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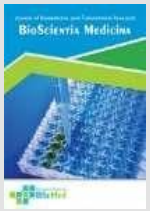

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Diagnosis and Management of Refeeding Syndrome

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A B S T R A C T

Refeeding syndrome (RFS) is described as a syndrome of electrolyte abnormalities and changes in body fluids with metabolic abnormalities in malnourished patients who receive refeeding either orally, enteral, or parenterally. Patients at risk for RFS are patients who have lost 10% of their previous body weight in the last 3-6 months, cancer patients who are on chemotherapy, geriatric patients with malnutrition, and patients with anorexia. Clinical manifestations are caused by electrolyte changes that affect neurons, heart and muscle disorders with various symptoms, and even death. The specific characteristics of RFS are the presence of hypophosphatemia and accompanied by other symptoms of electrolyte imbalance such as changes in sodium levels, changes in glucose, protein, fat metabolism, vitamin B1 deficiency, hypokalemia, and hypomagnesemia. The principle of management of RFS is to correct biochemical abnormalities and electrolyte and fluid imbalances. Preventive steps that can be taken are identifying individuals at risk for RFS, monitoring refeeding and administering an appropriate diet regimen.

1. Introduction

Malnutrition is an important problem in the elderly. About 50% of the elderly population is at high risk of malnutrition. Malnutrition can worsen the condition of the elderly population with various comorbidities, and malnutrition can even become a disease for the elderly. Nutritional therapy is given to reduce malnutrition, reduce mortality, and length of hospital stay. However, nutritional therapy, if not done properly and correctly, can cause complications. One of the complications of nutritional therapy is refeeding syndrome, which is a chemical change and complications that occur as a consequence of providing nutrition to malnourished patients. Refeeding syndrome was first introduced at the end of the second world war due to the large number of deaths that occurred in prisoners of war after starting a normal diet after a long period of starvation.[1]

Hernandez et al. reported the incidence of RFS is 14% in geriatric patients, 25% in patients with malignancy, and 28% in patients with anorexia nervosa, and most commonly occurs within the first 3 days after nutritional therapy. The main risk factor for RFS is malnutrition. Other risk factors are anorexia nervosa patients, prolonged fasting, chronic alcoholism, no intake > 7 days, postoperative patients, undergoing radiation therapy, malignancy patients,

pathological weight loss, stroke (neurological disorders), renal abnormalities, HIV/AIDS, malabsorption disorders (such as inflammatory bowel disease, chronic pancreatitis, cystic fibrosis), old age, uncontrolled diabetes mellitus, chronic consumption of diuretics (electrolyte loss) and chronic consumption of antacids (salt Al/Mg phosphate binders).[2,3]

Refeeding syndrome is caused by altered metabolic pathways in response to hunger. Acute starvation is defined as the absence of food for 1-3 days that result in the use and depletion of carbohydrate stores for nearly 24 hours. Long periods of starvation (starvation of more than 3 days) cause metabolic changes that involve lipolysis and decreased protein breakdown. The existence of this energy mobilization leads to the loss of the mass body and the loss of intracellular electrolytes, especially phosphate. Clinical symptoms vary from moderate to severe, ranging from mild nausea and vomiting, respiratory problems, heart problems, hypotension, arrhythmias, delirium, coma, and even death.[4,5]

Refeeding syndrome is a potentially life-threatening condition and often goes undiagnosed, but it can be treated and prevented, so it requires the vigilance and caution of health workers in treating patients who are at risk of developing RFS. Based on this background, the authors are interested in doing a review entitled the diagnosis and management of refeeding syndrome.

Pathogenesis of refeeding syndrome

Refeeding syndrome often occurs within 72 hours of starting nutritional therapy. Refeeding syndrome arises when a catabolic process changes to an anabolic process after a long period of starvation. When starving, in the first 24-72 hours, blood glucose levels will begin to fall, and the concentration of insulin will decrease while glucagon levels will increase, causing mobilization of glucose stores, especially from glycogen. Due to a lack of glucose-6-phosphatase and Glut-2 transporters, glycogen from striated muscle can only supply glucose to myocytes, while glycogen from the liver is catabolized and provides glucose for all body.[6]

These changes in early compensatory mechanisms help supply glucose to tissues glucose-dependent (brain, renal medulla, red blood cells), but after 72 hours, When glucose reserves from the liver and striated muscle are used up and decreased, the body will try to compensate for the state of lack of energy by changing metabolism and hormone regulation, the body will be in a state of catabolism.[6]

