Refeeding syndrome as treatment complication of anorexia nervosa

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Summary

Refeeding syndrome (RS) is one of the serious complications during treatment of anorexia nervosa. It includes hormonal and metabolic changes that occur during the process of refeeding in chronically malnourished patient when nutrition is introduced in an excessive and improper amount. RS manifests in water-electrolyte imbalances, including hypophosphatemia (the most important diagnostic marker), hypokalemia, hyponatremia, hypomagnesaemia, fluid retention, vitamin deficiency and metabolic acidosis. It applies to either oral and parenteral supplementation. In the treatment of malnourished patients with anorexia nervosa, it is essential to establish an initial caloric amount that will stimulate weight gain from the beginning of treatment, increase its effectiveness while minimizing the risk of RS. Recent research suggests that the current recommendations may be too stringent in this respect and require further updating. Awareness of the risks associated with RS, including significant mortality, appears to be currently insufficient also among physicians. There is a need for far more specialized multidisciplinary centers for patients with anorexia nervosa and also appropriate algorithms and standards of care for that population. The aim of this paper is to systematize the current knowledge about RS and RS prevention, to increase awareness of its occurrence and present the results of the latest research on safe resupplementation of patients suffering from anorexia nervosa.

Key words: refeeding syndrome, anorexia nervosa

Introduction

Anorexia nervosa (AN) is a serious mental disorder whose incidence is currently estimated at 0.2–0.8% in adults and 0.5–1% in children, with men accounting for circa 10% of all patients [1]. Young women are most commonly affected, although in recent years there has also been an upward trend in other age groups. AN is characterized by the patient's need to lose weight, intentionally maintaining too low body weight and considerable fear of 'weight gain'.

Diagnostic criteria according to ICD-10 of the World Health Organization (10th revision of the International Statistical Classification of Diseases and Related Health Problems) [2] and DSM-5 issued by American Psychiatric Association (Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders) [3] are summarized in table 1.

Table 1. **Diagnostic criteria for anorexia nervosa**

ICD-10	DSM-5
significant weight loss by at least 15% of the expected weight for age and height, in adults BMI below 17.5; weight loss caused by the patient's intentional action (i.e., avoiding 'fattening' products, restrictive physical exercise, using laxatives or vomiting); distorted body image, accompanied by fear of gaining weight, obesity, despite considerable underweight; numerous hormonal disorders (absence of menstrual cycles in women, libido and potency decrease in men); if onset is pre-pubertal, the sequence of pubertal events is delayed or even arrested.	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 the minimally normal one. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight. 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.
A patient is diagnosed with AN if the above symptoms occur. In other cases, atypical anorexia is diagnosed.	There are two types of anorexia restricting type – during the last three months, the individual has not engaged in recurrent episodes of binge eating or purging behavior. This subtype describes presentations in which weight loss is accomplished primarily through dieting. binge-eating/purging type – during the last three months, the individual has engaged in recurrent episodes of binge eating or purging behavior.

Consequences of chronic malnutrition for the patient's health are very serious. AN is characterized by the highest mortality of all mental disorders. About 10–20% of patients die from AN complications [1], while duration of the illness increases the risk of death [4]. Among the main causes of death are suicide and sudden cardiac arrest [1]. The consequences of AN affect all important systems and organs: cardiovascular complications such as bradycardia, arrhythmias, peripheral edema, hematological complications in all blood cell lines and musculoskeletal complications, which might impair mobility. Serious electrolyte, biochemical and hormonal disorders also occur. For this reason, the cooperation of specialized non-psychiatric institutions in the initial care of severely debilitated patients in unstable somatic condition is of paramount im-

portance. This care should be focused on the normalization of existing disturbances, stabilization of the somatic state and safe introduction of nutritional treatment, including refeeding syndrome prophylaxis.

Refeeding syndrome – definition and prevalence

Refeeding syndrome (RS) was first described after World War II in victims released from concentration camps, when they were restarted oral nutrition after a long period of starvation. Other commonly used name of the disease is food shock syndrome. In addition to patients suffering from AN (mainly restricting type), it may also occur in people with cancer, malabsorption, or alcoholism [1].

There is no unambiguous definition of RS, which significantly impedes the interpretation of medical data. It is most often described as acute hormonal-metabolic disturbance in severely debilitated patients who were fed too fast and were given too much food, both orally and parenterally. It manifests itself by water-electrolyte imbalances, including hypophosphatemia (the most important diagnostic marker), hypokalemia, hyponatremia, hypomagnesemia, fluid retention, vitamin deficiency and metabolic acidosis (table 2). Since there is no clear definition, different research groups adopt different criteria for RS diagnosis. Most of them accept only hypophosphatemia and other electrolyte disturbances as the criterion of inclusion, while others take into account also clinical symptoms. This results in a lack of clear data to estimate the incidence of the syndrome.

