Medical complications of anorexia nervosa and bulimia nervosa

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Purpose of review

This review focuses on recent publications concerning medical complications in patients with eating disorders, including anorexia nervosa and bulimia nervosa.

Recent findings

Recent literature continues to reflect that multiple organ systems are frequently affected by eating disorders. The literature underscores the frequently cited risk of premature death in those with anorexia nervosa. A plethora of dermatologic changes have been described, some signaling serious underlying pathophysiology, such as purpura, which indicates a bleeding diathesis. Much of the literature continues to delineate the fact that diabetic patients with eating disorders are at high risk of developing diabetic complications. Gastrointestinal complications can be serious, including gastric dilatation and severe liver dysfunction. Acrocyanosis is common, and patients with anorexia nervosa are at risk of various arrhythmias. Low-weight patients are at high risk for osteopenia/osteoporosis. Nutritional abnormalities are also common, including sodium depletion and hypovolemia, hypophosphatemia and hypomagnesemia. Resting energy expenditure, although very low in low-weight patients, increases dramatically early in refeeding.

Summary

Medical complications are common and often serious in patients with eating disorders, particularly those with anorexia nervosa.

Keywords

anorexia nervosa, bulimia nervosa, diabetes, medical complications, premature death

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Abbreviations

ABA	activity-based anorexia
BMDz score	bone mineral density *z* score
BMI	body mass index
FFM	fat-free mass
REE	resting energy expenditure

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Introduction

Eating disorders are known to result in a variety of potentially serious medical complications. These are usually most severe in patients with anorexia nervosa because of the complications attendant to starvation but many can also be seen in patients with bulimia nervosa, mainly attributed to the purging behaviors in which these patients engage, including self-induced vomiting and laxative abuse [1]. The purpose of this article is to review recent literature on the medical complications encountered in these patients.

Mortality

Although most studies have found substantially increased standardized mortality ratios for eating disorders [2], a recent report by Korndorfer *et al.* [3] from Olmstead County in Minnesota did not find this increase, a finding that has been of considerable debate in the literature [4]. A recent brief paper by Birmingham *et al.* [5••], however, includes a succinct overview of this literature, finding that standardized mortality ratios have varied anywhere from 0.71 to 17.8, and adding data finding a standardized mortality ratio of 10.5 (95% confidence interval = 5.5–15.5), again suggesting a markedly exaggerated risk of premature death in patients with anorexia nervosa.

Skin

An excellent review of the dermatologic signs seen in patients with eating disorders has recently been published by Strumia [6••]. This interesting review documents that a variety of dermatologic abnormalities can be seen in patients with eating disorders including xerosis (dry, scaly skin), lanugo-like body hair (fine, downy dark hair on the back, abdomen, and forearms), telogen effluvium (hair loss and a positive 'hair pull test'), acne, carotenoderma (carotene deposition in the tissues and yellowing of the skin because of excess ingestion of carotenoid-rich vegetables), acrocyanosis (circulatory changes resulting in cold, blue, and occasionally sweaty hands or feet), pruritis, purpura (caused by thrombocytopenia), stomatitis, and nail dystrophy. Patients with anorexia nervosa and bulimia nervosa who self-induce vomiting may also demonstrate Russell's sign (the presence of scar/callus formation over the dorsal surface of the hand, as the hand is used to stimulate the gag reflex to induce vomiting).

Endocrine

There has been an ongoing debate in the literature as to whether eating disorders are more common than would be expected by chance in girls and young women with

type 1 diabetes. Some reports have found higher than expected prevalences and others have not. Mannucci *et al.* [7••] recently reported a meta-analysis of the controlled trials on the prevalence of eating disorders in patients with type 1 diabetes, which included in total 748 controls and 1587 women with type 1 diabetes. They did not find that the prevalence of anorexia nervosa, using either Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM III-R) or DSM-IV criteria, was higher among type 1 diabetic patients. They, however, did find an increased prevalence of bulimia nervosa and an increased prevalence of the combined disorders among type 1 diabetic patients. Treatment issues regarding diabetic patients with eating disorders were also recently reviewed [8].

