Eating Disorders: A Review of the Literature with Emphasis on Medical Complications and Clinical Nutrition

Lyn Patrick, ND

Abstract

Eating disorders, including anorexia nervosa, bulimia nervosa, binge-eating disorder, and atypical eating disorder (eating disorder not otherwise specified or NOS), are estimated to occur in 5-10 million young and adult women and one million males in the United States. The etiology of eating disorders is complex and appears to include predisposing genetic factors and serotonin dysregulation, as well as psychological factors that include a history of trauma and childhood sexual abuse. Both anorexia nervosa and bulimia nervosa are medical conditions complicated by multiple neuroendocrine dysfunctions, nutritional deficiencies, and psychiatric diagnoses. Medical complications, specific nutritional deficiencies, and research involving the therapeutic use of inositol and zinc are reviewed.

(*Altern Med Rev* 2002;7(3):184-202)

Introduction

Only 0.25-4 percent of females fit the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for anorexia or bulimia. The prevalence of disordered eating, however, is estimated to be much greater. One-third of patients treated for eating disorders in clinic settings do not qualify as either bulimic or anorexic under the DSM criteria (Tables 1, 2, and 3), therefore falling under the classification of atypical eating disorders.

Five to ten percent of post-pubescent females are considered to be eating-disordered.[4] Atypical eating disorders are estimated to occur in 3-6 percent of middle-school age females and 2-13 percent of high school-aged females.[4] Ten percent of 13-year old females report the use of self-induced vomiting in an attempt to lose weight, and 25-35 percent of college-age women are estimated to engage in binging and purging as a weight management technique.[4] Thirty-three percent of female college athletes report practicing binging, self-induced vomiting, and regular laxative, diuretic and diet pill use as a means to control weight.[4] Athletes, both male and female, are considered at high risk for diagnosable eating disorders, with an estimated incidence of 10-20 percent.[5] The most common eating disorder in athletes involves exercise bulimia – using exercise as a form of weight reduction along with the use of laxatives, emetics, diuretics, and stimulants.[5]

Anorexia nervosa has the highest mortality of any psychiatric diagnosis, estimated at 10 percent occurring within 10 years of diagnosis,[6] and is the leading cause of death in young females 15 to 24 years of age.[7] Death occurs due to suicide, infection, or succumbing to the effects of chronic starvation.

Mortality for bulimia nervosa is expectedly less, approximately one percent occurring within 10 years of diagnosis.[7] These figures are deceiving, however, because up to 50 percent of anorexics become bulimic somewhere during the course of their disease, but still carry the primary diagnosis of anorexia nervosa. The medical complications of bulimia, however, are

Lyn Patrick, ND – Medical writer/researcher; Associate editor of *Alternative Medicine Review*; past Medical Director of Mirasol, Inc., a residential treatment program for women with eating disorders in Tucson, Arizona. Correspondence address: 21415 Hwy 140, Hesperus, CO 81326. E-mail: lpatrick@frontier.net

Table 1. *ICD-10 and DSM-IV Diagnostic Criteria for Anorexia Nervosa*[2,3]

1.Weight loss at least 15 percent below normal for age/height or failure to make expected weight gain during growth period, leading to body weight less than 85 percent of expected.

2. Weight loss is self-induced by avoidance of high caloric foods, self-perception of body weight or shape as being too fat or big, and intense fear of gaining weight with denial of the seriousness of current low body weight.

3. In postmenarcheal females, amenorrhea defined by the absence of at least three consecutive menstrual cycles. (Amenorrhea is also considered if menses only occur following hormone administration). In males, the disorder, also involving the hypothalamic-pituitary gonadal axis, manifests as loss of sexual interest and potency.

Specific Types:
1. Restricting type: absence of binge-eating or purging behavior during current episode of anorexia nervosa.

2. Binge-eating/purging type: regular binge-eating and purging behavior during current episode of anorexia nervosa.

considerable and can persist long after clinical remission is achieved.

Fortunately, research looking at treatment follow-up in a population of anorexics enrolled in a university treatment program found full recovery was achieved in 75.8 percent.[8] Although achieving recovery required substantial amounts of time (57-79 months), this research indicates that treatment programs can be effective in what is considered the most difficult psychiatric condition to treat. Bulimics also appear able to recover; a six-year outcome study showed 59.9 percent achieved a good outcome and were no longer symptomatic.[9]

Genetic Susceptibility

Although the etiology of eating disorders is complex, several national studies have clearly defined histories of childhood physical or sexual abuse as predisposing risk factors for developing eating disorders.[10,11] There is also compelling evidence that genetic predisposition, premature birth, birth trauma,[12] and biochemical individuality also play a significant role in the eventual development of an eating disorder.

Both anorexia nervosa and bulimia nervosa are statistically more common among family members than in the general population, and there is a cross-transmission of both conditions, i.e., a family member of someone with

Table 2. *ICD-10 and DSM-IV Diagnostic Criteria for Bulimia Nervosa*[2,3]

1.Recurrent episodes of overeating in a discreet period of time (example: within any two-hour period) at least twice a week over a period of three months.

2. A sense of loss of control during the episode accompanied by a strong desire or sense of compulsion to eat.

3.Recurrent, inappropriate compensatory behavior following bingeing to prevent weight gain: periods of food restriction, self-induced vomiting, laxative misuse or use of diuretics, enemas, appetite suppressants, thyroid preparations or other medications to prevent weight gain. Diabetics who have bulimia may choose to neglect their insulin treatment.

4. Self-perception of being overweight and morbid fear of becoming fat.

5. Behavior does not occur exclusively during episodes of anorexia nervosa.

Specific types:
1. Purging type: engages in self-induced vomiting or misuse of laxatives, diuretics, etc.
2. Nonpurging type: fasting or excessive exercise are the only compensatory behaviors.

anorexia nervosa is more at risk for developing bulimia nervosa than someone with no family history.[13] The same study also shared findings that suggest atypical eating disorders (binge-eating, etc.) also have familial heritability.

Because it is difficult to definitively separate genetics from environment in familial studies, eating disorder studies involving twins have provided important data concerning heritability. Multiple studies have shown the risk for developing either anorexia or bulimia is significantly greater in identical twins than in fraternal twins and these genetic effects emerge only after puberty.[14] In 50-83 percent of bulimia nervosa cases studied, heredity was determined to be a factor.[15]

Comorbidity, the association of two or more pathologies, also occurs in those with eating disorders and their family members. In family members with eating disorders, there is a 2.0-3.5 times increased occurrence of bipolar or unipolar depression.[13] In another example of comorbidity, a significant 3- to 4-fold higher lifetime risk for substance use disorders occurs in bulimics, relatives of bulimics, or binging anorexics when compared to relatives of anorexics or controls without eating disorders or a family history of eating disorders.[16]

Serotonin Dysregulation

Serotonin regulation has been shown to be a significant factor in eating disorders. Clinical research suggests that alterations in the serotonin system can affect feeding behaviors. Specifically, serotonin increases satiety responses, which are impaired in bulimics.[17] Insulin resistance, which may be present in anorexia and bulimia, impairs the body's ability to produce serotonin from L-tryptophan.[17] Acute dieting and weight loss can cause low levels of plasma L-tryptophan.[18] Compulsive exercising may also be related to changes in serotonin metabolism induced by food restriction. For example, research has shown a reduction of symptoms in compulsive exercisers when given the selective serotonin reuptake inhibitor (SSRI) fluoxetine.[19]

Low levels of serotonin have been reported in low-weight anorexics.[20-22] The lack of serotonin as a substrate has been suggested as the reason that anorexics do not typically respond to the SSRI-class antidepressant therapies.[23] Not all studies of cerebrospinal fluid (CSF) tryptophan and serotonin levels in anorexics have shown significantly lower serotonin levels,[24] and it remains to be seen whether anorexics without purging behaviors have different serotonin dysfunctions than anorexics with bulimic tendencies.

