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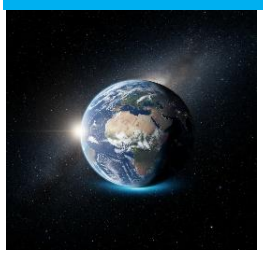

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Systemic Consequences of Anorexia Nervosa: Multiorgan Dysfunction and Long-Term Complications

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ABSTRACT

Background. Anorexia nervosa is a serious eating disorder marked by constant restriction of food intake, fear of gaining weight and disturbances in body image perception. While it is primarily categorized as a psychiatric illness, prolonged undernutrition leads to extensive medical complications that involve multiple organ systems and substantially increase mortality. These systemic effects are frequently overlooked, despite their critical role in disease severity and clinical outcomes.

Aim. The aim of this study was to present anorexia nervosa as a complex multisystem condition by outlining the key pathophysiological processes and medical complications affecting major organ systems, and emphasize the necessity of early diagnosis, coordinated multidisciplinary care, and long-term medical observation.

Material and methods. This review synthesizes current evidence by examining literature from 2019-2025 available on PubMed and Google Scholar using the keywords „anorexia nervosa", „malnutriton", „medical complications".

Results. It has been found that anorexia nervosa causes widespread medical complications that involve many organ systems, including the skeletal, endocrine, reproductive, digestive, cardiovascular, haematopoietic and respiratory system. The most serious consequences include sudden cardiac death, severe osteoporosis, infertility, obstetric problems and

dysregulation of multiple hormonal axes. Even after restoration of normal nutrition, some complications may not fully resolve.

Conclusions. Anorexia nervosa is a life-threatening disorder with systemic consequences that extend beyond weight loss, affecting multiple organs and physiological systems. Therefore, rapid intervention, comprehensive care and constant medical surveillance are crucial to improve long-term treatment outcomes.

Key words: anorexia nervosa, malnutrition, energy deficiency, medical complications, multidisciplinary care

Introduction

Anorexia nervosa (AN) is a serious and potentially fatal eating disorder characterized by deliberate restriction of food intake, extreme fear of weight gain, and distorted perception of body shape and size [1]. The precise diagnostic criteria according to the latest classification are presented in Table 1. The estimated yearly prevalence is 3.6% in women and 0.3% in men [2]. The disease is often chronic, with many individuals experiencing persistent symptoms long after the onset of the disorder, and has the highest mortality rate of any psychiatric disorder (around 10%) [3,4]. This is partly related to the fact that patients with AN have higher prevalence of depression throughout their lives and higher rates of suicide attempts than individuals without eating disorders [3,5]. However, around half of all deaths are caused by physical complications resulting from starvation [4]. Despite its severity, treatment options remain limited, as there are no approved medications available, and psychological therapies typically show moderate long-term effectiveness, particularly among adults [1]. AN affects individuals of all genders worldwide and most often develops during the transition from adolescence to early adulthood, with the average age of onset occurring between 15 and 19 years [6]. Over the years, anorexia has been observed at increasingly younger ages. It is particularly common among boys, who tend to develop this disorder earlier than girls [7]. Therefore, screening in early childhood is recommended, as it allows for the detection of behavioural patterns that may signal the later onset of eating disorders and associated risk factors. Early warning signs in younger children include a lack of interest in food, eating slowly

under pressure from parents, and even selective eating habits. Attention should also be paid to children who consume most of their calories in liquid form. In teenagers, on the other hand, it is possible to observe avoidance of eating in the presence of others, a sense of guilt while eating, as well as compulsive excessive physical activity or changes in the way they dress [8]. The prevalence of this disorder is expected to increase with rising social pressure related to physical appearance and the growing influence of the media, to which society is exposed at an increasingly younger age [3].

Table 1. Diagnostic criteria for AN according to DSM-5 [9].

