnight salivary cortisol levels (38) are all commonly, though not universally, elevated in women with anorexia nervosa. Although the clinical manifestations of hypercortisolemia in this cachetic group of patients may appear to be inconsistent with those observed in patients with Cushing’s syndrome, with closer examination there are several parallels. In women with anorexia nervosa, higher urine free cortisol levels predict truncal fat accumulation with weight gain (39), and in adolescent girls, higher overnight cortisol levels predict weight gain (40). Moreover, overnight blood cortisol levels are inversely associated with bone mineral density and positively associated with severity of depression and anxiety symptoms in women with anorexia nervosa (32). Therefore, hypercortisolemia may also contribute to the severe bone loss incurred and the highly prevalent psychiatric comorbidities in women with anorexia nervosa.

GH resistance

The fact that serum GH concentrations increase with fasting was first reported in 1963 in Science concurrently with a description of the development of the first GH assay sensitive and specific enough to detect changes of a clinically relevant magnitude (41). Later it was reported that GH burst frequency, burst mass, and burst duration are higher in women with anorexia nervosa than healthy controls, resulting in a 4-fold higher daily pulsatile GH secretion and 20-fold increase in basal GH secretion (42). Misra et al. demonstrated that this relative GH elevation extends to adolescents with anorexia nervosa compared with healthy adolescents, who themselves experience endogenous GH secretion in excess of that of healthy adults (43). However, despite elevated GH levels in patients with anorexia nervosa, IGF-I levels are not increased, as would be expected. To the contrary, chronic starvation causes a state of GH resistance in the liver, and IGF-I levels are low in women (44) and adolescents (43) with anorexia nervosa compared with healthy controls. The suppression of IGF-I is not an artifact of binding globulin abnormalities. This was shown by Stoving et al. using a kinase receptor activation assay to measure IGF-I bioactivity, which was found to be low in women with anorexia nervosa (45). In a recent study, Fazeli et al. investigated whether the state of GH resistance can be overcome with supraphysiologic recombinant human GH administration. In a 12-week randomized, placebo-controlled study administering a mean maximum daily dose of 1.4 ± 0.1 mg/d, serum IGF-I levels did not increase significantly compared with placebo (46). In addition, fat mass and leptin levels decreased. These data suggest that GH resistance in states of under-nutrition is not easily overcome and support the estab-
lished role of GH as a mediator of lipolysis, independent of IGF-I.

**Skeletal dysregulation**

Bone loss is a severe and prevalent complication of anorexia nervosa in women, with 90% of young women having a T score of less than −1.0 and 40% less than −2.0 (47) and is characterized by decreased bone formation and increased resorption (44). A study of 214 women with anorexia nervosa, mean age 25 yr, demonstrated osteopenia in 52% and osteoporosis in 35%, with fewer than 15% of women having normal bone mineral density at all skeletal sites tested (14). The annual rate of decline in bone mineral density at the spine and hip is approximately 2.5% in adults with anorexia nervosa (48). Adolescence is a critical time for bone mass accrual, and studies have shown that adolescent girls with anorexia nervosa do not experience the usual linear increase in bone mass during puberty (49), resulting in lower bone mineral density at the spine and hip than in healthy adolescents of comparable bone age (33). This deficit places them at risk of attaining lower-than-normal peak bone mass and may make them more vulnerable to developing osteoporosis and fractures later in life. In recent years, novel imaging techniques have made it possible to assess bone microarchitecture, and with microcomputed tomography techniques, it has been shown that bone volume and trabecular thickness become abnormal early in the course of the disease in adolescent girls, even before decreases in bone mineral density are detectable by conventional dual energy x-ray measurements (50). Bone microarchitectural parameters, including trabecular thickness and separation, are abnormal in adults with anorexia nervosa as well (51), and IGF-I levels are strong predictors of abnormal bone microarchitectural parameters (51). In addition, bone strength in women with anorexia nervosa has been modeled by finite element analysis and found to be lower than in healthy controls (52) (Fig. 1). The clinical effects of low bone mineral density, abnormal skeletal microarchitecture, and reduced bone strength are an elevated fracture rate reported at 30% (14) and seven times that expected for age and sex (53).