Table 2. **Main features of refeeding syndrome**

Hypophosphatemia
Hypomagnesemia
Hypokalemia
Disorders of glucose management
Fluid retention
Vitamin deficiency (thiamine)

Pathomechanism of refeeding syndrome

Pathomechanism of RS is complex, leading to abnormalities in the metabolism of glucose, electrolytes and vitamin B1 (thiamine) [5]. During long-term hunger (shortage of glucose supply), insulin levels drop and glucagon levels rise. The organism uses alternative energy sources and produces glucose from substitutes such as amino acids and triglycerides in order to gain energy. It leads to glycogenolysis in the liver, lipolysis in fatty tissue, and, with use of glycerol and amino acids, gluconeogenesis

in muscles. Ketone bodies and free fatty acids become the main source of energy [6]. As a result of the above processes, large amounts of ions are consumed, leading to their deficiencies [1].

After a long period of starvation, when the body is provided with relatively excessive amount of food, insulin level increases, leading to rapid movement of potassium, magnesium and phosphorus ions into the cells, significantly enhancing their serum deficiency and resulting in deep electrolyte disturbances..

Phosphorus – the main marker of RS

Phosphorus is the dominant intracellular ion, important compound of cell membrane, and, most importantly, the component of energy transfer compounds (ATP – adenosine triphosphate and ADP – adenosine diphosphate), which regulate all processes occurring in cells. Phosphorus deficiency results in cellular dysfunction and can have multiple consequences: weakened myocyte contraction strength (in the case of respiratory muscles and cardiomyocytes it may lead to respiratory failure, decreased ejection fraction and heart failure) or impaired neutrophil function, which increases the risk of infection and other hematological complications [5, 7]. In extreme cases, due to atrophy of the myocardium, there is an increased risk of overload [8]. Other common complications of hypophosphatemia are gastrointestinal disorders accompanied by nausea and vomiting. If the described symptoms last longer, they may lead to the development of neurological disorders – paresthesia, convulsions, delirium, and paralysis [5].

In one large cohort study conducted in intensive care units, hypophosphatemia was reported in 34% of patients after initiation of a nutritional therapy [9]. According to current standards of pharmacological treatment, interventions should be implemented when phosphorus concentration drops below 0.8 mg/dl; levels below 0.5 mg/dl are defined as alarming [1]. After initiation of feeding, the highest decrease in phosphate levels can be expected on day 2 and 3, while the lowest values were observed on day 5 [10]. Kameoka et al. [11] identified three risk factors for refeeding hypophosphatemia during nutritional replenishment in hospitalized patients with AN: initial significantly lower body mass index, older age, and higher blood urea nitrogen (BUN). There was no correlation between hypophosphatemia and total energy intake.

In addition to phosphorus deficiency, other dyselectrolitemias (mainly potassium and magnesium deficiency) may cause a variety of complications, including the most dangerous – ventricular arrhythmias, the most common cause of death in patients with RS [12]. Insulin, due to its antinatriuretic properties, promotes fluid retention and hypovolemic hyponatremia, manifested by peripheral edema, pul-

monary stasis, and circulatory failure [13]. For this reason, fluid supplementation should be cautious.

Due to increased tissue resistance to endogenous glucose after a period of starvation, hyperglycemia and, as a consequence, metabolic acidosis may develop in early days of refeeding. Excess glucose also leads to lipogenesis (stimulated by insulin) increasing the risk of fatty liver, hypercapnia and respiratory failure [6].

Patients with malnutrition may have multiple vitamin deficiency, including thiamine (vitamin B1), further deepened in the refeeding process [5]. Vitamin B1 is an essential cofactor in carbohydrate metabolism. Thus, their high supply increases demand for thiamine. For this reason, it is important to observe the patient for acute vitamin B1 deficiency and for Wernicke encephalopathy and Korsakoff's syndrome which are associated with disturbance of consciousness, vision problems, symptoms of acute peripheral neuropathy, and sudden cardiac complications [13].

Prophylaxis of refeeding syndrome

First of all, prevention of RS involves identification of high risk patients. It is highly important since mortality in advanced RS can be as high as 70% of cases [14]. In 2006, the National Institute for Health and Clinical Excellence (NICE) identified RS risk factors (table 3) [15].

