Psychiatr. Pol. 2022; 56(1): 89–100
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/126233

Mortality in extremely low BMI anorexia nervosa patients – implications of gastrointestinal and endocrine system dysfunction

Monika Suszko[1], Jacek Sobocki[1], Christian Imieliński[2]

[1] Prof. W. Orlowski Independent Public Clinical Hospital of the Medical Center for Postgraduate Education, Department of General Surgery and Clinical Nutrition

[2] Prof. W. Orlowski Independent Public Clinical Hospital of the Medical Center for Postgraduate Education, Department of Medical Sexology and Psychotherapy

Summary

Anorexia nervosa is a chronic disease classified as an eating disorder. It has a multifactorial aetiology and should be treated by a multidisciplinary team of specialists. Anorexia has many signs and symptoms, and usually affects young women. The complex clinical picture of anorexia is formed by numerous somatic and psychological symptoms. A high risk of mortality is associated with complications in all organs and systems. Body mass index (BMI) is an indicator in the diagnosis of anorexia, and BMI <15 kg/m² defines an extreme state in a patient. Data from a literature review and clinical practice show that a BMI <10 kg/m² is not uncommon. A specific BMI value associated with a particular medical complication has not been established, but many relationships have been reported. This article presents gastrointestinal and endocrine complications related to anorexia. It explains metabolic adaptations activated by the body to enable the survival of patients with very low body mass index (the lowest reported BMI was only 6.7 kg/m²).

Key words: anorexia nervosa, BMI, mortality

Introduction

Anorexia nervosa *(*AN) is a disease classified as an eating disorder. It is characterised by an intense fear of gaining weight, self-imposed food restriction, and a strong desire to lose weight (by excessive exercise and/or the use of laxatives) [1]. The clinical picture includes both psychological and somatic symptoms. Anorexia is associated with a significant increase in the risk of complications in all organs and systems (cardiovascular, central nervous system, gastrointestinal, as well as disorders

of acid-base and water-electrolyte homeostasis). Because of the wide spectrum of symptoms, chronic nature, high mortality and prevalence, anorexia is one of the most serious chronic diseases affecting girls and young women in developed countries. The treatment of anorexia is multistage and requires the cooperation of a multidisciplinary team of specialists. An accurate estimation of the prevalence rate of anorexia is difficult, since most gathered data concern hospitalised patients [2].

Anorexia is diagnosed based on criteria in the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders. Fourth edition) and ICD-10 (International Classification of Diseases and Related Health Problems. Tenth revision). According to DSM-IV, anorexia is diagnosed based on the following criteria: refusal to maintain bodyweight at or above minimally normal weight for height/age (less than 85th percentile); intense fear of gaining weight, even though underweight; disturbed by one's body weight or shape; self-worth influenced by body weight or shape. Recently, amenorrhea was dropped as a diagnostic criterion in DSM-5. The reason for this was the fact that anorexia also affects men, girls before menarche, and individuals on hormone therapy. DSM-5 also classifies atypical anorexia nervosa, which includes restrictive behaviours in individuals who do not have low body weight.

The main symptom of anorexia is low body weight and low body mass index (BMI). The DSM-5 classification includes four levels of severity of anorexia nervosa depending on the BMI value: extreme (BMI <15 kg/m^2), severe (BMI 15-15.99 kg/m^2), moderate (BMI 16-16.99 kg/m^2) and mild (BMI ≥17 kg/m^2) [1].

Aetiology of anorexia nervosa

There are multiple risk factors for anorexia nervosa. The psychopathology of eating disorders is thought to result from the combined effect of many biological, psychological, sociological and environmental factors. Genetics and personality predispositions are also involved [3].

A review of the literature has revealed that the risk factors for AN include obstetric and perinatal complications, as well as neonatal factors (birth defects, prematurity, low birth weight). Personality traits formed during childhood, including anxiety, depression, perfectionism, and low self-esteem have been identified as risk factors for the development of anorexia. Puberty is associated with many changes (e.g. in hormone levels affecting the functioning of neurotransmitters in the brain) and creates a particular predisposition to anorexia [1].