Neuroendocrine and nutritional factors are important determinants of bone loss and bone recovery. Normalization of reproductive function is the strongest predictor of skeletal recovery, and recovery of menses predicts an increase in bone mineral density independent of changes in weight (48). In addition, in a comparison of bone mineral density in 74 women with anorexia nervosa and 42 women with all of the characteristics (psychiatric and weight) of anorexia nervosa, except for amenorrhea, bone mineral density was marked lower in amenorrheic women than eumenorrheic women (mean T score −1.9 vs. −0.9 at the posteroanterior spine) (5). However, of note, eumenorrheic women with anorexia nervosa also had lower bone mineral density than expected for healthy women of comparable age, suggesting that hypogonadism is an important, but not the only, factor responsible for bone loss in women with anorexia nervosa. However, it is important to consider another interpretation of these data, which is that amenorrhea may simply be a marker of degree of undernutrition and/or degree of global endocrine dysregulation. In addition, bone mineral density is lower in amenorrheic women with anorexia nervosa than in normal-weight women with functional hypothalamic amenorrhea (54). These data suggest that nutritional factors are important determinants of bone mineral density, possibly due to both direct mechanical effects and effects on neuroendocrine modulators of skeletal metabolism. BMI is an important determinant of bone mineral density in women with anorexia nervosa, with lean body mass the most important component (49), perhaps due to the anabolic pull of muscle on bone. Recent evidence suggests that enteric and pancreatic peptides, including peptide YY (PYY) (55, 56) and amylin (57), may also play a role in mediating the effects of nutritional intake on bone. Overnight PYY levels are strongly inversely associated with bone mineral density, particularly at the spine, in women with anorexia nervosa (56), and fasting PYY levels are inversely associated with markers of bone turnover in adolescent girls with anorexia nervosa (55). Hypercortisolemia is prevalent in anorexia nervosa (32, 36) and appears to play a role in the etiopathology of bone loss (32), consistent with data in patients with hypercortisolemia of other causes, for example Cushing’s disease and exogenous glucocorticoid administration. Vitamin D and calcium intake are comparable in women with anorexia nervosa and healthy women of comparable age (58) and therefore are not likely to be important pathogenetic factors. Likewise, albumin levels, a marker of hypoproteinemia, are not reduced in

**FIG. 1.** Bone microarchitecture is abnormal in women with anorexia nervosa and bone strength is reduced. Shown are flat-panel volume computed tomography images of the distal radius in a woman with anorexia nervosa (A) and a healthy control (B). [Adapted from C. J. Walsh et al.: Women with anorexia nervosa: finite element and trabecular structure analysis by using flat-panel volume CT. *Radiology* 257:167–174, 2010 (52), with permission. © Radiological Society of North America.]
women with anorexia nervosa and are elevated in a subset of women with anorexia nervosa (14), possibly from hemoconcentration, but hypoproteinemia has not been ruled out as a potential etiologic factor in the development of bone loss in anorexia nervosa.

An interesting new area of investigation is the effect of starvation on bone marrow fat, which is elevated in women (59) and adolescents (60) with anorexia nervosa, and may be causatively related to bone loss, a theory that is supported by the strong inverse association between bone marrow fat and bone mineral density (59). These human data are consistent with a published report demonstrating elevated bone marrow fat and reduced bone mineral density in calorically restricted mice (61). Bone and fat cells share a common mesenchymal precursor stem cell within bone marrow, capable of differentiating into adipocytes or osteoblasts. However, it is not understood whether increased bone marrow fat is implicated in the pathogenesis of bone loss in anorexia nervosa or represents default into the fat lineage as a result of impaired osteoblastogenesis. It is also unknown whether fat from this depot secretes adipokines that modulate reproduction or other functions. Studies have demonstrated that GH/IGF-I (62), leptin (63), and peroxisomal proliferator-activated receptor-γ agonists (64) may influence the differentiation pathway. One study found that levels of Pref-1 (preadipocyte factor-1), a member of the epidermal-like growth factor protein family, are higher in women with anorexia nervosa than healthy controls and correlate positively with bone marrow fat (65).

