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THE ENDOCRINOPATHIES OF ANOREXIA NERVOSA

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Abstract

Objective—To describe the hormonal adaptations and alterations in anorexia nervosa.

Methods—We performed a PubMed search of the English-language literature related to the pathophysiology of the endocrine disorders observed in anorexia nervosa, and we describe a case to illustrate these findings.

Results—Anorexia nervosa is a devastating disease with a variety of endocrine manifestations. The effects of starvation are extensive and negatively affect the pituitary gland, thyroid gland, adrenal glands, gonads, and bones. Appetite is modulated by the neuroendocrine system, and characteristic patterns of leptin and ghrelin concentrations have been observed in anorexia nervosa. A thorough understanding of refeeding syndrome is imperative to nutrition rehabilitation in these patients to avoid devastating consequences. Although most endocrinopathies associated with anorexia nervosa reverse with recovery, short stature, osteoporosis, and infertility may be long-lasting complications. We describe a 20-year-old woman who presented with end-stage anorexia nervosa whose clinical course reflects the numerous complications caused by this disease.

Conclusions—The effects of severe malnutrition and subsequent refeeding are extensive in anorexia nervosa. Nutrition rehabilitation is the most appropriate treatment for these patients; however, it must be done cautiously.

INTRODUCTION

Anorexia nervosa (AN) is a psychiatric illness with devastating consequences. The incidence of AN is currently around 8 per 100 000 persons per year, and the prevalence rate of AN is 0.3% in young females (1). The diagnostic criteria for AN include refusal to maintain a weight of at least 85% of that expected for height, extreme fear of gaining weight, disturbed perception of body image, poor insight into the consequences of being underweight, and amenorrhea. More than 90% of patients with AN are women (2).

All organs are affected by this state of disordered eating and starvation. Severe malnutrition leads to electrolyte disturbances and can ultimately cause multiorgan system failure. Many

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DISCLOSURE

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of the hormonal aberrancies described in AN are essentially protective, aiming to conserve metabolic energy during prolonged periods of caloric restriction. The purpose of this article is to outline the metabolic derangements seen throughout the endocrine system in persons with AN. The most clearly understood endocrine disturbances of AN are those related to the hypothalamic-pituitary axis: thyroid, adrenal, and gonadal. AN also has dramatic effects on normal growth, bone turnover, nutrient metabolism, and appetite regulation.

To characterize the hormonal adaptations and alterations in anorexia nervosa, we performed a PubMed search of the English-language literature related to the pathophysiology of the endocrine disorders observed in anorexia nervosa, and we describe a case to illustrate these findings.

CLINICAL CASE

A 20-year-old woman was admitted to the hospital with end-stage AN, severe malnutrition, electrolyte instability, and a prolonged QT interval. She was consuming 200 calories a day. On admission her temperature was 96.6°F, pulse rate was 41 beats per minute, and blood pressure was 118/89 mm Hg. She was 162.6 cm tall and weighed 30.8 kg (68 lb). Her body mass index (BMI) was 11.7 kg/m². Physical examination revealed an extremely cachectic woman. She had shallow breathing and bradycardia. Her skin was cool, and her extremities had profound atrophy. She exhibited poor insight into her condition.

Laboratory test results on admission were notable for neutropenia, hypokalemia, hypoglycemia, and transaminitis. Her albumin concentration was 3.5 g/dL. Liver enzyme assessment included an aspartate aminotransferase level of 287 U/L and an alanine amino transferase level of 323 U/L. An electrocardiogram showed sinus bradycardia. Other laboratory tests showed the following values: thyroid-stimulating hormone, 4.62 mIU/L (reference range, 0.35–5.50 mIU/L); total triiodothyronine (T₃), 28 ng/dL (reference range, 60–181 ng/dL); total thyroxine (T₄), 5.8 µg/dL (reference range, 4.5–10.9 µg/dL); and a free thyroxine index of 2.3. A cosyntropin-stimulation test was performed with a robust response from 18.7 to 42 µg/dL. The 24-hour urinary cortisol excretion was 283 µg/24 h (reference range, 4–50 µg/24 h).