The risk of eating disorders is much higher in women. Dissatisfaction with body appearance, its shape and size, is a risk factor for the development of all eating disorders. The perceived pressure to be thin from the media, and the internalisation of the thin beauty ideal produces body dissatisfaction. However, social and cultural pressures alone do not explain the occurrence of eating disorders [3].

The susceptibility to anorexia is associated with neuroendocrine abnormalities in the pituitary-hypothalamic axis. Disorders in the regulation of food intake are associated

with the secretion of neuropeptides and neurotransmitters. The mental performance of patients depends on the stage of anorexia nervosa, its duration and severity [4].

Studies on the structure of the brain in subjects with anorexia nervosa have provided inconsistent results and reflect the heterogeneity of approaches, and take into account various limiting criteria. Faster loss of weight and stronger restriction of solid and liquid food is associated with a smaller volume of grey matter in the brain, which may not necessarily be linked with the pathophysiology of AN. Research by Frank [5] has revealed larger left medial orbitofrontal gyrus rectus volume in both adolescents and adults with anorexia nervosa. The orbitofrontal cortex (OFC) is responsible for controlling human behaviour and instincts, and for social functioning, for example, through integrity with the limbic system, which controls desires [5]. Studies investigating anomalies in the area of the orbitofrontal cortex and the insular cortex in subjects with anorexia explained why, despite not eating, they feel no hunger [4]. A larger volume of the orbitofrontal cortex may contribute to the ability to stop food intake before satisfying hunger [5]. Anomalies in the anterior part of the insular cortex are associated with changes of self-perception and interoceptive awareness. Therefore, patients with AN may suffer from a fundamentally and physiologically altered sense of self. Cerebellar dysfunction, at least in part, can affect some aspects of AN psychopathology, such as obsessive behaviour, compulsive rituals and perseveration. Although anorexia nervosa is associated with changes in the brain, these changes normalise as the patient recovers from the disease. Thus, these changes probably do not contribute to the neurobiological aetiology of AN [4].

Anorexia nervosa is a hereditary disease and data indicate that relatives of patients with AN have an 11 times higher risk of developing AN. The heritability rate estimated for anorexia nervosa is 0.48-0.74. Significant genetic correlations were reported between AN and BMI [6]. Studies revealed that estradiol moderates genetic influences on eating disorders. This is one of the most important epigenetic mechanisms of disease development. High estradiol status is associated with the magnitude of genetic effects regardless of age and physical signs of puberty [7]. Genetic and epigenetic factors contributing to AN have not been explained in detail. Genome-wide association studies *(*GWAS), despite inconclusive results, are expected to identify genetic markers of AN [6].

Complications related to anorexia nervosa

Unlike other psychiatric disorders, eating disorders are associated with a high incidence of medical complications. Deficiencies associated with malnutrition may be a predisposing factor for organ dysfunction. Dysfunction may affect almost all systems and organs. Dehydration, severe hypotension, arrhythmia and heart failure can cause critical reduction of organ perfusion. Some of the complications can be permanent and do not subside even after successful treatment of AN and normalisation of body weight [2].

Gastrointestinal system

Gastrointestinal symptoms are frequently reported by patients with anorexia nervosa. Salvioli et al. [8] examined 48 patients with eating disorders (including 39 with AN), and found postprandial fullness in 96%, abdominal distension in 90%, and abdominal pain and gastric distension in more than 50% of patients. There was also a significant correlation between gastroesophageal symptoms and values of the hypochondriasis scale. The presence of gastrointestinal symptoms is related to psychopathological traits. Oesophageal and gastrointestinal symptoms resolved in patients with normal hypochondriasis and hysteria scores [8].

Despite the fact that dysphagia is frequently reported in patients with AN, the lack of documented abnormalities in oesophageal motility may suggest other swallowing disorders [9]. Malnutrition leads to weakening of the throat muscles, and the ingested food, both liquid and solid, may be accidentally aspired. It is worth considering a diet including foods with more acceptable texture or the temporary insertion of a feeding tube, until sufficient weight gain is achieved and swallowing function has improved [3].

