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Refeeding syndrome as a serious complication of treatment of patients with anorexia nervosa - a literature review

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Abstract

Introduction and purpose of the work: Refeeding syndrome (RFS) is an acute, life-threatening hormonal and metabolic disorder that appears in the initial period of treatment in patients with anorexia nervosa with moderate or severe malnutrition as a result of inadequately managed nutritional therapy. The purpose of this article is to describe and draw special attention to this serious complication, as well as to summarize the latest research and guidelines on nutritional rehabilitation in these patients. Information was collected from the English-language databases Google Scholar and PubMed.

State of knowledge: Due to the chronic state of malnutrition and significant electrolyte and vitamin deficiencies in patients with anorexia nervosa, the process of refeeding is associated with the risk of acute electrolyte disturbances such as hypophosphatemia, hypokalemia, and

hypomagnesemia, which can lead to severe cardiac, respiratory, hematologic, and neurological complications. Symptoms usually appear within 2 to 5 days of initiating refeeding. Currently, the lack of a standardised definition and the non-specificity of the symptoms make it difficult to both estimate the incidence and diagnose refeeding syndrome.

Summary: The latest research proves that, compared to previous protocols, a safe start to the nutritional process may be based on a moderately increased starting caloric intake, as this results in faster weight gain and shortens the treatment time. HCR has been proven to be safe and effective, without significantly increasing the risk of refeeding syndrome. Additionally, it is crucial to monitor the levels of phosphates, magnesium and potassium and early supplementation of these electrolytes to prevent and alleviate the symptoms of refeeding syndrome. Further research is still needed to optimize nutritional protocols that take into account individual patient needs and minimize the risk of refeeding syndrome.

Key words: refeeding syndrome, anorexia nervosa, hypophosphatemia, refeeding hypophosphatemia

INTRODUCTION

Anorexia nervosa (AN) is an eating disorder involving deliberate, chronic starvation, which consequently leads to excessive weight loss. This is also accompanied by excessive physical activity, which further contributes to cachexia. The incidence of this disorder varies with age and gender and mainly affects young women. According to statistics, it is 0.8–6.3% in women and 0.1–0.3% in men [1]. Anorexia is strongly associated with mental disorders such as depression, anxiety, obsessive compulsive disorder and personality disorders. Anorexia has the highest mortality rate of all psychiatric disorders [2,8], with suicide being the leading cause of death [3]. In addition, the consequences of excessive food restriction affect all important systems and organs. These include cardiovascular complications such as cardiac arrhythmias, bradycardia, haematological complications involving all cell lines, and musculoskeletal complications that may impede independent mobility. Severe electrolyte, biochemical and endocrine disturbances also occur [1]. Treatment of anorexia nervosa requires an integrated approach that includes psychotherapy and appropriate nutritional supplementation. The most important thing is to limit further weight loss and monitor serious complications such as refeeding syndrome [5].

OBJECTIVE

The aim of this study is to draw attention to a serious complication of the treatment of patients suffering from anorexia, i.e. refeeding syndrome, and to increase awareness of its occurrence, as well as to summarize the latest research and guidelines on RFS prevention and nutritional rehabilitation in these patients.

METHODS

Information was collected based on a review of current knowledge from English-language databases: Google Scholar and Pubmed. The available literature from 2019-2024 was reviewed to characterise the issue of refeeding sydrome. Particular attention was paid to publications on refeeding syndrome in association with anorexia. Search keywords included: refeeding syndrome, anorexia nervosa and hypophosphatemia.

STATE OF KNOWLEDGE

Refeeding syndrome-definition

Refeeding syndrome is defined as medical complications resulting from fluid and electrolyte shifts following aggressive nutritional rehabilitation [7]. Other common terms include refeeding syndrome and food shock syndrome [2]. This is a potentially fatal complication of calorie reintroduction in patients treated for anorexia nervosa [6]. This is a potentially fatal complication of calorie reintroduction in patients treated for anorexia nervosa [6]. It occurs primarily during the first phase of intensive feeding by both enteral and parenteral routes, with enteral feeding posing the highest risk of RFS [4,12]. Consequently, it can lead to potentially fatal complications such as cardiac arrest, arrhythmia, coma, convulsions and sudden death [10].