As anorexia nervosa is frequently chronic, weight recovery is not achievable for many patients, and relapses occur. In addition, bone mineral density recovery to normal does not always follow weight recovery. Therefore, the development of therapies to address this complication is of critical importance. Studies have capitalized on addressing the known neuroendocrine abnormalities associated with the disease, as well as data using therapies proven effective in postmenopausal women. However, estrogen, an effective therapy in postmenopausal women, is ineffective in women with anorexia nervosa. Two randomized, placebo-controlled studies have shown that oral estrogen administration alone is ineffective—at replacement doses (66) or as oral contraceptives (67)—to increase bone mineral density in adults with anorexia nervosa. These results were unexpected, as one might hypothesize that estrogen would be an ideal therapy in this hypogonadal population, and may reflect the known effects of oral estrogen to suppress IGF-I production by the liver (68). In support of this hypothesis, a randomized, placebo-controlled study showed that recombinant human IGF-I (rhIGF-I) replacement plus oral contraceptive administration was more effective (2.8% increase in spine bone mineral density over 9 months compared with placebo) than rhIGF-I alone (1.4% increase) or oral contraceptives (no significant increase) alone or than placebo (69). A recent randomized, placebo-controlled study demonstrated efficacy of risedronate in adults with anorexia nervosa (70), consistent with an earlier small open-label pilot study (71). In this study, bone mineral density increased at the posteroanterior lumbar spine by 3%, lateral spine by 4%, and hip by 2% over the 1-yr study period. Of note, the mean bone mineral density of the treated group remained below normal for age; therefore, further studies are warranted to determine how to optimize bone mineral density in women with anorexia nervosa. In addition, although the published data on bisphosphonate administration during pregnancy are reassuring (72, 73), there are limited data available, and therefore bisphosphonates should be prescribed with caution in women of reproductive age. Other therapies that have been shown to be effective for postmenopausal bone loss have not been tested in this population. The question of whether bone mass responds positively to exercise in this disease has been raised, and a recent study confirmed that excessive moderate loading exercise has a deleterious effect on bone mineral density in underweight women with anorexia nervosa, in whom exercise is largely discouraged by providers due to the negative effects on energy balance; however, in the same study, a beneficial effect was observed in women who were weight recovered from the illness (74).

When considering therapies for osteoporosis, adolescent girls with anorexia nervosa need to be approached separately from adults due to the differences in skeletal physiology, and one cannot extrapolate efficacy data from adults to adolescents. Adolescence is a period of time in which there is rapid bone mass accrual, leading to peak bone mass and tonically increased bone turnover. In contrast, in adolescent girls with anorexia nervosa, markers of bone metabolism—both formation and resorption—are suppressed (75). Whether a physiologic estrogen replacement strategy and/or rhIGF-I replacement would be effective to preserve or increase bone turnover and mass in adolescents with anorexia nervosa is unknown. Clinical trials have not identified any effective therapy for bone loss for this group. One randomized, placebo-controlled study of bisphosphonate therapy in adolescent girls demonstrated increases in bone mineral density compared with baseline values but not compared with placebo (76). In that study, both groups gained weight, which was the most important determinant of the increases in bone mineral density observed (76). Similarly, a trial of DHEA therapy in adolescent girls and young adults combined did not
show efficacy after controlling for increases in weight that occurred during the treatment period (77).

**Endocrine Recovery with Weight Gain**

Weight gain in women with anorexia nervosa is followed by partial recovery of endocrine function. The hypogonadotropic hypogonadism observed in women with anorexia nervosa is thought largely to be functional, and in their original studies characterizing LH pulsatility, Boyar et al. demonstrated reversibility of LH secretory dysregulation with weight gain (15, 16). However, subsequent studies have reported that amenorrhea persists in approximately 15% of women despite weight recovery (78), but the underlying causes are not understood. Persistence of psychologic symptoms characteristic of eating disorders despite weight normalization and lower leptin levels may play a role (79), and the latter may reflect lack of complete resolution of body composition abnormalities, in particular relatively lower fat mass despite weight gain. GH resistance appears largely to be reversible with weight gain, with a stepwise normalization of IGF-I levels (42, 45, 80), as does hypercortisolemia, though the latter appears to persist in a subset of women who have gained weight to normal (37, 81–83), consistent with data showing hypercortisolemia in a subset of normal-weight women with functional hypothalamic amenorrhea from overexercise or stress (32). Longer-term weight normalization may be necessary for resolution of hypercortisolemia in some women with anorexia nervosa (81). Bone mineral density improves with recovery from anorexia nervosa, but not to normal (84), highlighting the importance of developing effective therapies for this complication so that women with a history of anorexia nervosa will not experience an increased risk of fractures later in life. Recovery of spontaneous menses appears to be more important for skeletal recovery than weight gain itself, which is inadequate to reverse bone loss in most women (48, 85).

