

# Medical Complications in Adolescents with Anorexia Nervosa: A Review of the Literature

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## ABSTRACT

The purpose of the current article is to summarize the evidence-based medical complications and treatments that are both common and unique to adolescents with anorexia nervosa (AN). Recent literature relating to the cardiovascular complications, refeeding syndrome, alterations in linear growth, impaired bone mineral accretion, and structural and functional brain changes was reviewed. The literature suggests that the medical complications in adolescents with AN are different from those reported in adults. The unique clinical presentation, the early onset, and the unknown impact of these

complications underscore the need for early identification and treatment of AN in adolescents. AN is a serious disorder with significant and often life-threatening medical complications. The increasing growth of evidence highlights the importance of early identification and treatment by an interdisciplinary team of health care providers who have expertise in managing adolescents with AN and their medical sequelae. © 2005 by Wiley Periodicals, Inc.

**Keywords:** medical complications; adolescents; anorexia nervosa

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## Introduction

Anorexia nervosa (AN) in adolescents can cause significant medical complications in every organ system in the growing and developing body.<sup>1</sup> Critical to the ongoing advancement of our understanding of AN in adolescents is the steady growth of evidence on the identification and management of the multitude of medical complications. Although many of these medical complications improve with nutritional rehabilitation and recovery from the eating disorder, some are potentially irreversible. As such, the long-term implications of these medical complications that typically begin in the formative years of adolescence are unknown. The current article summarizes the evidence-based literature on common medical complications that have been specifically studied in adolescent populations with AN over the past 20 years. We will focus on the cardiovascular and metabolic complications with a particular emphasis on refeeding syndrome, alterations in linear growth, impaired bone mineral accretion, and reference to structural and functional brain

changes, all of which have been studied in adolescents with AN.

## Cardiovascular Complications

AN is a life-threatening condition, with significant risk of death due to cardiac complications. One third of the deaths in adults with eating disorders are due to cardiac complications.<sup>2</sup> There are no such data regarding adolescents with AN.

Cardiac involvement is present in the early stages of the disorder in adolescents with AN.<sup>3,4</sup> In fact, even with a short duration of illness, there are both functional and structural cardiac abnormalities that appear to be reversible with early identification and treatment.<sup>3</sup>

Upon reviewing the adolescent eating disorder literature, the most common reported cardiovascular complications include electrocardiographic abnormalities such as sinus bradycardia,<sup>1,3–5</sup> decreased voltage and prolonged QTc,<sup>1,3–7</sup> orthostatic hypotension,<sup>8</sup> increased vagal tone,<sup>9,10</sup> poor myocardial contractility, mitral valve prolapse (MVP), reduction in left ventricular wall thickness and mass,<sup>3,9,11</sup> and silent pericardial effusion.<sup>11,12</sup>

Electrocardiographic abnormalities are present in most adolescents with AN.<sup>3,4,6,7</sup> Sinus bradycardia is reported to be present in 35–95% of adolescents with AN,<sup>1,3–5</sup> and is believed to be due to the reported increased vagal tone<sup>4,9,10</sup> and decreased metabolic rate.

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In one study, adolescents with AN had significantly lower heart rates and lower left ventricular forces (indicated by diminished R-wave in V<sup>6</sup>) compared with matched controls. Increased clinical disease severity (as measured by body mass index [BMI]) was significantly correlated with increased bradycardia and decreased left ventricular forces. No life-threatening arrhythmias were documented and there was no mortality reported among these adolescents.<sup>4</sup> Current recommendations suggest that adolescents with severe sinus bradycardia, defined as a heart rate <50 beats per minute during the day or <45 beats per minute at night, be admitted to a hospital for cardiac monitoring and gradual weight gain.<sup>13</sup>