She had intermittent hypotension, hypothermia, and hypoglycemia during her hospitalization. She was restless and exhibited excessive activity, rapidly lapping hospital corridors. Medically, her condition warranted admission to the intensive care unit; however, she refused for fear of activity restriction. She was recommended to eat 500 calories per day with a plan to slowly increase to a goal of 1200 calories per day. However, she did not adhere to these recommendations. She also refused any carbohydrates, including glucose tablets when her blood glucose concentration was 25 mg/dL. It was discovered that she was hiding food and purging. Supplemental nutrition and total parenteral nutrition were eventually started, and she was transferred to the intensive care unit to monitor for refeeding syndrome.

Her condition markedly worsened. While receiving total parenteral nutrition, her electrolytes were maintained with supplementation, but her liver enzyme concentrations tripled. She developed notable edema and tachycardia. Despite this, she continued to resist supplemental nutrition. During her hospitalization, she fell from bed and developed an acute subdural hematoma requiring urgent neurosurgical operation. Postoperatively, her laboratory values slowly normalized with progressive feeds. The patient was discharged to an inpatient rehabilitation facility on cycled tube feeds and a regular diet at a weight of 34 kg (74.9 lb) (42 days after admission when her weight was 30.8 kg).

HYPOTHALAMIC-PITUITARY-GONADAL AXIS

Secondary amenorrhea is a common clinical and diagnostic feature of AN. Likewise, primary amenorrhea is characteristic of the prepubertal anorexic girl. Normal puberty and menarche are delayed with even a 10% to 15% loss of normal body weight. Interestingly, this same degree of weight loss in postmenarchal women precedes amenorrhea in 20% of women with AN (3). Thus, even early abnormal eating behaviors, particularly with restrictive fat intake, can disrupt gonadotropin secretion and lead to amenorrhea (4).

Women with AN are hypoestrogenic secondary to hypothalamic dysfunction. Disturbed gonadotropin-releasing hormone (GnRH) secretion leads to abnormal gonadotropin pulsatility, resulting in insufficient ovarian stimulation for ovulation and ultimately decreased estrogen production. There is also loss of the positive feedback response where low estrogen levels normally stimulate gonadotropin secretion. Of note, there is also decreased aromatization of androgens to estrogens in fat tissue (secondary to lack of adipose), however this plays a minor role in the overall hypoestrogenic state (3,5). Pulsed GnRH injections can induce menses in women with hypogonadotrophic amenorrhea, as in AN, indicating normal pituitary and ovarian responsiveness to appropriate hypothalamic stimulation (3,6).

Menstrual abnormalities in hypothalamic dysfunction are manifestations of disturbed secretion of GnRH. Decreased caloric intake changes the pulsatility of GnRH causing abnormal responses of luteinizing hormone and follicle-stimulating hormone (FSH). Specifically, the gonadotropins have immature secretion patterns, with an increased follicle-stimulating hormone to luteinizing hormone (LH) ratio and decreased frequency and amplitude of luteinizing hormone bursts (4,7). Qualitative differences in the glycosylation patterns of gonadotropins are described in AN (8,9). These hormonal aberrations result in a prolonged follicular phase and an insufficient luteal phase (10). Marked caloric restriction impairs luteinizing hormone pulsatility (11). Thus, there is inadequate gonadotropin stimulation to initiate ovulation, consistent with hypothalamic amenorrhea (12). Hypothalamic amenorrhea in AN is associated with a partial gonadotropin deficiency, but with nutritional rehabilitation and maintained weight recovery, this deficiency is potentially reversible (4,13).

Amenorrhea in active AN is a protective physiologic adaptation to prevent pregnancy at a time of compromised nutrition. Luteal deficiency has been observed historically in times of famine and food rationing such as those in World War I and World War II (10). Infertility results from both anovulation and self-imposed restrictions on sexual activity in AN (3). Of note, silent eating disorders are not uncommon in women seeking therapy for infertility (14). In a study by Stewart et al, 58% of women with either amenorrhea or oligomenorrhea had evidence of an eating disorder (15).

Once appropriate weight gain (90% of the predicted weight for height) is achieved and maintained, menses often resume within a year (16). Establishing regular menstrual cycles is an important milestone for women recovering from AN (17). Fertility is often restored with appropriate treatment of the eating disorder; however, persistent amenorrhea remains more common in women who have recovered from AN than in the general population (18). Resumption of menses is best assessed biochemically with a rise in serum estradiol levels (16).