Recently several papers have examined the personality, temperament, and character in type 1 diabetic patients with eating disorders. Pollock-BarZiv and Davis [9] studied 51 women with type 1 diabetes intensively using interviews and self-report questionnaires. Fourteen of the patients appeared to show significant eating disorder symptoms. Weight preoccupation was associated with the presence of an eating disorder, and borderline personality characteristics were related to withholding insulin as purging mechanism and poor glycemic control. Grylli *et al.* [10] screened a sample of 199 adolescents with type 1 diabetes for eating disorders, finding that those with either full syndromal or subthreshhold eating disorders had higher mean scores on a measure of harm avoidance and lower scores on self-directedness. Peveler *et al.* [11••] performed a very interesting study in which 87 patients who had been interviewed at baseline (age 11–25 years) were recontacted and 63 (72%) were reinterviewed 8–12 years later (age 20–38 years) using the Eating Disorder Examination. Thirteen individuals met criteria at either baseline or follow-up for an eating disorder and seven evidenced significant eating disorder psychopathology. Thirty-one (35.6%) misused insulin for weight control purposes, and there was a strikingly significant relationship between disordered eating habits, insulin misuse, and the risk of developing microvascular complications. Grylli *et al.* [12•] also reported that adolescents with type 1 diabetes and disordered eating behavior also reported poorer physical and psychosocial quality of life than type 1 diabetic adolescents without disordered eating. These studies add to a growing body of literature that suggests that whether or not eating disorders are more prevalent in patients with type 1 diabetes, clearly the presence of an eating disorder markedly worsens the likelihood of an untoward outcome and impaired quality of life for patients with type 1 diabetes.

Gastrointestinal complications

Several case reports of gastric dilatation recently appeared in the literature. Lunca *et al.* [13] reported the case of a 22-year-old borderline mentally retarded man who experienced massive gastric dilatation with evidence of mucosal necrosis after binge eating. Lo *et al.* [14] also reported massive gastric dilatation and necrosis in a 26-year-old woman with a diagnosis of anorexia nervosa, and Barada *et al.* [15] reported acute gastric dilatation in a young woman. All three of these cases were managed conservatively with decompression and did well.

Other gastrointestinal problems are frequently seen in these patients. In a study by Winstead and Willard [16], 13 patients at an inpatient eating disorders unit were interviewed on their gastrointestinal histories. Eight (62%) had previously seen a gastroenterologist or primary care physician for gastrointestinal complaints and of these, six (46%) had sought treatment for these gastrointestinal complaints before ever seeking treatment for their eating disorder. Five (38%) had undergone an endoscopy, an upper gastrointestinal barium contrast radiograph, or a lower gastrointestinal barium contrast radiograph. This suggests that family physicians, internists, and gastroenterologists should have a high index of suspicion about the possible presence of an eating disorder among young women who present with gastrointestinal complaints.

Chial *et al.* [17] reviewed the manifestations and management of anorexia nervosa from the perspective of a gastroenterologist. Following an overview of the diagnosis, comorbidity, and multiple organ system dysfunction, the gastrointestinal manifestations were reviewed in detail. These included delayed gastric emptying, gastric motor dysfunction, an impaired sense of hunger and satiety, delayed small bowel transit time, and constipation, as well as case reports of gastric dilatation, spontaneous rupture of the stomach, pancreatitis, necrotizing colitis, and perforated ulcer. The paper also provides an overview of refeeding, and treatment in general.

Gendall *et al.* [18••] examined childhood gastrointestinal complaints in women with bulimia nervosa. One hundred and thirty-five women with bulimia nervosa were assessed regarding various gastrointestinal problems. One-third of the participants reported gastrointestinal complaints or constipation in childhood. Women with gastrointestinal complaints tended to be younger, to have an earlier onset of bulimia nervosa, and to have an earlier onset of self-induced vomiting, compared with women without gastrointestinal complaints. Other interesting recent reports underscore other possible gastrointestinal problems including parotid gland swelling [19], gastritis [20], acute liver damage [21], and dental complications [22].

Cardiovascular/pulmonary complications

Cardiovascular and pulmonary complications have been well recognized in patients with eating disorders and

include the risk for arrhythmias, acrocyanosis, as noted above, and pneumomediastinum [1]. Acrocyanosis was recently studied by Klein-Weigel *et al.* [23]. Using photoplethysmographic sonography of the brachial artery and capillary microscopy in symptomatic patients, they demonstrated typical microvascular features of acrocyanosis including dilated efferent capillary loops and venoles and reduced capillary flow velocities. Roche *et al.* [24••] studied abnormalities of the QT interval in patients with anorexia nervosa before and after refeeding, finding that the QT/RR slope was significantly enhanced in patients with anorexia nervosa, probably reflecting autonomic imbalance, and that this was reversible after refeeding. They stressed the potential clinical importance of this as the enhanced QT/RR slope has also been demonstrated in patients with life-threatening ventricular arrhythmia. Krantz and Mehler [25] reported a case of anorexia nervosa characterized by tachycardia in which the patient was found to have indolent lower left extremity cellulites. As bradycardia is usually seen in these patients, this case was meant to alert clinicians to the fact that tachycardia should prompt a search for other potentially life-endangering conditions. Ohwada *et al.* [26] reported evidence of ampulla cardiomyopathy, which is characterized by extensive akinesis of the apical region with hypercontraction of the basal segment of the ventricle, in three young women with anorexia nervosa, all of whom had experienced a hypoglycemic coma. Sundararaghavan *et al.* [27] reported an interesting case of the acute onset of chest pain, which was evaluated in the emergency room and found to be secondary to a spontaneous pneumomediastinum in a patient with anorexia nervosa.