The evidence for prolongation of the QTc interval and increased QTc dispersion in adolescents with AN is both conflicting and controversial. The QTc is the method of assessing the duration of ventricular repolarization. The length of the QT interval is dependent on the heart rate. The QT interval is "corrected" for heart rate and this is denoted as the QTc. Normal corrected QTc intervals are <0.44 s.<sup>4</sup> The issue of prolongation of the QTc interval has received a great deal of attention because of its association with sudden ventricular arrhythmias and death in adults who lost weight rapidly through a liquid protein modified fast or AN.<sup>2</sup> Lupoglazoff et al.<sup>6</sup> found prolongation of the QTc interval (QTc > 0.44 ms) in 25% of adolescents with AN. Another study<sup>1</sup> found that 32% of adolescents with AN had a prolonged QTc, although prolongation was defined as >0.425 s and there were no controls for comparison. In contrast, other studies in adolescents with AN have found no prolongation of the QTc interval (prolonged QTc interval was defined as  $\geq$ 0.44 ms or as >0.44 ms).<sup>1,3,4</sup> Because the finding of a prolonged QTc interval may still be concerning, a normal QTc should not reassure the clinician that the adolescent with AN is not severely ill.

In addition, there are reported inconsistencies with respect to increased QTc dispersion in adolescents with AN. It has been hypothesized that increased QTc dispersion reflects increased spatial differences in myocardial recovery time and may predispose patients to arrhythmias.<sup>14</sup> In the literature on adults with eating disorders, the electrocardiographic finding of increased QTc dispersion has been associated with ventricular arrhythmias and sudden death. Unlike Panagiotopoulos et al.,<sup>4</sup> who did not find increased QTc dispersion in adolescents with AN versus controls, both Mont et al.<sup>3</sup> and Swenne and Thurfjell<sup>7</sup> reported increased dispersion of the QTc interval.

The electrocardiographic abnormalities found in some studies need to be interpreted with caution as

they may lack control groups, have relatively small sample sizes, and vary in the type of methods and techniques used to measure the QT interval and corrected heart rate.<sup>1,5</sup>

Finally, it is also important to remember that electrocardiographic abnormalities in adolescents with AN should not only be taken as a feature of the disorder. Clinicians need to be aware that there may be other potential causes of abnormal electrocardiographic changes including metabolic and electrolyte disturbances (e.g., hypokalemia), a possible genetic etiology, or drug effects (e.g., prescribed medications, illicit drug use, or complimentary and alternative medications). Pharmacotherapy is currently being used more frequently in adolescents with AN as one component of a more comprehensive treatment.<sup>15</sup> Pharmacotherapy in AN has focused on the use of antidepressants (for which there is no evidence of effectiveness in low-weight patients with AN) with a recent interest in the use of atypical neuroleptics. Published studies using atypical neuroleptics have reported varying increases in the QTc interval. This literature needs to be interpreted with caution as there is a lack of consistent methodology in evaluating the QTc changes and there also remains a dearth of well-conducted case-control studies in interpreting absolute risk to life when using these medications.<sup>16</sup> Until more is known, the use of baseline and follow-up electrocardiography could facilitate the management of such adolescents who are treated with pharmacotherapy.

Orthostatic heart rate and blood pressure changes are common in adolescents with AN on admission to hospital.<sup>8</sup> Orthostatic changes place adolescents with AN at increased risk of syncope. One explanation for the observed orthostatic changes is that starvation leading to low body weight may result in atrophic peripheral muscles, resulting in decreased venous return to the heart. Recent evidence has shown that normalization of orthostatic pulse changes occurs after approximately 3 weeks of nutritional rehabilitation when subjects reach 80% of their ideal body weight (IBW). It has been suggested that the resolution of orthostasis can be used as an objective measure of medical stability in adolescents with AN.<sup>8</sup>

The incidence of MVP appears to be increased in patients with eating disorders.<sup>17</sup> MVP in AN is believed to develop as a consequence of weight loss with an associated reduction in left ventricle mass, resulting in a relatively large and redundant mitral apparatus.<sup>18</sup> MVP has been reported in 33% of adolescents with AN examined by echocardiography.<sup>19</sup> In another study, echocardiographic

evaluation confirmed the auscultation reported diagnosis of MVP found in 10 of 43 adolescents as well as in an additional 6 individuals, giving an overall incidence of 37% (i.e., 16 of 43 patients). This was in contrast to the 4% of control individuals. Cardiac arrhythmias were found in 5 patients with AN, all of whom had echocardiographic findings of MVP. This suggests that MVP might have an associated arrhythmogenic propensity that poses an additional risk to these adolescents.<sup>20</sup> Although it is not yet clear, MVP may resolve with weight restoration.<sup>21</sup>

Reports have demonstrated that adolescents with AN have loss of cardiac muscle detected by a decrease in left ventricular wall thickness.<sup>3,9,11,22</sup> Furthermore, reduced cardiac output also has been documented in adolescents with AN at initial assessment.<sup>3,17</sup> In one study, the majority of adolescents with AN had decreased left ventricular mass and cardiac output at the basal state, indicating early structural and functional heart involvement.<sup>3</sup> After refeeding, these adolescents had a consistent increase in cardiac dimensions, wall thickness, ventricular mass, and cardiac output, reflecting reversibility of these abnormalities.

