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Advances in Understanding and Managing Refeeding Syndrome: A Comprehensive Review

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Abstract
BACKGROUND: Refeeding syndrome (RFS) is a potentially serious complication that can occur during the reintroduction of nutrition in individuals who have experienced a period of malnutrition or starvation. The pathophysiology of RFS is multifaceted and primarily driven by shifts in electrolytes, fluids, and metabolic substrates, including phosphate, potassium and magnesium, as well as thiamine deficiency. RFS can be easily overlooked due to the wide range of clinical presentations, from asymptomatic electrolyte disturbance to multiorgan failure. It is vital to recognize the condition to identify at-risk patients and implement preventive measures.
OBJECTIVES: This review article aims to increase awareness of refeeding syndrome, educate physicians and other healthcare professionals, especially those outside of nutrition support teams, and provide a concise overview of the existing knowledge and suggested guidelines regarding RFS.
CONCLUSIONS: Although refeeding syndrome is potentially fatal, its occurrence is preventable. During the initial 2-5 days of increased calorie intake, it is crucial to monitor the concentrations of phosphate and other electrolytes, as well as to check for any new symptoms. The key components of RFS therapy include slow increases in feeding rates, phosphate and potassium replacement, fluid management, and thiamine supplementation. Further research is required on refeeding syndrome, including epidemiological studies, investigations into pathophysiology such as the role of magnesium, and large-scale randomized controlled clinical trials to establish a consensus on management.

Keywords: refeeding syndrome, phosphate, magnesium, potassium, nutrition support

Introduction

Refeeding syndrome is a potentially life-threatening condition that occurs in individuals undergoing refeeding after prologned periods of fasting or restricted calorie intake. It occurs hours to days after initiation of refeeding: orally, enterally or parenterally, and is characterised by electrolyte imbalances and organ dysfunction. RFS signifies the transition from a catabolic to an anabolic metabolic state.1–3 Until recently, there was no established universal definition

of refeeding syndrome.2,3 In 2020, the American Society for Parenteral and Enteral Nutrition (ASPEN) proposed that RFS be conceptualised as a decrease in serum concentrations of either phosphorus, potassium, and/or magnesium, or the presentation of thiamine deficiency, occuring shortly (within hours to days) following the onset of caloric intake in an individual who has experienced a prolonged period of undernourishment.2 Developing a standard definition of RFS facilitates the estimation of RFS incidence and the formulation of well-designed, controlled trials aimed at developing effective strategies for its identification, prevention, and treatment.

The aim of this study is to raise awareness of the refeeding syndrome among clinicians and researchers. This will contribute to a more accurate diagnosis and a better understanding of this syndrome, with an emphasis on prevention and appropriate interventions.

Methods

The databases searched for this study were PubMed (National Library of Medicine), the Cochrane Library, and Excerpta Medica dataBASE (EMBASE). The search strategy included keywords such as refeeding syndrome, phosphate, potassium, and magnesium. The search was limited to human studies. Furthermore, we conducted manual searches of references in identified studies and reviews.

History

Refeeding Syndrome (RS) was initially identified during World War II when prisoners of war, survivors of concentration camps, and individuals who had endured famine exhibited unforeseen morbidity and mortality upon undergoing nutritional repletion.4,5

In 1944 Keys et al. conducted a prospective, randomised-controlled trial widely known as the Minnesota Starvation Experiment. This landmark study explored effects of famine in young, healthy conscientious objectors with a belief in non-violence and a desire to make a meaningful contribution during the war. Participants underwent semi-starvation, with most losing >25% of their weight. After the initial phase, the men underwent a 3-month rehabilitation period during which they were randomly assigned to one of four energy intake groups. Each energy level was further divided into two protein levels, and each protein level was further divided into two vitamin levels. This study initiated research on starvation and refeeding. It remains relevant today as it provides insight into obesity, weight gain, malnutrition management, and eating disorders.6,7

Incidence

The incidence of refeeding syndrome (RFS) remains unclear due to the use of varying definitions and high data heterogeneity.8–10 In 2021, Cioffi et al. conducted a meta-analysis to estimate the incidence of RFS in adults, taking into account the criteria set by the American Society of Parenteral and Enteral Nutrition (ASPEN) as well as refeeding hypophosphatemia (RH), which is often considered a hallmark of RFS. Analysis of 35 observational studies showed RFS incidence varying from 0% to 62% and RH invidence 7% to 62%. Patients from Intensive Care Units and ones with initial calorie intake greater than >20 kcal/kg/day appeared to exhibit a greater occurrence of both RFS and RH.11