Food restriction may cause the development of gastroparesis (called delayed gastric emptying). Bloating, abdominal pain and early satiety are the main symptoms of this condition. Abnormalities in gastric emptying, which can be assessed by scintigraphy, eventually resolve with weight gain [10]. A rare complication of gastroparesis is gastric dilatation, which should be diagnosed by abdominal X-ray. This anomaly may lead to abdominal compartment syndrome (ACS). Progressive acute gastric dilatation increases intra-abdominal pressure (IAP), which threatens the function of many organs. In patients not diagnosed for this problem, acute gastric dilation may result in hemodynamic complications and, consequently, even death [9].

Functional disorders of the gastrointestinal system in patients with anorexia equally often include constipation and bloating. Reported data indicate that constipation affects about 67-83% of patients with AN. Functional constipation may be caused by restricted food intake or poor nutrition and hypokalaemia [10]. Many patients with chronic constipation have colonic distention due to rectal motor dysfunction, and this can inhibit gastric emptying [9]. It is unclear whether the delayed gastrointestinal transit, as a pre-existing physiological condition, predisposes patients to eating disorders, or delayed transit is a consequence of starvation. Approximately 41-52% of individuals with eating disorders have irritable bowel syndrome (IBS) and functional symptoms may persist even after recovery. Abdominal radiological tests may be useful in the diagnosis of these patients [10].

Another complication diagnosed in patients with anorexia is superior mesenteric artery syndrome (SMAS; Wilkie's syndrome). It is caused by the compression of the third and final portion of the duodenum between the aorta and the superior mesenteric artery. Significant loss of visceral (mesenteric) fat in patients with AN contributes to aortomesenteric angle reduction. The symptoms of SMAS include loss of appetite, postprandial abdominal pain along with early satiety, nausea and vomiting. Contrast-

enhanced abdominal computed tomography is useful in diagnosing SMAS. Treatment of SMAS is aimed at restoring normal body weight and mesenteric fat [10].

Abnormal levels of hepatic transaminases (aspartate transaminase – AST and alanine transaminase – ALT) have been reported in 43-53% of patients with anorexia nervosa on admission to hospital. Suggested aetiologies include ischaemic hepatitis caused by liver hypoperfusion, fatty liver disease with oxidative stress caused by low glutathione levels, and starvation-induced autophagy of hepatocytes [11]. It was clinically proven that the risk factors for increased levels of transaminases (greater for ALT than AST) are young age (<30 years), low BMI, restrictive anorexia nervosa (ANR) and male sex. Hanachi et al. [12] reported that ALT and AST levels normalised after four weeks of enteral nutrition in 96% of patients with AN. In addition, a significant correlation between elevated ALT levels during nutritional therapy and delayed onset of weight gain was recently demonstrated. The incidence of liver enzyme disorders also correlated with hypoglycaemia and the development of hypophosphataemia during refeeding [3].

Patients with more severe malnutrition require careful, progressive nutritional management, because excessive caloric intake may cause temporary fatty liver disease, detectable on ultrasound examination. It is suggested that fatty liver disease is a consequence of an imbalance between hepatic triacylglycerol synthesis and secretion with reduced lipoprotein synthesis, due to restricted availability of amino acids [13]. In malnourished patients the initial autophagic reaction allowing them to cope with nutrient deprivation is probably induced as the hepatoprotective mechanism by preventing hepatocyte cell death and liver insufficiency. When malnutrition progresses and BMI decreases, transaminase levels reach their peak, which is followed by liver insufficiency. Cell death occurs through autophagy, and hepatocytes are formed from numerous autophagosomes. Therefore, liver histological analysis does not disclose features of necrosis or apoptosis, despite a significant increase in detected levels of transaminases. Rare cases of acute liver damage were reported in patients with anorexia nervosa [14].

