Dutch consensus statement on Refeeding syndrome

Introduction

Disease related malnutrition is a common problem in health care. The refeeding syndrome is defined as the severe and potentially fatal shifts in fluid and electrolytes that may develop when initiating oral, enteral or parenteral nutrition of severely malnourished patients.

Purpose of this consensus statement

The potential fatal consequences of the refeeding syndrome are commonly acknowledged. Many aspects of the syndrome such as the direct cause, incidence, symptoms, prevention and treatment are unknown because of the lack of data from large patients series. Although the refeeding syndrome is univocally presented, patients present themselves with many different symptoms. In some patients deviations of many electrolytes are present and in others only the serum phosphate level is reduced. Some patients have mild symptoms, other have severe to lethal symptoms. Moreover, there is no unequivocal evidence on the best strategy for prevention and treatment of the refeeding symptoms. Because of these reasons it is not possible to tie the refeeding syndrome to a protocol. This consensus statement gives guidance to the definition, prevention, recognition and treatment of refeeding.

Causes

In case of an inadequate intake or loss of nutrition elements, fluid deficiencies of vitamins, electrolytes and trace minerals will occur. When the body experiences inflammation, it will be in a catabolic state in which insulin concentrations are low. By starting nutrition (oral, enteral, parenteral or an intravenous glucose supply), the body will be stimulated to process and store these nutrients. The insulin levels will rise, which will stimulate the glucose-uptake, -combustion and glycogen storage in the cells. In this process, electrolytes (potassium, magnesium, phosphate) will be retained from the blood flow into the cells. This will lead to a drastic decrease of the serum electrolyte levels. These low levels of electrolytes can cause complications such as cardiac arrythmia, neurological complications and respiratory insufficiency. Besides this, the water-soluble thiamine will be rapidly depleted because it is needed as a cofactor in the glycolysis. Malnourished patients often have a (latent) thiamine deficiency that becomes manifest after the supply of carbohydrates with symptoms as encephalopathy, cardiomyopathy and lactic acidosis. Furthermore, insulin will induce the water and salt retention in the kidney which can result in heart failure.

The refeeding syndrome encompasses the metabolic changes that occur when initiating oral, enteral or parenteral feeding (especially carbohydrates) of severely malnourished patients with vitamin and electrolyte deficiencies. It needs to be emphasised that not all symptoms will be clinically manifest in every patient in the same way. This is dependent on the deficiency status, the illness and medication use. Monitoring the refeeding

syndrome is essential to prevent clinical complications from occurring. A distinction can be made between 'biochemical refeeding syndrome' and 'symptomatic refeeding syndrome'. In table1 the characteristics of both types are given.

Table 1 Biochemical and symptomatic refeeding syndrome characteristics

Biochemical refeeding syndrome	**Symptomatic refeeding syndrome**
Increase in insulin	Insulin stimulates the glucose metabolism and induces water and salt retention, possibly leading to edema and heart failure
Hypophosphatemia	Reduced respiratory, cardiovascular, and neuromuscular functioning. Possible symptoms include muscle weakness, respiratory insufficiency, heart failure, seizures, and arrhythmia
Hypokalemia / hypopotassemia	Muscle weakness, respiratory insufficiency, arrhythmia, ileus, concentration disorders in the kidney
Hypomagnesemia	Muscle cramps, hypocalcaemia, arrhythmia, seizures
Thiamine deficiency	The body store of thiamine (vitamin B_1) is sufficient for at most 7 days. It is a co-factor in aerobic glucose consumption. A shortage leads to an anaerobic glucose metabolism resulting in an increase in lactate (lactate acidosis, heart failure). In addition, the Wernicke Korsakoff syndrome may manifest.

Patients at risk of refeeding syndrome

Identification of high-risk patients is important as early recognition and treatment can prevent the refeeding syndrome or attenuate the clinical symptoms. Groups at risk of developing a refeeding syndrome include patients who have been malnourished for a long time, have had prolonged minimal food intake or patients who could have severe shortages of any vitamins or electrolytes. The characteristics described in **table 2,** can be used to identify high-risk patients.