Bulimia nervosa, in the majority of studies, also appears to be characterized by altered serotonin metabolism.[17] Bulimics have reduced responses to serotonin challenges when given serotonin agonists and low levels of the major serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA), indicating reduced serotonergic activity.[17,25]

Serotonin dysregulation has been implicated in several psychiatric disorders occurring in bulimia and family members of bulimics: substance abuse, alcoholism, major depressive disorder, anxiety, suicidality, and impulsivity.[26-30]

Binging and vomiting have also been shown to decrease serotonin synthesis, and binge frequency has been inversely correlated with CSF concentrations of serotonin.[31,32] Even after one or more years in recovery, women with bulimia were found to still have increased core eating-disorder

Table 3. *Atypical Eating Disorders*[2]

1. Atypical anorexia: key symptoms are present but patient doesn't meet all criteria (menstruates or doesn't have significant weight loss). Patients with physical illnesses that result in weight loss do not qualify.

2. Atypical bulimia nervosa: all of criteria are met except frequency or duration of episodes (less than twice a week or less than three-month duration).

3. Inappropriate compensatory behavior in an individual of normal body weight after eating normal amounts of food (example: self-induced vomiting after eating a normal meal).

4. Binge-eating disorder: recurrent binge eating in the absence of compensatory behaviors like those of bulimia nervosa.

5. Repeatedly chewing and spitting out large amounts of food without swallowing

symptoms when compared to healthy controls.[33] They had normal dopamine and norepinephrine levels but increased levels of 5-HIAA, used to assess serotonin levels. Increased 5-HIAA levels after recovery are also found in anorexia. This phenomenon is not well understood and has been described as a possible "rebound" effect of the recovery process.[17]

The Use of Antidepressants, Serotonin Precursors, and Inositol in Eating Disorders

It is well substantiated in the medical literature that those diagnosed with bulimia nervosa respond to antidepressants.[23] However, they are not as effective as cognitive-behavioral therapy and there is little evidence antidepressant therapy alone is effective.[34,35] It is not known whether the mechanism of antidepressant medication in bulimia is the same as in depression. SSRIs have been shown to be useful only at high dosages (60 mg fluoxetine) in bulimia – higher than are usually used in antidepressant therapy. Also, the presence of diagnosed depression in a bulimic patient is not predictive of whether the antidepressant will be effective for the treatment of bulimia.[23]

Research with both 5-hydroxytryptophan (5-HTP) and L-tryptophan in eating disorders has been conducted primarily to investigate how these serotonin precursors affect the serotonin pre- and post-synaptic receptors in the brains of bulimics. When bulimic females were given a tryptophan-free diet for seven hours, they experienced a significant decline in positive mood, an increase in ratings of obsessive body image concerns, and subjective loss of control with food.[36] These findings support others that have found tryptophan depletion to lower mood in other subgroups of recovered patients with seasonal affective disorder and depression, aggression, substance dependence, and autism.[37]

L-tryptophan, given intravenously at a single dose of 100 mg/kg to both bulimics and controls, was ineffective at reducing meal size when compared to a similar serotonin agonist m-chlorophenylpiperazine.[38] When given intravenously (0.4mg/kg) in a single dose, 5-hydroxytryptophan resulted in a blunting of the prolactin response.[39] This is an indication that the subjects had low serotonin levels and so did not have the same prolactin-elevating effects seen in the controls that are expected with the production of serotonin. There is also some evidence from this study that the bulimic subjects may have had a lower brain uptake of 5-HTP than the controls. The same response, the blunting of prolactin in response to tryptophan, has also been reported for patients with major depression.[40]

The only published trial of L-tryptophan in the treatment of bulimia, using a double-blind design, involved the use of 1 gram of L-tryptophan and 45 mg of pyridoxine three times daily.[41] The author reported significant improvements in the subjects' mood and significant decreases in bulimic behavior.

There have been no clinical trials with 5-HTP in bulimia or anorexia; but there has been research in the area of obesity. One double-blind, placebo-controlled trial assessed the effect on obese subjects of 300 mg 5-HTP three times daily for two six-week periods.[42] The first period was with no dietary restriction and a second six-week period combined 5-HTP with a 1200 kcal/day diet. The placebo group had no decrease in dietary intake or weight loss while the treatment group reported a significant decrease in both caloric intake and weight loss during both periods. The authors of this study theorized that 5-HTP was effective because it reduced binge eating and carbohydrate cravings, although the study did not include an assessment of frequency of binge eating.

As a result of prior investigations establishing the application of inositol in depression, panic disorder, and obsessive-compulsive disorder (a pharmacological pattern that was similar to the application of SSRIs), a study was conducted to assess the effect of inositol in bulimia nervosa and binge-eating disorder.[43] Twelve patients, nine with bulimia and three with binge-eating disorder were given 18 grams of inositol or placebo in a double-blind crossover design of six weeks on either treatment or placebo. Evaluations were based on a group of psychometric tests conducted every

two weeks. At the end of the 12-week trial, there were significant improvements in the inositol-treated subjects in the area of binge eating (measured by the Visual Analog Scale of severity of binge eating). Five patients improved at least 50 percent compared to one patient in the placebo group showing 50 percent improvement. One patient in the treatment group who had been unresponsive to fluoxetine continued on inositol for six months with complete symptom remission. These results are significant in that they are comparable to those reported for bulimics treated with fluoxetine.[44] Side effects – mild abdominal pain, flatulence, or soft stools – were minimal and remitted with a lower dose of 12 grams daily.

Medical Complications

The medical complications of eating disorders are varied and complex. Many individuals with eating disorders are also substance abusers – 12-18 percent of anorexics and 30-70 percent of bulimics – complicating the consequences of caloric restriction and purging.[45] A brief review of the most commonly affected systems follows.

Electrolyte Abnormalities

Because fluid loss and fluid restriction are common in eating disorders, electrolyte abnormalities are frequent occurrences.[46] The most serious and frequently documented is potassium loss due to self-induced vomiting, and diuretic or laxative abuse.[47] Hypokalemia can result in cardiac symptoms, specifically arrhythmias and EKG abnormalities. Serum levels are often normal, but intracellular potassium may be low enough to create symptoms.[46] If chronic, it can lead to constipation, skeletal muscle myopathy, and nephropathy. Low magnesium is also common and may be a factor in restoring potassium levels. One study examining 175 eating-disordered individuals found 25 percent had low serum magnesium levels that correlated with muscular weakness, diminished concentration, muscular cramping, paresthesias, arrhythmias, and recent memory loss.[48]

Commonly known as "the refeeding syndrome," phosphate can drop to potentially fatal levels as a result of oral or parenteral refeeding in anorexia nervosa.[49,50] Hypophosphatemia can also occur as a result of vomiting, excessive exercise, laxative, diuretic, or antacid use[51] (antacids are frequently used in bulimia as self-treatment for reflux esophagitis and gastritis), or binge eating.[52] Low intracellular phosphate levels (serum levels commonly remain normal) usually occur along with low magnesium and potassium levels and can manifest as respiratory distress, signs of pneumonia, cardiomyopathy, skeletal myopathy, and neuropathy.[49] Low phosphate levels during the time of peak bone mass attainment have been correlated with osteoporosis in anorexia nervosa.[53] The high incidence of scoliosis in ballet dancers has also been related to phosphate depletion due to dietary restriction.[51] Phosphorus has been used prophylactically in refeeding of severely underweight patients to prevent hypophosphatemia and its sequelae.[54]

Although serum potassium has been used as a frequent laboratory screening tool for bulimia,[55] urine sodium-to-chloride ratios appear to be the best predictor of bulimic behavior. A ratio of greater than 1.21 was found in 51 percent of bulimic subjects with a five-percent false-positive rate.[56] The same study also found an increased urine anion gap was a significant predictor of bulimia.[56]

Cardiovascular Effects

Cardiovascular problems occur frequently, particularly in the presence of electrolyte abnormalities. Bradycardia, hypotension, orthostatic hypotension, and symptoms of dizziness and fainting often occur as a result of starvation and dehydration.[47] Sinus arrhythmias are common and do not require intervention, but ventricular arrhythmias are a well-accepted cause of death in eating disorders. Ipecac abuse (in one study 28 percent of bulimics admitted to using this emetic) can cause irreversible cardiac pathologies and fatal cardiomyopathies because it accumulates in cardiac tissue.[57] Chronic purging by either vomiting or diuretic/laxative use can cause hypovolemia

that leads to a hyperaldosterone state in an attempt to conserve body fluid. After the cessation of purging, reflex edema may occur that is temporary and benign, although anxiety-provoking in the patient.[57]