Acute pancreatitis is another rare complication in patients with AN, but it has been reported in patients at the early stages of nutritional therapy. Possible aetiology involves the relationship between malnutrition and duodenal stasis and the transformation of trypsinogen to trypsin. This leads to the subsequent activation of other proteases, which, as a result of bile reflux, cause damage to pancreatic cells [2].

Endocrine system

People with anorexia nervosa have a number of functional abnormalities in the endocrine system [15]. Various adipokines, such as resistin, adiponectin and leptin, as well as gastrointestinal hormones, ghrelin and anorexigenic neuropeptide PYY, play an important role in transmitting information between peripheral and hypothalamic appetite control centres. The level of leptin, an anorexigenic hormone secreted by

adipocytes after a meal, is significantly lower in women with AN [16]. In contrast, the levels of ghrelin, an appetite-stimulating hormone secreted by the stomach fundus, are elevated, probably in response to low energy status. A negative correlation between the level of ghrelin and BMI and body fat mass was reported. Clinical studies demonstrated the association between the parameters of endogenous ghrelin and levels of growth hormone (GH), cortisol, total triiodothyronine (T_3), and luteinizing hormone (LH) [17]. Paradoxically, the level of PYY hormone is elevated in patients with anorexia nervosa, as it is secreted by intestinal cells in response to food intake, which is reduced [18].

Hypercortisolaemia, which appears to result directly from malnutrition, has been reported in patients with AN. A study by Misra et al. [19] revealed that cortisol half-life trended higher in girls with AN, and cortisol levels did not reduce after a single oral glucose load. The authors of this report suggested that sustained weight recovery for a longer period of time may be necessary to see changes in other secretory characteristics and in cortisol response to an oral glucose load. This study also showed a negative correlation between cortisol and glucose and insulin levels, and documented that low glucose levels are a major factor stimulating cortisol secretion in AN. Thus, in malnourished individuals, cortisol is additionally involved in maintaining adequate blood glucose levels. The relationship between nutritional status and cortisol secretion was also confirmed by correlation analyses of cortisol and leptin levels [19]. Strong negative correlations between cortisol levels and markers of bone formation have also been reported. Therefore, high cortisol levels in patients with AN may be a factor responsible for bone loss [3]. In addition, high cortisol levels in patients with AN were negatively correlated with BMI and body fat mass [2].

In patients with malnutrition growth hormone is released more frequently, resulting in resistance to GH, and thereby reducing the level of insulin-like growth factor I (IGF-I). A positive correlation between the levels of IGF-I, an important anabolic hormone, and BMI and body fat mass was reported. IGF-I values vary depending on the state of undernutrition; for example, four days of fasting was associated with a 40% reduction in IGF-I levels, which normalized after the start of iv hyperalimentation [20]. Resistance to growth hormone may be an adaptive response to malnutrition. Low IGF-I levels help preserve energy by reducing expenditure on the growth of tissues, including the growth and maintenance of bone mass. GH levels probably increase as a result of positive feedback in the pituitary gland through low IGF-I levels [16], as well as in response to high ghrelin levels. During fasting and long-standing malnutrition, ghrelin receptors stimulate GH secretion, thus ensuring blood glucose levels sufficient for survival [17]. Increased GH levels may also be important for the mobilisation of fat reserves during nutritional deficiency. Therefore, elevated GH levels may be necessary for energy mobilisation, while low IGF-I levels help reduce energy consumption [16].

A strong correlation between thyroid hormone levels and nutritional status, i.e. BMI and body fat mass was reported [18]. The study indicated that levels of thyroxine (T_4) and T_3 in girls with AN were lower than in the control group. No changes were observed with regard to thyrotropic hormone (TSH) levels. Positive correlations between

total T_4 and T_3 and leptin levels, but negative correlations between these hormones and ghrelin were found [21]. Thus, low levels of leptin and ghrelin peaks in patients with AN can contribute to a decline in thyroid hormone levels [18]. These mechanisms are an adaptive response allowing the body to reduce its metabolic rate and therefore energy expenditure, as suggested by the fact that increases in T_3 with weight recovery are associated with increases in resting energy expenditure [16].