The shift from carbohydrate metabolism to fat and protein catabolism will produce glucose and ketones for energy. This shift to protein catabolism leads to the loss of body mass, which will affect important organs, such as the heart, lungs, liver, kidneys, and intestines. Atrophy of the myocardium causes poor contraction and reduced cardiac output. Liver disorders will lead to decreased protein synthesis and further disruption of metabolic processes. Atrophy of the gastrointestinal system leads to malabsorption and impaired motility, thereby exacerbating malnutrition and increasing the risk of infection.[7]

During refeeding, the absorbed glucose causes an increase in the glucose level, thereby increasing insulin and decreasing glucagon secretion. The result of these changes is the synthesis of glucagon, fat, and protein. Anabolic conditions require minerals such as phosphate and magnesium as well as cofactors such as thiamine. Insulin stimulates the absorption of potassium through cells (via the Na-K-ATPase symporter), where magnesium and phosphate are also transported. Water is drawn into the intracellular compartment by the process of osmosis.[8]

Decreased serum levels of phosphate, potassium, and magnesium further contribute to the clinical manifestations of RFS. Symptoms of RFS are variable, unpredictable, can occur without warning, and often too late. Symptoms occur due to changes in serum electrolytes that affect the cell membrane potential, which interferes with the function of nerves, heart, and skeletal muscle cells. Suppose mild electrolyte abnormalities can be asymptomatic. The most common symptoms are nausea, vomiting, lethargy, respiratory insufficiency, heart failure, hypotension, arrhythmias, delirium, coma, and death. Low serum

albumin concentration can be an important predictor of hypophosphatemia, although albumin is not nutritional.[9]

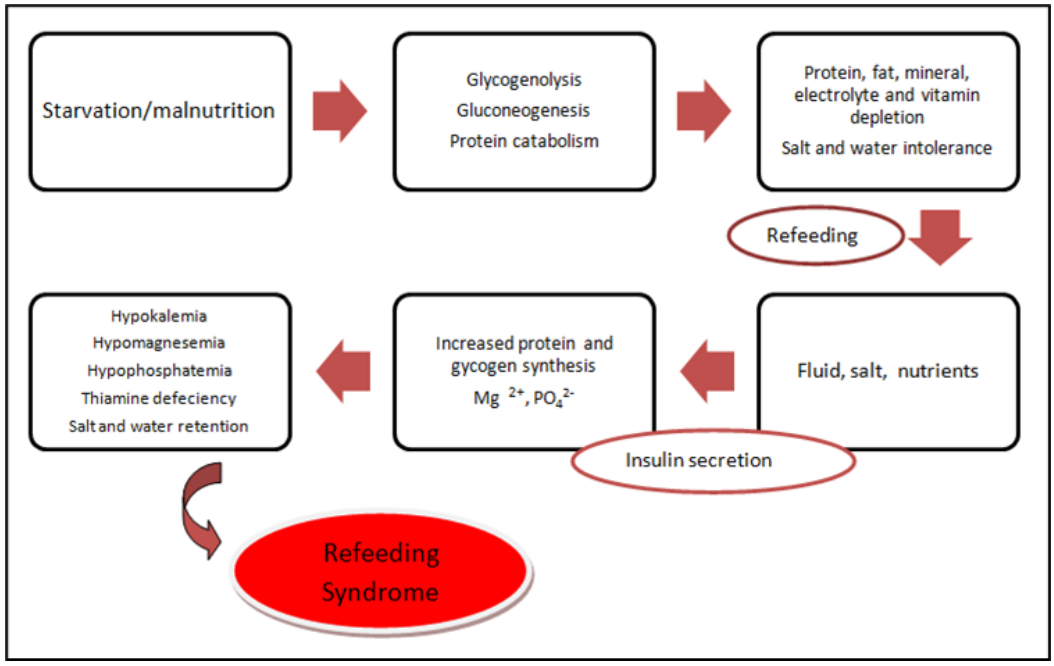

Figure 1. Pathogenesis RFS[12]

After starvation, glucose intake suppresses gluconeogenesis by releasing insulin and suppressing glycogen. If consumed in large quantities, glucose consumption can cause hyperglycemia, osmotic diuresis, dehydration, metabolic acidosis, and ketoacidosis. Excess glucose can also cause lipogenesis, which can lead to fatty liver, increased CO_2 production, hypercapnia, and respiratory failure.[10,11]

Diagnosis of refeeding syndrome

The diagnosis of RFS is based on clinical and electrolyte disturbances. The critical time of RFS is the first 72 hours. If in the first 72 hours there is an electrolyte imbalance accompanied by clinical symptoms such as peripheral edema, respiratory failure, or heart failure, it is said to be a manifest RFS. If there is an electrolyte imbalance without clinical symptoms, it is said to be an imminent RFS.[11]