Historical background

Although refeeding syndrome was first described many years ago, its incidence is still difficult to determine because there is no universally accepted definition [7].

The historical context of the re-feeding syndrome is based on clinical observations from World War II. The first information on this syndrome appeared when doctors noticed serious complications in starved people, especially prisoners of war and concentration camp victims, who were given food after a prolonged period of starvation. This phenomenon began to be

analysed in more detail when attempts were made to restore these people to health by giving them standard, caloric food. They then experienced rapid drops in electrolytes, especially phosphate, as well as hypoglycaemia, oedema and cardiovascular disorders, which were sometimes fatal.

Refeeding syndrome, as a distinct clinical entity, began to be defined in the 1950s, when scientists began to document the effects of sudden resumption of feeding after periods of fasting in various population groups, including people with chronic diseases requiring nutritional support [15].

A breakthrough in understanding the physiological mechanisms of RFS took place in the 1970s and 1980s, when studies showed that a sudden increase in carbohydrates after a period of starvation causes a rapid increase in insulin levels and a rapid movement of electrolytes such as phosphate, potassium, and magnesium into cells. This results in severe deficiencies of these electrolytes in the serum, leading to multi-organ complications.

In the 1980s and 1990s, refeeding syndrome was recognized as a common complication in cachectic and anorexic patients who were beginning the proces of intensive refeeding. Practical guidelines, including studies by the National Institute for Health and Care Excellence (NICE), recommended implementing a strategy of gradually increasing calories and monitoring electrolyte levels to prevent the occurrence of RFS [17,19,20].

Pathophysiology

Refeeding syndrome develops as a result of a sudden metabolic change after a period of prolonged starvation. In malnourished individuals, the body enters a state of catabolism in which fat and protein reserves become the primary source of energy and insulin levels fall, leading to depletion of glycogen reserves and electrolyte disorders. After starting nutritional therapy, especially with a sudden increase in carbohydrate intake, the body goes into a state of anabolism and there is a rapid increase in insulin levels in the blood, which causes numerous metabolic changes. Insulin stimulates glucose uptake and causes a shift of key electrolytes, such as phosphate, potassium and magnesium, from the extracellular space to the interior of the cells, leading to their deficiency in the blood [7,9,11]. As a consequence of the above mechanisms, hypophosphatemia occurs, which is the main indicator of this syndrome, hypokalemia, hypomagnesemia, metabolic acidosis and vitamin deficiency - mainly thiamine, which plays a key role in energy processes, including glycolysis. The increase in insulin also increases sodium and water retention in the body.

Clinical symptoms

Symptoms usually appear within 2-5 days of restarting feeding, and their severity depends on the previous degree of malnutrition and comorbidities. They can range from mild to severe and life-threatening [14].

The most relevant aetiological factor in this syndrome and the main target for clinical monitoring is low serum phosphorus, known as refeeding hypophosphatemia (RH). RH occurs in up to 38% of anorexic patients and is used as an indicator for the development of RFS [13,21]. Hypophosphatemia (< 1 mmol/l) is often the initial symptom of refeeding syndrome [24]. Phosphorus is essential for ATP production and its deficiency can lead to impairment of the heart, skeletal muscle and respiratory system. Clinical manifestations may include impaired cardiac contractility, arrhythmias and breathing difficulties due to dysfunction of the respiratory muscles (including the intercostal muscles and diaphragm) [16,18]. Phosphorus deficiency can also cause nausea and vomiting, which can subsequently lead to the development of neurological disorders - paresthesias, convulsions, delirium and paralysis [2]. Hypophosphatemia can also cause serious haematological complications such as haemolytic anaemia due to reduced production of 2,3-bisphosphoglycerate (2,3-DPG) and ATP. The development of haemolytic anaemia occurs as a result of impaired membrane pumps and impaired metabolic pathways, particularly inhibition of glycolysis or insufficient magnesium supply. Anaemia is manifested by pallor, yellowing of the skin and general weakness. In addition, there are immunological disturbances due to neutrophil dysfunction (impaired chemotaxis) manifested by susceptibility to infection and bleeding.

