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Review Article

Refeeding Syndrome – Underestimated Clinical Problem in Everyday Practice

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Introduction

Refeeding syndrome (RFS) is a series of metabolic and electrolyte changes that occur as a result of reintroduction and/or increased calorie delivery after a period of reduced intake [1]. It manifests as acute electrolyte deficiency with associated fluid retention and glucose disturbances as a result of oral, enteral or parenteral nutrition in malnourished patients [2].

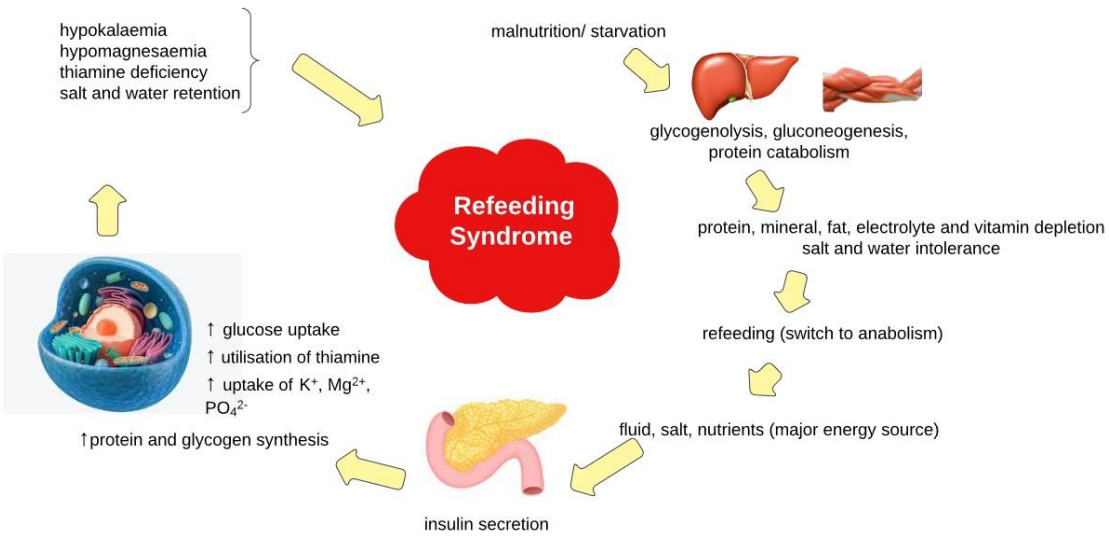
Despite the fact that the first reports on the symptoms of RFS date back to the 5th century BC and were confirmed and detailed in the 1940s, there is still insufficient awareness of it among doctors and nurses. Considering that 30-55% of patients admitted to hospitals are malnourished at the time of admission, the appropriate implementation of nutrition and the treatment of possible symptoms of the Refeeding Syndrome is clinically important[3, 4].

The first cases of Refeeding Syndrome described in detail date back to the end of the Second World War, when prisoners of war released from concentration camps, starved for months, began to take their meals. Many of them died within days of liberation [5]. Following these observations, Keys conducted an experiment in which he studied the physical and psychological effects of long-term dietary restriction and subsequent re-feeding in 36 study participants. The majority of subjects experienced severe emotional distress, depressive symptoms, social withdrawal, isolation, decreased concentration and decreased metabolic rate, slowed respiration rate and heart rate, swelling of the extremities during the periods [6]. Further observations were made by Schnitker and Burger. A number of starved inmates developed severe symptoms such as heart failure, peripheral oedema and neurological disorders after a normal diet was restored, and one inmate died within the next few days [7]. These observations led to the first description of Refeeding Syndrome (RFS).

Pathogenesis of RFS

RFS is an intense physiological response to glucose reintroduction (re-feeding) after a prolonged phase of starvation or restricted food intake[8]. The exact pathophysiological mechanisms remain unclear, but assumptions are based on the processes shown in Fig.1.

