The Eating Disorders
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Chapter 19

Pathophysiologic and Clinical Aspects of Medical, Endocrine, and Nutritional Abnormalities and Adaptations in Eating Disorders

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Anorexia nervosa, bulimia, and related eating disorders are a heterogeneous group of primary psychiatric disorders whose incidence has approached epidemic proportions in recent years [1,2]. Patients with eating disorders may have numerous secondary medical, hypothalamic, endocrine, metabolic, and nutritional abnormalities [2-38,58-60], some of which may be or become severe enough to be life-threatening. Further, it has been suggested that some of the psychologic abnormalities in patients with anorexia nervosa may be secondary to starvation and undernutrition rather than intrinsic to the syndrome of anorexia nervosa [39]. Response of the primary disorder to psychotherapy is associated with restoration of near-normal weight and reversal of the secondary medical, hypothalamic, endocrine, metabolic, and nutritional abnormalities. However, patients with bulimia may sustain irreversible damage to the gastrointestinal tract and the oral cavity as a result of emesis or laxative abuse.

This review will provide some general perspectives regarding the pathogenesis, incidence, severity,and evolution of the abnormalities in patients with anorexia nervosa, bulimia, and related eating disorders, and the adaptation to starvation, undernutrition, emesis, or laxative or diuretic abuse. Subsequently, those specific abnormalities that are most significant for the diagnosis, evaluation, and management of these patients will be emphasized.

GENERAL PERSPECTIVES

Anorexia nervosa has been appropriately described as starvation in the midst of plenty. Unlike other settings where starvation and malnutrition occur, patients with anorexia nervosa have access to all foods and nutrients. They will selectively eat some things, albeit usually in meager quantities, and assiduously avoid others. Characteristically, they will eat little or no carbohydrate except as may be present in low-calorie fruits and vegetables, and little or no fat except as may be present in protein foods. However, their total caloric intake and relatively high protein intake further diminishes protein breakdown and conserves lean body mass (see below). The vitamin content of those foods they do eat, often supplemented by (calorie-free) vitamin supplements, militates against vitamin deficiency in all but the most severe cases. Most patients with eating disorders are young and otherwise medically well. Many tolerate severe and protracted undernutrition, severe fluid and electrolyte depletion, protracted emesis, or inordinate laxative or diuretic abuse with minimal or no detectable clinical or laboratory abnormalities. When findings in

older patients; patients with cardiac, gastrointestinal, neoplastic, or other systemic diseases; and patients with protein-calorie malnutrition are extrapolated to patients with eating disorders [38], the potential risks are exaggerated and exceed what is commonly observed [3,9].

The resilience of patients with anorexia nervosa further is facilitated by two prompt normal physiologic adaptations to starvation or to carbohydrate deprivation:

1. About 80% to 90% of the more active circulating throid hormone, triiodothyronine (T3), comes from extrathyroidal conversion of thyroxine (T4). Within days, peripheral conversion of T4 to T3 is inhibited, and T3 levels are decreased. In patients with anorexia nervosa, mean T3 levels are usually about half those of normal controls [4,9-12,17). Findings such as cold intolerance, constipation, dry skin, bradycardia, carotenemia, hypercholesterolemia, and decreased basal metabolic rate provide further evidence for an apparent protective hypometabolic adaptation.
2. The needs of glucose-dependent tissues such as the CNS normally are met by food intake and by breakdown of liver glycogen to glucose. Within hours of starvation, glycogen stores are depleted, and glucose can be provided only by gluconeogenesis from the amino acid constituents of proteins. Within days, stimulation of lipolysis and ketogenesis provides ketones at levels high enough to be used by the CNS as an alternate fuel [40]. Glucose requirements and protein breakdown are diminished and lean body mass is conserved.