Another element whose reduction in serum is a component of the refeeding syndrome is potassium. Hypokalaemia can lead to electrochemical membrane potential abnormalities, resulting in potentially fatal arrhythmias and even cardiac arrest. Supraventricular arrhythmias, e.g. atrial fibrillation, are much more common in this syndrome, and significant electrolyte deficiencies can lead to ventricular arrhythmias. These are the most common cause of death in patients with RFS [25].

An additional component of this syndrome is hypomagnesaemia. Magnesium is a cofactor for many enzymes, e.g. the sodium-potassium pump, and its deficiency can lead to cardiac dysfunction and complications from the muscular and nervous systems such as ataxia, seizures and paresthesias.

Vitamin B1 (thiamine) deficiency is also very common in the re-nutrition syndrome. When nutrients are reintroduced after a period of starvation, the need for thiamine increases significantly because it is a cofactor for glucose-dependent metabolic pathways. Its deficiency

results in neurological disorders, Wernicke's encephalopathy (visual abnormalities, ataxia, confusional state, hypothermia, coma) or Korsakov's syndrome (retrograde and subsequent amnesia, confabulations), as well as oculomotor disorders (horizontal ophthalmoplegia). Thiamine deficiency can also lead to insufficient ATP production in cardiomyocytes, which can result in oedema, congestive failure and cause cardiac arrhythmias [7,18].

In addition, the refeeding syndrome poses the risk of oedema and cardiovascular overload, which can lead to complications such as heart failure. This happens as a result of an increase in insulin, which increases sodium and water retention in the body.

Risk factors for refeeding syndrome in patients with anorexia nervosa

Patients with long-term anorexia are at particular risk of developing refeeding syndrome (RFS) due to the metabolic and electrolyte disturbances and cachexia that occur. Patients who have a very low body mass index (BMI less than 16 kg/m²) are particularly susceptible to the risk of RFS. They have significant deficiencies in energy stores, electrolytes and micronutrients, which promotes sudden electrolyte changes when starting a diet.

Pre-existing electrolyte disturbances or vitamin deficiencies occurring prior to the onset of re-alimentation are also an additional adverse factor. There is also an increased risk of RFS in patients who have lost more than 15% of body weight in the past 3-6 months. Such rapid weight loss often leads to depletion of intracellular stores of phosphate, potassium and magnesium, which are essential for ATP synthesis and stable cellular function. It is also worth paying attention to drugs often used by patients suffering from anorexia nervosa, such as diuretics, laxatives or psychotropic drugs, which have a negative effect on electrolyte disturbances and the body's defense mechanisms and may therefore increase the risk of refeeding syndrome [22,23].

Diagnostic criteria

The American Society for Parenteral and Enteral Nutrition (ASPEN) published consensus recommendations on RFS in 2020, defining standardised diagnostic criteria for future studies. RFS is defined as a decrease in serum phosphate, potassium and/or magnesium of 10-20% (mild), 20-30% (moderate) or > 30% (severe), with or without organ damage, within 5 days of resumption of previously significantly reduced calorie intake [16].

Diagnostics

Early diagnosis of RFS in patients with anorexia is crucial to prevent serious complications. Diagnosis is based on monitoring electrolytes (mainly phosphate, potassium and magnesium levels), cardiac function (ECG) and performing blood gas tests to assess acid-base balance.

