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REVIEW

Medical complications of anorexia nervosa and their treatments: an update on some critical aspects

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Abstract Anorexia nervosa has the highest mortality rate of any psychiatric disorder. Many of the deaths are attributable to medical complications which arise as the malnutrition and weight loss worsens. Every body system may be adversely affected by anorexia nervosa. Yet, remarkably, most of the medical complications of anorexia nervosa are treatable and reversible with optimal medical care, as part of a multidisciplinary team who are often involved in the care of these patients. Herein, we will describe the medical complications of anorexia nervosa and their treatments.

Keywords Anorexia nervosa · Medical complications · Body systems · Cardiac · Osteoporosis

Introduction

Anorexia nervosa is associated with many different medical complications which increase in incidence and severity as weight loss becomes more pronounced. These complications are a direct result of weight loss and malnutrition. Almost every body system can be adversely affected by anorexia nervosa, some of which even have permanent adverse effects even if there is a successful program of nutritional rehabilitation and weight restoration. Anorexia nervosa has the highest mortality rate of any psychiatric disorder, many times higher than that seen in aged-matched controls. Recent studies have demonstrated that the standard mortality rate for patients with anorexia nervosa approaches 12 times those of age-matched controls [1, 2]. Thus, given the typically young age of people afflicted with anorexia nervosa, it is critical to understand these complications and their treatments to help the primary treatment team achieve a successful outcome. Herein, we provide a thorough review of the different body systems adversely affected by anorexia nervosa and their treatments.

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Bone

One of the most concerning complications of anorexia nervosa is that of bone mineral density loss. This is both because the rapidity of its development and the fact that the reduction in bone density may be permanent [3]. Patients with anorexia nervosa very commonly have impaired bone structure and reduced bone strength, termed osteopenia if the loss is moderate, and osteoporosis if it is severe. In fact, according to a recent study, 85 % of women with a diagnosis of anorexia nervosa also have osteoporosis or osteopenia [4]. Furthermore, a study of 310 women with anorexia nervosa and 108 normal controls showed a lifetime fracture prevalence as being 59.8 % higher in those with anorexia nervosa as compared to controls [5]. This also applies to adolescents with anorexia nervosa in that they have an increased risk of long=term future fragility fractures [6].

One group of researchers set out to study patters of bone loss among patients with anorexia nervosa as compared to post-menopausal women. The most concerning finding was that the bone inner structure in anorexia nervosa was

degraded to a similar extent as in menopause [7]. Individuals who develop anorexia nervosa during adolescence are of especially great concern as normal bone accrual typically continues through the mid-20s and is thus interrupted by the disease. Adolescents with anorexia nervosa may never reach normal peak bone mass as they typically begin to lose bone before ever reaching optimal bone density and structure.

Another study in anorexia nervosa set out to determine whether age of onset of anorexia nervosa correlated with decreased bone density. Interestingly, adult anorexia nervosa patients with the onset of their amenorrhea before age 18 had significantly lower spinal bone density than those developing amenorrhea later, independent of duration of amenorrhea [8]. This highlights the importance of early diagnosis and intervention among adolescents with anorexia nervosa and decreased bone mineral density, and the basis for the widely accepted practice of obtaining a DEXA scan after 9–12 months of the disease or amenorrhea and every 2 years thereafter while the DEXA scans are abnormal.

The pathogenesis of osteoporosis among patients with anorexia nervosa differs from the disease process in postmenopausal women. In the latter, it is only due to increased bone resorption, but in anorexia nervosa it is also due to decreased bone formation. Interestingly, predictors of bone mineral density loss vary by anatomical location with the spine more affected than cortical bone sites. Duration of amenorrhea was again the only factor associated with decreased lumbar spine bone mineral density, and lower IGF-1 levels were the only significant independent predictors for decreased hip bone density [9]. One study utilized MRI to evaluate differences in bone morphology in women with anorexia nervosa as compared to age-matched controls. Anorexia nervosa subjects had higher marrow fat content which correlated inversely with less bone mineral density [10].

Males with anorexia nervosa are also at great risk for osteopenia and osteoporosis [11]. Lowest body mass index (BMI) and illness duration predict lumbar *Z*-scores [12]. In a prospective study of hypogonadal men with anorexia nervosa, low testosterone levels correlated directly with degree of bone mineral density loss, and testosterone replacement was effective in normalizing bone mineral density over time [13].