Table 3. **RS high-risk patients according to the National Institute for Health and Clinical Excellence (NICE)**

The patient has at least one factor of the following:
BMI lower than 16 kg/m^2
Weight loss greater than 15% within the last 3–6 months Little or no nutritional intake for more than 10 days Low levels of electrolytes prior to refeeding
or the patient has two or more of the following:
BMI 16–18.5 kg/m^2 Weight loss greater than 10–15% within the last 6 months Little or no nutritional intake for 5–10 days A history of alcohol abuse or drugs including antacids, diuretics, chemotherapy or insulin.

BMI <15 kg/m^2 is an indication for hospitalization in AN; almost all hospitalized patients demonstrating the above value are high-risk RS patients.

The next steps should involve a systematic assessment of the patient's condition and gradual introduction of nutritional treatment. The initial period of refeeding is particularly important, because in most studies RS was observed in the first 72 hours of feeding [16].

Initial calorie supply

Too rapid introduction of caloric overload results in a development of RS. Thus, establishing a safe level of caloric intake in the proposed diet is a key issue. During a hospitalization period the recommended weight gain should be gradual and range from 0.5 to 1.5 kg per week. According to widely applied recommendations – in order to minimize the risk of RS, initially the food intake should be low and it should be increased slowly ("start low and go slow") depending on the risk of RS. Authors of the Management of Really Sick Patients with Anorexia Nervosa (MARSIPAN), developed in 2014, recommend commencing a supply of 20 kcal/kg/day in AN patients with moderate risk of RS development. Later on, the supply should be increased by 10–20% every 2–3 days to 1800–2200 kcal/day or more, if required. For patients with a high risk of RS (significant ECG deviations, severe electrolyte disturbances, unstable somatic condition, BMI <12 kg/m^2), more restricted supply (5–10 kcal/kg/day) is advisable. It then should be gradually increased, to 20 kcal/kg/day until somatic stabilization [17]. The NICE guidelines are more rigorous in this matter (maximum 10 kcal/kg/day) [15].

Current controversies

Recent studies undermine the above recommendations and show that in young people with AN it is not necessary to implement such a high caloric restriction at the beginning of the refeeding process. The authors postulate that higher caloric diet (1500–2500 kcal/day) and faster energy supply (by 250 kcal/day) is therapeutically more effective (reduced initial weight loss and shortened hospitalization period) without increasing the risk of RS [18, 19]. The authors of a large retrospective study comparing the efficacy of different initial caloric intakes have shown that with the increase in dietary calorie intake in adolescents with AN, the risk of developing RS does not increase [20]. The authors of the study found that higher calorie intake had an effect on the effectiveness of treatment – it shortens the duration of hospitalization at a similar risk of RS. None of 310 patients developed RS, with 47 people developing hypophosphatemia which was continuously supplemented. Researchers associate hypophosphatemia with the initial level of malnutrition but not with the calorie content of the diet. Interestingly, the authors also hypothesized that if carbohydrates initiate insulin burst, the development of hypophosphatemia may depend more on carbohydrate content than on total caloric load.

Similar findings have been reported by the authors of first randomized trial in which 18 patients aged 10–16 years were randomized to 2 groups with a diet starting at either 500 kcal/day or 1200 kcal/day. The latter diet was associated with a higher BMI after 10 days but not with a higher rate of medical problems, including hypophosphatemia.

The authors of the study found that hypophosphatemia occurred in patients with a low BMI and reduced white blood cells at admission [21].

On the other hand, the authors of a prospective study on weight gain in adolescent population with AN concluded that the use of current guidelines effectively prevent the onset of RS [22]. They have, however, noticed that the use of these guidelines increases the risk of initial weight loss and significantly delays weight gain, as well as prolongs hospitalization. In 2015, the International *Journal of Eating Disorders* published a systematic review of studies on refeeding in AN [23]; its authors concluded that current guidelines for patients with mild or moderate malnutrition are too restrictive and recommend increasing the caloric intake in both groups. However, it is not clear enough whether an increase in the caloric intake in people with severe malnutrition is safe. The authors also point out the need for systematic supplementation of possible electrolyte deficiencies as a necessary condition in prophylaxis of RS.