There seems to be an association between "silent" pericardial effusions (pericardial effusion with no associated clinical signs or symptoms) and AN.<sup>11,12</sup> One study described 10 hospitalized adolescents with AN with pericardial effusions discovered on echocardiography.<sup>12</sup> No clinical signs or symptoms of heart failure were observed. In 8 of these adolescents, pericardial effusion remitted with weight rehabilitation.<sup>12</sup> The pathophysiology for the development of pericardial effusion in AN is unknown although there is a correlation with low BMI<sup>11</sup> and weight restoration.<sup>12</sup> The clinical significance remains unclear.

Cardiac complications have the potential to have detrimental consequences. Although there are very few studies that have examined the cardiac involvement in adolescents with AN, it appears that such involvement is present in the early stages of the disorder and from all accounts is reversible.<sup>3</sup> This emphasizes the need for early identification and prompt treatment of adolescents with AN. Gradual weight restoration with careful cardiac monitoring will re-establish normal cardiac structure and function.<sup>3</sup>

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## Refeeding Syndrome

Refeeding syndrome is well described in adolescents with AN. It is defined as severe shifts in fluid and

electrolyte levels, in particular phosphate levels, from extracellular to intracellular spaces in severely malnourished patients who have total body phosphorus depletion and are undergoing refeeding, whether orally, enterally, or parenterally.<sup>23</sup> Refeeding syndrome is of particular concern in severely malnourished adolescents with AN. Refeeding syndrome consists of cardiovascular, neurologic, and hematologic complications, and can be associated with significant morbidity and mortality.

The consequences of serum hypophosphatemia resulting from refeeding have been documented in adolescents with AN. Adverse effects of hypophosphatemia include cardiac failure, muscle weakness, immune dysfunction, and death. In one study, severely malnourished hospitalized adolescents with AN underwent nutritional rehabilitation and developed hypophosphatemia. Three-fourths of these adolescents reached a phosphorus nadir within the first week of hospitalization.<sup>24</sup> In Fisher et al.,<sup>25</sup> severely malnourished young people with AN developed significant hypophosphatemia along with other clinical features of the refeeding syndrome with oral feeds. That report emphasized the need for hospitalization with close medical monitoring and slow oral refeeding. Refeeding in hospitalized adolescents with AN has shown that a minimum 4-day weight gain criterion between 0.36 kg and 0.55 kg was associated with weight gain without the accompanied complications of refeeding.<sup>26</sup>

Cardiac sequelae are secondary to and occur early in the cascade of events that arise during refeeding. Congestive heart failure results from the decreased ventricular mass and myofibrillar atrophy, causing decreased stroke volume and reduced capacity of the cardiovascular system. Kohn et al.<sup>27</sup> described acute cardiac complications—arrhythmias (bradycardia), pericardial effusion, hypotension, and cardiac arrest—in 3 adolescents with AN admitted to hospital for refeeding. All patients were <70% IBW and developed life-threatening complications associated with refeeding. Two of the 3 developed hypophosphatemia, all had cardiac arrhythmias documented within the first week of hospitalization, and all had delirium during or after the second week of refeeding. Treatment recommendations included early administration of supplemental phosphorous, gradual increase in prescribed nutrition, and close monitoring of electrolyte levels and cardiac status.

In conclusion, descriptive studies have illustrated that refeeding syndrome can result from the use of oral, parenteral, or enteral nutrition in malnourished adolescents with AN. Slow refeeding, gradual increase in calories, close inpatient medical monitoring including careful observation of the cardiac

status, daily monitoring of serum phosphorus levels during the first week of hospitalization,<sup>24</sup> and the possible addition of phosphorus supplementation, are required to prevent the development of refeeding syndrome in severely malnourished adolescents with AN.