Skeletal system

Several recent studies have examined the issue of the skeletal complications associated with eating disorders, particularly anorexia nervosa. These are well recognized complications [28], but many gaps remain in our knowledge of the causes, course, and effective treatments for these. A recent report by Misra *et al.* [29] reinforces the high frequency with which such complications occur. These investigators examined 60 individuals presenting with anorexia nervosa and compared them with 58 normal controls. Bone mineral density was measured and the results show z scores less than or equal to -1 in 41% of the individuals with anorexia nervosa, and less than or equal to -2 in 11% of the anorexia nervosa sample. This was in contrast with the control sample in which bone mineral density z (BMDz) scores less than or equal to -1 were found in 23% (for BMDz < -2, 2.0%). In this study, body mass index (BMI), amount of lean body mass, and age at menarche were all predictors of diminished bone mineral density.

Another study also recently examined the question of predictors of bone mineral density, with the interesting findings that may have substantial importance for our approach to treating anorexia nervosa and its psychiatric comorbidities. In this study, Konstantynowicz *et al.* [30••] examined bone mineral density in 14 women with anorexia nervosa plus comorbid major depression and 31 women with anorexia nervosa but no major depression. BMDz scores were lower (i.e., worse) in individuals with anorexia nervosa and comorbid depression as compared with those without (-2.6 vs. -1.7), and this difference was both statistically and clinically significant. In addition, overall level of depression symptoms was inversely correlated with total body bone mineral density, as well as bone mineral density measured at the lumbar spine. These correlations were fairly high ($r = -0.4$ for total body and $r = -0.6$ for lumbar spine).

Finally, there remain no clearly identified effective treatments for diminished bone mineral density in anorexia nervosa, and there is evidence to suggest that weight restoration alone is not sufficient [31]. A recent study compared alendronate with placebo, given in conjunction with calcium and vitamin D for 1 year [32•]. In this study, alendronate treatment was associated with substantial improvements in femoral neck and lumbar spine bone mineral density, whereas placebo treatment was not. As in other studies, low body weight at intake into the study predicted lower bone mineral density at follow-up.

Leptin

Leptin is a hormone secreted by fat cells, which appears to have important roles in the regulation of body intake and body weight. It may be particularly important in food deprivation [33•] and thus may be important in understanding anorexia nervosa.

Recent work using a commonly employed animal model of anorexia nervosa has helped to expand our understanding of the way in which leptin might work in individuals with anorexia nervosa [34]. This study examined rats with activity-based anorexia (ABA) that developed a combination of physical hyperactivity plus food refusal. Previous work has suggested that leptin administration reduces the degree of semistarvation-induced hyperactivity seen in this animal model [35]. This study compared rats with ABA with those allowed to exercise ad-lib and with rats that were sedentary. All three groups received intracerebral ventricular leptin. In ABA rats, decreased running-wheel activity, diminished food intake, and increased temperature were seen. No changes in activity were seen in the ad-lib or sedentary groups, with only minimal changes in temperature, but food intake was decreased. This complex set of findings (diminished hyperactivity in ABA rats but also diminished food intake) may serve to temper enthusiasm about leptin as a treatment for anorexia nervosa.

Another study has attempted to examine the question of leptin function in humans with anorexia nervosa [36]. This study examined 23 women with anorexia nervosa and 21 controls, all adolescents, and involved frequent sampling of leptin, growth hormone, cortisol, and ghrelin. Detailed studies of leptin release showed lower amounts of pulsatile and total leptin release in anorexia nervosa, and fine-grained analysis showed that this was because of lower levels of basal and burst leptin release.