Restoration of appropriate signaling in the hypothalamic-pituitary-ovarian axis appears to be facilitated by a variety of hormones. In women with AN, elevations in baseline cortisol are predictive of increased body fat content, which in a study by Misra et al was shown to be a good indicator of menstrual recovery in anorexic adolescent girls (19). Interestingly, in a

study of female endurance athletes by Rickenlund et al, menstrual frequency was negatively correlated with cortisol concentration (20). The initial serum concentrations of follicle-stimulating hormone, inhibin B, and anti-Müllerian hormone may also correlate with the degree of ovarian suppression and may predict the resumption of ovulation with weight gain (17).

HYPOTHALAMIC-PITUITARY-THYROID AXIS

Individuals with AN often exhibit clinical features of hypothyroidism such as bradycardia, hypothermia, hypotension, dry skin, and reduced metabolic rate. Biochemically, anorexic patients have a constellation of thyroid hormone abnormalities similar to sick euthyroid syndrome with notably low T_3 levels and low to normal T_4 levels due to decreased peripheral conversion (21). Patients with AN generally have normal to below-normal thyroid-stimulating hormone levels (22). These patients are generally not considered to be hypothyroid despite evidence of peripheral thyroid hormone deficiency as documented by delayed Achilles reflex half-relaxation time and subsequent improvements with exogenous T_3 (23). Overall improvements in thyroid hormone profiles are observed with nutritional rehabilitation (12).

Altered thyroid hormone levels in individuals with AN are multifactorial. In AN, as in any condition of chronic illness or starvation, there is decreased peripheral deiodination of T_4 to T_3 with increased conversion to inactive reverse T_3 (24). The presence of carbohydrates appears to be important in stimulating the peripheral conversion of T_4 to active T_3 (25). Hypothalamic release of thyrotropin-releasing hormone may be impaired in AN, preventing the typically robust thyroid-stimulating hormone response to low peripheral thyroid hormone levels (23). Exogenous thyrotropin-releasing hormone can illicit a normal or delayed response in thyroid-stimulating hormone, and this delay in response reverses with weight gain (26).

Malnutrition and subsequently low insulinlike growth factor 1 (IGF-1) levels likely cause thyroid atrophy in AN (27). A decrease in overall thyroid volume has been observed in anorexic patients compared with age-matched control participants; atrophy of the thyroid may further exacerbate depressive symptoms and ongoing starvation (27).

As previously mentioned, the biochemical thyroid abnormalities seen in AN generally correct with weight gain. Unfortunately, the psychologic problems and personality traits are not rectified with weight gain alone. Thus, thyroid dysfunction is not the sole etiology of the psychologic pathology observed in AN, but it is possible that abnormal thyroid function may exacerbate existing psychologic problems (28).

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Individuals with severe AN must maximize the physiologic stress response to chronic starvation for survival. Thus, these patients generally exhibit hypercortisolemia (29). Elevated cortisol levels in patients with AN result from increased cortisol pulsatility and secretory burst frequency, as well as decreased T_3 -regulated metabolism of cortisol (30). The circadian rhythm of cortisol secretion is preserved in AN (12,31). Cortisol secretion is also stimulated by hypoglycemia and hypoinsulinemia, conditions commonly seen in AN (30).

Dynamic testing of the hypothalamic-pituitary-adrenal axis in AN reveals abnormal suppression of cortisol production with either an oral glucose load (30) or from dexamethasone in conjunction with very robust responses to corticotropin stimulation and weak responses to corticotropin-releasing hormone stimulation (30–32). The poor cortisol

response to corticotropin-releasing hormone is suggestive of hypersecretion of corticotropin-releasing hormone as a means of overcoming cortisol resistance. This may be explained by glucocorticoid receptor abnormalities (33). Pituitary corticotrophs remain responsive to the inhibitory effects of free fatty acids in AN even in the setting of hypercortisolemia (34). Chronic corticotropin-releasing hormone elevations may also be partly responsible for maintaining the state of chronic starvation (5).

Hypothalamic-pituitary-adrenal axis hyperactivity is an established feature of AN and depression. AN is also associated with alterations in vasopressin secretion, manifesting as problems with appropriate dilution of urine (35). Vasopressin has a greater involvement in hypercortisolemia of depression, while corticotropin-releasing hormone appears to have a dominant role in hypothalamic-pituitary-adrenal axis hyperactivity in AN (36). Patients with AN and high cortisol levels do not typically display features of Cushing syndrome, as they have low baseline levels of adipose tissue and cortisol resistance (5,30).