A	Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.
B	Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
C	Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Etiology

The exact etiology of AN remains unknown, but it is believed to be multifactorial and to include genetic, social, personality, hormonal, and sexual factors [10]. Sociocultural risks include pressure to meet unrealistic ideals of physical appearance, exacerbated by their exposure on social media. Psychological and individual factors include low self-esteem, perfectionism, and emotional dysregulation. Already existing mental health disorders, including anxiety, depression, and post-traumatic stress disorder, as well as neurodevelopmental disorders such as autism and attention deficit hyperactivity disorder, further increase susceptibility to AN. Risk factors for anorexia also include stressful life events, a family history of eating disorders and weight control, and growing up in a non-traditional family environment [11,12]. Research indicates that genetic factors have a strong influence on AN, and that many genes may contribute to its onset. Twin studies suggest that heredity accounts for approximately 28% to

74% of the risk of developing this disorder [13]. Interestingly, AN shows higher heritability than other eating disorders. Genetic studies have identified numerous loci in biological pathways that may play a role in its etiology, including genes associated with serotonin, dopamine, opioid signalling, appetite regulation and the endocannabinoid system [14]. Unfortunately, current research results are insufficient to establish a definitive molecular diagnosis of AN and do not yet allow for the development of specific, reliable genetic diagnostic tools [8]. In addition, the gut-brain axis has recently been increasingly linked to central nervous system health. Therefore, dysbiosis or gut microbiota imbalance may also be contributing to the development of this AN [15,16].

Medical complications

The skeletal system

It is well known that low body weight in AN results in decreased bone mineral density [17]. Multiple major factors likely contribute to the bone disease observed in AN patients. These include inadequate nutrient intake, vitamin D deficiency, hypogonadism, elevated serum cortisol levels, decreased insulin-like growth factor levels, resistance to growth hormone, as well as amenorrhea in women and low testosterone levels in men [18]. Decreased leptin secretion, which is a result of low body fat, inhibits the hypothalamic-pituitary-gonadal axis. This causes decreased levels of estrogen and testosterone, leading to accelerated bone resorption and reduced bone formation. As a result, the likelihood of osteopenia, osteoporosis, and bone fractures increases [19]. AN primarily affects young women during the critical period of peak bone mass development [20]. Therefore, studies show that 54% of women with AN are diagnosed with osteopenia, and 38% with osteoporosis. Importantly, the increased risk of bone fractures persists even when the patient achieves remission [19]. No improvement in bone mineral density, despite weight gain and adequate nutrition, can lead to height loss and chronic pain [18]. Osteopenia and osteoporosis associated with eating disorders are challenging to manage, with few effective pharmacological treatment options available. Consequently, early identification of individuals at highest risk, along with targeted preventive and therapeutic interventions, is essential to mitigate this problem [19]. For this reason, it is recommended that all patients with a disease duration exceeding one year or a history of amenorrhea lasting longer than six months undergo screening dual-energy X-ray absorptiometry. Nevertheless, regaining

body weight and resuming menstruation remain the basis of treatment, with calcium and vitamin D being essential components for bone regeneration [18].

The endocrine system

Persistent starvation in anorexia nervosa causes a series of adaptive hormonal changes that lead to disturbances in the regulation of various endocrine axes. Many of these abnormalities are largely reversible upon restoration of normal body weight, as they represent a physiological response to energy deficiency. However, endocrine dysfunction plays a key role in the development of somatic complications of anorexia nervosa, as certain hormonal and metabolic changes that go beyond adaptive mechanisms may remain despite treatment and cause neuropsychiatric symptoms [21].

Regarding hypothalamic-pituitary-thyroid axis, starvation induces a reversible adaptive reduction in thyroid hormones, resulting in a hypothyroid-like state that conserves energy while TSH usually remains normal. These changes contribute to common clinical features of AN, such as bradycardia, cold intolerance, hair loss, and constipation. This adaptive response does not justify replacement therapy with thyroid hormones, as such therapy may worsen energy deficiency. Treatment should instead focus on nutritional rehabilitation [22].