**Etiology of Anorexia Nervosa**

**Heritability**

Studies have reported heritability of between 56 and 84% (86–89) for anorexia nervosa, suggesting a probable genetic disposition to the disease. However, as yet, no clear genetic picture has emerged, possibly because heritability is likely multifactorial and complex. Close to 200 genetic-association studies have identified putative genetic candidates implicated in regulatory pathways for appetite, energy, neurotransmission, reward, neuroendocrine, and inflammatory systems. Rask-Andersen et al. recently re-viewed these studies and reported that 128 polymorphisms of 43 genes have demonstrated associations, and they identified five genes for which the strongest data have been generated (90). These included one appetite-regulating gene (Agouti-related protein), two genes that are associated with reward pathways (catechol-O-methyl transferase and opioid receptor δ CNR1) and two genes that are associated with regulation of mood and psychiatric disorders [brain-derived neurotrophic factor (BDNF) and small-conductance calcium-activated potassium channel].

**Appetite dysregulation**

Recent studies evaluating the regulation of appetite, reward, and psychiatric comorbidities in women with anorexia nervosa have yielded interesting insights into the disease that may provide clues to its pathophysiologic basis. Although women with anorexia nervosa restrict their caloric intake, it is not clear whether they experience normal sensations of hunger, and there is increasing evidence of appetite hormone dysregulation in women with the disorder. Concentrations of a number of orexigenic and anorexigenic hormones, which signal the need and lack of need for nutrient intake, respectively, have been investigated. It has been known for some time that levels of the anorexigenic hormone leptin, secreted by adipocytes after meals, is lower in women with anorexia nervosa compared with lean controls (19, 91), and this follows logically from the fact that the source of leptin, adipocytes, is greatly reduced in mass in women with anorexia nervosa. However, elevation of the anorexigenic hormone PY (55, 92), which is secreted by intestinal L cells, is not as simple to explain and appears paradoxical, as it is released in response to food intake, which is reduced in anorexia nervosa. This raises the possibility that PY or related pathways may be implicated in some way in the etiology of the eating disorder, but this would be entirely speculative. Ghrelin, which is released by oxyntic cells of the stomach, (93–95) has also been found to be elevated in anorexia nervosa, though one recent study reported decreased ghrelin levels in women with a binge/purge subtype (96). A recent study demonstrated an exaggerated decrease in ghrelin levels with insulin infusion during a euglycemic hyperinsulinemic clamp, which the authors hypothesized might lead to an elevated sensation of satiety (97). The orexigenic hormone elevation has largely been explained as adaptive, i.e. an “attempt” to stimulate appetite and increase nutritive intake. Whether one possible factor contributing to the development of anorexia nervosa in a subset of women is a resistance to the effects of orexigenic hormones to stimulate appetite and, if so, whether such resistance predisposes women to the disorder or whether this elevation is simply acquired as a result of chronic
starvation, is unknown. To address the question of whether anorexia nervosa is associated with ghrelin resistance, Hotta et al. performed a pilot study, administering ghrelin to five subjects, ages 14–35, hospitalized for anorexia nervosa, and reported an increase in hunger and food intake (98). The results of this study suggest that patients with anorexia nervosa are capable of responding to the orexigenic effects of ghrelin but does not address the question of whether relative ghrelin resistance is a characteristic of anorexia nervosa. This study was small and was not placebo-controlled; therefore, further studies are needed to investigate the putative role of ghrelin and other orexigenic hormones in the pathophysiology of anorexia nervosa. PYY and cortisol have also been shown to be independently and positively associated with degree of eating disorder cognition (99), further evidence of a possible link between appetite regulation and the etiopathology of anorexia nervosa.