Food restrictions and excessive exercise reduce glycogen reserves in the liver and lead to the impairment of hepatic gluconeogenesis. Failure to maintain safe blood glucose levels in severe stages of AN may cause sudden death. Rare cases of reactive hypoglycaemia together with elevated levels of insulin secretion were reported in patients with anorexia nervosa after a rapid increase in energy intake. Reportedly, type 1 diabetes in patients with AN is associated with a higher risk of mortality. The glucose level in patients with AN is difficult to control. Mild hyperglycaemia (glucose levels lower than 250 mg/dl) is even acceptable in these patients during the early stages of nutritional treatment [2]. However, some patients with insulin-dependent diabetes can induce weight loss by reducing their insulin doses, thus inducing hyperglycaemia and osmotic diuresis, which accelerates microangiopathy [3].

Changes also affect sex hormones in both men and women with anorexia. Patients with AN have low levels of gonadotropins and significant oestrogen and testosterone deficiency. Low levels of gonadotropin-releasing hormone (GnRH), LH, and follicle-stimulating hormone (FSH) were also observed. The LH levels can be higher in patients with other endocrine disorders, such as polycystic ovary syndrome (PCOS) [15]. Most often, the absence of menstruation in patients with anorexia is a secondary complication and usually results from the loss of 10-15% of the normal body weight. Approximately 20% of patients may experience amenorrhoea before reaching significant weight loss. The incidence of fertility problems increases in patients with AN due to the absence of ovulation and decreased libido. Anorectic pregnant women are at higher risk of foetal abnormalities, miscarriages, caesarean section, as well as perinatal mortality [2].

Mortality in anorexia nervosa

Anorexia nervosa has the highest mortality rate of any psychiatric disorder, most likely because of complications. Most deaths of patients with AN are a direct consequence of starvation and cardiac complications [3]. Fifty percent of deaths in patients with anorexia are due to sudden cardiac events and developed arrhythmia, but are not due to the prolonged QT interval as was previously believed. Higher risk of death in critically ill patients is associated with hypoglycaemia. Leukocytopaenia and the associated increased risk of infection are also considered to be the leading cause of death in AN [15].

The reported standardised mortality ratio (SMR) was 0.71 for a 27-year observation period, 5.86 [22] and 12.8 [23]. These differences in SMR values may partly be attributed to the duration of the follow-up period in the analysed patients. Shorter stud-

ies revealed higher values of SMR. The weighted mortality rate (i.e. deaths per 1000 person-years) reported in a meta-analysis was 5.1 for AN, and one in 5 individuals who had died committed suicide [22]. The authors of a 21-year observational study reported that 50.6% of patients fully recovered, 10.4% still met diagnostic criteria for anorexia nervosa, and 15.6% of patients died [24]. Another study revealed the mortality rate at 6.6% [23]. Analysis of data from a Japanese database for 669 patients revealed 0.7% in-hospital mortality. Five patients who died had a BMI lower than 11 kg/m² [25]. Another study demonstrated that among 41 patients with severe AN (mean BMI: 10.1 ± 0.57 kg/m²) one patient died, two had myocardial infarction, two had acute pancreatitis, and five suffered from mental confusion [26]. According to the report, 14 patients with BMI lower than 11 kg/m² were admitted to hospital, and only seven of them survived [27].

Factors related to the mortality of hospitalised patients with AN remain unclear. Studies have demonstrated a strong correlation between the age of patients with anorexia and the risk of mortality. A higher survival rate is observed in young patients, and the disease gets worse with age [1].

BMI as a prognostic factor for the treatment of AN

Body mass index is one of the most useful and widely available measures of nutritional status. Kawai et al. [28] empirically demonstrated that body temperature and blood pressure fluctuated significantly depending on the patient's condition, which is why these parameters are more difficult to use as guidelines for the need for urgent hospitalisation. The researchers suggest that BMI is easier to use than the above-mentioned parameters, and its use may contribute to the prevention of serious medical complications.