For young women, a reasonable general guideline for ideal body weight would be 100 lb for 5 ft plus 5 lb for each additional inch in height. Patients with eating disorders who are less than 20% below ideal body weight almost always are asymptomatic and have no clinical or laboratory abnormalities except as will be discussed. Patients between 20% and 40% below ideal body weight begin to have clinical and laboratory abnormalities that are infrequently life-threatening. Patients 40% or more below ideal body weight usually are symptomatic and have clinical and laboratory abnormalities that almost invariably are life-threatening [9]. Among other variables that may affect the incidence and severity of the abnormalities include the percent weight loss from premorbid weight, the rate of weight loss, the total weight loss, the duration of undernutrition, and the susceptibility of the individual patient [9].

Two specific exceptions to the above are:

1. Amenorrhea may occur before or concurrent with onset of weight loss in up to one third of patients with anorexia nervosa and may persist following normalization of weight. These patients [14] exhibit an immature 24-hour pattern of luteinizing hormone (LH) secretion characteristic of prepubertal or pubertal girls, a physiologic as well as psychologic regression from adulthood to childhood.
2. Significant and sometimes life-threatening clinical and laboratory abnormalities due to emesis or laxative or diuretic abuse may occur in normal-weight or overweight patients.

Findings reported as individual values, range of values, or percent abnormal values, comparison of findings from different reports, and observation of large numbers of patients [9] indicate that the incidence and severity of clinical and laboratory abnormalities among patients are extremely variable. It should be emphasized that laboratory evaluation usually provides the initial evidence for these abnormalities.

The use of weight as the sole or primary criterion for assessment of medical and nutritional status has several significant limitations:

1. The patient has an overriding concern about weight and is extremely fearful of, threatened by, and resistant to weight gain.
2. Despite repeated explanations and reassurance, the patient almost invariably reacts adversely to the rapid and sizable weight gain that is associated with refeeding edema or cessation of purging (a quart of body fluid weighs 2 lb).
3. The patient can readily manipulate weight before weight-ins by eating, drinking, wearing heavy clothing, or loading clothing with heavy objects.
4. There may be little or no correlation between the absolute weight or the percentage below ideal or premorbid body weight and the presence, severity, and evaluation of clinical and laboratory abnormalities.

However, it must be emphasized to the patient with undernutrition that weight gain is a prerequisite for improvement of medical and nutritional status.

HYPOTHALAMIC, ENDOCRINE AND METABOLIC ABNORMALITIES IN PATIENTS WITH ANOREXIA NERVOSA

The protective hypometabolic adaptation of decreased peripheral conversion of T4 to T3 and the resultant marked diminution in T3 levels has been described. Total T4 levels (T4 is normally 99.96% bound to plasma proteins) usually have been found to be lower than in normal controls but within the normal range [3-6,9-13,17]. However, dialyzable free T4 levels, felt to be

the most sensitive parameter of thyroid function, have been found to be normal [3,4,6,9,17]. That there is hypothalamic dysfunction or a protective hypothalamic hypometabolic adaptation has been suggested [4,5,8,10-13] by the findings of normal basal pituitary throid stimulating hormone (TSH) levels and quantitatively normal and temporally normal or delayed response to TSH to hypothalamic thyrotropin releasing hormone (TRH). In addition to the clinical and laboratory findings described, other hypothyroid-like alterations in glucocorticoid and androgen metabolism have been reported in patients with anorexia nervosa [15,17].

These perturbations in hypothalamic-pituitary-thyroid status may be seen in patients with other forms of caloric deprivation, with various severe nonthyroidal illnesses, with certain medications, and after major surgery [41], and have been dubbed the "euthyroid sick syndrome."

The physiologic regression of the 24-hour pattern of LH secretion to a prepubertal or pubertal pattern previously has been described. Basal LH and follicle stimulating hormone (FSH) levels have been found to be low [3-6,8,16]. FSH and LH responses to gonadotropin-releasing hormone (GnRH) have been reported to be normal, blunted, temporally delayed, and discordant [4,5,8,16]. As would be anticipated in amenorrheic women with low FSH and LH levels, plasma estradiol levels are low [4,8].