High risk patients
The patient fulfils **one or more** of the following characteristics: ■ BMI <16 kg/m^2 ■ >15% undesired weight loss in the last 3-6 months ■ >10 days with no or negligible food intake (estimated <100 kcal/24 h) ■ Low plasma values of electrolytes before starting feeding (potassium, phosphate, magnesium) The patient has **two or more** of the following characteristics: ■ BMI <18.5 kg/m^2 ■ >10% undesired weight loss in the past 3-6 months ■ >5 days with no or negligible food intake (estimated <100 kcal/ 24 h) ■ Chronic (excessive) alcohol abuse

Table 2. Characteristics to identify patients at high risk of the refeeding syndrome

Due to restricted food intake, weight loss or high losses of nutrients or a combination of these, certain patient groups have a higher risk at developing the refeeding syndrome than other patients. Therefore, given the possible fatal consequences, these groups should always be screened on the risk of refeeding syndrome before (re)starting nutritional therapy.

High-risk patient groups are:

Patients with a low nutrient intake and / or unintentional weight loss

- Long-lasting fasting or a low caloric diet
- Chronical swallowing problems or other neurological disease
- Anorexia nervosa
- Chronic (excessive) alcohol abuse
- Depressed older adults (> 70 years)
- Cancer patients
- Chronical infectious diseases (AIDS, tuberculosis)
- Postoperative patients

Patients who have large losses of nutrients and / or a diminished nutrient absorption

- Chronical inflammatory bowel diseases (IBD)
- Dysfunction of the gastrointestinal tract (e.g. cystic fibrosis)

- Chronic pancreatitis
- Short bowel syndrome
- Chronic use of high dosages of diuretics (loss of electrolytes)
- Chronic use of antacids (magnesium an aluminium salts bind to phosphate)
- Post-bariatric surgery

Prevention & Treatment

The prevalence and severity of the refeeding syndrome symptoms are dependent on different symptoms and therefore difficult to predict accurately. These factors are the severity of malnutrition, quick restart of nutrition and the administration of too large amounts of nutrition without adequate supplementation of vitamins and electrolytes. In addition, conditions that worsen/cause vitamin and electrolyte deficiencies, such as alcohol abuse and gastro intestinal diseases are factors that play a role in the development of the refeeding syndrome. Treatment is based on prevention, monitoring of biochemical and symptomatic changes and if necessary, anticipation by reducing the 'feeding' speed or by supplementing electrolytes, fluids or vitamins.

This treatment plan is divided in (1) laboratory control, (2) supplementation, (3) feeding recommendations (4) fluids and (5) monitoring.

The plan is developed to give a possible strategy to increase the identification of the (early) signs of refeeding syndrome. The elements can be adjusted in order to match the procedures of a specific institution. It is advisable to found a working group in each institution that will have the knowledge of the recent publications on the refeeding syndrome, defines the multidisciplinary responsibility in the care process and educates relevant health care workers.

1. Laboratory control

Specify the laboratory assessments and the vitamins, trace elements and electrolytes that need to be supplemented before the start and during the build-up of the feeding (intravenous or otherwise) and interpret the results on a daily basis. **(Table 3)**

Table 3. Laboratory control in case of high-risk of the refeeding syndrome

Measurement?	***When?***	
	Before start of the feeding (day 0)	**During the build-up of the feeding (daily on day 1 to 4-10)[1]**
Sodium	X	
Potassium	X	X
Phosphate	X	X
Magnesium	X	X
Calcium	X	On indication[2]
Creatinine	X	
Glucose	X	
Albumin	X	On indication[3]

[1.] For at least 4 days, continue if laboratory results are aberrant or show clinically relevant variations,

[2.] With severe hypocalcemia and/or other electrolyte disorders,

[3.] To evaluate the calcium level (add or subtract 0.02 mmol/L Ca for each gram of albumin under or above a total serum albumin of 40 g/L, respectively).