Hypothalamic-pituitary-adrenal axis hyperactivity appears reversible. Normalization of cortisol levels is observed with weight gain; however, normal corticotropin responsiveness to corticotropin-releasing hormone takes longer to fully resolve (31). One could postulate that as hypercortisolemia reflects responsiveness to stress, it may also reflect adrenal reserve, which could explain the potential use of cortisol levels as a marker for menstrual recovery. In other words, ovarian function may parallel adrenal function in that women with higher cortisol levels may be better equipped to respond to the stress of malnutrition and in turn may also have an increased likelihood of ovarian recovery with nutrition rehabilitation.

GROWTH HORMONE RESISTANCE AND IGF-1 DEFICIENCY

Growth hormone (GH) secretion and activity are also affected by severe malnutrition. These individuals have increased basal and pulsatile secretion of GH (37). GH-releasing hormone elicits an exaggerated response of GH in conditions of severe starvation (38). A positive correlation exists between BMI and levels of IGF-1 and insulinlike growth factor binding protein 3. Hepatic IGF-1 production is inhibited by malnutrition, and low IGF-1 levels stimulate increased GH secretion. This ultimately leads to acquired GH deficiency secondary to GH resistance (37,39). Interestingly, obesity is associated with reductions in both basal and pulsatile GH secretion (40).

Impaired linear growth is common in adolescents with AN secondary to the hormonal abnormalities mentioned thus far (deficiencies in thyroid and sex hormones and elevations and resistance to cortisol and GH). Nutritional intervention results in variable degrees of catch-up growth; however, permanent short stature may be observed in adolescents (39).

BONE METABOLISM

Bone health is compromised very early in the disease course of AN. AN is especially damaging to bone health in adolescents, as malnutrition during these formative years interferes with the accumulation of peak bone mass (12). More than 50% of adolescents with AN have evidence of osteopenia and 25% have osteoporosis (41). Women with AN have even more dramatic problems, with more than 90% having evidence of reduced bone density and 38% meeting diagnostic criteria for osteoporosis (42). Individuals with the bingeing/purging subtype of AN are at greater risk for developing osteoporosis compared with the restricting subtype (43). AN may have very long-term effects on bone health. Osteopenia has been documented to persist for more than 10 years after the initial diagnosis (44). Increased risk of fracture may persist years after the original diagnosis of AN (45).

There are qualitative and quantitative problems with the bones in AN. In general, trabecular bone appears to be affected more than cortical bone, and a greater degree of recovery is observed in trabecular bone than in cortical bone (41,44,46). Bone changes in AN are related to both bone density and absolute size of bones, with decreased bone density in large part attributed to estrogen deficiency and reduced bone size related to malnutrition (47).

Abnormal bone metabolism in AN is multifaceted and appears to result from an osteoblastic abnormality (48,49). In most cases there is a severe nutritional deficiency. Excessive exercise is also a major factor in bone loss in individuals with AN as it helps them achieve low body weights and perpetuates hypothalamic amenorrhea leading to associated bone loss (39). Hormonal aberrancies including low estrogen, androgen, T₃, IGF-1, and leptin levels, as well as elevated catecholamine and glucocorticoid concentrations, contribute to decreased bone density in AN (41).

Women with AN have increases in markers of bone resorption with decreases in markers of bone formation (50,51). This contrasts with postmenopausal women with osteoporosis who have concurrent increases in both bone formation and resorption and with adolescents with AN who have a generalized reduction in bone turnover (51). With sufficient weight gain, markers of bone formation (osteocalcin and bone alkaline phosphatase) increase and bone resorption decreases (C-telopeptide breakdown products) paralleling an increase in bone density in as little as 3 months (48). Severely ill patients with AN receiving parenteral hyperalimentation have rapid biochemical evidence of increased bone formation before any significant weight gain. Interestingly, this increase in osteocalcin is not associated with a reciprocal decrease in bone resorption during early nutrition rehabilitation (52). GH resistance may have a role in the low bone turnover state seen in AN (37).