Pathophysiology

The underlying mechanisms of refeeding syndrome (RFS) are likely associated with the transition from catabolic to anabolic metabolic pathways that occurs when undernourished individuals resume feeding.1

In the initial stages of starvation, there is a decrease in both blood glucose and insulin levels, accompanied by an elevation in glucagon concentrations, which triggers the breakdown of glycogen in the liver as well as lipolysis of triacetylglycerol in fat reserves generating fatty acids and glycerol. Tissues utilize these components for energy, and in the liver, they are further converted into ketone bodies.8,12 When the glycogen stores are exhausted,

gluconeogenesis is triggered in the liver. This process involves using amino acids (derived from muscle breakdown), lactate, and glycerol to synthesize glucose. The newly synthesised glucose is then used by the brain and red blood cells as an energy source. These alterations lead to a shift in the body's primary energy source from carbohydrates to protein and fat. The basal metabolic rate can decrease by up to 20-25%.1,8

Extended periods of fasting lead to a significant depletion of intracellular minerals, particularly phosphate, potassium, and magnesium. Although these minerals have normal concentrations in the serum, their renal excretion is reduced, and phosphate is released from cells into the bloodstream. Therefore, blood phosphate levels may remain within the normal range despite depleted cellular stores.13,14

Insulin and carbohydrates

The introduction of nutrients, particularly carbohydrates, triggers an increase in insulin secretion, leading to a rapid shift from fat to carbohydrate metabolism.15 Insulin facilitates the activity of the sodium-potassium ATPase, aided by magnesium as a co-factor. This symporter transports glucose and potassium into the cells while expelling sodium. Additionally, the release of insulin promotes anabolic processes that necessitate minerals, enhancing the cellular uptake of phosphate, potassium, and magnesium, along with coenzymes like thiamine.11

Electrolyte shift and depletion of the mineral pool, may result in significant hypophosphatemia, as well as low extracellular concentrations of magnesium and potassium, though not necessarily a complete depletion of these minerals. Additionally, insulin exerts an anti-natriuretic effect on renal tubules, leading to a reduction in urinary sodium and water excretion. This can result in rapid fluid overload, potentially leading to congestive cardiac failure, arrhythmias, and pulmonary edema1,16

Hypophosphatemia

Phosphate is mainly an intracellular mineral and plays a crucial role in energy production and transfer, serving as a component of adenosine triphosphate (ATP).15 It is essential for numerous enzymatic processes within cellular metabolic pathways.16

During the refeeding process, increased production of phosphorylated intermediates leads to heightened utilization of phosphate which in turn results in a reduction in the generation of ATP and 2,3-diphosphoglycerate. This can cause impaired cardiac and respiratory functions as well as reduced oxygen release to the tissues.18

Hypokalemia

Potassium is an intracellular mineral that plays a crucial role in maintaining the sodium–potassium membrane gradient. In RFS serum concentrations of potassium decrease due to insulin stimulation of the Na+/K+ ATPase.19 Hypokalemia leads to an imbalance in the electrochemical membrane potential, causing impaired transmission of electrical impulses.20 This can result in arrhythmias, cardiac arrest, and neurologic symptoms, such as weakness, hyporeflexia, respiratory depression, and paralysis21–23

Hypomagnesemia

Hypomagnesemia has been acknowledged as a feature of RFS. However, the specific mechanism leading to its development in RFS and its direct significance in the morbidity of the syndrome have not been fully clarified. Magnesium serves as a cofactor for the phosphorylation of adenosine triphosphate (ATP), and it plays a crucial role in maintaining neuromuscular and enzymatic functions. Hypomagnesemia may hinder the reuptake of potassium in the nephron and also impede its cellular transport, which exacerbates hypokalemia.24,25

Thiamine deficit

Thiamin deficiency may also manifest as a consequence of RFS because it serves as a cofactor in ATP production. Thiamin deficiency can lead to neurological abnormalities, encompassing confusion, encephalopathy (such as Wernicke's syndrome and Korsakoff psychosis), oculomotor issues (primarily horizontal ophthalmoplegia), hypothermia, and, in severe cases, coma.26,27

Thiamin also plays a role in the conversion of lactate to pyruvate. In individuals with thiamin deficiency, lactic acidemia may occur, even in the absence of acute liver injury.28 Thiamin deficiency can also result in a reduced production of ATP in cardiac myocytes, potentially leading to congestive heart failure, a condition known as wet beriberi.29