It should be kept in mind that BMI and body weight do not always reflect the patient's actual physical status. Many patients with anorexia often drink large amounts of water before the scheduled medical appointment, and the hydration distorts test results. El Ghoch et al. [29] suggested a BMI cut-off ≤16.5 kg/m^2 as a clinical threshold for determining AN severity. BMI is used to determine the target body weight during treatment, with obvious adjustment for the baseline body weight and stage of puberty. In addition, the demand for energy during realimentation in patients with AN is associated with the initial BMI. In short-term weight-restored adult females with AN, BMI, but not body fat percentage or distribution, at inpatient discharge is associated with long-term normal weight maintenance [30].

There are no studies that determine what BMI value is associated with a particular medical complication, but many relationships have been reported [12]. Survival of patients with very low BMI is possible because of complex metabolic adaptations [31]. It is unclear, however, whether the metabolic adaptation is due to a reduction in fat-free body mass or due to the activation of energy-preserving mechanisms. Patients with anorexia nervosa and a mean BMI of 15.6 kg/m² had a reduced basal metabolic rate

(BMR) adjusted to fat-free mass (FFM) compared to patients who recovered from AN and controls with normal body weight. Several mechanisms could be responsible for changes in energy expenditure and metabolic adaptations to weight loss, including alterations in hormone levels, thyroid metabolism, insulin secretion and leptin levels [32].

According to the DSM-5 classification, extreme anorexia nervosa is diagnosed in patients with BMI <15 kg/m². The clinical implications of low BMI include a significant risk of chronic anorexia and death associated with emaciation. Hebebrand et al. [27] reported that BMI lower than 13 kg/m² was considered a cut-off value for weight loss and poor prognosis. Starving patients with BMI 13-14 kg/m² satisfy the demand for energy by converting fat into protein. It is believed that the rate of BMI reduction during starvation increases even more due to the metabolism of fatty acids that have the highest calorific value. When all fat reserves are depleted during starvation, other proteins in muscles (including the myocardium), blood and cell membranes are degraded [28].

Many adaptations in patients with extremely low BMI have been reported. One report presents the case of a 27-year-old woman from Japan with a BMI of 8.5 kg/m², admitted to hospital due to coma. Her condition strongly suggested the involvement of severe hypoglycaemia in the pathogenesis of central pontine myelinolysis *(*CPM). The patient survived but suffered permanent neurological damage [33]. However, even lower BMI values have been documented. One case report described a 29-year-old woman successfully treated in a specialist medical centre. Her BMI was 7.8 kg/m² on admission. She was fully conscious and had acceptable values of blood pressure, heart rate and body temperature, unexpected for a patient with such a low BMI [31]. The case of a 29-year-old woman with a BMI of 7.6 kg/m² was reported in 1990 [34].

It would seem that the body mass index of a live person could not be lower than that. A review of studies and clinical data revealed that the lowest BMI value ever recorded in AN patients was 6.7 kg/m². On admission to hospital a 31-year-old woman had a body weight of 19 kg with a height of 168 cm. After 10 days of nutritional therapy the patient suffered from an acute mitral valve endocarditis. Echocardiographic assessment furthermore showed severely impaired left and right ventricular function. Chronic malnutrition, as well as septic endocarditis that caused myocardial insufficiency resulting in an increased risk of death, renal failure and pneumonia were observed in this patient [35].

Conclusions

Anorexia nervosa is a multifactorial and multistage disease. AN is associated with the risk of many medical complications, and their severity increases with the decrease in the patient's body weight. Most of these complications, often serious ones, resolve after weight gain and nutritional treatment. Complex metabolic adaptations allow for the survival of patients even if they have extremely low BMI. The value of BMI beyond which survival is impossible cannot be clearly established. It is not certain if a BMI of

6.7 kg/m² is the critical and final cut-off value. However, the incidence of anorexia nervosa is clearly increasing, and this problem requires further and more detailed research.