Fig. 1.Pathophysiology of the Refeeding Syndrome (adapted from Stanga Z. et el.) [9]



In a catabolic state (due to reduced food intake or starvation), insulin production is reduced, glucose oxidation takes place only in glucose-dependent tissues such as the brain, renal medulla and red blood cells. Glycogen stores are reduced, leading to the activation of gluconeogenesis and the production of glucose from endogenous amino acids, which are released by increased proteolysis. This process results in reduced muscle mass, causing functional weakness and weight loss. Vitamin and electrolyte levels are reduced and their stores are depleted. After a few days, lipolysis increases, leading to increased levels of free fatty acids in the circulation. Free fatty acids stimulate ketogenesis in the liver, leading to a high production of ketone bodies, which become the body's main energy providers. If refeeding begins, glucose becomes the main energy supplier, causing hyperglycaemia and consequently an increase in insulin secretion. Anabolic processes are stimulated, leading to intracellular shifts of glucose, water and electrolytes, resulting in a potentially severe drop in serum micronutrient levels. The resulting electrolyte imbalance can cause life-threatening complications such as arrhythmia, cramps or tetany. At the same time, thiamine deficiency can lead to neurological and cardiorespiratory symptoms of beri-beri disease. The more impaired the nutritional status of the patient , the greater the risk of RFS and the greater the severity of its symptoms[1, 10, 11].

Thiamine is an essential cofactor in carbohydrate metabolic pathways, enabling the conversion of glucose to adenosine triphosphate (ATP) in the Krebs cycle. In thiamine deficiency, glucose is converted to lactate, leading to metabolic acidosis. Thiamine deficiency can also cause neurological (Wernicke's encephalopathy) or cardiovascular disorders (the so-called 'wet' form of beri-beri disease)[12, 13]

Clinical consequences resulting from electrolyte changes and thiamine deficiency may include.[14-16]:

- tachycardia, tachypnoea, oedema
- hyper/hypotension, cardiomyopathy, sudden cardiac arrest
- pulmonary oedema
- paresthesias, convulsions
- constipation, abdominal pain, diarrhoea
- metabolic acidosis

The relationships between electrolyte deficiencies and symptoms are shown in Fig.2.

Fig.2. Electrolyte disturbances and symptoms associated with Refeeding Syndrome [11, 17-19]

Hypophosphatemia	nausea, vomiting, heart failure, arrhythmias, haemolytic anaemia, pancytopenia, rhabdomyolysis, acute tubular necrosis, cranial nerve palsy, muscle paralysis, disorientation, coma.
Hypomagnesaemia	Hypocalcaemia, cardiac arrhythmias, tachycardia, tremor, ataxia, confusion, irritability, paresthesias, abdominal pain, convulsions, tetany.
Hypokalaemia	Arrhythmia, hyporeflexia, low blood pressure, paralytic bowel obstruction, paresthesias, spasms, muscle paralysis, respiratory depression, myoglobinuria, polyuria, metabolic alkalosis.
Thiamine deficiency	Wernicke's encephalopathy, syndrome Korsakoff

Carbohydrate intolerance, fluid intolerance	hyperosmolarity, hepatic steatosis. Dehydration, peripheral oedema, heart failure, low blood pressure, pre-renal renal failure, sudden death

Prevention of Relapse Syndrome

In order to prevent the onset of RFS symptoms, risk factors need to be kept in mind and assessed for each patient in whom enteral nutrition, parenteral nutrition or extended oral diet is initiated [16]. Risk factors for the relapse syndrome are shown in Fig.3.

Fig.3. Risk factors for Relapse Syndrome [10]

"small" risk factors	"large" risk factors	groups of patients at high risk
• BMI < 18.5 kg/m²	• BMI<16 kg/m²	• starvation
• unintentional weight loss >10% in the last 3-6 months.	• unintentional weight loss >15% in the last 3-6 months.	• history of bariatric surgery
• insufficient intake for >5 days	• insufficient intake for >10 days	• short bowel syndrome
• history of alcohol dependence, insulin therapy, chemotherapy, use of diuretics, antacids	• low concentrations of potassium, phosphates, magnesium prior to the inclusion of nutrition	• oncology patients

It is worth noting that patients at high risk of Refeeding Syndrome are also patients at high nutritional risk according to the NRS 2002 scale. This scale is compulsorily completed in every hospitalised patient (Fig.4). A score equal to or higher than 3 points requires the inclusion of nutritional treatment. In this situation, RFS prevention should be kept in mind.

