Refeeding syndrome – management and recommendations

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Abstract

Refeeding syndrome (RFS) is a potentially life-threatening complication. It comprises acute deficiencies of micronutrients, fluid and electrolyte imbalances, as well as disturbances of organ function and metabolic dysregulation that results from a too rapid or inadequate refeeding in patients with severe malnutrition.

According to the literature, the principal characteristic of a RFS is the hypophosphataemia. Moreover, this complex syndrome can be accompanied by hypokalemia, hypomagnesaemia, alterations in the glucose-, protein- and lipid-metabolism and thiamine deficiency, and can lead in a multi organ failure or even death. In this review, the current pathophysiological understanding of RFS and practical advice on diagnosis, monitoring and therapeutic measures in at-risk patients are discussed.

Keywords: Refeeding syndrome; malnutrition; hypophosphataemia.

1. Introduction

The refeeding syndrome (RFS) comprises life-threatening complications, as consequence of too fast and inadequate refeeding in malnourished, catabolic patients. It is characterized by electrolyte disorders (hypophosphataemia, hypo-magnesaemia, hypokaliaemia) as well as a liquid dysbalance with consecutive sodium retention and organ function impairment [1]. Additional to the electrolyte disorders, also changes in the glucose-, protein- and lipid-metabolism, as well as vitamin deficiencies are described [2], leading to a multi-organ failure or even death. The most relevant clinical symptoms of RFS are tachycardia, tachypnea and peripheral oedema [3].

The first report about the RFS appeared after the second world war, as the refeeding of the starving prisoners ended often in cardiac insufficiency and neurological complications [4]. The "Minnesota experiment" was conducted in the same year: male, healthy volunteers received only 50% of their energy requirement. The starving men were aggressive, depressive, anxious and weren`t able to concentrate. Several showed peripheral oedema, lower cardiac and breathing frequency, as well as a lowered body temperature [5].

There exists no consistent definition of RFS in the literature. Thereby, epidemiologic data are varying and a reliable diagnosis is difficult. Several case series showed potential life-threatening complications, but till now, large randomized controlled trials are largely missing. Consequently, the RFS is often not recognized and therefore treated inadequately, resulting in differing prevalence data. A recent systematic review on RFS [6] found important differences in definitions used for RFS with mainly three groups. First, hypophosphatemia as the only definition criteria. Second, any electrolyte disturbances including hypophosphatemia. Third, electrolyte disturbances with additional clinical signs and symptoms. Moreover, this systematic review found a large variety in incidence rates of RFS depending highly on the definition criteria used and the patient population. For example the prevalence of RFS (hypophosphataemia <2.5 mmol/L) in

oncological patients with artificial nutrition was 25% [7] and in patients with anorexia nervosa 28% [8]. A prevalence of even 48% is documented in malnourished patients. Additionally, this patient population showed a prolonged hospitalization and a higher mortality rate [9]. In a study with malnourished oncologic patients starting with an artificial nutrition, a RFS occurred in 24.5%. Whereby it was observed more frequently in enteral nutrition (37.5%) as in parenteral nutrition (18.5%) [7,10].

2. Pathophysiology

Till now, the detailed mechanism of RFS is not known in detail. Responsible for the manifestation of RFS are metabolic or hormonal changes, caused by a too fast and over-aggressive refeeding (oral, enteral or parenteral) after the prior starvation period. The pathophysiological pathway is shown in Figure 1. This reduced energy intake leads to a catabolic state with impaired insulin secretion and increased glucagon release [11].