Gastrointestinal Effects

Gastrointestinal complications in eating disorders are complex and can be life-threatening. Swollen submandibular glands and parotid glands as well as esophagitis, esophageal spasm, and esophageal tearing and potentially fatal ruptures can occur from constant vomiting.[47] Bulimics may have esophageal disorders that are undiagnosed and contribute to involuntary vomiting.[58] Gastric dilatation may result from binging in either disorder or refeeding in anorexia. Acute pancreatitis can occur as a result of binge eating or in anorexics who are refed. Long-term laxative abuse can cause pancreatic damage and inhibit normal insulin release.[59] Atrophy of the pancreas has been observed in anorexics and, although the size of the pancreas appears to revert to normal with recovery and increases in body weight, it is unknown whether pancreatic function returns to normal.[60] Abnormal motility, reflected in delayed gastric emptying, increased transit time, constipation, loss of peristalsis, irritable bowel syndrome, steatorrhea, and melanosis coli (a dark brown discoloration of the colon secondary to laxative abuse) can have a variety of causes including binge eating, purging, food restriction, laxative abuse, electrolyte deficiency (potassium, magnesium), and dehydration.[47]

Endocrine Imbalances

Hypothalamic-Pituitary-Adrenal Axis

Sustained elevations of cortisol have been documented in anorexia in multiple studies,[60-64] along with proportionately decreased levels of DHEA, DHEA sulfate, and androstenedione.[65] Studies in bulimics have not consistently found elevated cortisol levels.[64] A more recent study, however, did find elevated cortisol and ACTH levels in normal-weight bulimic women.[66] The reason for hypercortisolemia in anorexics is quite simply that starvation increases cortisol output. Studies of even short-term fasting of 2.5 days in midluteal-phase women have shown a 1.7-fold increase in cortisol output over baseline.[67]

Evidence of elevated cortisol in bulimics may reflect their propensity to restrict food intake, a pattern that often leads to binging and purging behavior, or may reflect a biochemical state predisposing them to depression. Increased baseline cortisol as a result of alterations of the hypothalamic-pituitary-adrenal axis (HPA) is a well-replicated finding in the neurobiology of depression.[68-71] Elevated cortisol, both in plasma and saliva, has been found to be predictive of major depression in both adult females and male and female adolescents and children.[72,73] Women with a history of childhood abuse and a diagnosis of major depression exhibit exaggerated cortisol responses to stress when compared to healthy women or women with a history of childhood abuse and no diagnosis of major depression.[74] The HPA axis appears to have a reciprocal modulating relationship with serotonin.[17] Serotonin regulation deficits result in hypercortisolemia and may, in part, be responsible for the elevated cortisol levels in underweight anorexics as well as normal-weight bulimics.[75] Clearly, weight gain is necessary for the normalization of the HPA axis in anorexia nervosa. The use of adjunctive therapies to address existing elevated cortisol levels in bulimia is warranted. Studies have not directly addressed the ability of serotonin-directed antidepressants to reduce cortisol levels in bulimia.

Studies addressing the application of phosphatidylserine, a phosphorylated amino acid found in the CNS, that has been shown to lower cortisol levels and improve symptoms of depressive disorders, are warranted in bulimics.[76]

Thyroid Function

Thyroid function is commonly abnormal in both anorexia and bulimia.[77,78] The most common laboratory findings are normal thyroxine (T4), normal thyroid stimulating hormone (TSH), and subnormal triiodothyronine (T3), although one study documented low levels of all thyroid hormones in a population of bulimics.[77] These findings correlate with symptoms of fatigue, hypothermia, constipation, bradycardia, and

hypercholesterolemia, even if T4 levels are normal.[79] Signs and symptoms of either "sick euthyroid syndrome" (normal T4 and TSH, and decreased T3) or frank hypothyroidism do not necessarily normalize with increased body mass index or remission of binge eating and purging. One study revealed that bulimics, after seven weeks of abstinence, actually had lower levels of free thyroxin, free triiodothyronine, reverse triiodothyronine, and thyroid-binding globulin, than during periods of active binging and vomiting.[77] The authors speculated that binging may have actually raised thyroid hormone levels even though they were still lower compared to controls at the time of active bulimia. There is also some evidence that thyroid atrophy takes place in anorexia.

Blunted or decreased responses to exogenous TSH are common in anorexia, and there was evidence of significant decreases in thyroid volume in a population of 22 anorexics.[80] The authors of this study expressed their concern about the role thyroid atrophy and related symptomology could play in the continuation of both depression and anorexic behavior. Although depression of triiodothyronine and increased production of reverse T3 is an automatic physiological reaction to starvation,[81] the HPA axis may also be involved in eating-disorder thyroid dysfunction. Elevated plasma cortisol was inversely related to the TSH response to exogenous thyrotropin-releasing hormone (TRH) in 16 females with anorexia and low serum total T3 levels.[79]

Hypothalamic-Pituitary-Gonadal Axis and Bone Loss

Amenorrhea is a classic feature of anorexia nervosa and is considered not only to be a result of caloric restriction and weight loss, but also a dysfunction of the hypothalamic-pituitary-gonadal (HPG) system. A variety of factors (HPA axis, thyroid dysfunction, exercise, etc.) alter gonadotropin-releasing hormone pulsing and result in lowered levels of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH).[82] Bulimics are also at risk of HPG dysfunction and may experience irregular menses even if they are normal weight.[47]

Over 50 percent of all patients with anorexia nervosa have evidence of significant osteoporosis[83] and the rate of bone loss appears to be equal to that of menopause, i.e., five percent per year.[84] The consequences are striking. In one study of 27 anorexics followed for 25 months, the relative risk for nonspinal fracture was 7.1 compared to normal women in the same age group. Gains in bone density did not depend on whether the women took calcium or estrogen, regained their menses, attained 80 percent of ideal body weight, or exercised significantly.[85] Even young women who recover before 15 years of age have been shown to have long-term decreased bone density in the lumbar spine and femoral neck.[86] A study examining premenopausal anorexics who had been in recovery for a mean of 21 years still had significantly lower femur bone density measurements than age-matched controls.[87]

Estrogen administration alone has not been shown to prevent progressive bone loss in current diagnosed anorexics[88] and increases in weight alone appear to be insufficient in reversing bone mineral density losses.[89] Bone loss in anorexia has been linked to the metabolic consequences of starvation and weight loss, including metabolic acidosis, hypoestrogenism, malnutrition, elevated cortisol, low insulin levels that may reduce calcium absorption, and decreased hepatic production of insulin-like growth factor-1.[90]

DHEA, IGF-1, and Bone Loss Reversal

Both DHEA[91] and insulin-like growth factor (IGF-1) have been shown to improve bone turnover markers in women with anorexia nervosa.[92] IGF-1 is a nutritionally-dependent bone-synthesizing hormone that has been shown to stimulate osteoblast and collagen function *in vivo*.[92] In a study of 23 anorexic women (aged 18-29 years), the lowest dose of IGF-1 significantly increased a marker of bone formation (type I procollagen carboxyl-terminal propeptide) and left markers of resorption unchanged. Levels of IGF-1, which had previously been abnormally low in all subjects, were brought to above normal. The need for subcutaneous injection of recombinant human IGF-1 may limit its practical application

in further studies. There is, however, evidence that DHEA stimulates IGF-1 levels in postmenopausal women.

DHEA, given in either 50, 100, or 200 mg/day doses, to 15 young women with anorexia resulted in significant changes in both markers of bone formation and bone resorption after three months.[91] A dose of 50 mg was sufficient to restore DHEA levels to normal physiologic levels. At this dosage, markers of bone resorption (urinary N-teleopeptides) decreased, and markers of formation (serum osteocalcin) increased, both significantly. Menses resumed in 53 percent of the women in the study. A trial of 50 mg DHEA in postmenopausal women was also effective at increasing levels of growth hormone and IGF-1, as well as osteocalcin.[93]

The effect of normalizing physiological levels of DHEA in anorexia nervosa may have added efficacy in reversing bone loss. Both osteoporosis and major depressive disorder are now known to share an association with increased cortisol, a hyperactive HPA axis, and a resistance to dexamethasone suppression, all of which are present in anorexia nervosa.[94] In a recent study, 31 patients with major depressive disorder were found to have evidence of altered HPA-axis function. They had a significantly elevated incidence of osteoporosis which correlated with chronic hypercortisolemia. DHEA has antiglucocorticoid activity and has been shown to correlate positively with IGF-1 binding proteins, increasing the biological activity of IGF-1.[95]

The effect of DHEA in treating major depressive disorder[96] and improving depression and anxiety scores in females with adrenal insufficiency[97] may potentially be as important in treating anxiety and depression characteristic of anorexia nervosa.