Fig.4. NRS 2002 scale

Deterioration of nutritional status		Severity of illness (increased demand on nutrients)	
0 = none	correct nutritional status	0 = none	normal demand
1 = mild malnutrition	weight loss >5% during 3 months Or food intake <50-75% in the past week	1 = mild malnutrition	hip fracture, chronic diseases especially with complications - cirrhosis, COPD, diabetes, cancer
2 = medium malnutrition	weight loss >5% during 2 months or BMI 18.5-20.5 kg/m^2 with associated poor general condition or a food intake in the range of 25-60% of normal requirements in the last week	2 = medium malnutrition	major abdominal procedures, stroke, severe pneumonia, post-operative renal failure, chemotherapy, malignant haematological diseases
3 = severe malnutrition	weight loss >5% during 1 month (>15% over 3 months) or BMI < 18.5 kg/m ^{2} with associated poor general condition or food intake between 0-25% of normal requirements in the last week	3 = severe malnutrition	head injury, Bone marrow transplant, patients requiring intensive medical therapy
1 = if patient's age >70 years			
Total number of points =			

When starting to feed a patient, risk factors should be taken into account and the amount of kcal, composition and feeding rate should be adjusted accordingly (Figure 5).

Fig.5 Prevention of RFS in hospitalized patients receiving nutritional treatment [10]

	risk-free	low risk	high risk	very high risk
		1 "small" factor	1 "large" factor or 2 "small" factors	• BMI<14 kg/ m² • weight loss>20% • starvation>15 days
1-3 days		15-25 kcal/kg/d	10-15 kcal/kg/d	5-10 kcal/kg/d
4 day		30 kcal/kg/d	15-25 kcal/kg/d	10-20 kcal/kg/d
5 day			15-25 kcal/kg/d	10-20 kcal/kg/d
6 day			30 kcal/kg/d	10-20 kcal/kg/d
Day 7-9				20-30 kcal/kg/d
over 10 days				

RFS prevention

- identification of patients at risk of RFS
- assessment of electrolyte concentrations and correction of deficiencies before starting feeding
- administration of thiamine before feeding
- selecting an appropriate supply: 10-15kcal/kg/24h for the first 3 days of nutritional treatment
- evaluation of symptoms and test results following the inclusion of nutrition

Recognition of RFS

RFS can occur in up to 62% of hospitalized patients, depending on their nutritional status and general condition [20].

In 2017. ASPEN (American Society for Parenteral and Enteral Nutrition) proposed the following diagnostic criteria for RSF:

Decrease in serum phosphorus, potassium and/or magnesium (occurring within 5 days of reintroduction of nutrition):

- by 10%-20% (mild form)
- by 20%-30% (moderate form)
- by >30% and/or organ dysfunction due to reduction in any of the organs and/or due to thiamine deficiency (severe) [1, 21, 22]

RFS treatment

Currently, there are no standardized, evidence-based guidelines for the treatment of RFS. However, it is assumed, based on previous studies, that an effective risk assessment strategy, development of a nutritional care plan and monitoring of patients at risk of RFS can significantly reduce the morbidity and mortality associated with this syndrome [10, 23-25].

If symptoms of the Refeeding Syndrome are already present, nutritional support should be reduced and hypophosphatemia, hypokalaemia and hypomagnesaemia should be corrected immediately, while treating the patient's other health problems [26, 27]. Moderately or severely ill patients with seizures, significant oedema or serum phosphorus levels <2 mg/dl should be hospitalized for intravenous electrolyte supplementation and close monitoring.

In summary, when symptoms of RFS occur, it is important to [16, 23, 28]:

1. stop the supply of nutrition

2. assess electrolyte concentrations

3. replenish electrolyte deficiencies

4. administer thiamine

5. reintroduce feeding at the correct dose and rate

Summary

Refeeding Syndrome is a potentially fatal metabolic complication of nutritional treatment.

Correct assessment of need and estimation of RFS risk are key to the correct inclusion of oral, enteral and/or parenteral nutrition.

Prompt recognition of RFS symptoms and appropriate diagnostic and therapeutic management makes it possible to reduce or resolve symptoms.

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