Many different therapeutic options have been studied for treating bone disease in patients with AN and they have variable results. Estrogen replacement with oral contraceptive pills makes empiric sense in these hypogonadal women; however, there is a lack of evidence that exogenous estrogen is truly beneficial. The absence of a significant response to exogenous estrogen likely reflects ongoing inhibition of IGF-1 by oral estrogen and the persistence of low bone formation in patients who have yet to undergo successful nutritional rehabilitation (51). Although bisphosphonates evaluated in this population did improve bone density, maintenance of a healthy body weight has much greater influence on increasing bone density in the long term (53). There is also obvious concern with using bisphosphonates in young women with AN, as once recovered, these women may desire to become pregnant and the safety of these medications during pregnancy has not been established. These drugs have a long half-life and may be released from the bone over time. Studies of bisphosphonates in pregnant rats have shown abnormal calcium homeostasis and altered fetal bone development (54). Menatetrenone (vitamin K₂) has shown some promise in patients with AN in terms of decreasing the loss of vertebral bone density, increasing markers of bone formation, and decreasing markers of bone resorption (55). Dehydroepiandrosterone is abnormally low in individuals with AN, and these low levels are likely associated with bone loss in this disease. Although dehydroepiandrosterone may offer improvements in some of the psychologic aspects, there are no marked improvements in bone density with exogenous dehydroepiandrosterone use (56).

Recombinant IGF-1 promotes bone formation and reduces bone resorption. It has positive effects on bone health (stimulation of bone metabolism and activation of vitamin D to 1,25-dihydroxycholecalciferol) in patients with GH deficiency (57). Patients with AN have functional GH deficiency secondary to GH resistance and could potentially benefit from recombinant IGF-1 therapy. Combinations of recombinant IGF-1 for its anabolic properties

and oral contraceptive pills for their antiresorptive qualities have shown beneficial effects on bone density (49).

Overall restoration and maintenance of a healthy weight have the greatest effect on bone density in patients with AN (41,42,58). Nutrition rehabilitation and behavioral support with body weight maintenance are essential and should be the mainstay of therapy to attempt to reverse the severe bone loss associated with AN. Unfortunately, deficits in bone accrual in adolescence may result in permanently decreased bone density despite weight recovery (59).

NUTRIENT METABOLISM IN ANOREXIA NERVOSA AND REFEEDING SYNDROME

Patients with severe AN can survive conditions of extreme malnutrition. The percentage of body fat is generally a better predictor of nutritional status than BMI (41). Many patients with severe AN maintain normal albumin levels in contrast to patients with other marasmic conditions.

Generally, patients with AN have relatively low glucose and insulin levels and high glucagon levels during the active disease state with persistent abnormalities in glucose metabolism through recovery. Patients who have recovered from AN continue to have a reduced insulin response to caloric intake and there remains a metabolic preference to use glucose over fat stores (60). Cholesterol levels are frequently elevated and should be monitored closely. Patients with severe AN generally have hypercholesterolemia with normal free fatty acid levels that are attributed to accelerated cholesterol metabolism (61).

The prevalence of vitamin D deficiency appears to be significantly lower in women with AN than in healthy control participants (62). However, vitamin D deficiency should be treated with oral supplementation to achieve serum 25-hydroxyvitamin D levels greater than 30 ng/mL to avoid further insult to bone metabolism. Vitamin supplementation is very common in AN, and this supplementation may prevent vitamin deficiencies in these severely undernourished patients (63).

Refeeding the severely malnourished patient requires frequent monitoring to avoid fatal consequences. Slow, careful introduction of nutrients must be initiated with particular attention to maintaining normal electrolyte levels and avoiding drastic fluid shifts. Macronutrient ratios must be thoughtfully considered to avoid refeeding syndrome. Proteins and fats present less of a metabolic threat than carbohydrates (64). Ingested carbohydrate stimulates insulin release, and the introduction of insulin to the starved system poses a variety of severe hemodynamic and electrolyte consequences. Specifically, insulin stimulates antinatriuresis and intracellular influx of electrolytes—potassium, magnesium, and phosphorous. The sodium retention caused by increased insulin levels can lead to hypervolemia and resultant cardiac and respiratory failure. The hypophosphatemia, hypokalemia, and hypomagnesemia encountered during refeeding can also lead to potentially fatal consequences such as arrhythmias, respiratory failure, neuromuscular weakness, and encephalopathy. Avoiding thiamine deficiency with reintroduction of carbohydrates is particularly important to minimize the risk of permanent neurologic compromise (65). Patients with a BMI less than 16 kg/m², significant recent weight loss, and preexisting electrolyte deficiencies are at especially high risk for developing refeeding syndrome (66).