Blood Sugar Metabolism and Diabetes Mellitus

A group of anorexic females displayed lower fasting and postprandial glucose levels compared to healthy females after ingesting a 75 gram glucose load.[98] In bulimia, the theory that post-purging glucose and insulin levels resulting from purging may initiate further binge-and-purge episodes was tested in bulimic subjects.[99] Bulimics who purged a test meal had significant drops in glucose and insulin after purging the test meal, while glucose and insulin levels after a non-purged meal were comparable to controls. The authors of this study proposed that the hypoglycemia resulting from purging may contribute to consequent binge/purge episodes.

Another group of bulimics given 25 grams of glucose in a double-blind, placebo-controlled trial reported depression, fatigue, anxiety, and confusion five minutes post-injection.[100] The bulimics receiving saline did not report mood changes that were elevated above those at baseline; whereas, the bulimics had increasing symptoms as time elapsed – up to 60 minutes post-injection. The bulimics receiving glucose also reported increased urges to binge 10 and 60 minutes post-injection. Blood sugar level declines correlated with mood in bulimics given glucose, but not controls. When blood sugar levels were compared, bulimics had lower glucose levels than controls.

The incidence of eating disorders in young females with type 1 diabetes appears to be significantly more common than in non-diabetic young women. The incidence of bulimia or atypical eating disorders in 356 young women ages 12-19 was twice that of 1,098 matched controls.[101] Conscious omission of insulin is the most commonly used method of purging in this group (insulin omission is listed as a diagnostic symptom of bulimia in the DSM-IV) and eating-disordered diabetics have a three-fold increased risk for diabetic retinopathy.[102] In fact, eating disorders in diabetes are more predictive of complications such as retinopathy than the actual duration of diabetes.[102] The authors suggest that clinicians should suspect eating disorders in their young female patients who have unexplained poor control and episodes of ketoacidosis.

Nutrient Deficiencies

Zinc

A significant amount of research has attempted to evaluate the role of zinc in eating disorders.[103] Several symptoms of zinc deficiency,

including weight loss, appetite loss, specific forms of dermatitis, amenorrhea, and depression are also commonly seen in anorexia nervosa.[104] Because zinc deficiency has a wide range of biochemical effects that are seen in eating disorders – alteration of prolactin, thymulin (a zinc-containing thymic hormone), estrogen,[105] cortisol,[106] and the opioid feeding system;[107] lowered testosterone;[108] reduced insulin efficiency;[109] defective insulin-like growth factor-1 signaling pathways;[110] and alterations in serotonin metabolism[111] – there is adequate reason to investigate the potential therapeutic effect of supplemental zinc.

Zinc deficiency also reduces leptin concentrations.[112] Leptin is a peptide produced by adipose cells and affects hypothalamic activity involved in appetite regulation.[113] Leptin receptors are also found in reproductive tissues and low levels of leptin may contribute to reproductive dysfunction.[103] Low levels of leptin are found both in underweight anorexics[114] and normal-weight bulimics.[115,116] Low leptin in bulimics and anorexics may also contribute to low thyroid hormone levels and abnormalities in the HPG axis found in both eating disorders.[117,118]

In protein-energy malnutrition, a state that many anorexics achieve, there is a disruption of the small intestinal mucosal absorptive capacity with a resultant decreased capacity for zinc absorption.[119] The acquired zinc deficiency, in turn, perpetuates an altered or "dysfunctional" epithelial barrier and may result in diarrhea, which perpetuates malabsorption.[120]

Diet history and recall studies have found women with anorexia nervosa at high risk for deficiencies of zinc, as well as calcium, vitamin D, folate, vitamin B12, magnesium, and copper.[121,122] Evidence of zinc malabsorption also exists in anorexia.[123]

Clinical studies assessing the incidence of zinc deficiency in eating disorders are not all in agreement. Six studies found significantly low plasma, serum, or urine zinc in anorexic patients[124-130] and two found zinc deficiency in significant numbers of bulimic patients.[128,129] Three studies found no difference between serum or plasma zinc levels in populations of patients with anorexia nervosa and controls.[131,132] However, as researchers in the field of zinc nutriture have pointed out, there is currently no universally accepted single measure to assess zinc status in humans, and plasma zinc is considered a poor measure of marginal zinc deficiency.[133]

The need for additional zinc during weight restoration in malnutrition and eating disorders has been evident in several studies.[134-136] The stated goal of zinc supplementation in anorexia nervosa in clinical trials has been to increase rate of recovery as evidenced by increases in body mass index.[130] In one clinical trial using either 50 mg of zinc gluconate (14 mg elemental zinc) twice daily or placebo,[16] female anorexic patients on zinc were able to achieve a statistically significant increase in rate of weight gain.[130] In an open study of 20 females with anorexia given 45-90 mg of zinc sulfate daily, the authors found 17 had increased their weight by more than 15 percent at follow-up. One patient had a weight gain of 57 percent within 24 months and one patient had a weight gain of 24 percent within three months. None of the study subjects lost weight after starting zinc therapy and 13 experienced the return of their menses within 1-17 months.[137] In other open trials and patient cases the use of zinc supplementation has been shown to improve weight gain.[138-141]

Zinc supplementation may also benefit psychological as well as growth and developmental parameters in anorexia nervosa. A placebo-controlled study of 15 adolescents, conducted through the Stanford University Pediatrics Department, first looked at evidence of zinc deficiency using 24-hour urinary excretion.[125] The mean zinc loss in the treatment group was significantly lower than the control group. The adolescents with anorexia were then given 50 mg elemental zinc/day for six months. On follow-up, the treatment group had statistically significant improvements in mood and anxiety, in addition to greater weight and height gain, improved taste function, resolution of skin abnormalities, and greater advancement of sexual maturation.

Zinc supplementation has also been studied in bulimia. Forty-seven female bulimic patients were given 120 mL of liquid zinc sulfate for an average of 8.3 days.[142] Patients had significant improvement in both reduction of "fat anxiety"

Table 4. *Anorexia Nervosa Supplement Trials*

Supplement	Effect	Reference
50 mg elemental zinc for 6 months	Significant decreases in measures of anxiety and depression, increased weight gain, sexual maturation, improved taste function.	15 adolescents in double-blind, placebo-controlled randomized trial for 6 months[125]
45-90 mg zinc sulfate	85 percent of patients had greater than 15-percent increase in weight.	20 females in open study[137]
50 mg zinc gluconate	Significant increase in daily body mass index (weight) gain.	35 females in double-blind, placebo-controlled randomized trial for 24.6-31.5 days[130]
50 mg DHEA	Significant increase in markers of bone formation, significant decrease in markers of bone resorption.	15 females in a double-blind, placebo-controlled, randomized trial of 50, 100, or 200 mg. DHEA for 3 months[91]

and "weight vigilance" on the Multidimensional Body-Self Relations Questionnaire and the "drive for thinness" and "body dissatisfaction" on the Eating Disorder Inventory (EDI). No information was available concerning changes in frequency of binge-purge episodes or weight changes. In the same article, Schauss also reports favorable outcomes in both anorexia and bulimia with the use of 9.1-18.2 mg daily dosage of elemental zinc in a liquid zinc sulfate form (40-80 mL). That dosage is maintained for 6-15 days or until taste acuity improves according to the zinc taste test[140] and the patient can then switch to an encapsulated zinc supplement.[143]

Thiamine, Riboflavin, Magnesium, and Essential Fatty Acids

Thiamine deficiency has been documented in 38 percent of a sample of 37 anorexics using erythrocyte transketolase activation.[144] Thiamine deficiency has been shown to cause depression, paresthesia, weakness, dizziness, myalgia, palpitations, hypotension, bradycardia at rest, sinus arrhythmias on exertion, cognitive changes, and classic anorexia.[145] It is relevant that individuals with eating disorders are at high risk for abuse of diuretics and alcohol, and often have high simple carbohydrate loads, increasing risk for thiamine deficiency. Wernicke's encephalopathy, a