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## Linear Growth

Impaired linear growth and the possibility of permanent short stature are significant medical complications in adolescents with AN. There are reports in the pediatric literature of children and adolescents with AN presenting with growth failure or short stature.<sup>28–30</sup> Reports regarding catch-up growth after weight restoration include failure to gain any height,<sup>30</sup> incomplete catch-up growth,<sup>31</sup> and complete catch-up growth.<sup>30,32</sup> Small sample size, variation in the duration of follow-up, and lack of premorbid growth data may explain these inconsistent results.

Growth retardation has been attributed to several hormonal changes that have been well documented in patients with AN. These include low levels of thyroxine (T4) and triiodothyronine (T3), elevated levels of cortisol, low levels of sex hormones, and changes in the growth hormone (GH)–insulin-like growth factor (IGF) axis. Recent studies in adolescents with AN have demonstrated the dramatic alteration in the GH–IGF axis. These changes are believed to contribute to the alterations in linear growth.

During normal puberty, levels of sex steroids increase, which, in turn, result in increased levels of GH and IGF-I, a bone trophic hormone that stimulates longitudinal bone growth.<sup>33</sup> The action of GH on bone is mediated through IGF-I. Studies of adolescents with AN reported decreased adult height<sup>29,34</sup> and low serum levels of IGF-I.<sup>35</sup>

More recently, studies have shown that adolescents with AN have a state of GH resistance, with high<sup>35</sup> or normal basal levels of GH<sup>36</sup> and inappropriately low levels of IGF-I and growth hormone binding protein (GHBP).<sup>36,37</sup> Undernutrition is known to inhibit IGF-I production in the liver, causing an increase in GH levels through reduction in negative feedback. GH action, however, as measured by IGF-I, is impaired despite these elevated GH levels. In addition, levels of IGFBP-3, the main carrier protein of IGF-I, which is regulated by both GH secretion and nutrition, are low, indicating further alteration in GH action. Furthermore, significantly greater basal GH secretion and increased

pulse frequencies have been reported in adolescents with AN compared with healthy adolescents.<sup>35</sup> These indices of GH normalize with weight recovery.<sup>36</sup> Low levels of serum IGF-I due to undernutrition also correlate with low BMI in AN.<sup>35,36</sup> These studies suggest that GH resistance and IGF-I deficiency significantly contribute to reduced growth in adolescents with AN. Current studies are underway to determine whether these alterations in GH physiology impact the rate of linear growth, recovery, and final adult height.

Finally, the timing of the onset of AN with respect to puberty may also be important to alterations in linear growth. One report describes adolescent females with AN who present before menarche and have a long history of poor weight gain and growth retardation compared with those who develop the disorder when they are postmenarcheal.<sup>38</sup> In another prospective study, adolescents who developed AN in early puberty and before menarche presented with growth retardation compared with those who developed the disorder when they were postmenarcheal. Although this group of adolescents demonstrated catch-up growth with nutritional intervention, they did not reach their full genetic height potential. The peak height velocity was reported to be lower than expected and occurred later than anticipated.<sup>34</sup> Understanding GH physiology and the impact on linear growth rate before and during pubertal development requires further attention.

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## Osteoporosis

Osteopenia is a frequent, early, and serious complication in adolescents with AN. Adolescence is a critical time for the attainment of peak skeletal mass. Because the majority of bone mineral accretion occurs by the middle of the second decade of life, the development of AN during these formative years can result in the reduction of bone mineral density (BMD) and long-term morbidity. One study reported that there was a threefold increase in long-term risk of fractures later in life in people who had a history of AN.<sup>39</sup>

The pathogenesis of bone loss in adolescents with AN is associated with impaired bone formation and increased bone resorption. Most adolescent girls with AN have low BMD that involves trabecular and cortical bone.<sup>40,41</sup> Studies have shown that adolescents with AN have significantly reduced bone mass compared with age-matched<sup>41</sup> and bone age-matched controls.<sup>42</sup> In

one study,<sup>41</sup> the lumbar bone density of two-thirds of adolescents with AN was more than 2 *SD* lower than the normal values for their age. Of note, the changes in bone density occurred very early in the course of the illness, with one half of these adolescent girls having had a diagnosis of AN for <1 year. In addition, BMD in adolescents with AN has been shown to be significantly correlated with BMI, age at onset, and the duration of illness.<sup>41</sup>

The possible mechanisms of low bone mass observed in adolescents with AN are complex. A number of identified factors have been shown to influence the attainment of peak bone mass in adolescents with AN: hypoestrogenemia, decreased levels of IGF-1, increased cortisol levels, physical activity, poor nutrition, low calcium and vitamin D intake, and low body mass. Together, these factors put adolescents with AN at risk for early osteopenia.

