Medical Complications of Anorexia Nervosa and Bulimia Nervosa

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KEYWORDS

- Medical complications
- Eating disorders
- Anorexia nervosa
- Bulimia nervosa

KEY POINTS

- Anorexia nervosa and bulimia nervosa are multisystem diseases with medical complications affecting all body systems.
- The medical complications of anorexia nervosa are due to malnutrition and weight loss. Additional complications of anorexia nervosa, binge-eating/purging type are due to the frequency and mode of purging behaviors.
- The medical complications of bulimia nervosa are due to the frequency and mode of purging behaviors.

INTRODUCTION

Unlike other psychiatric disorders that do not inherently manifest with somatic complications, eating disorders are multisystem diseases with significant medical complications affecting all body systems. Eating disorders have been noted to have among the highest mortality of all mental health disorders, with mortality in anorexia nervosa (AN) approaching 6% per decade.\textsuperscript{1} Although about one-quarter of these deaths in AN are related to suicide, greater than 50% are attributed to medical complications.\textsuperscript{1} The purpose of this article is to discuss the medical complications of AN and bulimia nervosa (BN) as well as the recommended interventions. Unless otherwise specified, AN will refer to both AN-R (restricting subtype) and AN-BP (binge/purge subtype).

SKIN

In decreasing order of frequency, the skin manifestations of AN include xerosis (dry skin), hypertrichosis lanuginosa (lanugo hair), telogen effluvium (hair loss), nail fragility,
and acrocyanosis. Purpura and easy bruisability are also found in AN, related to thrombocytopenia. These skin changes are in part an expected physiologic adaption to the malnutrition and associated hypothermia commonly present in individuals with eating disorders. Lanugo presents as fine, minimally pigmented hairs mostly on the face, back, or abdomen. It is not a sign of virilization and likely serves as a heat-conserving mechanism. Acrocyanosis is a condition of skin arteriole constriction and venous dilatation of unknown cause. It has been hypothesized to serve as an energy-saving mechanism. Xerosis likely develops secondary to various nutrient deficiencies as well as reduced sebaceous gland secretion and altered composition of the secreted sebum. Telogen effluvium manifests as a diffuse pattern of hair loss due to an increased number of hairs in the telogen phase, the resting phase when hair loss occurs. Individuals who engage in purging via self-induced vomiting may manifest with Russell sign, thickening of the skin over dorsal surface of the knuckles, and is considered a pathognomonic sign for AN-BP and BN. Male patients with AN may be less prone to develop lanugo and may present with a higher frequency of striae distensae (stretch marks). All these conditions improve with weight restoration and cessation of vomiting.

**HEAD, EARS, EYES, NOSE, THROAT**

Lagophthalmos, the inability to fully close the eyelids, leads to symptoms of eye irritation due to ocular surface drying. Lagophthalmos is presumed to be secondary to orbital fat wasting and is proportional to the extent of weight loss. It is treated with lubrication and weight restoration. Autophonia, the hyperperception of one’s own voice and breathing, is another occurrence in severe AN. It is thought to be secondary to loss of fatty tissue surrounding the eustachian tube. Improvement is seen with weight restoration. Oropharyngeal dysphagia is a relatively common symptom in this population as well, due to weakness of the swallowing muscles. Dysphagia can be well managed in consultation with a speech therapist and with dietary modification leading to strengthening of the swallowing muscles.

Complications specific to those who engage in self-induced vomiting include dental erosion of the lingual surface of the teeth known as perimylyolysis, increased incidence of dental caries, and sialadenosis, a swelling of the major salivary glands, including the parotid gland, often occurring a few days after purging ceases. Perimylolysis and dental caries seem to develop as a result of food choices, changes in salivary composition, and increased contact of gastric acid with the teeth as a result of vomiting. Sialadenosis can be treated with sialagogues (ie, hard candies such as lemon drops or LifeSavers) to encourage saliva production, heating pads, and anti-inflammatory medications; rarely, pilocarpine may be required for refractory cases. Subconjunctival hemorrhage and epistaxis can also develop as a result of forceful retching.

**PULMONARY**

The lungs are relatively spared compared with the other body systems. However, there are case reports of spontaneous pneumothorax, pneumomediastinum, and the pulmonary function changes of obstructive lung disease. Development of pneumomediastinum appears to be secondary to nontraumatic alveolar rupture and not secondary to esophageal perforation. Hence, purging does not appear to increase the risk of spontaneous pneumothorax. Supportive care seems to be adequate in most cases, although chest tube intervention may occasionally be warranted. Aspiration pneumonia also occurs with increased frequency in those with AN and BN due to either oropharyngeal weakness or purging via emesis.
CARDIAC

Sudden cardiac death is a potential cause of the high mortality in those with eating disorders. Sudden cardiac death can be attributed to various functional and structural causes, including myocardial scarring and cardiac atrophy,\textsuperscript{21,22} as well as various cardiac arrhythmias. The impact of QT dispersion (inter-lead QT variability on electrocardiogram) toward sudden death and predisposition to unstable arrhythmias seems likely, although medications and duration of disease may be a further influence.\textsuperscript{23–27} However, QT prolongation is not inherit to AN or BN, and when present, should result in a search for secondary causes of QT prolongation, such as electrolyte derangements and offending medications.