Table 5. *Bulimia Nervosa Supplement Trials*

Supplement	Effect	Reference
L-tryptophan 1 gram tid Vitamin B-6 45 mg tid	Significant decrease in frequency of bingeing and purging	comment [41]
Inositol 12-18 grams qd	50 percent of patients had significant decrease in binge eating	12 females in double-blind, placebo-controlled randomized trial for 6 wks.[43]
Zinc 120 mL liquid zinc sulfate	Significant decreases in psychometric testing specific to eating disorder	12 females in open study for a median of 8.3 days[142]

potentially fatal condition if untreated, has been diagnosed in bulimia nervosa.[146]

Riboflavin deficiency in anorexia has been documented in studies of plasma and by erythrocyte glutathione reductase (a riboflavin coenzyme) activity.[132,147] Riboflavin deficiency due to deficiency of conversion cofactors has also been documented in anorexia.[148] This phenomenon has been hypothesized to be due to low triiodothyronine levels in anorexia nervosa, as T3 is necessary for the production of riboflavin mononucleotide. Because both riboflavin and T3 have been shown to be deficient even after refeeding in anorexics, malabsorption and thyroid replacement even in "sick euthyroid syndrome" should be considered.[148]

Magnesium deficiency has been documented in 25 percent of 175 patients in an inpatient treatment setting.[48] In this group, 19 were normal-weight bulimics, six had restrictive or bulimic anorexia, and 13 had obesity and depression (the remaining patients had thought disorders). Serum magnesium levels below 1.8 mEq/L, when compared to eating-disorder patients with normal serum magnesium levels, correlated with symptoms of muscular weakness and cramping, restlessness, paresthesias, decreased concentration, cardiac arrhythmias, hypertension, and diminished short-term memory. The authors also reported that symptoms occurring in the magnesium-deficient patients improved following either intramuscular or oral magnesium replacement and returned when the oral magnesium supplementation was discontinued. It is important to note that in eight patients with low magnesium levels who had cardiac arrhythmias, magnesium replacement normalized each patient. The cardiac abnormalities included supraventricular tachycardia, atrial fibrillation, and EKG changes, including S-T segment depression, widening of QRS interval with peaked T waves, prolonging of the P-R interval, and S-T segment depression.[48]

Dietary restrictions in anorexia nervosa often exclude sources of dietary fat.[149] Essential fatty acid deficiencies have been found in anorexia nervosa.[150] An assessment of eight patients with anorexia nervosa found polyunsaturated fatty acid deficiencies in plasma phospholipids that were, however, more complex than simple essential fatty acid deficiencies.[151] The implications of this type of aberration are not clear, but the authors stated that anorexia affects the fluidity of plasma phospholipids to a similar extent as is seen in cirrhosis and Crohn's disease.

Winston et al,[144] and Hoffman et al,[48] suggest routine screening be done for thiamine and magnesium deficiency in eating-disordered patients, or, more cost-effectively, thiamine and magnesium supplementation be routinely given to all anorexics. In the same manner, it would be logical to suggest nutrient repletion for the nutrients that have been found to be deficient in anorexics: potassium, phosphorus, magnesium, zinc, thiamine, and riboflavin. Other nutrient deficiencies that have been assessed in the diets of women with anorexia nervosa – calcium, folate, vitamin B1, B2, B12, and copper – may also need to be addressed.[121] Table 4 summarizes supplement trials for anorexia. Table 5 summarizes supplement trials for bulimia.

Conclusion

Since the incidence of eating disorders in 15- to 24-year-old females appears to be rising,[152] the necessity for comprehensive treatment of the eating-disordered patient is vital. As eating disorders clearly involve a wide spectrum of gastrointestinal, neurological and endocrine disorders, adequate screening and assessment of patients with eating disorders is necessary, particularly since these patients are seen more and more frequently in private practice settings. Bone density assessments may be important in bulimics with intermittent menstruation as well as those with anorexia and amenorrhea. Alternatives to standard oral contraceptive hormone therapy in eating-disordered women with low bone density may need to be explored. Adrenal function, particularly levels of cortisol and DHEA, may need to be assessed in those being treated for anxiety or depression and low bone density. Attention to nutritional deficiencies may contribute to improved physiological and neurological functioning and assist the psychotherapeutic process. More research is needed to assess the role of inositol, zinc, and serotonin precursors in the treatment of anorexia nervosa and bulimia nervosa.

References

1. Hoek HW. The distribution of eating disorders. In: Brownell KD, Fairburn CG, eds. *Eating Disorders and Obesity: A Comprehensive Handbook*. New York: Guilford Press; 1995:207-211.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* Washington, DC: 1994.
3. World Health Organization. ICD-10 *Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research*. Geneva, Switzerland: 1993.
4. Costin C. *Eating Disorder Sourcebook*. Los Angeles, CA: Lowell House; 1999:18-19.
5. Sungot-Borgen J. Eating disorders among male and female elite athletes. *Br J Sports Med* 1999;33:434.
6. Sullivan P. Course and outcome of anorexia nervosa and bulimia nervosa. In: Fairburn CG, Brownell KD, eds. *Eating Disorders and Obesity* 2nd ed. New York, NY; Guilford Press; 2002:226-232.
7. Sullivan PF. Mortality in anorexia nervosa. *Am J Psychiatry* 1995;152:1073-1074.
8. Strober M, Freeman R, Morrell W. The long-term course of severe anorexia nervosa in adolescents: survival analysis of recovery, relapse, and outcome predictors over 10-15 years in a prospective study. *Int J Eat Disord* 1997;22:339-360.
9. Fichter MM, Quadflieg N. Six-year course of bulimia nervosa. *Int J Eat Disord* 1997;22:361-384.
10. Rorty M, Yager J, Rossotto E. Childhood sexual, physical, and psychological abuse and their relationship to comorbid psychopathology in bulimia nervosa. *Int J Eat Disord* 1994;16:317-334.

11. Wonderlich SA, Brewerton TD, Jocic Z, et al. Relationship of childhood sexual abuse and eating disorders. *J Am Acad Child Adolesc Psychiatry* 1997;36:1107-1115.
12. Cnattingius S, Hultman CM, Dahl M, Sparen P. Very preterm birth, birth trauma, and the risk of anorexia among girls. *Arch Gen Psychiatry* 1999;56:634-638.
13. Strober M, Freeman R, Lampert C, et al. Controlled family study of anorexia nervosa and bulimia nervosa: evidence of shared liability and transmission of partial syndromes. *Am J Psychiatry* 2000;157:393-401.
14. Bulik CM, Sullivan PF, Wade TD, Kendler KS. Twin studies of eating disorders: A review. *Int J Eat Disord* 2000;27:1-20.
15. Strober M, Bulik C. Genetic epidemiology of eating disorders. In: Fairburn CG, Brownell KD, eds. *Eating Disorders and Obesity* 2nd ed. New York, NY; Guilford Press; 2002:238-242.
16. Lilenfeld LR, Kaye WH, Greeno CG, et al. A controlled family study of anorexia nervosa and bulimia nervosa: psychiatric disorders in first-degree relatives and effects of proband comorbidity. *Arch Gen Psychiatry* 1998;55:603-610.
17. Brewerton TD. Toward a unified theory of serotonin dysregulation in eating and related disorders. *Psychoneuroendocrinology* 1995;20:561-590.
18. Goodwin GM, Cowen PJ, Fairburn CG, et al. Plasma concentrations of tryptophan and dieting. *BMJ* 1990;300:1499-1500.
19. Altemus M, Glowa JR, Murphy DL. Attenuation of food-restriction-induced running by chronic fluoxetine treatment. *Psychopharmacol Bull* 1993;29:397-400.
20. Brewerton TD, Brandt HA, Lesem DT, et al. Serotonin in eating disorders. In: Coccaro E, Murphy DL, eds. *Serotonin in Major Psychiatric Disorders.* Washington, DC: American Psychiatric Press; 1990:153-184.
21. Hassanyeh F, Marshall EF. Measures of serotonin metabolism in anorexia nervosa. *Acta Psychiatr Scand* 1991;84:561-563.
22. Kaye WH, Gwirtsman HE, George DT, et al. CSF 5-HIAA concentrations in anorexia nervosa: reduced values in underweight subjects normalize after weight gain. *Biol Psychiatry* 1988;23:102-105.
23. Walsh BT. Pharmacological treatment of anorexia nervosa and bulimia nervosa. In: Fairburn CG, Brownell KD, eds. *Eating Disorders and Obesity* 2nd ed. New York, NY; Guilford Press; 2002:325-329.
24. Gerner RH, Cohen DJ, Fairbanks L, et al. CSF neurochemistry of women with anorexia nervosa and normal women. *Am J Psychiatry* 1984;141:1441-1444.
25. McBride PA, Anderson GM, Khait VD, et al. Serotonergic responsivity in eating disorders. *Psychopharmacol Bull* 1991;27:365-372.
26. Lee MA, Meltzer HY. Neuroendocrine responses to serotonergic agents in alcoholics. *Biol Psychiatry* 1991;30:1017-1030.
27. Borg S, Kvande H, Liljeberg P, et al. 5-Hydroxyindoleacetic acid in cerebrospinal fluid in alcoholic patients under different clinical conditions. *Alcohol* 1985;2:415-418.
28. Rosenthal NE, Davenport Y, Cowdry RW, et al. Monoamine metabolites in cerebrospinal fluid of depressive subgroups. *Psychiatry Res* 1980;2:113-119.
29. Coccaro EF, Siever LJ, Klar HM, et al. Serotonergic studies in patients with affective and personality disorders. Correlates with suicidal and impulsive aggressive behavior. *Arch Gen Psychiatry* 1989;46:587-599.
30. van Praag HM, Kahn RS, Asnis GM, et al. Denosologization of biological psychiatry or the specificity of 5-HT disturbances in psychiatric disorders. *J Affect Disord* 1987;13:1-8.
31. Kaye WH, Gwirtsman HE, George DT. The effect of bingeing and vomiting on hormonal secretion. *Biol Psychiatry* 1989;25:768-780.
32. Jimerson DC, Lesem MD, Kaye WH, Brewerton TD. Low serotonin and dopamine metabolite concentrations in cerebrospinal fluid from bulimic patients with frequent binge episodes. *Arch Gen Psychiatry* 1992;49:132-138.
33. Kaye WH, Greeno CG, Moss H, et al. Alterations in serotonin activity and psychiatric symptoms after recovery from bulimia nervosa. *Arch Gen Psychiatry* 1998;55:927-935.
34. Attia E, Haiman C, Walsh BT, Flater SR. Does fluoxetine augment the inpatient treatment of anorexia nervosa? *Am J Psychiatry* 1998;155:548-551.