2. Supplementation

Recommendations for supplementation in patients with the refeeding syndrome should be made carefully, adjusted to the individual patient's situation and in consultation with the treating doctor.

Vitamins

Supplement at least 30 minutes before starting or restarting feeding:

■ 100-300 mg thiamine (oral, enteral, intramuscular, or intravenous)

Supplement on days 1 - 3 from start or restart of feeding:

■ once daily 100-300 mg thiamine

■ once daily multivitamins and trace elements complex (vitamins preferably at least 200% ADH, trace elements at least 100% ADH). Realize that enteral / parenteral nutrition is supplemented with micronutrients.

If there is an indication of severe undernutrition or multiple deficiencies of vitamins, minerals, or trace elements

are expected, it is recommended to continue the thiamine, multivitamin and trace elements supplements from day 4 – 10

■ once daily 100 mg thiamine

■ once daily multivitamins, mineral complex (vitamins preferably at least 200% ADH, trace elements at least 100% ADH)

Electrolytes:

Supplement electrolytes in case the patient has clinically relevant low plasma concentrations **(table 4)**.

Table 4. Electrolyte supplementation recommendations in refeeding syndrome (NB adjust in case of renal insufficiency)

Electrolyte	Concentration	Proposed supplementation	Testing
Phosphate	Mild to moderate 0.3-0.8 mmol/L	15-30 mmol/d oral or IV	Daily
	Severe <0.3 mmol/L (*with a rapid drop (>0.3 mmol/L/d) or life-threatening hypophosphatemia*)	0.25-1.0 mmol/kg over 8-12 hours IV	Every 6 hours
Potassium	Mild to moderate 3.0-3.4 mmol/L	4.5 mmol/h for 3 h IV followed by 2-3.5 mmol/h IV with a maximum of 90 mmol/d + frequent testing	daily
	Severe < 3.0 mmol/l	30-80 mmol/d IV or oral	Daily
Magnesium	Mild to moderate 0.5-0.7 mmol/L	13-34 mmol/d oral or 10-15 mmol/d IV	Daily
	Severe <3.0 mmol/L	2-4 mmol/kg/d IV or 120-240 mmol/d IV or oral	Every 6 hours

3. Feeding recommendations: Oral, enteral, parenteral

■ Start with 10 kcal/kg/d (preferably 50-60% carbohydrates, 30-40% fat, 15-20% protein)

■ Build up 5-10* kcal/kg daily, until requirements are fully covered within 4-10

■ Avoid extra glucose (oral, enteral, intravenous) during the build-up phase (or compensate with feeding)

■ Anticipate the risk of developing refeeding syndrome. If there are no biochemical and/or symptomatic changes and none appear later, the feeding can be increased more quickly.

* If there is a clinical manifestation of the refeeding syndrome:

■ build up by 5 kcal/kg daily

■ if electrolyte supplementation is required: continue feeding (not necessary to stop), but perhaps temporarily delay increasing the feeding rate, depending on the severity of the electrolyte drop(s) and until the electrolyte(s) stabilise.

4. Fluid

■ Maintain an even fluid balance of maximum positive fluid balance of 500 ml (adjust to requirement depending on the patient's clinical situation, e.g. dialysis)

■ Average requirement is 20-30 ml/kg/d total fluids, adjust to requirement until adequate hydration is achieved.

5. Monitoring

■ Evaluate the nutrition recommendations and adjust as necessary

■ Monitor the electrolytes, fluid balance, and weight (fluctuations) daily during build-up of nutrition

■ Carry out additional tests (renal function, heart rate, etc.) according to the patient's clinical status

Outpatient setting

In home care it will be more difficult to monitor patients with a high risk of the refeeding syndrome and admission to the hospital will be the best strategy. When hospital admission is not possible, the five steps of the treatment plan can be carried out by the general practitioner and home care dietitian, possibly with assistance of the facilities (laboratory) of a near hospital.

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