While the best way to prevent osteoporosis in anorexia nervosa is with weight restoration and resumption of menses, more commonly the focus is what to do once it is present. Adequate vitamin D (levels >50 mmol/L) and calcium intake (1200 mg) are needed for bone health, but by themselves are not likely to improve bone mineral density in patients with anorexia nervosa [14, 15]. Bisphosphonates have been shown to be effective in patients with anorexia nervosa who have osteoporosis, but need to be used judiciously given their known adverse side effects [16]. Very recently, the first study on the use of teriparatide for the osteoporosis of anorexia nervosa was published and demonstrated favorable effects to improve bone mineral density [17]. There are a few randomized controlled studies which demonstrate that oral estrogen–progesterone combinations are not effective in the osteoporosis of anorexia nervosa [18]. However, recent data indicate that transdermal estrogen may increase bone density especially in adolescents with anorexia nervosa and loss of bone density [19]. There are not as yet any studies on the potential efficacy of romosozumab in anorexia nervosa [20]. After treatment is initiated, it is reasonable to recheck a DEXA scan in 2 years to reassess their bone density, because the cost and consequence of noncompliance with therapy and with ongoing osteoporosis is substantial due to lifetime fracture risk and health-care utilization [21].

Hematologic

Hematologic abnormalities are quite common among patients with anorexia nervosa and may affect all three cell lines (white cell, red cells and platelets). A cross-sectional study of women with anorexia nervosa with a mean BMI of 16.8 kg/m^2 revealed anemia in 38.6 %, leukopenia in 34.4 % and thrombocytopenia in 5 %. Leukopenia was significantly correlated with a lower percent of ideal body weight [22]. Another retrospective study analyzed men and women with severe anorexia nervosa admitted to an inpatient medical unit with a mean BMI of 12.2 kg/m^2. Among these inpatients, 83 % had anemia, 79 % had leukopenia and 25 % had thrombocytopenia. Seventeen percent developed thrombocytosis during refeeding [23].

The most commonly cited cause of pancytopenia among severely malnourished patients is gelatinous marrow transformation. Histopathologically, marrow with gelatinous transformation includes features such as hypoplasia, fat atrophy and gelatinous infiltration [24]. As fat stores are used up by catabolism, the adipose tissue collapses and is replaced by gelatinous marrow [24]. This finding is seen in patients with protein catabolic conditions and severe malnutrition, including patients with eating disorders, acquired immune deficiency syndrome, alcoholism, malignancies and congestive heart failure. Treatment generally involves restoration of weight and proper nutrition which leads to normalization of blood counts over the ensuing weeks to months [25–27]. Several case studies of patients with anorexia nervosa have demonstrated gelatinous transformation of marrow on bone marrow biopsy [28, 29]. It is not standard of care to utilize hematopoietic growth factors (darbepoetin and pegfilgrastim), as they are unnecessary

since nutritional rehabilitation will suffice to restore normal bone marrow.

Anemia among patients with anorexia nervosa is typically normocytic and not often associated with iron deficiency. A cross-sectional study of 12 patients admitted to an adolescent inpatient unit with a mean BMI of 14.8 kg/m^2 revealed 75 % developed anemia during their hospitalization and only one patient had a low serum iron level [30]. Another study reported 6 % of the anemias being due to iron deficiency [23].

Liver dysfunction has been suggested as a cause for thrombocytopenia among patients with anorexia nervosa in two case reports [31, 32]. Deficiency of thrombopoietin (which is generated in the liver and regulates platelet production) has been suggested as the specific underlying cause of thrombocytopenia in anorexia nervosa.

Neurologic

Starvation and nutrient deficiency among patients with anorexia nervosa may have deleterious effects on the central nervous system. Case reports speak on the development of Wernicke–Korsakoff syndrome due to thiamine deficiency in the setting of anorexia nervosa [33, 34]. Wernicke's encephalopathy is characterized by the triad of ataxia, global confusion and ophthalmoplegia. Without thiamine supplementation, Wernicke's encephalopathy, which is reversible, may progress to Korsakoff syndrome which is characterized by amnesia and confabulations. Thus, it is critical to prescribe 7–10 days of thiamine supplementation to patients with anorexia nervosa as they begin to refeed.