References

1. Zipfel S, Giel KE, Bulik CM, Hay P, Schmidt U. *Anorexia nervosa: Aetiology, assessment, and treatment.* Lancet Psychiatry 2015; 2(12): 1099–1111.
2. Mehler PS, Brown C. *Anorexia nervosa – Medical complications.* J. Eat. Disord. 2015; 3: 11.
3. Westmoreland P, Krantz MJ, Mehler PS. *Medical complications of anorexia nervosa and bulimia.* Am. J. Med. 2016; 129(1): 30–37.
4. Kaye WH, Wierenga CE, Bailer UF, Simmons AN, Bischoff-Grethe A. *Nothing tastes as good as skinny feels: The neurobiology of anorexia nervosa.* Trends Neurosci. 2013; 36(2): 110–120.
5. Frank GK. *Advances from neuroimaging studies in eating disorders.* CNS Spectr. 2015; 20(4): 391–400.
6. Yilmaz Z, Hardaway A, Bulik C. *Genetics and epigenetics of eating disorders.* Adv. Genomics Genet. 2015; 5: 131–150.
7. Klump KL, Keel PK, Sisk C, Burt SA. *Preliminary evidence that estradiol moderates genetic influences on disordered eating attitudes and behaviors during puberty.* Psychol. Med. 2010; 40(10): 1745–1753.
8. Salvioli B, Pellicciari A, Iero L, Di Pietro E, Moscano F, Gualandi S et al. *Audit of digestive complaints and psychopathological traits in patients with eating disorders: A prospective study.* Dig. Liver Dis. 2013; 45(8): 639–644.
9. Chial HJ, McAlpine DE, Camilleri M. *Anorexia nervosa: Manifestations and management for the gastroenterologist.* Am. J. Gastroenterol. 2002; 97(2): 255–269.
10. Sato Y, Fukudo S. *Gastrointestinal symptoms and disorders in patients with eating disorders.* Clin. J. Gastroenterol. 2015; 8(5): 255–263.
11. Nadelson AC, Babatunde VD, Yee EU, Patwardhan VR. *Expanding the differential diagnosis for transaminitis in patients with anorexia nervosa.* J. Gen. Intern. Med. 2017; 32(4): 486–489.
12. Hanachi M, Melchior JC, Crenn P. *Hypertransaminasemia in severely malnourished adult anorexia nervosa patients: Risk factors and evolution under enteral nutrition.* Clin. Nutr. 2013; 32(3): 391–395.
13. De Caprio C, Alfano A, Senatore I, Zarrella L, Pasanisi F, Contaldo F. *Severe acute liver damage in anorexia nervosa: Two case reports.* Nutrition 2006; 22(5): 572–575.
14. Kheloufi M, Boulanger CM, Durand F, Rautou PE. *Liver autophagy in anorexia nervosa and acute liver injury.* Biomed. Res. Int. 2014; 2014: 701064.
15. Warren MP. *Endocrine manifestations of eating disorders.* J. Clin. Endocrinol. Metab. 2011; 96(2): 333–343.
16. Schorr M, Miller KK. *The endocrine manifestations of anorexia nervosa: Mechanisms and management.* Nat. Rev. Endocrinol. 2017; 13(3): 174–186.
17. Misra M, Miller K, Kuo K, Griffin K, Stewart V, Hunter E et al. *Secretory dynamics of ghrelin in adolescent girls with anorexia nervosa and healthy adolescents.* Am. J. Physiol. Endocrinol. Metab. 2005; 289(2): E347–E356.