Prevention of refeeding syndrome

A key aspect of the treatment of patients with anorexia is weight gain and the prevention of refeeding syndrome. Regular monitoring of laboratory parameters is essential, as well as the introduction of appropriate preventive measures.

There is no clear scientific position yet on the amount of calories that a person at risk of RFS should consume [26]. Publications and recommendations produced before 2015 were based on a cautious introduction and a gradual increase in calorie supply during the initial phase of nutritional rehabilitation [27]. At that time, the 'start low, go slow' principle was followed (start low in calories, increase slowly). Refeeding in the United States started at about 1200 calories per day, with a slow increase of about 100 calories per day (kcal/d). In Europe and the UK, increasing calories by 200-600 kcal/d was recommended. Low calorie refeeding (LCR) aimed to minimise the risk of developing refeeding syndrome [28,29].

More recent studies are increasingly questioning this approach, as LCR has been shown to be associated with prolonged hospital stays and leads to excessively slow weight gain, which delays full rehabilitation and may even lead to weight loss in patients who are already severely malnourished [10,30]. Additionally, it has been shown that even with low calorie intake, RFS is still documented [27,32].

A number of studies have been published in recent years demonstrating the safety and efficacy of higher calorie intake. Higher calorie refeeding (HCR)-initial intake ≥2000 kcal/day and increasing by 200 kcal-has been shown not to be associated with a higher incidence of refeeding syndrome (RFS) [23]. In addition, it has been pointed out that more rapid normalisation of body weight is associated with lower costs- this is an important aspect both organizational and economic.

Koerner et al. [23] conducted a retrospective review of medical records of 103 severely underweight (BMI <13 kg/m^2) adults with anorexia nervosa. The initial weight restoration strategy was based on oral intake of 2000 kcal/d from the first day of treatment and resulted in an average weight gain of 1040 g/week over four weeks. Combined with close medical

monitoring and phosphate and thiamine supplementation, accelerated refeeding was shown not to increase the risk of RFS in severely malnourished adult patients with AN.

Cuntz et al.[33] conducted an observational study to verify whether rapid refeeding improves the health status of patients with severe cachexia. Patients received three meals with an average total energy value of 2000 kcal per day from the first day after admission. Phosphate (1024 mg/day) and thiamine (200 mg/day) were routinely supplemented. This study showed that rapid nutrition under close medical supervision, with additional phosphate and thiamine supplementation and electrolyte substitution whenever necessary, was safe even in extremely malnourished patients with mental anorexia. Apart from hypervolaemia, there was no evidence of refeeding syndrome.

Dalenbrook et al. [30] conducted a retrospective chart review of patients with AN aged 12-20 years and with a body mass index (BMI) < 15 kg/m². All patients received 2000 kcal/day from day one and routinely received no prophylactic phosphate replacement. After four weeks of treatment, severely malnourished adolescents with AN achieved the recommended weight gain targets of between 0.5 and 1 kg/week, without anyone developing refeeding syndrome (RFS). Only nine patients (7.5%) developed mild hypophosphatemia. It was shown that HCR was not associated with RFS even in severely malnourished adolescents with AN.

Golden et al. [31] in a randomised controlled trial reported one-year results of clinical remission and readmissions of patients with anorexia treated with a higher calorie diet (2000 kcal per day, increasing by 200 kcal per day). Follow-up visits took place after 10 days and at 1, 3, 6 and 12 months after discharge. At each visit, the patient's height, weight and vital signs were recorded. Clinical remission at 12 months after discharge was defined as weight restoration (≥95% of median BMI) plus mental health recovery as measured by a global Eating Disorder Examination Questionnaire (EDE-Q) score within 1 SD of community norms. This multicentre RCT found that at 1 year, clinical remission rates did not differ between HCR and LCR. HCR was not associated with higher rates of medical readmissions, number of hospital readmissions or an increase in total hospital days after initial admission. In contrast, higher-calorie refeeding (HCR) was associated with more rapid weight gain and shorter hospital stay without an increased risk of electrolyte abnormalities, cardiovascular abnormalities or refeeding syndrome.