Monitoring and supplementation

In the initial period of refeeding, a regular assessment of the patient's condition – body weight, cardiovascular parameters (heart rate monitoring), presence of edema, fluid balance, and laboratory results – is necessary. The electrolyte concentrations (phosphates, Ca^{2+}, K^+, Mg^{2+}) and glucose should be tested daily for the first 5–7 days. The first dose of thiamine –100 mg should be given before the introduction of refeeding and then continued at doses of 100 mg/day for the first 5 days [1]. Regular prevention of electrolyte imbalance, preferably intravenously, is also necessary for RS prophylaxis. According to NICE guidelines (table 3), the simultaneous initiation of nutrition and alignment of electrolyte imbalance is recommended [15]. Daily doses are as follows: 2–4 mmol/kg of potassium, 0.3–0.6 mmol/kg of phosphorus, calcium and 0.2 mmol/kg intravenously or 0.4 mmol/kg orally of magnesium [6].

If RS appears, nutrition should be stopped and existing electrolyte imbalance should be aligned. Serious complications (heart failure, arrhythmia, respiratory failure, hematological disorders) involve the need for specialist consultations and implementation of appropriate treatment, including hospitalization. According to clinical practice, in the case of RS development the patient should be provided with half of the baseline caloric intake after having been stabilized.

Collaboration in treating AN

Unfortunately, there is still lack of multi-specialty centers treating AN and appropriate algorithms for specialized care. At present, the problem of inadequate referral of patients who are severely debilitated due to AN seems to be a major problem for
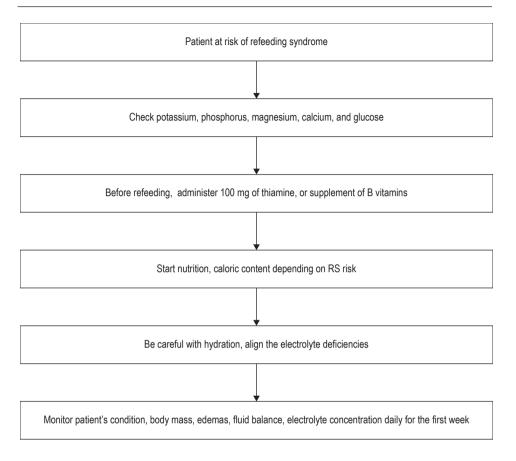
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│                    Patient at risk of refeeding syndrome                   │
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│           Check potassium, phosphorus, magnesium, calcium, and glucose     │
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│      Before refeeding,  administer 100 mg of thiamine, or supplement of B vitamins │
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│             Start nutrition, caloric content depending on RS risk          │
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│             Be careful with hydration, align the electrolyte deficiencies   │
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┌─────────────────────────────────────────────────────────────────────────┐
│ Monitor patient's condition, body mass, edemas, fluid balance, electrolyte concentration daily for the first week │
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Figure 1. **Recommendations for treating patients with increased RS risk – based on the 2006 NICE guidelines**

psychiatric outpatient clinics usually lacking internal medicine support. There is widespread conviction that BMI lower than 13.5 is a life threatening condition associated with a high risk of sudden death. For this reason, extremely emaciated patients (BMI <13) should be referred to an internal ward (or intensive care unit in the case of acute complications) where their somatic status should be stabilized at first, and then nutritional treatment should be introduced according to the prophylaxis regimen. Only after stabilizing the somatic state and achieving a safe BMI, patients can be transferred to a psychiatric ward and undergo further treatment of AN.

Recapitulation

Malnutrition in the course of AN leads to many disorders in the functioning of the organism and promotes development of RS. Although it is a relatively rare complication, it should be remembered for its high mortality rate. In its prophylaxis, it is essential to identify high-risk patients and then to introduce a safe caloric load, to monitor patients' condition systematically and to compensate possible electrolyte deficiencies. The initial caloric level should stimulate weight gain from the onset of treatment, increase its effectiveness while minimizing the risk of RS. Recent research suggest that current recommendations may be too stringent and require further updating. Following stages of treatment should be carried out in adapted units. At first, stabilizing the somatic state and avoiding serious somatic complications in patients should be conducted in internal medicine wards. After stabilizing the somatic state, treatment should be continued in psychiatric units, preferably in centers specializing in eating disorders.

AN treatment should involve multidisciplinary approach including nutritional, internal medicine, psychiatric and psychological care. For this reason it is also important to develop appropriate cooperation procedures between specialist centers and to create effective and safe treatment for AN patients also in the context of RS. The specifics of the treatment of eating disorders, its prevalence and serious eating disorders-related risks, but also special requirements (highly trained staff and other well-defined conditions), should cause establishing a nationwide network of highly specialized units to be one of the main targets in development of psychiatric care. The current situation should be considered as highly insufficient.

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