Other common cardiac manifestations of AN include mitral valve prolapse and pericardial effusion. Mitral valve prolapse occurs in individuals with AN and is related to changes in left ventricular dimensions causing laxity of the mitral valve.\textsuperscript{28,29} Pericardial effusion also develops in about one-third of individuals with AN, is of unclear cause, and correlates with the level of malnutrition.\textsuperscript{30} Both of these conditions are generally reversible with weight restoration.\textsuperscript{30,31}

The most common clinical findings include sinus bradycardia and hypotension. Sinus bradycardia is a nearly universal finding in AN,\textsuperscript{32} likely a manifestation of increased vagal tone.\textsuperscript{33} Junctional rhythms and other bradyarrhythmias will occasionally develop as well.\textsuperscript{34} Patients with marked bradycardia (pulse <35 beats/min) should be monitored with telemetry, but no other intervention or use of a pacemaker is generally required. Bradycardia generally resolves with adequate weight restoration.

Those with AN-BP and BN may be at increased risk for arrhythmias due to electrolyte imbalance. These electrolyte and acid base disorders, as a result of purging behaviors, are likely the cause of the elevated mortality in AN-BP relative to AN-R, and in BN.\textsuperscript{35} A cardiomyopathy may also develop if individuals used an excessive amount of Ipecac as a form of purging, or in some cases, as a result of chronic malnutrition in the absence of Ipecac use.\textsuperscript{36}

GASTROINTESTINAL

Gastrointestinal (GI) complaints of bloating, early satiety, abdominal discomfort, nausea, and constipation are commonly reported in this population. Many of these symptoms are likely the result of slowed GI motility, which is a common finding in those with AN.\textsuperscript{37,38} This diminished motility tends to normalize with weight restoration.\textsuperscript{39–41} Gastric-emptying studies are rarely needed for diagnosis of gastroparesis given the near universal finding of prolonged gastric emptying as the severity of weight loss increases; furthermore, gastric emptying times do not correlate well with reported symptoms,\textsuperscript{42} suggesting a functional component to these symptoms in AN and BN as well.\textsuperscript{42,43} It is unclear if there is a higher incidence of pancreatitis that would contribute to these symptoms, although several potential mechanisms could be postulated regarding an increased risk for those with eating disorders.\textsuperscript{44} The constipation and associated straining along with stimulant laxative abuse predispose to development of rectal prolapse.\textsuperscript{45} Patient education regarding normalization of gastric and intestinal motility, and thus improvement in abdominal discomfort, bloating, and constipation, can be expected with weight restoration. Prokinetic or motility agents, such as metoclopramide, and osmotic agents, such as polyethylene glycol, are first-line pharmacologic treatments for gastroparesis and constipation, respectively, and may be required temporarily during early refeeding. However, metoclopramide should be used at lower doses to minimize the risk for potential adverse effects of tardive dyskinesia and QT
prolongation. Macrolide antibiotics may also be tried, cautiously, for symptoms of delayed gastric emptying.

Superior mesenteric artery (SMA) syndrome is a less frequent cause of abdominal pain and emesis in AN. The true prevalence of this condition in AN is unknown, and weight loss is the greatest risk factor leading to its development. As extent of malnutrition increases, the fat pad that normally supports the SMA is lost, causing its medial migration and resultant total or incomplete compression of the duodenum between the SMA and the aorta. Surgery is not recommended as a first-line treatment because weight restoration, using a soft or liquid oral diet or placement of a feeding tube and bypassing the mechanical obstruction, is successful in most cases. Computed tomographic scan can provide anatomic diagnosis, but upper GI series provides a more functional diagnosis. SMA syndrome also predisposes to the rarely encountered gastric dilatation. Gastric dilatation can be diagnosed with a plain abdominal radiograph and should be treated with nasogastric suction as well as a surgical consult given the increased risk for vascular insufficiency, gastric necrosis, and perforation.

Individuals with AN-BP and BN are at increased risk for esophageal complications due to reflux of gastric acid through the weakened lower esophageal sphincter as a result of purging. A higher incidence of gastroesophageal reflux is reported in BN, which may further contribute to serious complications, such as esophageal adenocarcinoma. However, endoscopic findings in those reporting reflux seem to be noted less frequently than expected, suggesting there may be a functional component. Individuals may also develop Mallory-Weiss tears and/or esophageal rupture due to recurrent vomiting. A trial of H2 antagonists and/or proton pump inhibitors along with cessation of purging is the recommended treatment of acid reflux with consideration of an upper endoscopy.