There exists a large amount of concern over the potential for patients with anorexia nervosa to sustain alterations in brain structure along with long-term cognitive deficits. One study examined decision-making deficits in 22 patients with anorexia nervosa (before (average BMI 15.78 kg/m^2) and after weight restoration to a BMI $>$18.5 kg/m^2) as compared to controls. Decreased volume in the left orbitofrontal cortex, which is involved in decision-making and the processing of rewards and punishments, and lower BMIs were associated with worse performance among patients with anorexia nervosa [35].

Another study used MRI to evaluate differences in brain structure in patients with anorexia nervosa. Those affected had significantly lower whole-brain volume, significantly higher volume of cerebrospinal fluid and significantly lower gray matter volume. There was also a negative correlation between duration of illness and gray matter volume [36]. Similarly, there is evidence of focal gray matter atrophy in the cerebellum of patients with anorexia nervosa, which is correlated with disease duration [37].

With clear evidence that anorexia nervosa-related malnutrition causes anatomical changes in the brain, the question of reversibility remains critically important especially given the young age of onset of many cases of anorexia nervosa. A study of 40 women with greater than 1 year of recovery from anorexia nervosa, who underwent an MRI, showed no significant differences in cerebrospinal fluid volume, or gray or white matter volume compared to controls [38]. Another study contrasts these findings. After weight restoration, results revealed a significant increase in gray matter among patients with anorexia nervosa; however, the anorexia nervosa group still had, on average, significantly less gray matter than controls. In addition, the degree of gray matter loss negatively correlated with duration of illness [39]. Thus, the definitive message about permanent neurocognitive deficits after a bout of anorexia nervosa is not currently known. However, emerging evidence is raising, anew, concern that anorexia nervosa may adversely affect long-term cognitive acumen.

Gastrointestinal

As a result of weight loss and malnutrition, especially as the BMI falls to the low teens, patients with anorexia nervosa may develop dysphagia [40]. This is as a result of weakness of pharyngeal muscles and uncoordinated patterns of swallowing. As a consequence they may complain of coughing with eating and have a history of aspiration pneumonia. This improves with weight restoration of stimulation techniques.

A substantial portion of these patients will have delayed gastric emptying due to gastroparesis. There is no known exact BMI below which this occurs, but it clearly worsens with more severe degrees of anorexia nervosa. Patients complain of early satiety, left upper abdominal fullness and nausea. Low-dose metoclopramide is very effective when given 30 min before meals to alleviate these symptoms. Small particle-sized feeds may be of benefit early in the course of refeeding to mitigate this issue [41, 42]. The gastroparesis is not permanent and will resolve with ongoing weight gain.

Somewhat related is the entity known as acute gastric dilation [43]. This is an idiopathic complication which is rarely seen in those patients who have more severe degrees of anorexia nervosa, but needs to be considered in the evolution of the complaint of severe upper abdominal pain and distention in the early phases of refeeding due to the risk of undiagnosed gastric perforation. A plain abdominal radiograph will demonstrate the gastric dilation, and the treatment involves a brief course of nasogastric suction and then assumption of caloric intake utilizing liquid food sources for a few days.

Also, a complaint of the more severe cases of anorexia nervosa is the superior mesenteric artery (SMA) syndrome. It develops as a result of weight loss and atrophy of a fat pad which normally cushions the angle between the aorta and the SMA. As a result of the loss of this fat pad, the SMA compresses the luminal diameter of the duodenum and causes a mechanical small bowel obstruction and the attendant symptoms of nausea, vomiting, early satiety and abdominal pain. Diagnosis is made by computer tomography (CT) scan. Once again, treatment involves altering the caloric sources to a softer more liquid consistency, smaller more frequent meals and ongoing weight gain. Surgery is rarely, if ever, indicated in the SMA syndrome of anorexia nervosa.

Just as there is slowing of gastric emptying, there is also reflex hypofunctioning of the colon due to lack of oral intake in anorexia nervosa. Therefore, it is not uncommon for these patients to complain constipation as they begin to refeed. This is reversible over time and easily treated with an osmotic laxative given on a daily basis.

There are also hepatic changes which occur in anorexia nervosa. Hepatic transaminase levels (AST–ALT) are frequently elevated, especially with more severe degrees of weight loss [44]. This is referred to as hepatic apoptosis or autophagy. Generally, it is solely due to starvation and normalizes with nutritional rehabilitation. Less commonly, these enzymes rise to abnormal levels with refeeding which can be due to deposition of carbohydrates and fat in the liver, referred to as hepatic steatosis. If needed, a liver ultrasound can easily differentiate if it is apoptosis or steatosis, since the treatment in the former is ongoing caloric restoration, whereas in the latter it is to reduce the carbohydrate content of the diet [45].