35. Walsh BT, Wilson GT, Loeb KL, et al. Medication and psychotherapy in the treatment of bulimia nervosa. *Am J Psychiatry* 1997;154:523-531.
36. Smith KA, Fairburn CG, Cowen PJ. Symptomatic relapse in bulimia nervosa following acute tryptophan depletion. *Arch Gen Psychiatry* 1999;56:171-176.
37. Van der Does AJ. The effects of tryptophan depletion on mood and psychiatric symptoms. *J Affect Disord* 2001;64:107-119.
38. Brewerton TD, Murphy DL, Jimerson DC. Testmeal responses following m-chlorophenylpiperazine and L-tryptophan in bulimics and controls. *Neuropsychopharmacology* 1994;11:63-71.
39. Goldbloom DS, Garfinkel PE, Katz R, Brown GM. The hormonal response to intravenous 5-hydroxytryptophan in bulimia nervosa. *J Psychosom Res* 1996;40:289-297.
40. Cowen PJ, Charig EM. Neuroendocrine responses to intravenous tryptophan in major depression. *Arch Gen Psychiatry* 1987;44:958-966.
41. Mira M, Abraham S. L-tryptophan as an adjunct to treatment of bulimia nervosa. *Lancet* 1989;2:1162-1163.
42. Cangiano C, Ceci F, Cascino A, et al. Eating behavior and adherence to dietary prescriptions in obese adult subjects treated with 5-hydroxytryptophan. *Am J Clin Nutr* 1992;56:863-867.
43. Gelber D, Levine J, Belmaker RH. Effect of inositol on bulimia nervosa and binge eating. *Int J Eat Disord* 2001;29:345-348.
44. No authors listed. Fluoxetine in the treatment of bulimia nervosa. A multicenter, placebo-controlled, double-blind trial. Fluoxetine Bulimia Nervosa Collaborative Study Group. *Arch Gen Psychiatry* 1992;49:139-147.
45. Bulik CM, Sullivan PF, Epstein LH, et al. Drug use in women with anorexia and bulimia nervosa. *Int J Eat Disord* 1992;11:213-225.
46. Mitchell JE, Pyle RL, Eckert ED, et al. Electrolyte and other physiological abnormalities in patients with bulimia. *Psychol Med* 1983;13:273-278.
47. Pomeroy C, Mitchell J. Medical complications of anorexia nervosa and bulimia nervosa. In: Fairburn CG, Brownell KD, eds. *Eating Disorders and Obesity* 2nd ed. New York, NY: Guilford Press; 2002:278-285.
48. Hall RC, Hoffman RS, Beresford TP, et al. Hypomagnesemia in patients with eating disorders. *Psychosomatics* 1988;29:264-272.
49. Solomon SM, Kirby DF. The refeeding syndrome: a review. *JPEN J Parenter Enteral Nutr* 1990;14:90-97.
50. Beumont PJ, Large M. Hypophosphataemia, delirium and cardiac arrhythmia in anorexia nervosa. *Med J Aust* 1991;155:519-522.
51. Haglin L. Hypophosphataemia in anorexia nervosa. *Postgrad Med J* 2001;77:305-311.
52. Kaysar N, Kronenberg J, Polliack M, Gaoni B. Severe hypophosphataemia during binge eating in anorexia nervosa. *Arch Dis Child* 1991;66:138-139.
53. Crosby LO, Kaplan FS, Pertschuk MJ, Mullen JL. The effect of anorexia nervosa on bone morphometry in young women. *Clin Orthop* 1985;Dec:271-277.
54. Fisher M, Simpser E, Schneider M. Hypophosphatemia secondary to oral refeeding in anorexia nervosa. *Int J Eat Disord* 2000;28:181-187.
55. Wolfe BE, Metzger ED, Levine JM, Jimerson DC. Laboratory screening for electrolyte abnormalities and anemia in bulimia nervosa: a controlled study. *Int J Eat Disord* 2001;30:288-293.
56. Crow SJ, Rosenberg ME, Mitchell JE, Thuras P. Urine electrolytes as markers of bulimia nervosa. *Int J Eat Disord* 2001;30:279-287.
57. Pomeroy C, Mitchell J. Medical issues in the eating disorders. In: Brownell K, Rodin J, Wilmore JH. *Eating, Body Weight, and Performance in Athletes. Disorders of a Modern Society*. Philadelphia, PA: Lea and Febiger; 1992:202-221.
58. Kiss A, Bergmann H, Abatzi TA, et al. Oesophageal and gastric motor activity in patients with bulimia nervosa. *Gut* 1990;31:259-265.
59. Brown NW, Treasure JL, Campbell IC. Evidence for long-term pancreatic damage caused by laxative abuse in subjects recovered from anorexia nervosa. *Int J Eat Disord* 2001;29:236-238.
60. Cuntz U, Frank G, Lehnert P, Fichter M. Interrelationships between the size of the pancreas and the weight of patients with eating disorders. *Int J Eat Disord* 2000;27:297-303.