The complete reversibility of low bone mass in adolescents with AN is unknown. Weight recovery has been shown to increase whole-body bone density, even before the return of menses.<sup>43</sup> In this same study, however, lumbar bone density remained significantly reduced and subsequent weight loss was associated with further decreases in bone density. Despite their gains in BMD, 8 patients had osteopenia of the spine or whole body, or both. Similarly, in other follow-up studies,<sup>44,45</sup> approximately 50% of the young women with AN had persistent osteopenia >10 years after the initial study. Finally, one-third of young women who recovered from AN during adolescence had persistent osteopenia of the lumbar spine.<sup>43</sup> Such persistence suggests that BMD deficits may not be completely reversible.

The treatment of osteoporosis in adolescents with AN should emphasize the importance of weight recovery and the resumption of menses. Weight restoration is the safest and most effective way to increase bone mineralization in adolescents with AN.<sup>43</sup> Changes in body weight and composition (in particular increases in lean body mass), even before the return of menses, is important to bone mineralization. Weight at resumption of menses has been used as a biologic marker of health. In one study, 86% of adolescents who achieved a weight that was approximately 90% of their IBW resumed menses within 6 months. This weight was approximately 2 kg greater than the weight at which the adolescents lost their menstrual periods (menstrual threshold weight).<sup>46</sup>

Calcium is important for attaining skeletal health during adolescent growth and development. Dietary calcium requirements increase during periods

of peak velocity of growth and bone mineral content.<sup>47</sup> In general, both healthy adolescents and adolescents with AN consume less calcium than the recommended dietary intake.<sup>41,47</sup> Although there is evidence to suggest that calcium intake increases BMD in healthy children and adolescents,<sup>48</sup> no association has been found between calcium intake and bone mass in adolescents with AN.<sup>41</sup> Vitamin D is crucial to the absorption of calcium. Current recommendations for adolescents with AN include a treatment regimen of daily calcium intake of 1,300–1,500 mg during the preteen years and continuing through adolescence<sup>49,50</sup> and at  $\geq 400$  IU per day of vitamin D intake.<sup>50</sup>

To date, there is no evidence that hormone replacement therapy (HRT) effectively reverses or prevents bone loss in adolescents with AN. A 1-year<sup>51</sup> prospective observational study in adolescents with AN who received either estrogen-progestin or no hormonal treatment had no significant differences in absolute values or in the net change of lumbar-spine or femoral-neck BMD between the two groups at follow-up. In addition, Munoz et al.<sup>52</sup> also studied the effect of oral estrogen/progestin administration on bone loss in young women with AN. Thirty-eight young women with AN (mean age = 17.3 years) were treated with estrogen/progestin treatment for 1 year. The estrogen/progestin-treated group had no significant change in BMD, even after the follow-up period and partial recovery of weight.

Despite the lack of conclusive evidence demonstrating the effectiveness of HRT for preventing bone loss or restoring the deficits in adolescents with AN, it is not uncommon for health care providers to support the use of HRT in adolescents with AN. One survey found that >75% of physicians treating adolescents with AN used HRT to treat older teens.<sup>53</sup> One of the main concerns with the use of HRT is that the resumption of monthly hormone-induced withdrawal bleeding may be misinterpreted as the return of normal menstrual function, adequate weight restoration, and therefore, recovery. Studies are needed to address whether this potential misunderstanding could make adolescents more complacent about the treatment process.

The relationship between bone density and physical activity in adolescents with AN is complex. Although incorporating high-impact exercise has been shown to increase BMD (femoral head) in healthy children, no relationship has been found between the amount<sup>42</sup> or type of physical activity<sup>41</sup> in adolescents with AN. Furthermore, the intensity,

frequency, and duration of activity that promotes bone mineralization are unknown.