**Reward circuitry dysregulation**

The question of whether dysregulation of reward circuitry contributes to the pathophysiology of anorexia nervosa has also been raised in the context of a reported anhedonia in response to eating (100). In a binge/purge rodent model, investigators induced food addiction, including characteristic withdrawal and relapse, as well as cross-tolerance to alcohol and cocaine (101, 102). Although these data are more directly applicable to bulimia nervosa than anorexia nervosa, they raise the possibility that dysregulation of reward pathways could play an etiologic role in the development of eating disorders.

**Neuromodulator dysregulation**

Another possibly important clue to the pathophysiologic basis of anorexia nervosa is the high prevalence of psychiatric comorbidities, including depression, which is observed in 50 to 75% of patients (103, 104). In addition, this population is enriched with specific personality traits, including perfectionism, which persists after recovery from eating disorders (105) and neuroticism, which is a risk factor for the development of anorexia nervosa (86). Moreover, clinical observations that psychotropic medications that bind serotonin and dopamine receptors result in weight gain have led investigators to consider whether these neurotransmitters might be involved in the pathogenesis of the eating disorder. However, until recently, this line of investigation has proven difficult. For example, in 1984, Kaye et al. reported decreased 5-hydroxyindoleacetic acid, a major metabolite of serotonin, in women with anorexia nervosa, which increased to normal with weight recovery (106), suggesting a putative pathophysiologic communality with depression. However, the authors could not rule out or control for the possible confounding contribution of dietary tryptophan, of which 5-hydroxyindoleacetic acid is also a metabolite. More recently, BDNF, a peptide that has been implicated in the pathogenesis of major depressive disorder, has been studied. In a mouse model in which BDNF was conditionally knocked out in brain tissue, mice develop hyperphagia and weight gain, as well as anxiety (107). BDNF levels have also been found to be lower in women with anorexia nervosa compared with controls (108). Because in this study levels were also lower in normal-weight women with bulimia nervosa, these findings appear to be independent of nutritional status, but whether these findings reflect the cause or effect of an eating disorder and whether peripheral levels reflect brain concentrations remain unknown. The development of sophisticated genetic and imaging techniques may enhance the ability of investigators to determine the role of endogenous psychoactive molecules and their receptors and neural pathways in the development of eating disorders.

**Treatment of Anorexia Nervosa**

The primary goals of recovery remain weight restoration and psychiatric recovery, and a team approach, which may include a psychiatrist or psychologist, primary care physician, and nutritionist, is the standard of care. Inpatient therapy is required for patients of extremely low weight, suicidality, and/or severe medical or psychologic comorbidities. A number of specific psychologic approaches have been studied, but few randomized, controlled trials have been performed. A review of randomized, controlled anorexia nervosa treatment trials in 2007 concluded that there was little evidence for efficacy of any specific treatment strategy, but that cognitive behavioral therapy may reduce the risk for relapse in women who have achieved weight recovery (109). A more recent randomized, controlled trial demonstrated improved outcomes with both individual and family-based psychotherapy in adolescent girls, with family-based therapy demonstrating a small advantage in durability of treatment effect (110). Despite the increasing use of psychotropic medications, clinical trials have mostly been disappointingly negative in demonstrating antidepressant effects on the disease itself (111) or psychiatric comorbidities (112) and have been plagued by difficulty retaining study subjects (113). Similarly, studies of the efficacy of atypical antipsychotics, of which there are few controlled trials, do not provide evidence of efficacy for weight gain in women with anorexia nervosa (114). Therefore, identification of
effective therapies for this disorder and its complications is critical.

Conclusions

Anorexia nervosa is a primary psychiatric disorder complicated by serious endocrine disorders, including hypogonadism, hypercortisolism, hyponatremia, and severe bone loss, for which there are few effective therapies. Further research will be important to increase our understanding of the etiopathology of the disease and its complications and to identify effective therapies for anorexia nervosa itself and its attendant consequences.

Acknowledgments

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