Draffin et al. [21] conducted a pilot study of 23 children and adolescents under 18 years of age with anorexia nervosa to compare the effects of a low-carbohydrate (<40% total energy from carbohydrate) and standard (50-60% total energy from carbohydrate) feeding protocol on serum phosphate levels. Participants considered to be at high risk of RFS were those who

consumed minimal carbohydrates for 7-10 days. They were started on a meal plan providing 1500 kcal/day (6300 kJ). All other participants were started on a meal plan providing 2000-2500 kcal/day (8400-10 500 kJ). Study participants were randomly assigned to a low-carbohydrate eating plan that provided less than 40% of total energy from carbohydrate or a standard carbohydrate eating plan that provided 50–60% of total energy from carbohydrate. Phosphates were not routinely administered to the subjects. Serum phosphate levels were monitored daily for the first week and twice weekly thereafter. Clinical status, including weight gain, was monitored throughout the admission period. The study showed that no patient in either diet group developed hypophosphatemia associated with refeeding. In addition, it was confirmed that a calorie-equivalent, low-carbohydrate oral diet (<40% of total energy) starting at a minimum of 1500 kcal/day offered no advantage over a standard carbohydrate-based oral diet (50-60% of total energy) in reducing the incidence of refeeding hypophosphatemia and refeeding syndrome in patients hospitalised with anorexia nervosa. Serum phosphate levels did not fall below the range in any participant in the low-carbohydrate or standard group. One participant was cautiously administered a dose of oral phosphate in the context of a downward trend in serum phosphate levels without clinical markers of developing RFS.

Preventive electrolyte and vitamin supplementation

Guidelines published by ASPEN recommend routine supplementation of phosphate, potassium and magnesium in patients at high risk of RFS to reduce the risk of sudden electrolyte disturbances. It is recommended to administer phosphates prophylactically in the first days of refeeding in a dose determined individually for each patient, even in the absence of initial hypophosphatemia. Phosphate levels should be monitored daily.

Prophylactic supplementation of thiamine, as well as other B vitamins, is crucial especially in patients on long-term starvation. Thiamine (usually in doses of 100-200 mg per day) is recommended for patients at high risk of deficiency, for the first 3-5 days of refeeding, followed by lower doses in subsequent weeks. Recommendations for the frequency of phosphate monitoring have also been increased and should be daily for the first 5-7 days of refeeding [34-36].

CONCLUSIONS

Anorexia nervosa is an eating disorder characterized by extreme restriction of food intake,

intense fear of gaining weight, and distorted body image, and is also associated with the highest mortality rate of all mental disorders. When treating patients with anorexia, medical personnel must be aware of the risk of serious complications in these patients, such as refeeding syndrome. This is a serious, potentially fatal, but avoidable complication of anorexia treatment. The key to prevention is an interdisciplinary approach combining gradual restoration of proper nutrition with appropriate biochemical monitoring of the patient. Constant medical supervision and strict adherence to dietary recommendations are priorities for effective treatment and prevention of complications associated with refeeding syndrome. Recent research and clinical guidelines focus on the safe resumption of caloric intake, appropriate biochemical monitoring, and supplementation of key vitamins and electrolytes to reduce the risk of RFS in high-risk patients. Initiating higher-calorie feeding (HCR) has been shown to be safe for malnourished patients, including those with severe anorexia, provided that electrolytes such as phosphorus, magnesium, and potassium are closely monitored. This approach reduces the risk of severe hypoglycemia and shortens hospital stay without affecting the risk of refeeding syndrome. However, more research is needed on optimal feeding protocols, particularly in the context of tailoring calorie and electrolyte levels to individual patient needs. Furthermore, there is a paucity of research on the long-term effects of RFS, particularly in patients with eating disorders. A better understanding and awareness of the importance of this issue could significantly improve treatment outcomes and reduce the risk of complications.

Disclosure

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