Chronically elevated ACTH and cortisol levels in AN patients, along with an increased cortisol awakening response, reflect persistent activation of the hypothalamic-pituitary-adrenal axis. The inverse relationship between cortisol levels and body mass index supports the view that hypercortisolaemia is an adaptive response to starvation. This results in reduced bone mineral density, impaired immune function, visceral fat accumulation (during weight recovery), as well as insulin resistance. Despite these symptoms, pharmacological suppression of cortisol is not recommended, as hypercortisolaemia in AN represents a compensatory mechanism to preserve glucose homeostasis and blood pressure during prolonged malnutrition [22,23].

Long-term starvation also causes a state of resistance to growth hormone (GH), which is accompanied by elevated GH levels and low concentrations of insulin-like growth factor-1 (IGF-1). GH is involved in the process of gluconeogenesis in the liver, so its increased secretion, stimulated by an increase in ghrelin levels, has the adaptive task of maintaining euglycaemia despite food deficiency. In a chronic condition secondary to these processes, GH resistance

increases in the liver in order to restrict the consumption of gained energy for the body's growth. [22,24]. The result of these mechanisms is reduced growth during puberty. However, there is insufficient evidence that the treatment with recombinant GH is beneficial. GH levels normalise with a restoration of normal body weight, without additional replacement therapy [25].

In the course of AN, the secretion of hormones stored in the posterior lobe of the pituitary gland may also be disrupted. Hyponatraemia in this disease is multifactorial, most commonly related to the syndrome of inappropriate antidiuretic hormone secretion (SIADH), renal malfunction, and excessive water intake for weight manipulation. It is mostly asymptomatic, however it may also result in serious symptoms such as vomiting, confusion, seizures, and coma. Accordingly, careful medical and therapeutic monitoring of sodium levels is required, and the use of selective serotonin reuptake inhibitors should be approached with caution due to their association with SIADH and limited evidence of efficacy in severely underweight patients [22,26]. In the case of oxytocin, nocturnal concentrations are reduced compared to the general population, while its levels after a meal show an increase, possibly reflecting inverse central–peripheral regulation. However, there is no evidence supporting oxytocin therapy in AN [22].

Eating disorders, including AN, are essentially characterised by disturbances in the physiological regulation of appetite, satiety and feelings of fullness, which depend on coordinated communication between peripheral tissues and hypothalamic centres that control food consumption [22]. Among the substances secreted by adipose tissue (adipokines), leptin and adiponectin are the most important in food intake. The exact mechanism through which adiponectin controls appetite is not fully understood, but its levels are often elevated in anorexia nervosa (AN) and decrease during nutritional rehabilitation. It shows an inverse association with body mass index [27]. Leptin, on the other hand, is a marker of long-term energy reserves, because physiologically, when the body receives sufficient energy stored in the form of fat, this hormone inhibits food consumption and reduces appetite [24]. In AN, its level is therefore significantly reduced due to a significant decrease in adipose tissue, but this does not stimulate food intake, but is associated with increased physical activity and excessive exercise. Low leptin levels may also contribute to hypothalamic amenorrhoea through reduced stimulation of gonadotropin-releasing hormone [22]. Although leptin replacement therapy remains controversial, monitoring leptin levels during and after treatment may help identify patients who may benefit from targeted relapse prevention strategies and closer follow-up [28]. Ghrelin, the main appetite-stimulating hormone circulating in the body, is constantly elevated in AN, but its effect appears to be weakened, indicating central ghrelin resistance and, consequently,

altered central reactivity despite strong hunger signals from the periphery [24]. Hormones produced in the intestines may also disrupt appetite regulation in eating disorders. Peptide YY, which physiologically reduces appetite, is released as a result of food intake, but its levels are paradoxically elevated in AN, which contradicts its role as an adaptive mechanism in chronic starvation. It is therefore possible that it plays a role in the pathogenesis of AN. Peptide YY levels may remain elevated even after returning to a normal body weight. In turn, reduced release of cholecystokinin (CCK), which affects the feeling of satiety, is mainly relevant in the course of binge eating disorders [22,24].