Mehanna et al. mention hypophosphatemia as the main criterion for RFS. In a systematic review study, 20 of 38 RFS patients had hypophosphatemia. Hypophosphatemia is common in the elderly and is an independent predictor of mortality in the form of a three times higher mortality rate. The more severe the degree of hypophosphatemia, the worse the prognosis.[13] Friedli et al. states hypophosphatemia when the phosphate level is >30% below the lower value or < 0.6 mmol/L or a decrease in the level of two types of electrolyte parameters.[11]

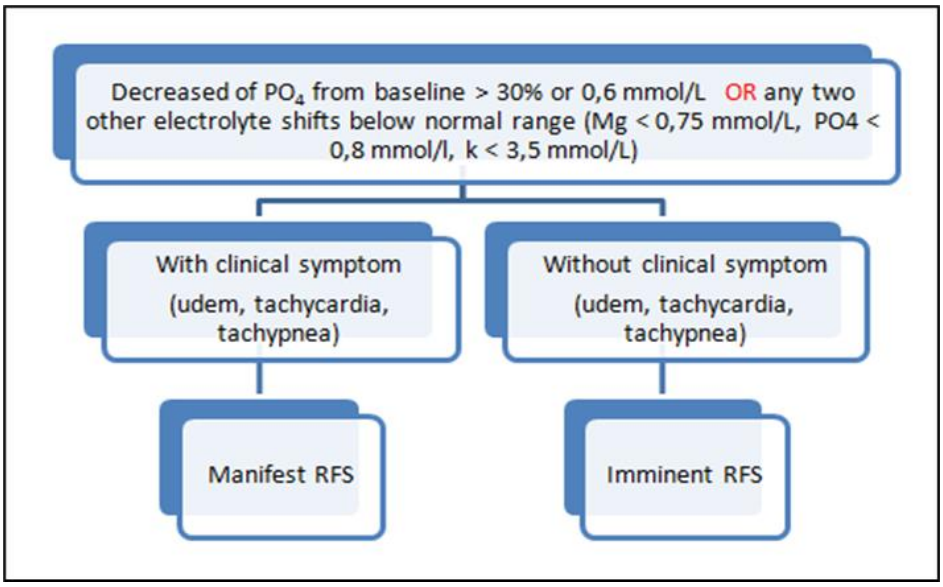

Figure 2. Diagnosis of RFS[11]

Management of refeeding syndrome

The management principle of RFS is the correction of biochemical abnormalities and fluid imbalances to normal levels whenever possible. Any patient who is malnourished, elderly, or at high risk for malnutrition should be screened for the risk of developing refeeding syndrome, and an assessment of nutritional status should be performed for those deemed at risk. The initial evaluation should involve a thorough history and targeted physical examination to identify risk factors and characteristics of malnutrition. Laboratory assessment should involve measurements of baseline electrolytes (phosphorus, magnesium, calcium, sodium), pre albumin, glucose, renal function, liver function, serum vitamin B12, and serum folate levels. Serum albumin has little value in the assessment or monitoring of nutritional status.[14]

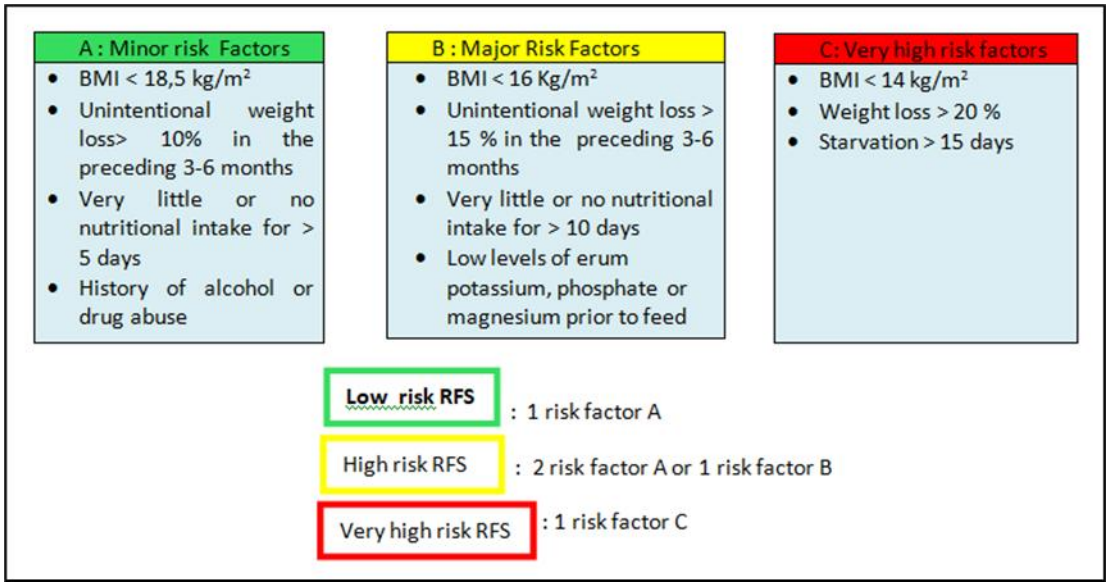

Figure 3. Early identification of RFS.[11]