NEUROENDOCRINE MEDIATION OF APPETITE

Leptin and ghrelin are 2 hormones that have major roles in energy balance. Leptin is a 167-amino acid protein product of the *LEP* gene (previously known as *OB*) expressed primarily in white adipose tissue. It circulates in the serum in either a free form or bound to leptin-binding proteins. It is secreted in a pulsatile rhythm with substantial diurnal variation (67). Leptin, secreted from adipose tissue, and insulin from pancreatic β cells circulate in proportion to adipose tissue stores, reflecting energy availability. Both leptin and insulin enter the central nervous system via a saturable uptake mechanism in the blood-brain barrier. These hormones bind to receptors in the arcuate nucleus of the hypothalamus, altering the expression of neuropeptides involved in regulating energy balance. Specifically, leptin and insulin interact in the central nervous system to inhibit the production of anabolic peptides such as neuropeptide Y and agouti-related peptide and lead to the up-regulation of catabolic peptides such as proopiomelanocortin and corticotropin-releasing hormone (68).

Ghrelin is produced mainly by the stomach. It is the only known gastrointestinal hormone that increases food intake. Ghrelin strongly stimulates GH secretion and regulates energy homeostasis (69). Plasma ghrelin levels are inversely correlated with body weight and are increased in humans after weight loss (70). The actions of ghrelin are mediated in concert with neuropeptide Y and agouti-related peptide in the hypothalamus.

In individuals with AN, leptin concentrations are lower because of reduced body weight and fat mass (71), and diurnal variation in leptin is decreased. In addition, these patients have lower concentrations of leptin in cerebrospinal fluid and a higher cerebrospinal fluid leptin to plasma ratio than healthy control participants. Soluble leptin receptor concentrations are also increased, resulting in a lower free leptin index. In contrast, plasma neuropeptide Y concentration in AN has been reported to be greater or equal to that of normal-weight women (72,73). Changes in leptin levels likely have a role in the neuroendocrine adaptation to starvation, leading to changes in other hormone concentrations that may have a protective effect in this energy-deficient state (74). For instance, leptin has been shown to stimulate GnRH pulsatility and release in vitro (75), to increase free T_4 and free T_3 in leptin-deficient children (76), and to prevent a decrease in total IGF-1 during fasting in healthy lean men (77).

Nutritional rehabilitation increases serum leptin concentration (78) while simultaneously decreasing the soluble leptin receptor and serum concentration of neuropeptide Y (79). However, these changes do not correspond to increasing body weight and BMI, suggesting further dysregulation of appetite and weight control mechanisms in AN.

The rise in leptin with increased caloric intake correlates with increasing gonadotropin levels, indicating that increasing leptin may be responsible for activation of the hypothalamic-pituitary-gonadal axis. Resumption of menses is associated with a significant increase in the free leptin index (80), suggesting that free leptin may be an important determinant of menstrual recovery. There are no differences between leptin and neuropeptide Y concentrations before and after dietary treatment in eumenorrheic vs amenorrheic patients with AN, indicating that leptin is a critical but not a sufficient signal for recovery of menstrual function. Observational studies show a threshold leptin level of 1.85 ng/mL may be necessary for sufficient increases in follicle-stimulating hormone and luteinizing hormone and for the complete recovery of the reproductive system (81). Further studies are needed to determine whether recombinant human leptin may provide benefits to women with AN who have regained weight but remain amenorrheic.

Fasting ghrelin levels are elevated in patients with AN and return to normal after partial weight recovery (82,83). High ghrelin levels appear compensatory to increase food intake

and to induce a state of positive energy balance (84). Reduced food intake despite chronic elevation of circulating ghrelin suggests decreased sensitivity to the orexigenic action of ghrelin in this condition (85). Patients with AN are less sensitive to ghrelin administration than healthy women with respect to GH response and appetite (86,87). It is unclear whether the acute ghrelin response to food intake is normal or impaired in women with AN, and this may depend on caloric content or macronutrient composition of meals (83,88,89).

CONCLUSION

AN is a severe psychiatric disorder that can lead to extreme malnutrition. Although alterations in the hormonal axes are initially adaptive, mitigating the devastating consequences of starvation, these abnormalities may have important complications. Abnormalities in the adrenal glands and thyroid gland generally reverse with nutrition rehabilitation; however, there may be long-lasting complications including short stature, infertility, and osteoporosis. These patients require close medical monitoring as interventions geared towards achieving a healthy weight are aggressively pursued.

Abbreviations

AN	anorexia nervosa
BMI	body mass index
GH	growth hormone
GnRH	gonadotropin-releasing hormone
IGF-1	insulinlike growth factor 1
T₃	tri-iodothyronine
T₄	thyroxine

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