The reproductive system

Anorexia nervosa is associated with profound dysregulation of the hypothalamic-pituitary-gonadal (HPG) axis, caused primarily by chronic energy deficiency, underweight and excessive physical activity. Impaired hypothalamic signalling causes inhibition of pulsatile gonadotropin-releasing hormone (GnRH) secretion, leading to decreased secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary gland [29]. Many neuroendocrine mechanisms contribute to the inhibition of the HPG axis in AN, including significantly reduced leptin levels secondary to decreased body mass and elevated cortisol levels resulting from hyperactivity of the hypothalamic-pituitary-adrenal axis. Additional metabolic and neuroendocrine mediators, such as ghrelin, insulin, peptide YY, opioids, and dopaminergic pathways, further inhibit GnRH pulsatility [30,31]. As a result, estrogen concentration in women and testosterone concentration in men decrease, manifesting as hypogonadotropic hypogonadism, which is one of the most common endocrine disorders in the acute phase of AN [32].

Clinically, women experience amenorrhoea and anovulation, resulting in fertility problems, as well as suppression of bone and endometrial growth. Amenorrhoea occurs in approximately 68-89% of women with AN and usually appears when body weight drops by 10-15% compared to baseline. Although restoration of body weight and energy availability is essential for recovery of reproductive functions, resumption of menses is frequently delayed and may remain absent in a subset of patients despite normalization of gonadotropin secretion, likely reflecting persistent metabolic imbalance and psychological stressors [29,31]. Fertility problems affect many patients with AN, with long-term studies showing that only approximately one-third of

women with this disorder give birth to a child [31]. In addition, a pregnancy itself may be at risk due to a higher incidence of obstetric complications such as miscarriage, abnormal placental implantation, hypertensive disorders, risk of bleeding, susceptibility to infection, gestational diabetes, and, as a result, preterm delivery and a higher rate of caesarean sections [29]. The optimal management of these pregnancies involves restoring proper nutrition and carefully monitoring clinical, biochemical and cardiovascular parameters, as well as prompt hospitalisation when weight gain is insufficient or signs of health instability appear [29]. Among men suffering from AN, HPG axis disorders lead to testosterone deficiency, which primarily results in sexual dysfunction and decreased libido [29,30].

The gastrointestinal system

Anorexia nervosa is associated with extensive disturbances in the structure of the gastrointestinal tract, motility, secretion and neuroendocrine regulation, mainly as a result of prolonged starvation and abnormal compensatory behaviours [33]. In many cases, gastrointestinal symptoms are the first sign of AN, which can delay the diagnosis of an eating disorder, as only digestive system-related medications are prescribed in the initial period. These complaints may be functional or organic in nature and include heartburn, dysphagia, nausea, vomiting, early satiety and abdominal pain [33, 34]. A common symptom is an abdominal fullness after a meal, resulting from documented delayed gastric emptying and prolonged transit time through intestines. In AN patients this feeling exacerbates the impression that they are unable to tolerate food, which is a significant problem in returning to normal nutrition [35]. Another particularly common symptom is constipation. It is believed that this is due to smooth muscle atrophy, electrolyte disturbances, altered intestinal transit and pelvic floor dysfunction, the latter being further exacerbated by the overuse of laxatives [33]. In addition, functional disorders are worth mentioning, as functional dyspepsia and Irritable Bowel Syndrome (IBS) are much more common in patients with AN than in healthy individuals and correlate with a lower body mass index and a longer period of malnutrition [33]. AN is also characterised by significant dysregulation of gastrointestinal and metabolic hormones, including elevated levels of cholecystokinin, peptide YY, gastrin, somatostatin, leptin, β-endorphin and vasoactive intestinal peptide, as well as impaired insulin secretion and sensitivity. These hormonal changes may contribute to reduced appetite and the perpetuation of restrictive eating behaviours [36]. Abnormalities also include: oral symptoms such as salivary gland hypertrophy and acidic saliva;