61. Boyar RM, Hellman LD, Roffwarg H, et al. Cortisol secretion and metabolism in anorexia nervosa. *N Engl J Med* 1977;296:190-193.
62. Walsh BT, Katz JL, Levin J, et al. Adrenal activity in anorexia nervosa. *Psychosom Med* 1978;40:499-506.
63. Walsh BT, Katz JL, Levin J, et al. The production rate of cortisol declines during recovery from anorexia nervosa. *J Clin Endocrinol Metab* 1981;53:203-205.
64. Gold PW, Gwirtsman H, Avgerinos PC, et al. Abnormal hypothalamic-pituitary-adrenal function in anorexia nervosa. Pathophysiologic mechanisms in underweight and weight-corrected patients. *N Engl J Med* 1986;314:1335-1342.
65. Winterer J, Gwirtsman HE, George DT, et al. Adrenocorticotropin-stimulated adrenal androgen secretion in anorexia nervosa: impaired secretion at low weight with normalization after long-term weight recovery. *J Clin Endocrinol Metab* 1985;61:693-697.
66. Mortola JF, Rasmussen DD, Yen SS. Alterations of the adrenocorticotropin-cortisol axis in normal weight bulimic women: evidence for a central mechanism. *J Clin Endocrinol Metab* 1989;68:517-522.
67. Bergendahl M, Iranmanesh A, Pastor C, et al. Homeostatic joint amplification of pulsatile and 24-hour rhythmic cortisol secretion by fasting stress in midluteal phase women: concurrent disruption of cortisol-growth hormone, cortisol-leutinizing hormone, and cortisol-leptin synchrony. *J Clin Endocrinol Metab* 2000;85:4028-4035.
68. Raadsheer FC, Hoogendijk WJ, Stam FC, et al. Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. *Neuroendocrinology* 1994;60:436-444.
69. Axelson DA, Doraiswamy PM, Boyko OB, et al. *In vivo* assessment of pituitary volume with magnetic resonance imaging and systematic stereology: relationship to dexamethasone suppression test results in patients. *Psychiatry Res* 1992;44:63-70.
70. O'Toole SM, Sekula LK, Rubin RT. Pituitary-adrenal cortical axis measures as predictors of sustained remission in major depression. *Biol Psychiatry* 1997;42:85-89.
71. Beck-Friis J, Ljunggren JG, Thoren M, et al. Melatonin, cortisol, and ACTH in patients with major depressive disorder and healthy humans with special reference to the outcome of the dexamethasone suppression test. *Psychoneuroendocrinology* 1985;10:173-186.
72. Harris TO, Borsanyi S, Messari S, et al. Morning cortisol as a risk factor for subsequent major depressive disorder in adult women. *Br J Psychiatry* 2000;177:505-510.
73. Goodyer IM, Herbert J, Tamplin A, Altham PM. Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. *Br J Psychiatry* 2000;177:499-504.
74. Ladd CO, Huot RL, Thrivikraman KV, et al. Long-term behavioral and neuroendocrine adaptations to adverse early experience. *Prog Brain Res* 2000;122:81-103.
75. Brewerton TD, Lydiard RB, Laraia MT, et al. CSF beta-endorphin and dynorphin in bulimia nervosa. *Am J Psychiatry* 1992;149:1086-1090.
76. Maggioni M, Picotti GB, Bondiolotti GP, et al. Effects of phosphatidylserine therapy in geriatric patients with depressive disorders. *Acta Psychiatr Scand* 1990;81:265-270.
77. Altemus M, Hetherington M, Kennedy B, et al. Thyroid function in bulimia nervosa. *Psychoneuroendocrinology* 1996;21:249-261.
78. Curran-Celentano J, Erdman JW Jr, Nelson RA, Grater SJ. Alterations in vitamin A and thyroid hormone status in anorexia nervosa and associated disorders. *Am J Clin Nutr* 1985;42:1183-1191.
79. Bannai C, Kuzuya N, Koide Y, et al. Assessment of the relationship between serum thyroid hormone levels and peripheral metabolism in patients with anorexia nervosa. *Endocrinol Jpn* 1988;35:455-462.
80. Stoving RK, Bennedbaek FN, Hegedus L, Hagen C. Evidence of diffuse atrophy of the thyroid gland in patients with anorexia nervosa. *Int J Eat Disord* 2001;29:230-235.
81. Melchior JC. From malnutrition to refeeding during anorexia nervosa. *Curr Opin Clin Nutr Metab Care* 1998;1:481-485.
82. De Cree C. Sex steroid metabolism and menstrual irregularities in the exercising female. A review. *Sports Med* 1998;25:369-406.

83. Grinspoon S, Herzog D, Klibanski A. Mechanisms and treatment options for bone loss in anorexia nervosa. *Psychopharmacol Bull* 1997;33:399-404.
84. Drinkwater BL, Nilson K, Chesnut CH 3rd, et al. Bone mineral content of amenorrheic and eumenorrheic athletes. *N Engl J Med* 1984;311:277-281.
85. Rigotti NA, Neer RM, Skates SJ, et al. The clinical course of osteoporosis in anorexia nervosa: A longitudinal study of cortical bone mass. *JAMA* 1991;265:1133-1138.
86. Hergenroeder AC. Bone mineralization, hypothalamic amenorrhea, and sex steroid therapy in female adolescents and young adults. *J Pediatr* 1995;126:683-689.
87. Hartman D, Crisp A, Rooney B, et al. Bone density of women who have recovered from anorexia nervosa. *Int J Eat Disord* 2000;28:107-112.
88. Klibanski A, Biller BM, Schoenfeld DA, et al. The effects of estrogen on trabecular bone loss in young women with anorexia nervosa. *J Clin Endocrinol Metab* 1995;80:898-904.
89. Baker D, Roberts R, Towell T. Factors predictive of bone mineral density in eating-disordered women: a longitudinal study. *Int J Eat Disord* 2000;27:29-35.
90. Bruni V, Dei M, Vicini I, et al. Estrogen replacement therapy in the management of osteopenia related to eating disorders. *Ann N Y Acad Sci* 2000;900:416-421.
91. Gordon CM, Grace E, Emans SJ, et al. Changes in bone turnover markers and menstrual function after short-term oral DHEA in young women with anorexia nervosa. *J Bone Miner Res* 1999;14:136-145.
92. Grinspoon S, Baum H, Lee K, et al. Effects of short-term recombinant human insulin-like growth factor I administration on bone turnover in osteopenic women with anorexia nervosa. *J Clin Endocrinol Metab* 1996;81:3864-3870.
93. Genazzani AD, Stomati M, Strucchi C, et al. Oral dehydroepiandrosterone supplementation modulates spontaneous and growth hormone-releasing hormone-induced growth hormone and insulin-like growth factor-1 secretion in early and late postmenopausal women. *Fertil Steril* 2001;76:241-248.
94. Vrkljan M, Thaller V, Lovricevic I, et al. Depressive disorder as possible risk factor of osteoporosis. *Coll Antropol* 2001;25:485-492.
95. Murialdo G, Barreca A, Nobili F, et al. Relationships between cortisol, dehydroepiandrosterone sulphate and insulin-like growth factor-1 system in dementia. *J Endocrinol Invest* 2001;24:139-146.
96. Wolkowitz OM, Reus VI, Keebler A, et al. Double-blind treatment of major depression with dehydroepiandrosterone. *Am J Psychiatry* 1999;156:646-649.
97. Arlt W, Callies F, Allolio B. DHEA replacement in women with adrenal insufficiency – pharmacokinetics, bioconversion and clinical effects on well-being, sexuality and cognition. *Endocr Res* 2000;26:505-511.
98. Gniuli D, Liverani E, Capristo E, et al. Blunted glucose metabolism in anorexia nervosa. *Metabolism* 2001;50:876-881.
99. Johnson WG, Jarrell MP, Chupurdia KM, Williamson DA. Repeated binge/purge cycles in bulimia nervosa: role of glucose and insulin. *Int J Eat Disord* 1994;15:331-341.
100. Blouin AG, Blouin J, Bushnik T, et al. A double-blind placebo-controlled glucose challenge in bulimia nervosa: psychological effects. *Biol Psychiatry* 1993;33:160-168.
101. Jones JM, Lawson ML, Danemen D, et al. Eating disorders in adolescent females with and without type 1 diabetes: cross sectional study. *BMJ* 2000;320:1563-1566.
102. Rydall AC, Rodin GM, Olmsted MP, et al. Disordered eating behavior and microvascular complications in young women with insulin-dependent diabetes mellitus. *New Engl J Med* 1997;336:1849-1854.
103. Shay NF, Mangian HF. Neurobiology of zinc-influenced eating behavior. *J Nutr* 2000;130:1493S-1499S.
104. Bakan R. The role of zinc in anorexia nervosa: etiology and treatment. *Med Hypotheses* 1979;5:731-736.
105. Prasad AS. Clinical, endocrinological and biochemical effects of zinc deficiency. *Clin Endocrinol Metab* 1985;14:567-589.
106. Brandao-Neto J, de Mendonca BB, Shuhama T, et al. Zinc acutely and temporarily inhibits adrenal cortisol secretion in humans. A preliminary report. *Biol Trace Elem Res* 1990;24:83-89.
107. Morley JE, Silver AJ. Anorexia in the elderly. *Neurobiol Aging* 1988;9:9-16.