Clinical manifestation

Symptoms of refeeding syndrome usually appear within 2-5 days of refeeding. The severity of the symptoms can range from mild to severe and life-threatening, depending on the level of malnutrition and any other health conditions the individual may have.30,31 RFS has a wide clinical spectrum, including neurologic, cardiac, and metabolic problems. Neuropsychiatric symptoms may include acute encephalopathy, Wernicke's encephalopathy, central pontine myelinolysis associated with sudden correction of hyponatremia, ataxia, coma, delirium, Korsakov's psychosis, paresthesia, and peripheral neuropathy. Cardiac problems, such as congestive heart failure with fluid overload and cardiac arrhythmias, can also occur. Renal and liver function should be monitored due to the increased risk of renal impairment, acute or chronic kidney disease, acute tubular necrosis, liver failure, or abnormal hepatic function tests. Gastrointestinal problems that interfere with feeding, such as nausea, vomiting, and constipation, may also occur. Patients may also experience metabolic issues, such as hyperglycemia, metabolic acidosis, lactic acidosis, osteomalacia, and rhabdomyolysis. Respiratory failure and ventilator dependency may result from diaphragm and other muscle weakness. Additionally, there may be hematologic abnormalities, such as anemia and thrombocytopenia, which increase the risk of infections. It is important to properly recognize and treat refeeding syndrome to avoid sudden death.2,3,12

Screening and risk factors

In general, the risk of refeeding syndrome is typically assessed subjectively by a clinician during the evaluation and initiation of enteral or parenteral nutrition. However, screening strategies to identify patients at risk of RFS are imprecise and insufficiently validated. There are several recommendations for assessing the risk of RFS, with the UK's National Institute for Health and Care Excellence (NICE) being the most widely used.36

Patient has one or more of the following:
- BMI less than 16 kg/m2
- unintentional weight loss greater than 15% within the last 3–6 months
- little or no nutritional intake for more than 10 days
- low levels of potassium, phosphate or magnesium prior to feeding.

Or patient has two or more of the following:
- BMI less than 18.5 kg/m2
- unintentional weight loss greater than 10% within the last 3–6 months
- little or no nutritional intake for more than 5 days
- a history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics.

Table 2: NICE Criteria for determining people at high risk of developing refeeding syndrome

Several patient populations are susceptible to RFS. Individuals receiving enteral nutrition are more at risk than those receiving oral or parenteral nutrition.37 Screening tools for malnutrition, such as the Short Nutritional Assessment Questionnaire (SNAQ), are also useful

in predicting RFS.38 The occurrence of RFS is heightened in individuals with diseases associated with malnutrition. Malnutrition is routinely assessed with screening tools such as Nutritional Risk Score (NRS 2002)39 or Subjective Global Assessment (SGA).40 A modern diagnosis of malnutrition takes into account the Global Malnutrition Index (GLIM) criteria.41 Patients at risk of RFS include those with eating disorders, anorexia nervosa42 and avoidant/restrictive food intake disorder (ARFID)43 in particular; dysphagia and esophageal dysmotility; hyperemesis gravidarum or protracted vomiting; malabsorptive states (eg, short-bowel syndrome, non-specific enterocolitis, cystic fibrosis); cancer, acquired immunodeficiency syndrome (AIDS); major stressors or surgery without nutrition for prolonged periods of time, postbariatric surgery; chronic alcohol or drug use disorder; failure to thrive, including physical and sexual abuse and victims of neglect, refugees, individuals experiencing food insecurity and homelessness.2,31

Biomarkers

Several biomarkers are being investigated to improve the detection of RFS. At present, none has been validated for diagnosis, risk assessment or monitoring of RFS. Some of the biomarkers being investigated are insulin-like growth factor (IGF1) and leptin. However, they have been developed for the management of malnutrition, not specifically for RFS. They also have low specificity, which could lead to undertreatment of malnutrition. Therefore, biomarkers such as IGF1 or leptin are not recommended for clinical use in the management of RFS.34,35

Diagnosis

Recognising refeeding syndrome is challenging. It is based on both clinical manifestations and laboratory findings. Clinical spectrum of RFS is wide with no specific signs of symtoms.13 A significant number of physicians are unfamiliar with (RFS), resulting in its status as an overlooked or neglected condition. Physicians with the highest level of expertise were seen to be those who specialise in critical care medicine.32,33

The ASPEN criteria define refeeding syndrome as a reduction in one or more serum electrolyte levels, including phosphate, potassium and/or magnesium, of 10-20% (mild), 20-30% (moderate) or >30% (severe). It also includes the occurrence of organ dysfunction within five days of starting nutrition in a malnourished patient.2