altered intestinal permeability, which may link the pathogenesis of AN with coeliac disease; and changes in the composition of the intestinal microflora, characterised by reduced microbial diversity [33,36]. The latter is currently the subject of much research into the pathogenesis of the disorder and possible therapeutic options [34]. The involvement of the liver, reflected in elevated transaminase levels, and dysfunction of the exocrine pancreas, characterised by reduced secretion of digestive enzymes, further illustrate the multisystemic impact of AN [36]. Some studies indicate a possible causal link between AN and an increased risk of acute gastritis and Crohn's disease [37].

Gastrointestinal complaints may partly reflect somatisation, whereby psychological pathologies are expressed through physical symptoms, potentially creating a self-perpetuating cycle that reinforces eating disorder behaviours and complicates recovery. Effective treatment should therefore address both the physiological consequences of malnutrition and the psychological focus on somatic symptoms, using psychoeducation and support strategies to prevent gastrointestinal complaints from becoming an obstacle to recovery [38]. Most of the abnormalities improve with feeding rehabilitation and weight restoration, but delayed gastric emptying and the associated feeling of fullness can persist for a long time, posing a serious therapeutic challenge when initially introducing adequate amounts of food [35].

The cardiovascular system and hematologic complications

As previously mentioned, anorexia nervosa is associated with the highest mortality rate among mental illnesses. Nearly one-third of these deaths are caused by cardiovascular disorders, most often as a result of sudden cardiac events [39]. Cardiovascular symptoms are primarily the result of adaptive physiological responses to prolonged starvation, such as increased parasympathetic (vagal) activity, decreased sympathetic activity, hypothermia, and reduced basal metabolic rate. These mainly include hypotension and sinus bradycardia [40,41]. Structural remodelling of the heart is commonly observed, resulting in a reduction of the mass and wall thickness of the left ventricle (LV). Despite this, the left ventricular stroke volume often remains similar to normal population parameters. Cardiac output is therefore reduced mainly because of bradycardia. Diastolic dysfunction of the heart muscle has also been described [41]. Additional echocardiographic findings may include mild pericardial effusion and mitral valve prolapse, reflecting abnormalities in the cardiac muscle and connective tissue secondary to malnutrition

[40]. The exact pathophysiology of these cardiac changes is not fully understood, but proposed contributing mechanisms include calorie restriction-induced myocardial remodeling, endocrine disturbances such as low triiodothyronine (T3) levels, altered growth factor signaling, changes in sodium balance, and increased levels of circulating Brain Natriuretic Peptide (BNP), which may contribute to a reduction in cardiac mass and heart rate [41]. Electrophysiological aberrations are common and clinically significant in anorexia nervosa. Sinus bradycardia, decreased QRS amplitude, nonspecific ST abnormalities, and, in some patients, QT prolongation and increased QT dispersion may be observed. QT interval-related alterations are particularly important because they have been recognized as markers of ventricular electrical instability and are linked to an increased risk of malignant arrhythmias and sudden cardiac death. They often occur in the presence of precipitating factors such as electrolyte disturbances - particularly hypokalemia - as well as sudden weight loss and a significant reduction in BMI [39,40]. Anorexia also has a significant adverse effect on the vascular system, characterized by peripheral vasoconstriction, endothelial dysfunction, and impaired microvascular reactivity, mainly caused by chronic malnutrition, autonomic imbalance, and hormonal disturbances. These vascular changes may contribute to clinical symptoms such as the Raynaud's phenomenon [42]. Given the high prevalence and potential mortality of cardiovascular complications, systematic assessment of the cardiovascular system is essential - including routine electrocardiography with careful assessment of heart rate, QT interval, and QT dispersion - especially in patients who are severely underweight and those who engage in purging behaviors [39].