Cardiac

For years, it has been known that the extreme weight loss of anorexia nervosa adversely affects the heart and causes shrinkage of the cardiac myofibrils and reduces exercise capacity. Indeed, as mentioned earlier, anorexia nervosa has a very high mortality rate, in part due to sudden cardiac death in this population. There are a number of cardiac issues in anorexia nervosa involving hemodynamics, myocardial structure and arrhythmias. In general, patients with anorexia nervosa are known to be bradycardic, and sinus bradycardia at rest is the most common cardiac rhythm found in these patients. Thus, a "normal" heart of 80 beats per minute may be a harbinger of impending instability in more severe cases of anorexia nervosa [46]. In addition, these patients are typically hypotensive with systolic blood pressures less than 90 mmHg. These vital sign changes are due to the increased vagal tone which is seen as anorexia nervosa becomes more severe and may represent an adaptive mechanism to conserve energy in the face of caloric deprivation [47]. While there are no studies which have definitively demonstrated below what heart rate these patients should be hospitalized, consensus seems to be a cardiac rhythm other than sinus or a heart rate below 40 beats per minute [48]. Bradycardia, hypotension and orthostasis all seem to resolve with weight restoration and without other specific treatment [49].

Structurally as would be expected, there is a decrease in left ventricular mass and cardiac mass with a concomitant decrease in cardiac output, reduced exercise capacity and fatigue [50]. Mitral valve prolapse, which may present with chest pain or palpitations [51], occurs in about one-quarter of these patients and resolves again with weight restoration. Increasingly, pericardial effusions have been noted in this population [52]. They are generally asymptomatic and again resolve with weight restoration. While there is no evidence of obstructive coronary artery in anorexia nervosa [53], recently cardiac fibrosis has been noted on cardiac MRI [54].

With regard to cardiac conduction system abnormalities in anorexia nervosa, QT prolongation has garnered much discussion as a putative cause for sudden cardiac death in anorexia nervosa. Currently, most evidence does not support that the QT interval is prolonged in anorexia nervosa as an inherent complication of anorexia nervosa. Rather, when present, there is a need to look for secondary causes beyond the anorexia nervosa itself [55]. In contrast, increased QT dispersion may be a new link between QT interval abnormalities and sudden death in anorexia nervosa [56]. This interlead variability in the QT interval may be a marker of ventricular irritability and a propensity toward Torsades de pointes. Or, decreased heart rate variability in anorexia nervosa may also be a marker of an abnormal heart muscle and the basis for the less than ideal cardiac prognosis in anorexia nervosa [57].

Pulmonary

Overall, the lungs seem to be fairly immune to the harms from anorexia nervosa. However, there are a few possible issues to be aware of. Spontaneous pneumothorax occurs in anorexia nervosa, possibly as a result of a defect in surfactant production. When it does occur, it can be difficult to keep the lung reexpanded [58]. There also appear to be changes in pulmonary function which are analogous to those seen in emphysema, but the etiology is not yet defined [59].

Endocrine

Finally, there are many endocrine-related medical complications found in patients with anorexia nervosa [60]. Overall, there is a reversion, soon after diagnosis and with ongoing weight loss, to a prepubertal state in which pituitary hypogonadism becomes evident with low LH and FSH levels. As a result, male and female patients with anorexia nervosa often have low serum testosterone and estrogen levels and impairments of fertility and sexual functioning [61, 62]. Euthyroid sick syndrome is also present and thus thyroxine (T_4) levels are found to be low. Cortisol levels are high in anorexia nervosa either due to increased production or decreased renal clearance, but its significance is unknown [63]. Leptin levels are low in anorexia nervosa [64], which may in part cause amenorrhea. Hypoglycemia is a poor prognostic sign in anorexia nervosa and is indicative of more advanced disease with depletion of hepatic gluconeogenic substrate. Plasma glucose levels <50 mg/dL should prompt increased vigilance and may speak of the need for hospitalization [65].

Conclusion

In summary, anorexia nervosa is associated with a litany of medical complications. Most of them are reversible with weight restoration via nutritional rehabilitation. The earlier they are diagnosed and treated, the better are the long-term chances of full recovery.

Compliance with ethical standards

Conflict of interest Dr. Philip S. Mehler and Dr. Carrie Brown declare that they have no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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