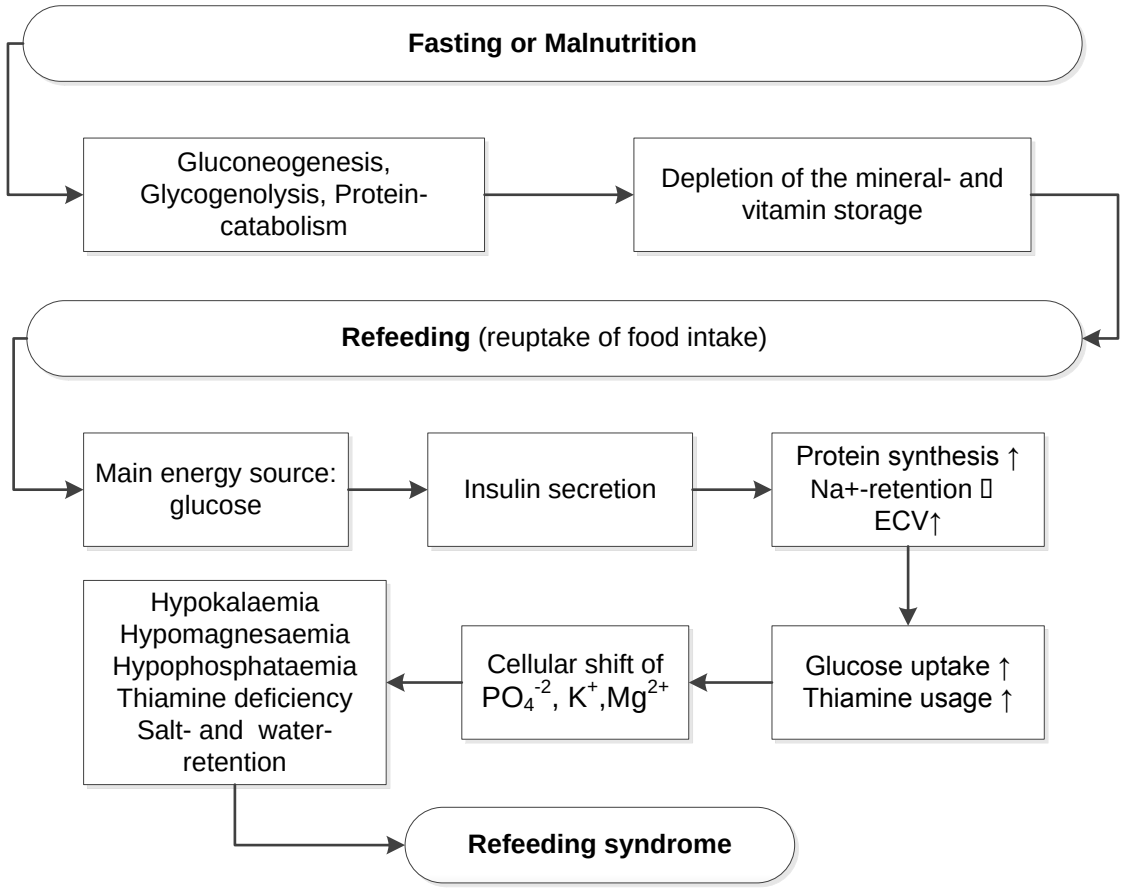

Figure 1. Pathophysiologic pathway of the refeeding syndrome [3,11]

A missing energy intake, especially glucose, leads to an onset of gluconeogenesis and later proteolysis. This leads to a reduction of body weight and a depletion of intracellular electrolyte- and vitamin storage [3]. The amino acids are released by an increased proteolysis in the periphery, whereby muscle mass gets lost. An increased lipolysis leads to a rise in free fatty acids, glycerol and ketone bodies in the blood. Glucose as the main energy source is replaced in this situation through free fatty acids and ketone bodies (ketogenesis) [12]. When refeeding is started after a longer starvation period and along with this, a sudden glucose uptake occurs, it comes abruptly to a change of the metabolism from catabolism to anabolism (glycolysis ↑, glucose oxidation ↑, lipolysis ↓, lipid oxidation ↓). The exogenous delivered glucose leads to a hyperglycaemia and to a stimulated insulin secretion. The intracellular uptake of phosphate, magnesium and potassium is a consequence of the enhanced insulin secretion and the resulting reuptake of the anabolic process. Consequentially, their serum concentrations are decreasing [1] and life-threatening complications can occur like arrhythmias, tetany and spasms. Low serum phosphate levels influence negatively energy generation in the form of ATP, because this pathway is phosphate dependent. This leads to muscle weakness, rhabdomyolysis, as well as hematological complications with symptoms like anaemia and reduced oxygen [3]. Severe hypophosphataemia (<0.32 mmol/L), an important characteristic of the RFS, occurs in refed patients mostly in the first three days [6]. Phosphate is used during the refeeding for the phosphorylation of glucose, because glucose can only be used in this form in the glycolysis. It has to be considered, that malnourished, catabolic patients can show normal serum phosphate levels, while the intracellular phosphate storage is already depleted (lipid oxidation doesn`t need phosphate-containing products) [13]. In addition to the intracellular electrolyte uptake, hyperglycaemia and hyperinsulinism are leading to sodium retention with consecutive volume overloading. This can lead to peripheral oedema or a risk for heart insufficiency (increase of

extracellular volume) [12]. The breakdown of carbohydrates and conversion into energy depends on vitamins from the B group, especially vitamin B_1 (thiamine). In a vitamin deficiency, the whole carbohydrate metabolism and therefore also the energy generation is impaired. Induced by the fast refeeding (glucose intake), thiamine storage is depleted, because the human body is only able to store a small amount of thiamine (storage for 14 days). The resulting thiamine-deficiency can lead into a Wernicke-encephalopathy or a lactic acidosis [3].