Those engaging in abuse of stimulant laxatives may be at risk for cathartic colon syndrome. Although speculative as to whether this condition develops with currently available stimulant laxatives, this condition is likely due to damage to the gut nerve plexus, creating a colon that is incapable of peristalsis and the propagation of fecal material. It is recommended that stimulant laxatives be discontinued for this reason. A harmless black discoloration of the colon, known as melanosis coli, can also develop with chronic laxative abuse.

HEPATIC

Abnormal liver function tests (aspartate aminotransferase/alanine aminotransferase [AST/ALT]) are a frequent manifestation of both starvation and refeeding in those with eating disorders. Starvation hepatitis is increasingly common with greater weight loss, normalizes with weight restoration, and is not usually associated with elevated bilirubin or alkaline phosphatase. It is thought to be due to autophagy. Abnormal elevations in the AST/ALT can also develop as a result of refeeding, causing steatotic changes. Treatment of refeeding hepatitis can require a decrease in the daily caloric intake and/or carbohydrate intake to improve the inflammatory changes. Ultrasound can differentiate these 2 conditions if diagnosis is in question, with normal findings in starvation but with echogenic changes in refeeding.

HEMATOLOGIC/IMMUNOLOGIC

Abnormalities in the complete blood count of patients with AN are commonly seen and may mimic other severe hematological diseases. Anemia, leukopenia, neutropenia, and, occasionally, thrombocytopenia can be seen, with a certain subset of patients having deficiencies in all 3 cell lines as weight loss becomes more severe. The
incidence of anemia, leukopenia, neutropenia, and thrombocytopenia has been studied in a community sample of both outpatient adolescents and severely ill adult patients. Age was inversely related to these changes, with younger patients having a higher proportion of cytopenias. Rates of leukopenia ranged from being present in 22% to 79% of patients and anemia in 22% to 83%, and thrombocytopenia was the least frequent. In the sickest population, pancytopenia was found in 23% of patients. The most notable determinants of severity of these cytopenias were related to age and body mass index (BMI), with younger populations and lower BMI individuals having the highest incidence. Interestingly, none of these abnormalities seemed to be due to a deficiency in iron, vitamin B12, or folate, and the investigators recommended not routinely testing for these deficiencies. The purported mechanism of diminished cell production likely involves decreased bone marrow cellularity and gelatinous marrow transformation. In addition, despite a marked reduction in the white blood cell count, most studies do not show an increase in infection risk in this population. These changes improve with weight restoration and improvement in nutrition, making the use of growth factors unnecessary. Thus, complete blood counts should be monitored when evaluating a patient with AN, and the severity of the counts may give an indication of the severity of the disease, but do not typically require any special precautions or treatments.

NEUROMUSCULOSKELETAL

Patients with AN develop significant muscular weakness and deconditioning, at least partially because of a proximal myopathy with type 2 muscle fiber atrophy that improves with weight restoration. Neurologic changes in AN include diffuse atrophy of gray and white matter. These neurologic changes are associated with various deficits on neuropsychological testing that are also found in BN, worsening with greater levels of malnutrition. Although the brain atrophy appears to mostly normalize with weight restoration, the cognitive deficits do not necessarily normalize with weight restoration. It is unclear if these persisting deficits are trait characteristics of the illness, perhaps contributing to development of the eating disorder, or if they are irreversible neurologic deficits developing secondary to the malnutrition.

ENDOCRINE

Multiple endocrine dysregulations develop in those with eating disorders, likely as physiologic adaptive mechanisms in response to the extreme starvation. Hypoglycemia is frequently observed because of depleted glycogen stores and lack of substrates for gluconeogenesis, with increased frequency as severity of malnutrition increases. Hypoglycemia is a common cause of sudden death in AN. The hypothalamic-pituitary-thyroid (HPT) axis is dysregulated in AN with low T3, low T4, and normal thyrotropin. Although a similar pattern is found in malnutrition, weight loss is unlikely the sole cause for these findings given a dysregulated HPT axis is also found in normal weight individuals with BN. Reduced estrogens and androgens are often found in this population as a result of decreased and dysregulated gonadotropin-releasing hormone pulsatility and a reversion to a prepubertal state, contributing to hypothalamic amenorrhea. This dysregulated gonadal axis is a result of leptin deficiency that is found in both AN and BN. The hypothalamic-pituitary-adrenal axis is dysregulated as well with the finding of increased cortisol levels. This hypercortisolemia increases gluconeogenesis and provides nutrients vital to organ function but may also contribute to a centripetal fat distribution during refeeding, mood-related symptoms, an increased risk of gastric ulcer, and
an increased risk of osteoporosis. Growth hormone resistance is also a common finding in AN, contributing to decreased insulinlike growth factor 1 levels and further contributing to the low-bone-mineral density frequently found in this population. Growth hormone resistance may partially develop as a consequence of the lipolytic effects of this hormone. These dysregulated hormonal pathways tend to normalize with weight restoration, with the possible exception of bone disease. In addition, fertility is generally restored after recovery from the eating disorder, although active AN can predispose to an increased risk for unplanned pregnancy due to ovulation in the absence of menses. An active eating disorder may also lead to negative birth outcomes, including an increased risk of small-for-gestational-age births and an increased risk of miscarriages. In addition, to the decreased leptin levels, other changes in appetite-regulating hormones, including increased ghrelin, peptide YY, and relatively increased adiponectin, have all been described in AN.