Phosphate correction, electrolytes, and thiamine supplementation have been accepted as initial steps in the management of RFS, although expert recommendations differ on various clinical aspects of nutrition. Phosphate levels in healthy patients can decrease after the administration of glucose either orally or parenterally, so some experts recommend caloric restriction when electrolyte and phosphate correction is performed. Doig et al. (2015) compared RFS patients on calorie restriction management with RFS patients on standard calories. Doig found that patients with RFS who were given calorie restrictions had higher phosphate levels, a lower incidence of infection, especially lung infections, better glucose control, and a higher 60-day life expectancy after discharge from the ICU compared to patients who received calories standard.[14]

The rate of refeeding depends on the severity of malnutrition. In moderate-risk patients who eat very little or nothing for >5 days, the recommendation is to provide nutrition <50% of energy requirements. If, after clinical monitoring and biochemical status, everything is in good condition, nutrition can be increased. If the patient falls in one of the high-risk categories, nutrition is given slowly with a maximum of 10 kcal/kg every 24 hours and can be increased until it reaches a total requirement 4-7 days later in severely malnourished patients (BMI kg/m^2 or very little or no nutritional intake for 2 weeks or more). NICE recommends that refeeding should be initiated at a maximum of 5 kcal/kg/24 hours, with cardiac monitoring at risk for cardiac arrhythmias. In this situation, fluid administration is necessary, but care is needed to avoid overload.[15,16]

Table 1. Nutrition and fluid management in the refeeding syndrome.[11]

	Low risk for RFS	**High risk for RFS**	**Very high risk for RFS**
Nutritional support	• Days 1-3 : 15-25 kcal/kg/d • Day 4 : 30 kcal/kg/d • From day 5 : full requirement	• Days 1-3 : 10-15 kcal/kg/d • Days 4-5 : 15-25 kcal/kg/d • Day 6 : 25-30 kcal/kg/d • From day 7 : full requirement	• Day 1-3 : 5-10 kcal/kg/d • Day 4-6 : 10-20 kcal/kg/d • Day 6 : 25-30 kcal/kg/d • Day 7-9 : 20-30 kcal/kg/d • From day 10 : full requirement
Fluid management	30-35 ml/kg/d	• Day 1-3 : 25-30 ml/kg/d • From day 4 : 30-35 ml/kg/d	• Days 1-3 : 20-25 ml/kg/d • Days 4-56 : 25-30 ml/kg/d • From day 7 : 30-35 ml/kg/d
Sodium restriction	No sodium restriction	Days 1-7 : < 1 mmol/kg/d	Days 1-10 : < 1 mmol/kg/d
Thiamin	Days 1-3 : 200-300 mg	Days 1-3 : 200-300 mg	Days 1-5 : 200-300 mg
Multivitamin	Days 1-10	Days 1-10	Days 1-10

The main points regarding RFS are alertness, prevention, diagnosis, and treatment. Refeeding syndrome can occur and progress rapidly within the first 72 hours after initiation of nutritional therapy, so an intensive clinical evaluation, including vital conditions and hydration status, is essential. Several studies have shown that prophylactic administration of phosphate and thiamine supplementation in patients at high risk of RFS is effective in preventing hypophosphatemia, RFS and mortality, and poor prognosis associated with refeeding.[11]

Prophylactic phosphate supplementation is considered in patients at high risk of developing RFS, even though phosphate levels are at a lower limit than normal. In patients with renal impairment, phosphate should be administered with caution. Leitner's (2016)

study on prophylactic phosphate administration in patients with restrictive eating disorders found that there was no incidence of refeeding syndrome in patients receiving prophylaxis. According to Leitner, phosphate administration can prevent the occurrence of refeeding syndrome and is relatively safe for patients because there are no adverse events that occur during prophylactic phosphate administration.[17]

2. Conclusion

Refeeding syndrome is a syndrome of electrolyte abnormalities and changes in body fluids with metabolic abnormalities in malnourished patients receiving oral, enteral, or parenteral refeeding with manifestations of neuromuscular and cardiovascular symptoms. Refeeding syndrome is established when there is hypophosphatemia with phosphate levels >30% below the lower value or <0.6 mmol/L or decreased levels of two types of electrolyte parameters. Important factors in the management of RFS are early identification of patients at risk, monitoring during refeeding, and administration of an appropriate regimen with the principle of correcting biochemical abnormalities and fluid imbalances to normal levels.

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