3. Criteria for identification of RFS

RFS can occur in oral, enteral or parenteral nutrition. But the highest probability to develop RFS exists with parenteral nutrition, followed by enteral and oral nutrition [14]. Patients with risk constellations, who are exposed to a high RFS-risk, are shown in Table 1 [15].

Table 1. Specific risk constellations for a RFS [15]

Patients with following risk constellations are exposed to a high RFS-risk at beginning of the refeeding:
- patients with anorexia nervosa
- patients after a hunger strike for several days (e.g. prisoners)
- already malnourished patients with temporary reduced nutritional intake (acute Crohn disease, after gastrointestinal infection, etc.)
- tumor patients, particularly after heavy weight loss
- alcoholics
- patients after bariatric surgery

The National Institute for Health and Clinical Excellence (NICE) determined recommendations for the diagnosis and management of RFS. The criteria are shown in Table 2 [16].

Table 2. Risk factors for RFS [16]

one of the following	**two of the following**
• BMI <16 kg/m^2	• BMI <18.5 kg/m^2
• unintentional weight loss >15% in the preceding 3-6 months	• unintentional weight loss >10% in the preceding 3-6 months
• very little or no nutritional intake for more than 10 days	• very little or no nutritional intake for more than 5 days
• low levels of serum K, PO_4,Mg^{2+} prior to feed	• history of alcohol or drug abuse

An impaired absorption of nutrients caused by massive vomiting or diarrhea, chronic intake of high doses of diuretics (especially in anorexia nervosa), as well as a dysfunction or inflammation of the gastrointestinal tract has to be considered [13]. The criteria for confirmation of the diagnosis of RFS are a result of the pathophysiologic and clinical symptoms (Figure 2) [1,10].

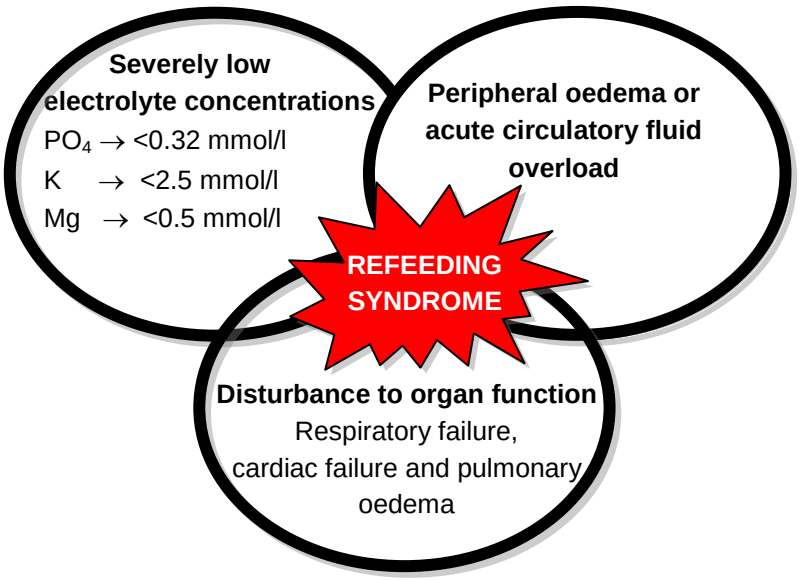

Figure 2. Criteria for confirmation of the diagnosis of a RFS [1,10]

Rio et al. investigated in their prospective cohort study a mixed in-patients population of 243 patients with artificial nutrition (87% enteral and 13% parenteral). 133 of these patients were considered as at risk for RFS. Only three patients developed a complete RFS. Independent predictors for a RFS were a reduced food intake of >10 days, a weight loss of >15% and low serum magnesium level prior the refeeding (<0.7 mmol/L). These predictors showed a sensitivity of

67% and a specificity of 80%. The specificity for weight loss of >15% was only 59.1%. Low phosphate- and potassium level prior to the refeeding showed in this study no significant association. The starving condition was the most reliable predictor, as described by the authors [10]. In general it is recommended, that hospitalized patients are screened for a risk of malnutrition, because this population is exposed to a higher risk to develop a RFS. There exist different screening methods for the detection of the nutritional risk. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommend the Nutritional risk screening (NRS 2002) for hospitalized patients [17]. The NRS 2002 includes the assessment of the nutritional status (weight loss, BMI, appetite) and the evaluation of the disease severity (stress metabolism). An age of >70 years is an independent risk factor to develop malnutrition and is considered in the calculation of the total score of the NRS 2002. A case-control study of Marvin et al. decided that the NRS 2002 is a more sensitive method for identifying risk factors than screening according to the NICE recommendations. The RFS was defined as the decrease of the serum phosphate concentration of >0.15 mmol/L on <0.80 mmol/L [18].