Nutritional issues

Historically, substantial attention has been paid to the nutritional aspects of anorexia nervosa and its treatment, and three recent reports helped to expand our knowledge in this area. First, Caregaro *et al.* [37•] published a recent report highlighting the importance of sodium depletion and hypovolemia and associated hemoconcentration in anorexia nervosa. They reported a sample of 14 individuals hospitalized for a mean of 24 days for anorexia nervosa treatment. Mean BMI at admission was 12.9, and at discharge, 14.2. Sixty-four percent of the sample had hypovolemia at intake laboratory assessment. In spite of this (or perhaps more accurately, because of this), hematologic measures, such as hematocrit, hemoglobin among others, were generally within the normal range at admission, but with adequate hydration, anemia became apparent in six out of the 14 individuals in this sample. The authors noted that such hemoconcentration due to hypovolemia may lead to falsely reassuring laboratory values when individuals present for eating disorders treatment.

Electrolyte disturbances have received attention in this area for long, but in the treatment of anorexia nervosa, hypophosphatemia has received the greatest emphasis. Birmingham *et al.* [38] reported a series of 50 individuals admitted for anorexia nervosa treatment; of these 50, 30 (60%) developed hypomagnesemia at some point during their hospitalization. Of note, only 16% of them had it at admission, whereas the others developed it during treatment, as late as 3 weeks into treatment. These results suggest the importance of continued monitoring of magnesium throughout the early and middle stages of treatment in order to detect the possible emergence of later in treatment hypomagnesemia.

Finally, a case report serves to emphasize the potential severity of nutritional deficiencies that can be encountered. This report described a 33-year-old woman with an eating disorder who had developed as a result of that vitamin A deficiency leading to corneal disease culminating in blindness [39].

Metabolism and body composition

A number of important clinical issues are encountered in the area of weight, energy expenditure, and refeeding. These include problems with understanding and estimating changes in body composition and energy expenditure, understanding marked changes in weight that can occur in treatment, and how to best monitor the changes in body compartments. Four recent papers have helped to illuminate further these areas. In the first of these, Van Wymelbeke *et al.* [40] followed resting energy expenditure (REE) at baseline and three points over the first 7 weeks of treatment in 87 women with anorexia nervosa. These investigators found that REE was substantially increased by day 8; the amount of this increase was substantially out of proportion to the change in fat-free mass (FFM) observed (13.4% change in REE vs. 1.8% change in FFM). Throughout the rest of the treatment, this marked disparity between changes in REE and FFM persisted.

Regional body composition and hormonal function are clearly linked, but the nature of this complex relationship has not been well understood. Misra *et al.* [41] examined a sample of 23 individuals with anorexia and 20 normal controls and attempted to correlate hormonal function with changes in body composition. Not surprisingly, differences were seen between controls and individuals with anorexia nervosa in terms of percentage of trunk fat, trunk/extremity fat ratio, trunk lean mass, and trunk/extremity lean-mass ratio. Interestingly, in the normal control group the area under the curve for growth hormone was inversely correlated with trunk fat and trunk extremity fat ration, but no such relationship was seen in anorexia nervosa. Nadir levels of cortisol, however, were inversely associated with extremity lean mass and directly correlated with trunk lean mass. The magnitude of these correlations was substantial (for external lean mass, $r = 0.49$, and for trunkal lean mass, $r = 0.48$).

For many patients the pace of weight gain in treatment is steady, but on occasions marked changes in weight can be seen. Yucel *et al.* [42] published a series of two cases in which marked weight gain (in one case 9 kg, in the other case 3 kg) was seen in the first week. These investigators emphasized the importance of this kind of edematous weight gain for clinical treatment.

Finally, as weight changes, there is some interest, both clinical and in research, in measuring the size of different body compartments. Piccoli *et al.* [43•] compared bioelectrical-impedance analysis with skin-fold thickness measurements in 74 women with anorexia nervosa. This study showed poor agreement between these methods in individuals below a BMI of 15, and these authors cautioned strongly against the use of such measures in these low-weight individuals.

Conclusion

Anorexia nervosa and bulimia nervosa represent psychiatric disorders wherein medical complications are

common, and in the case of anorexia nervosa, expected. In patients with anorexia nervosa every major organ system is involved, and the risk of mortality is substantial. Particular areas of concern are highlighted in the article and include dermatologic changes (some of which evidently need acute intervention; e.g., purpura), endocrine abnormalities (including mismanagement of diabetes), gastrointestinal problems (including the risk of gastric dilatation), cardiovascular/pulmonary problems (including arrhythmias and pneumomediastinum), severe electrolyte abnormalities, and bone demineralization. Physicians caring for these patients must be aggressive in pursuing, and when they are found in treating, these potentially life-endangering complications.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 460–461).

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