Although a critical body weight has been suggested as a prerequisite for maintenance or onset of menses [42], the clinical observation that women often become amenorrheic with little or no antecedent weight loss and may remain amenorrheic for months after restoration of a normal or near-normal weight suggests that factors other than weight are involved in the pathogenesis of amenorrhea in patients with anorexia nervosa. Stress-induced amenorrhea ("hypothalamic amenorrhea") in otherwise normal young women has long been recognized. That vigorous physical activity may be associated with delayed menarche and amenorrhea has been described more recently [43-45], but the significance is uncertain, since comparable vigorous physical activity ("obligatory" running) has been suggested to be an analogue of anorexia nervosa [46]. Finally, simple weight loss to about 20% below ideal body weight in nonanorectic women has been associated with amenorrhea and altered basal and post-GnRH, FSH, and LH levels [47].

Basal plasma cortisol levels have been found to be normal or elevated [3-6,17-19]. Diurnal variation of plasma cortisol levels has been found to be normal or absent [3-6,17,18]. Prolongation of the half-life of cortisol and decreased metabolic clearance rate of cortisol were thought to be responsible for the increased 24-hour mean cortisol level [17]. A subsequent study suggested that the cortisol production rate, initially thought to be normal [17], was elevated in proportion to body mass [19]. Dexamethasone suppression of plasma cortisol levels has been found to be impaired in patients with anorexia nervosa more than 20% below ideal body weight [20,21] and in patients with bulimia as well [22]. Bulimia was considered to be related to affective disorders and to be responsive to therapy with tricyclic antidepressants [48]. However, the clinical utility of the dexamethasone suppression test for psychiatric diagnosis and management has not been supported by recent critical evaluation [49,50].

Studies using recently available ovine corticotropin-releasing hormone (CRH) have shown marked basal hypercortisolism, normal basal corticotropin (ACTH) and marked reduction of the ACTH response to CRH in underweight women with anorexia nervosa [58]. However, hypercortisolism resolved and the ACTH response to CRH normalized respectively four weeks and six months after restoration of normal weight. This suggests that the abnormalities in the hypothalamic-pituitary-adrenal axis seen in anorexia nervosa are not intrinsic to the psychiatric disorder but rather are related to undernutrition. Further, normal weight bulimic women did not have significant hypercortisolism, and had a normal basal ACTH and a normal ACTH response to CRH.

The mean plasma concentration of the adrenal androgen dehydroisoandrosterone (DHA) recently was found to be similar to that of preadrenarcheal children. Like the immature 24-hour pattern of LH secretion, this represents another endocrine regression from adulthood to childhood [23].

Basal growth hormone (GH) levels have been found to be normal or increased [4-6]. An inverse relation between basal GH levels and dietary intake [5] and a direct relation between basal GH levels and severity of weight loss [4] have been noted. Both GH and cortisol are protective counterregulatory hormones that stimulate gluconeogenesis in response to the threat of hypoglycemia (see below). The presence of normal or elevated GH and cortisol levels readily distinguishes anorexia nervosa from hypopituitarism. Further, hypopituitarism now is known to be rarely associated with undernutrition.

Evidence for partial central diabetes insipidus using the fluid deprivation test with subsequent administration of exogenous antidiuretic hormone (ADH) has been found in one study [4] but not confirmed in another [7]. The distinction between diabetes insipidus and primary or psychogenic polydipsia may be difficult using the fluid deprivation test, and patients with anorexia nervosa frequently hoard and consume large amounts of noncaloric fluids. Abnormal levels of plasma and CSF arginine vasopressin recently were described

in patients with anorexia nervosa, but the causes and consequences were not determined [24]. In addition, impaired concentration of urine in patients with bulimia may result from nephrogenic diabetes insipidus induced by hypokalemic nephropathy [51].

It is of interest that qualitatively similar but quantitatively less dramatic perturbations in hypothalamic and endocrine status have been found in nonanorectic women with secondary amenorrhea associated with simple weight loss [47].

Frequent mild to moderate and occasional marked fasting hypoglycemia is seen in patients with anorexia nervosa and apparently is asymptomatic [9]. The adaptive stimulation of lipolysis and ketogenesis, which provides ketone bodies as an alterante fuel and diminishes glucose requirements, and the stimulation of gluconeogenesis by GH and cortisol have been described. It has been found that total fasting for 72 hours in normal women results in similarly marked and asymptomatic hypoglycemia [52]. It is reasonable to anticipate, but it remains to be established, that these observations mitigate the clinical significance of hypoglycemia in patients with anorexia nervosa. Accordingly, it still seems prudent to be concerned about moderate to marked fasting hypoglycemia in these patients.