4. Management and recommendations

Not all patients, who are refed, develop a RFS. Therefore, it is very important, that patients at risk are identified early by a well-educated multidisciplinary medical team and an adequate assessment and care plan are provided. According to the described cases in the literature, the NICE guidelines and the recommendations of Stanga et al., a procedure for prevention and treatment of the RFS can be proposed (Table 3 and 4) [11,16].

Table 3. Management of RFS (day 1-3), evidence grade D [11,16]

measure	**day 1-3**
energy intake	10-15 kcal/kg/day
	(50-60% carbohydrates, 30-40% lipids and 15-20% proteins)
electrolyte supplementation	prophylactic electrolyte supplementation (unless pre-refeeding serum levels are high):
	phosphate 0.5-0.8 mmol/kg/day
	potassium 1.0-2.2 mmol/kg /day
	magnesium 0.3-0.3 mmol/kg/day
fluid intake	20-30 ml/kg/day
	Sodium restriction <1 mmol/kg/day (if oedema develops, restrict further)
micronutrients supplementation	200-300 mg thiamine i.v. 30 minutes before first nutritional intake, afterwards daily i.v. or p.o.
	vitamins 200% of DRI
	trace elements 100% of DRI (no iron supplementation in the first week)
lab controls	K, PO_4,Mg^{2+}, glucose, Ca^{2+}, Na daily
clinical examination	blood pressure, pulse, oxygen saturation, hydration status, cardiopulmonary, weight

DRI = dietary reference intake

Table 4. Management of RFS (day 4-10), evidence grade D [11,16]

measure	**day 4-10**
energy intake	15-20 kcal/kg/day, on the 7. day: 20-30 kcal/kg/day
	(50-60% carbohydrates, 30-40% lipids and 15-20% proteins)
electrolyte supplementation	continue electrolyte supplementation in order to restore normal serum levels:
	phosphate <0.6 mmol/L → 30-50 mmol over 12 hours
	potassium <3.5. mmol/L → 20-40 mmol over 12 hours
	magnesium <0.5 mmol/L → 24 mmol $MgSO_4$ over 12 hours
fluid intake	25-30 mL/kg/day, on the 7. day: 30 mL/kg/day
micronutrients supplementation	vitamins 200% of DRI
	trace elements 100% of DRI
lab controls	K, PO_4,Mg^{2+} 2x/week, afterwards 1x/week
clinical examination	hydration status, cardiopulmonary, weight

DRI= dietary reference intake

In order to prevent a RFS, it is essential, that the hydration status is normalized before the refeeding and that the pulse, blood pressure and also the fluid balance are controlled continuously. The fluid content of the normal and supplemented nutrition and the tube feeds should be considered for the calculation of the total fluid intake. From the daily weight control it can be estimated, whether a pathological fluid accumulation or an improvement of the nutritional status is responsible for the weight gain. A weight gain of more than 0.3-0.5 kg/day or 1.5 kg/week implies more likely a fluid overload. The fluid balance should be carefully restored (normally 20-30 mL/kg/day). If there is no deficiency, also the sodium intake (salt) should be minimized by <1 mmoL/kg/day. Empirical supplementation of electrolytes and vitamins should be started before feeding is initiated (oral, enteral or parenteral). A continuous monitoring of especially sodium, potassium, phosphate and magnesium is crucial, also during the refeeding phase. The NICE guidelines recommend (evidence grade D) a high dosed administration of vitamins, electrolytes and minerals during ten days (100-200% of the daily recommended intake (DRI)). Thiamine should be given at least 30 minutes prior to the refeeding and afterwards daily 200-300 mg per oral or intravenous till the third day. A continuous monitoring is also necessary for the plasma glucose, calcium and kidney values. The risk for a hyperglycaemic drift is higher at the beginning, therefore, the blood glucose concentration should be monitored daily and the daily supplied amount of carbohydrates should initially not exceed 100 g. Furthermore, the energy and fluid intake should be instituted carefully and gradually increased over 1-10 days. In patients with a high risk, it is started with 10 kcal/day and in patients with a very high risk for a RFS even with 5 kcal/day. Moreover, a cardiac monitoring is recommended in the latter risk population, to detect and treat arrhythmias early [1,11,16].

5. Conclusion

Because of the increasing relevance of a nutritional therapy, it is necessary to

consider the potential occurrence of RFS, as a possible complication. Further clinical studies are necessary to clarify uncertainties about incidence, prevention and treatment. A recently published randomized controlled study by Doig et al. showed, that a reduction of the energy intake in critically ill patients with RFS was effective and improved the outcome (decrease of mortality rate) [19]. Nevertheless, further investigations are needed to confirm these and other findings, especially in non-critically ill patient populations. For this reason, a randomized controlled study (EFFORT) in several Swiss hospitals is currently ongoing, investigating the effect of a nutritional therapy in medical patients and generating important data regarding RFS.

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