108. Om AS, Chung KW. Dietary zinc deficiency alters 5 alpha-reduction and aromatization of testosterone and androgen and estrogen receptors in rat liver. *J Nutr* 1996;126:842-848.
109. Song MK, Rosenthal MJ, Naliboff BD, et al. Effects of bovine prostate powder on zinc, glucose, and insulin metabolism in old patients with non-insulin-dependent diabetes mellitus. *Metabolism* 1998;47:39-43.
110. Browning JD, MacDonald RS, Thornton WH, O'Dell BL. Reduced food intake in zinc-deficient rats is normalized by megestrol acetate but not by insulin-like growth factor-1. *J Nutr* 1998;128:136-142.
111. Sandstead HH. W.O. Atwater memorial lecture. Zinc: essentiality for brain development and function. *Nutr Rev* 1985;43:129-137.
112. Mantzoros CS, Prasad AS, Beck FW, et al. Zinc may regulate serum leptin concentrations in humans. *J Am Coll Nutr* 1998;17:270-275.
113. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature* 1998;395:763-770.
114. Eckert ED, Pomeroy C, Raymond N, et al. Leptin in anorexia nervosa. *J Clin Endocrinol Metab* 1998;83:791-795.
115. Halmi K. Physiology of anorexia nervosa and bulimia nervosa. In: Fairburn CG, Brownell KD, eds. *Eating Disorders and Obesity* 2nd ed. New York, NY; Guilford Press; 2002:267-271.
116. Jimerson DC, Mantzoros C, Wolfe BE, Metzger ED. Decreased serum leptin in bulimia nervosa. *J Clin Endocrinol Metab* 2000;85:4511-4514.
117. Pirke KM, Pahl J, Schweiger U, Warnhoff M. Metabolic and endocrine indices of starvation in bulimia: a comparison with anorexia nervosa. *Psychiatry Res* 1985:15;33-39.
118. Devlin MJ, Walsh BT, Katz JL, et al. Hypothalamic-pituitary-gonadal function in anorexia nervosa and bulimia. *Psychiatry Res* 1989;28:11-24.
119. Koo SI, Turk DE. Effect of zinc deficiency on the ultrastructure of the pancreatic acinar cell and intestinal epithelium in the rat. *J Nutr* 1977;107:896-908.
120. Wapnir RA. Zinc deficiency, malnutrition and the gastrointestinal tract. *J Nutr* 2000;130:1388S-1392S.
121. Hadigan CM, Anderson EJ, Miller KK, et al. Assessment of macronutrient and micronutrient intake in women with anorexia nervosa. *Int J Eat Disord* 2000;28:284-292.
122. Bakan R, Birmingham CL, Aeberhardt L, Goldner EM. Dietary zinc intake of vegetarian and nonvegetarian patients with anorexia nervosa. *Int J Eat Disord* 1993;13:229-233.
123. Dinsmore WW, Alderdice JT, McMaster D, et al. Zinc absorption in anorexia nervosa. *Lancet* 1985;1:1041-1042.
124. Rigaud D, Sogni P, Hammel P, et al. Anorexia nervosa: absence of sensitivity to nutritional protein markers. Study of 23 patients and comparison to a paired group with colonic Crohn's disease. *Ann Med Interne (Paris)* 1989;140:86-90. [Article in French]
125. Katz RL, Keen CL, Litt IF, et al. Zinc deficiency in anorexia nervosa. *J Adolesc Health Care* 1987;8:400-406.
126. Casper RC, Kirschner B, Sandstead HH, et al. An evaluation of trace metals, vitamins, and taste function in anorexia nervosa. *Am J Clin Nutr* 1980;33:1801-1808.
127. Lask B, Fosson A, Rolfe U, Thomas S. Zinc deficiency and childhood-onset anorexia nervosa. *J Clin Psychiatry* 1993;54:63-66.
128. McClain CJ, Stuart MA, Vivian B, et al. Zinc status before and after zinc supplementation of eating disorder patients. *J Amer Coll Nutr* 1992;11:694-700.
129. Humphries L, Vivian B, Stuart M, McClain CJ. Zinc deficiency and eating disorders. *J Clin Psychiatry* 1989;50:456-459.
130. Birmingham CL, Goldner EM, Bakan R. Controlled trial of zinc supplementation in anorexia nervosa. *Int J Eat Disord* 1994;15;251-255.
131. Kopala LC, Good K, Goldner EM, Birmingham CL. Olfactory identification ability of anorexia nervosa. *J Psychiatry Neurosci* 1995;20:283-286.
132. Van Binsbergen CJ, Odink J, Van den Berg H, et al. Nutritional status in anorexia nervosa: clinical chemistry, vitamins, iron, and zinc. *Eur J Clin Nutr* 1988;42:929-937.
133. Wood RJ. Assessment of marginal zinc status in humans. *J Nutr* 2000;130:1350S-1354S.
134. McClain CJ, Humphries LL, Hill KK, Nickl NJ. Gastrointestinal and nutritional aspects of eating disorders. *J Am Coll Nutr* 1993;12:466-474.
135. Castillo-Duran C, Heresi G, Fisberg M, Uauy R. Controlled trial of zinc supplementation during recovery form malnutrition: effects on growth and immune function. *Am J Clin Nutr* 1987;45:602-608.

136. Nishi Y. Zinc status in various diseases. *Hiroshima J Med Sci* 1980;29:69-74.
137. Safai-Kutti S. Oral zinc supplementation in anorexia nervosa. *Acta Psychiatr Scand Suppl* 1990;361:14-17.
138. Yamaguchi H, Arita Y, Hara Y, et al. Anorexia nervosa responding to zinc supplementation: a case report. *Gastroenterol Jpn* 1992;27:554-558.
139. Humphries LL, McClain MP, Vivian DB, et al. Anorexia nervosa, zinc supplementation and weight gain. In: Anderson H, ed. *Biology of Feast and Famine: Relevance to Eating Disorders, Symposium on Nutrition Research*. Toronto: University of Toronto; 1990:124-136.
140. Bryce-Smith D, Simpson RI. Case of anorexia nervosa responding to zinc sulphate. *Lancet* 1984;2:350.
141. Esca SA, Brenner W, Mach K, Gschnait F. Kwashiorkor-like zinc deficiency syndrome in anorexia nervosa. *Acta Derm Venereol* 1979;59:361-364.
142. Schauss A, Costin C. Zinc as a nutrient in the treatment of eating disorders. *Am J Nat Med* 1997;4:8-13.
143. Schauss A. Natural and conventional therapies in the treatment of eating disorders. *Int J Integr Med* 2000;2:30-39.
144. Winston AP, Jamieson CP, Madira W, et al. Prevalence of thiamin deficiency in anorexia nervosa. *Int J Eat Disord* 2000;28:451-454.
145. Williams RD, Mason HL, Power MH, et al. Induced thiamine (vitamin B1) deficiency in man: relation of depletion of thiamine to development of biochemical defect and of polyneuropathy. *Arch Int Med* 1943;71:38-53.
146. Reuler JB, Girard DE, Cooney TG. Current concepts. Wernicke's encephalopathy. *N Engl J Med* 1985;312:1035-1039.
147. Rock CL, Vasantharajan S. Vitamin status of eating disorder patients: relationship to clinical indices and effect of treatment. *Int J Eat Disord* 1995:18:257-262.
148. Capo-chichi CD, Gueant JL, Lefebvre E, et al. Riboflavin and riboflavin-derived cofactors in adolescent girls with anorexia nervosa. *Am J Clin Nutr* 1999;69:672-678.
149. Halmi KA, Falk JR. Common physiological changes in anorexia nervosa. *Int J Eat Disord* 1981;1:16-17.
150. Langan SM, Farrell PM. Vitamin E, vitamin A and essential fatty acid status of patients hospitalized for anorexia nervosa. *Am J Clin Nutr* 1985;41:1054-1060.
151. Holman RT, Adams CE, Nelson RA, et al. Patients with anorexia nervosa demonstrate deficiencies of selected essential fatty acids, compensatory changes in nonessential fatty acids and decreased fluidity of plasma lipids. *J Nutr* 1995;125:901-907.
152. Hoek HW. Distribution of eating disorders. In: Fairburn CG, Brownell KD, eds. *Eating Disorders and Obesity* 2nd ed. New York, NY; Guilford Press; 2002:233-237.