The association of hypercholesterolemia with anorexia nervosa is not commonly recognized but has been clearly demonstrated [25-27]. The elevation of total cholesterol was found to be related to an increase in low-density lipoprotein (LDL) cholesterol and to be reversible in patients who regained their original weight and began to menstruate [27]. Yet, patients with anorexia nervosa may have normal or low cholesterol levels as well [3,6,9,26,27]. The relative contributions of the protective hypometabolic adaptation of diminished peripheral conversion of T4 to T3 and of diet to the hypercholesterolemia and hypercarotenemia [28,29] of anorexia nervosa are not fully established.

No surprisingly, evidence for osteoporosis has been found in some women with anorexia nervosa [59,60], particularly after prolonged amenorrhea and undernutrition. Single photon absorptiometry has shown decreased cortical bone density in the distal forearm, and radiographs have shown vertebral compression fractures. A high level of physical activity may protect anorexic women against bone loss [59]. The effect of restoration of normal weight and resumption of menses on restitution of bone density is not yet known.

MEDICAL AND NUTRITIONAL ABNORMALITIES IN PATIENTS WITH ANOREXIA NERVOSA, BULIMIA AND RELATED EATING DISORDERS

Alterations in fluid status are common in patients with eating disorders [9]. Starvation or carbohydrate deprivation as well as emesis or laxative or diuretic abuse give rise to fluid depletion. Refeeding or cessation of purging are associated with fluid repletion and retention, and sometimes with dramatic edema. The effect of the accompanying rapid weight gain may be devastating to patients with eating disorders. Initial laboratory evaluation in patients with fluid depletion and decreased plasma volume frequently provides falsely high values, particularly for blood count and serum proteins. With fluid repletion and retention, laboratory values may fall precipitously, sometimes to falsely low levels. In such patients, some short-term weight loss usually is associated with ultimate restoration of normal fluid balance.

Patients with anorexia nervosa frequently have mild anemia and moderate to severe leukopenia with neutropenia or lymphopenia [3,9,30-32]. Thrombocytopenia has been found to be mild, infrequent, and asymptomatic [3,9,30-32]. The deficiency in all hematologic cellular elements appears to be a result of reversible bone marrow hypoplasia with increased gelatinous acid mucopolysaccharide ground substance in the marrow [30]. Sporadic cases of decreased granulocyte bactericidal activity and hypocomplementemia have been described in patients with anorexia nervosa and may contribute to increased susceptibility to infection [32]. In addition, significant lymphopenia may affect immune competence [53]. However, clinical observations do not support an increased susceptibility to infection [9,13], even in those patients with leukopenia, neutropenia, or lymphopenia.

Levels of serum proteins measured in routine multichannel automated chemistry profiles, ie, total protein and albumin, often are normal in patients with anorexia nervosa [9]. When present, significant hypoalbuminemia indicates severe or protracted undernutrition. However, because of its shorter half-life of six to eight days, serum transferrin levels, measured directly or calculated from measurement of total iron-binding capacity (TIBC), reflect significant protein deficiency much earlier than total protein or albumin levels [53]. Transferrin levels almost always are low in patients initially presenting with anorexia nervosa, and may be as low as half of normal values in patients with severe or protracted undernutrition [9].

Life-threatening potassium depletion and hypokalemia may occur as a result of emesis or laxative or diruetic abuse. Potent diuretics, eg, thiazides and furosemide, induce potassium depletion by increasing renal excretion of potassium as well as sodium. The potassium concentration of gastric fluid is relatively low, so only a small portion of the potassium depletion in patients with protracted emesis is a result of gastric potassium loss. However, loss of gastric fluid hy-

drochloric acid gives rise to metabolic alkalosis, and most of the potassium depletion in patients with protracted emesis is a result of increased renal potassium loss associated with chronic metabolic alkalosis. On the other hand, potassium depletion in patients with laxative abuse is a direct result of significant intestinal potassium losses in chronic diarrhea [51].