Low bone density, defined as a z score less than $-1$ for the diagnosis of osteopenia and less than $-2.5$ defined as osteoporosis, is common in patients with AN and can be very detrimental to patients long after they recover. This bone disease is thought to be related to several disruptions in the hypothalamic-hypogonadal axis. Because of the patient’s inadequate calorie intake, nonessential functions of the body begin to be suppressed or even shut down. Patients with anorexia have significant reductions in serum levels of estrogen and progesterone. Reduced sex hormones contribute to a decrease of bone formation and an increase in bone resorption, leading to the state of reduced bone density. This state of uncoupling is responsible for the severity of bone disease, notwithstanding the often young age of these patients. Misra and colleagues found, in a cohort of 60 adolescent outpatients with AN, that 41% of the patients had osteopenia and osteoporosis. Other studies show as high as an 85% incidence of low bone density as defined by a z score of less than $-1$. Duration of illness, age, and nadir BMI have been shown to be a significant factor in the severity of bone disease. In addition, these lower bone densities lead to a higher long-term incidence of fractures. Many of these patients, in addition to restriction, turn to compulsive exercise as a manifestation of anxiety or method of caloric burning. As opposed to postmenopausal women wherein exercise is beneficial for improving bone density, exercise in these patients is detrimental to bone mineral density. Treatment should be focused on weight restoration because studies have shown that weight restoration will lead to improvement in bone mineral density. Other medications, such as bisphosphonates, teriparatide, and others, have been used, but no definite guidelines currently exist. There are, however, randomized controlled trials that support the judicious use of bisphosphonates, teriparatide, and transdermal estrogen in patients with AN. Although transdermal estrogen has been shown to be effective, oral contraceptives (OCPs) and oral estrogen replacement have not been found to be effective, and furthermore, the withdrawal bleed from OCPs can lead to a false sense of recovery in patients.

**RENAL AND ELECTROLYTES**

Recurrent purging with secondary development of hypokalemia can predispose to hypokalemic nephropathy in AN-BP and BN. The true incidence of this condition in those engaging in purging is unknown, but when it occurs, it can result in end-stage renal disease and the need for hemodialysis. Individuals with AN-BP and BN who engage in frequent purging often develop electrolyte abnormalities along with excessive weight gain after the abrupt cessation of the excessive purging behavior. This condition, known as pseudo-Bartter syndrome,
tends to develop because of sustained increases in release of aldosterone as a result of chronic intravascular depletion, to reduce the risk of syncope, which in turn leads to sodium and water retention along with metabolic alkalosis and hypokalemia. Pseudo-Bartter syndrome should be treated with gentle fluid resuscitation and early initiation of an aldosterone antagonist, such as spironolactone. Hypophosphatemia during refeeding is one of the most dangerous complications that can develop in AN. Increased weight loss is one of the strongest predictors for development of hypophosphatemia, due to depleted total body phosphorous and further shifting of phosphorous intracellularly with refeeding. Phosphorous should be carefully monitored during refeeding and corrected with oral and, in more severe cases, intravenous supplementation.

Of note, electrolytes are usually normal in those primarily restricting food intake, but hypokalemia and metabolic alkalosis with the potential for acid-base disturbances are a frequent manifestation in BN and AN-BP. Hyponatremia is occasionally seen in patients with AN, most often because of diminished ability for free water clearance from an abnormal solute load in the urine. Hypovolemia can also be an additional cause for development of hyponatremia. Syndrome of inappropriate antidiuretic hormone does not appear to be a common cause of hyponatremia in this population. Less commonly, hypernatremia can also occur as the result of diminished fluid intake or neurogenic diabetes insipidus.

SUMMARY

In summary, the medical complications of AN are generally due to malnutrition and weight loss and their associated physiologic compensations. The complications of purging are due to the frequency and mode of these behaviors. Most medical comorbidities in eating disorders are effectively treated with nutritional rehabilitation and weight restoration, along with cessation of the purging behaviors.

REFERENCES