18. Misra M, Klibanski A. *The neuroendocrine basis of anorexia nervosa and its impact on bone metabolism.* Neuroendocrinology 2011; 93(2): 65–73.
19. Misra M, Miller KK, Almazan C, Ramaswamy K, Lapcharoensap W, Worley M et al. *Alterations in cortisol secretory dynamics in adolescent girls with anorexia nervosa and effects on bone metabolism.* J. Clin. Endocrinol. Metab. 2004; 89(10): 4972–4980.
20. Grinspoon SK, Baum HB, Peterson S, Klibanski A. *Effects of rhIGF-I administration on bone turnover during short-term fasting.* J. Clin. Invest. 1995; 96(2): 900–906.
21. Misra M, Miller KK, Kuo K, Griffin K, Stewart V, Hunter E et al. *Secretory dynamics of leptin in adolescent girls with anorexia nervosa and healthy adolescents.* Am. J. Physiol. Endocrinol. Metab. 2005; 289(3): E373–E381.
22. Arcelus J, Mitchell AJ, Wales J, Nielsen S. *Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies.* Arch. Gen. Psychiatry 2011; 68(7): 724–731.
23. Eckert ED, Halmi KA, Marchi P, Grove W, Crosby R. *Ten-year follow-up of anorexia nervosa: Clinical course and outcome.* Psychol. Med. 1995; 25(1): 143–156.
24. Zipfel S, Löwe B, Reas DL, Deter HC, Herzog W. *Long-term prognosis in anorexia nervosa: Lessons from a 21-year follow-up study.* Lancet 2000; 355(9205): 721–722.
25. Nakamura M, Yasunaga H, Shimada T, Horiguchi H, Matsuda S, Fushimi K. *Body mass index and in-hospital mortality in anorexia nervosa: Data from the Japanese Diagnosis Procedure Combination database.* Eat. Weight Disord. 2013; 18(4): 437–439.
26. Rigaud D, Tallonneau I, Brindisi MC, Vergès B. *Prognosis in 41 severely malnourished anorexia nervosa patients.* Clin. Nutr. 2012; 31(5): 693–698.
27. Hebebrand J, Himmelmann GW, Herzog W, Herpertz-Dahlmann BM, Steinhausen HC, Amstein M et al. *Prediction of low body weight at long-term follow-up in acute anorexia nervosa by low body weight at referral.* Am. J. Psychiatry 1997; 154(4): 566–569.
28. Kawai K, Yamashita S, Yamanaka T, Gondo M, Morita C, Nozaki T et al. *The longitudinal BMI pattern and body composition of patients with anorexia nervosa who require urgent hospitalization: A case control study.* Biopsychosoc. Med. 2011; 5: 14.
29. El Ghoch M, Pourhassan M, Milanese C, Müller MJ, Calugi S, Bazzani PV et al. *Changes in lean and skeletal muscle body mass in adult females with anorexia nervosa before and after weight restoration.* Clin. Nutr. 2017; 36(1): 170–178.
30. El Ghoch M, Calugi S, Chignola E, Bazzani PV, Dalle Grave R. *Body mass index, body fat and risk factor of relapse in anorexia nervosa.* Eur. J. Clin. Nutr. 2016; 70(2): 194–198.
31. Frølich J, Palm CV, Støving RK. *To the limit of extreme malnutrition.* Nutrition 2016; 32(1): 146–148.
32. Polito A, Fabbri A, Ferro-Luzzi A, Cuzzolaro M, Censi L, Ciarapica D et al. *Basal metabolic rate in anorexia nervosa: Relation to body composition and leptin concentrations.* Am. J. Clin. Nutr. 2000; 71(6): 1495–1502.
33. Bando N, Watanabe K, Tomotake M, Taniguchi T, Ohmori T. *Central pontine myelinolysis associated with a hypoglycemic coma in anorexia nervosa.* Gen. Hosp. Psychiatry 2005; 27(5): 372–374.
34. Taguchi H, Enzan H, Shibuya K, Sato H, Ikeda H, Hara H et al. *Gelatinous transformation of the bone marrow in anorexia nervosa: Report of two cases.* Journal of the Japan Society Reticuloendothelial System 1990; 30(3): 193–199.

35. Beholz S, Hotz H, Grosse J, Konertz W. *Biventricular assist device in extreme anorexia nervosa.* Interact. Cardiovasc. Thorac. Surg. 2002; 1(1): 35–37.

Address: Monika Suszko
Prof. W. Orlowski Independent Public Clinical Hospital of the Medical Center for Postgraduate Education
Department of General Surgery and Clinical Nutrition
00-416 Warszawa, Czerniakowska Street 231
e-mail: monika.suszko@wp.pl