Abnormalities in the course of AN are also evident in the blood count, where, as malnutrition progresses, a decrease in all three cellular lines can be detected. Leukopenia is the most common, but normocytic anemia and thrombocytopenia may also occur. These disorders are caused by a characteristic transformation of the bone marrow, in which the disappearing serous fat in the marrow is replaced by a substance rich in mucopolysaccharides, disrupting normal blood cell production. However, neutropenia does not carry an elevated risk of infection, so additional preventive measures are not required [24]. The severity of hematologic disorders is closely related to the progression of nutritional deficiencies. Normalisation of energy supply and weight gain usually result in rapid and complete restoration of peripheral blood parameters and proper bone marrow architecture, which in most cases makes invasive diagnostics or therapy with growth factors unnecessary [24,43].

The respiratory system

Long-term starvation in anorexia nervosa exerts a significant negative impact on the respiratory system, contradicting earlier assumptions that pulmonary function is largely preserved in this condition [44]. One of the main consequences is weakness and atrophy of the respiratory muscles, which may lead to dyspnea, reduced ventilatory capacity, and decreased oxygen delivery, particularly during periods of respiratory illness or physiological stress [24,45]. In addition to functional impairment, there are also structural alterations of the lungs, including emphysema-like changes, bullae formation, and bronchiectasis. According to research, they may be driven by loss of elastin, reduced surfactant production and altered cellular signaling cascades that promote apoptosis in the setting of severe undernutrition [45]. Patients with AN carry an increased risk of acute and potentially life-threatening pulmonary complications, such as pneumomediastinum and spontaneous pneumothorax. These may arise from mechanisms involving increased alveolar pressure resulting in alveolar rupture (Macklin effect) or oesophageal perforation caused by vomiting (Boerhaave syndrome) [24,44]. Furthermore, impaired pharyngeal muscle strength and swallowing disorders increase susceptibility to aspiration pneumonia, while immune dysfunction and structural lung disease may predispose to infections with opportunistic pathogens, including non-tuberculous mycobacteria [24,44]. Therefore, management of patients with anorexia nervosa requires increased vigilance for pulmonary complications and early diagnostic imaging in the case of respiratory symptoms or fever. Prevention is based mainly on effective nutritional rehabilitation, prevention of aspiration and infections, and careful performance of invasive procedures within the chest [45].

Conclusions

Prolonged malnutrition in anorexia nervosa results in extensive multisystem complications. The skeletal system is affected through impaired bone formation and increased resorption, leading to reduced bone density and a heightened risk of osteopenia, osteoporosis and fractures, often persisting beyond clinical remission. Endocrine disturbances reflect adaptive responses to energy deficiency but involve dysregulation of multiple hormonal axes, contributing to metabolic slowing, electrolyte imbalances, impaired growth and disrupted appetite regulation. Reproductive functions are compromised due to central suppression of gonadotropin secretion,

resulting in hypogonadism, amenorrhea, infertility, and increased obstetric risk. The gastrointestinal system exhibits structural, motility, and hormonal abnormalities that manifest as delayed gastric emptying, functional gastrointestinal disorders, and symptoms that can reinforce restrictive eating behaviors. Cardiovascular involvement is among the most serious complications, including autonomic imbalance, cardiac remodeling, electrophysiological instability, and vascular dysfunction, significantly increasing the risk of sudden cardiac events. Hematologic abnormalities arise from malnutrition-related bone marrow changes, leading to reversible cytopenias. Pulmonary complications include respiratory muscle weakness, structural lung changes and reduced ventilatory capacity, resulting in increased susceptibility to acute pulmonary events and infections.

Collectively, these findings underscore that anorexia nervosa is a serious, potentially fatal multisystem disease rather than an isolated psychiatric condition, necessitating early diagnosis, comprehensive multidisciplinary treatment, and long-term medical follow-up to reduce morbidity and mortality.

Disclossure

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