According to ASPEN criteria RFS is defined by reduction in serum level of

- phosphate
- magnesium
- or potassium

or organ dysfunction within 5 days after nutrition support initiation

% reduction in serum level of electrolytes	RFS severity
10-20	mild
20-30	moderate
>30	severe

Table 1: ASPEN criteria for refeeding syndrome diagnosis

RFS does not have a dedicated International Statistical Classification of Diseases and Related Health Problems (ICD) ICD-10 label. It is commonly coded as E87.8 ("other electrolyte disturbances") or E83.3 ("disturbances of phosphate metabolism"), with E87.8 being the preferred and more specific label for coding RFS.13

Management

There is a consistent view that prevention and management of refeeding syndrome requires identification of those at risk, close monitoring of nutritional intake, and careful electrolyte and fluid replacement. Well-trained healthcare professionals, including doctors, dietitians, nurses, and pharmacists, can significantly enhance patient outcomes when forming

specialized teams to provide nutritional support.36 Once the level of risk for RFS is identified, decisions regarding the administration rates of fluids and nutrition, correction of electrolyte imbalances, and the supplementation of essential vitamins and micronutrients (such as zinc, iron, and selenium) can be established.44

There is a lack of consensus and conflicting research regarding the determination of feeding rates to prevent RFS. Therefore, it is recommended to adopt an individualized approach when refeeding patients. The approach of reintroducing nutrition at a "low rate with slow advancement" may conflict with the goal of achieving rapid weight gain, especially in high-risk populations like individuals with anorexia nervosa.45 On the other side, several recent randomized trials conducted on critically ill patients advocate for a gradual initiation and progression of nutrition support therapy.46,47 Starting rates may vary from 15–25 kcal/kg/day for lower risk patients to 5–10 kcal/kg/day for the highest risk patients.44,48

It is important to adjust fluid balance as necessary to ensure proper hydration, and daily weight measurements should be closely monitored to prevent fluid overload. Recent findings suggest that maintaining a low sodium intake may help decrease the occurrence of refeeding edema. In cases of hyponatremia, it is crucial to avoid rapid correction to minimize the risk of central pontine myelinolysis. Patients at high risk of developing RFS should be on sodium restriction of less than 1 mmol/kg/day. Patients experiencing RFS are more susceptible to renal abnormalities, necessitating careful monitoring of renal function.3

Depending on the risk of developing RFS patients require supplementation of thiamine (200-300mg daily for 3 to 5 days) to reduce the risk of Wernicke's encephalopathy and Korsakoff's syndrome,8 multivitamins up to 200% and electrolytes according to their electrolyte serum levels and RFS severity: 1–1.5 mmol/Kg/day potassium, 0.2–0.4 mmol/Kg/day magnesium, 0.3–0.6 mmol/Kg/day phosphate.14,44,48

New technologies

While new technologies may not directly treat refeeding syndrome, they can play a role in its prevention, monitoring, and management. Attempts have been made to incorporate algorithms and machine learning models to improve the detection of RFS and subsequently improve patient care. A team in Leipzig, Germany developed and implemented a clinical decision support system (CDSS) embedded into the electronic health record system. The CDSS alerted physicians and nutrition support teams to patients at risk of RFS, based on clinical and laboratory data.13 Another team in Korea attempted to develop a machine learning model for RFS prediction.49 It's important to note that while technology can provide valuable tools, the prevention and management of refeeding syndrome primarily requires close medical supervision, careful planning and individualized treatment based on the patient's condition.

Conclusions

Refeeding syndrome is a potentially fatal, but preventable and treatable complication of oral, enteral or parenteral nutrition in malnourished individuals. Early identification and implementation of suitable interventions can lead to a decrease in both morbidity and mortality rates. Further research is needed in all areas related to RFS, including epidemiological studies, deeper understanding of the pathophysiology and the role of magnesium, and standardisation of treatment protocols in randomised clinical trials in specific patient groups. It may be beneficial to distinguish between patients with anorexia nervosa and whose who are critically ill, as well as between different age and comorbidity groups. Improving patient care in this area depends on prevention through increased clinician awareness and early involvement of specialised dietetic support.

Disclosure

Author's contribution

Conceptualization, Agata Mazur, and Magdalena Madera; methodology, Aleksandra Kublińska; software, Aleksy Bizan; check, Magdalena Madera, Sylwia Mazur and Aleksandra Kublińska; formal analysis, Roksana Zdunek; investigation, Emilia Nagórska; resources, Krzysztof Marcinkowski; writing - rough preparation, Agata Mazur; writing - review and editing, Natalia Dąbrowska; visualization, Karolina Strus; supervision, Sylwia Mazur; project administration, Agata Mazur
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