Recent studies have provided insight into geometric changes such as increases in bone cross-sectional area at different regions of the hip that support exercise-associated gains in bone strength in healthy, early-pubertal girls.<sup>54</sup> Further work using this type of technique would be useful in understanding the impact of exercise on bone strength in adolescents with AN.

Excessive exercise in adolescents with AN can perpetuate the low body weight, amenorrhea, and decreased sex hormone levels with subsequent bone loss. When an adolescent with AN is weight restored or is actively achieving weight restoration and is medically stable, closely monitored weight-bearing exercise can be considered.

Other treatment modalities have been studied for the prevention and treatment of osteoporosis. Dehydroepiandrosterone (DHEA) is a precursor to both estrogen and androgens and has been noted to be abnormally low in patients with AN. DHEA has been shown to stimulate bone formation and decrease markers of bone resorption in adolescent females with AN. In a pilot study, Gordon et al.<sup>55</sup> investigated the effect of short-term oral DHEA in young women with AN. Markers of bone resorption significantly decreased and markers of bone formation significantly increased. Menses resumed in 53% of the young women during treatment. Another study by the same group compared a 1-year course of oral DHEA treatment with HRT (20 µg of ethinyl estradiol and 0.1 mg levonorgestrel) in young women with AN. At the completion of the study, both the DHEA and HRT-treated groups had significantly reduced markers of bone resorption and the DHEA group had increased markers of bone formation. There was no significant change in lumbar BMD in either group and, after controlling for weight gain, there was no treatment effect detectable with respect to hip BMD.<sup>56</sup>

Researchers have studied the effect of IGF-1 on bone turnover markers and BMD in patients with AN. IGF-1 is a nutritionally dependent hormone that stimulates osteoblast function and collagen synthesis and is known to be abnormally low in AN. One group studied the effect of the short-term use of subcutaneous recombinant human IGF-1 (rhIGF-1) on bone turnover in older adolescents and young women with AN<sup>57</sup> and showed an increase in markers of bone formation. This same group also studied the effects of rhIGF-1 and oral contraceptive administration on BMD in AN. The study suggested potentially beneficial effects of combined IGF-1 and oral contraceptives on bone density in young women with AN.<sup>58</sup>

Bisphosphonates are analogs of pyrophosphate, bind to bone hydroxyapatite, and inhibit osteoclast-

medicated bone resorption. Bisphosphonates have been used to treat osteoporosis in children and adolescents with osteogenesis imperfecta,<sup>59</sup> diffuse connective tissue diseases,<sup>60</sup> and cerebral palsy,<sup>61</sup> as well as in children receiving steroids.<sup>62</sup> Alendronate, a bisphosphonate, is currently being studied in adolescents with AN.

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## Structural and Functional Brain Changes

There is strong evidence of structural and functional brain abnormalities in adolescents with AN. These are among the most common and early physical consequences of the disorder. Investigators have examined the brain of adolescents with AN using magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission tomography (SPECT), and proton magnetic resonance spectroscopy (1H-MRS).<sup>63</sup> In the current special issue, Lask et al. focuses on brain imaging in AN.<sup>64</sup>

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## Conclusions

For adolescents, AN is a serious disorder with significant medical complications. Medical complications such as alterations in linear growth, osteoporosis, and structural and functional brain changes are very serious. These medical complications may not be completely reversible and their impact later in life is unknown. Cardiac problems and refeeding complications can be life-threatening.

When considering the medical complications of adolescents with AN, a number of recurring themes are identified. The medical complications of adolescents with AN differ from those of adults with AN. These medical complications are unique in their clinical presentation and present early in the course of the illness. Any one of a number of these complications has the potential to have wide-ranging impact on the growth and development of adolescents with AN. Some of the medical complications are, in part, reversible if there is timely restoration of body weight, careful medical management, and ongoing monitoring. Finally, the long-term consequences of these medical complications remain unknown.

The unique clinical presentation, the early onset, and the unknown impact of these medical complications underscore the need for early identification

and treatment of AN in adolescents. An interdisciplinary team approach that includes health care providers who have expertise in managing adolescents with AN and their medical sequelae can result in a successful outcome.<sup>13,65,66</sup>

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