Small to moderate potassium loss usually is asymptomatic. Symptoms of moderate to severe potassium depletion and hypokalemia include skeletal and smooth muscle weakness and paralysis, cardiac arrhythmias and conduction abnormalities, and hypokalemic nephropathy, which may give rise to nephrogenic diabetes insipidus. When hypokalemia becomes significant and mandates treatment has been a subject of recent debate [54,55]. Even patients with emesis or laxative or diuretic abuse who have significant hypokalemia often have no symptoms or ECG abnormalities [9].

Surreptitious emesis or laxative or diuretic abuse may simulate Bartter's syndrome, a rare syndrome characterized by hypokalemic alkalosis, hyperaldosteronism, and hyperplasia of the renal juxtaglomerular apparatus. It may be differentiated from Bartter's syndrome by measuring serum or urinary laxative or diuretic levels and urinary chloride levels [56].

Renal function as measured by BUN and creatinine is affected by protein intake and catabolism and by fluid status as well as by intrinsic renal function in patients with eating disorders [9]. With normal fluid status and renal function, BUN, creatinine, and uric acid levels are normal or low. With significant fluid depletion, almost always associated with emesis or laxative or diuretic abuse, hypovolemia results in prerenal azotemia with BUN disproportionately more elevated than creatinine. Renal excretion of uric acid and of calcium may be compromised and hyperuricemia and hypercalcemia may ensue.

Orthostatic hypotension often is seen in patients with eating disorders. While reduction of plasma volume and significant electrolyte imbalance such as occurs in patients with emesis or laxative or diuretic abuse are known to induce orthostatic hypotension, the pathogenesis of orthostatic hypotension in patients with anorexia nervosa who have not purged is uncertain [57].

A variety of ECG changes have been observed in patients with eating disorders [3,9,33-35], some of which may be related to undernutrition, hypometabolic adaptation, and hypokalemia. The pathogenesis and significance of frequently nonspecific and occasional ischemic-like ST segment and T wave contour changes is uncertain. Arrhythmias and conduction abnormalities have caused the greatest concern. Prolongation of the QT interval has been observed [32,35] and recently was reported in an abstract [35] to be associated with the sudden death of three patients with anorexia nervosa. However, such ominous findings are most uncommon [3,9,34] in these patients.

Gastrointestinal symptoms and evidence for gastrointestinal dysfunction abnormalities are extremely common in patients with eating disorders. Symptoms and abnormalities may be related to undernutrition, hypometabolic adaptation, decreased food intake, binge eating, emesis, laxative abuse and hypokalemia. Irreversible damage to the gastrointestinal tract and to the oral cavity may ensur. Abnormal liver function tests, SGOT (AST) and SGPT (ALT) disproportionately more than GGTP are seen commonly [9] and presumably reflect hepatocellular injury as a result of moderate to severe undernutrition. Elevated serum amylase levels have been attributed to pancreatitis. However, salivary gland enlargement is seen occasionally in patients with bulimia [9,36] and is associated with elevated serum amylase levels [36]. The pathogenesis of the sialopathy is uncertain, but elevated serum amylase levels in untreated patients with eating disorders are more likely a result of sialopathy rather than of pancreatitis. Characteristic dental deterioration has been observed inpatients with eating disorders [37]. Dissolution of tooth enamel and altered caries response may occur as a result of emesis, abnormal diet, and alteration in the quality and composition of saliva.

SUMMARY

Patients with anorexia nervosa, bulimia, and related eating disorders have numerous secondary medical, hypothalamic, endocrine, metabolic, and nutritional abnormalities, some of which may be or become severe enough to be life-threatening. Some general perspectives regarding the pathogenesis, incidence, severity, and evolution of the abnormalities in these patients, and the adaptations that facilitate their resilience to starvation, undernutrition, emesis, or laxative or diuretic abuse have been provided. Specific abnormalities that are most significant for the diagnosis, evaluation, and management of these patients have been emphasized.

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