Refeeding syndrome: a clinical review

Refeeding syndrome can result in a wide variety of complications and may be life threatening. Although well described in hospital practice, refeeding syndrome is often under-recognized and inadequately treated.

Refeeding syndrome describes the severe electrolyte and fluid shifts associated with related metabolic abnormalities in malnourished patients undergoing refeeding orally, enterally or parenterally (Solomon and Kirby, 1990). It was originally described in Japanese prisoners of war after the Second World War, in whom feeding after a prolonged period of starvation precipitated cardiac failure (Schnitker et al, 1951). An early experiment in Minnesota, USA, further illustrated the physiological effect of semi-starvation in healthy subjects: 32 male volunteers were fed between 1500 and 1600 kcal/day for a 24-week period and, on average, lost 16 kg (23% weight loss) which resulted in cardiovascular reserve being significantly diminished, to the point of cardiac failure (Keys et al, 1950).

The current incidence of refeeding syndrome in hospital patients is unknown. A study of more than 10 000 hospital inpatients over a 1-year period found that the overall incidence of severe hypophosphataemia, a biochemical characteristic of the refeeding syndrome, was 0.43%, rising to 10.4% in patients with malnutrition (Camp and Allon, 1990). A concerning finding of this study was that hypophosphataemia was unrecognized or inappropriately treated in 42% of cases (Camp and Allon, 1990). In a prospective study of 62 critically ill patients admitted to an intensive care unit, 34% experienced refeeding hypophosphataemia and, of particular clinical relevance, the length of mechanical ventilation and hospital stay were significantly longer in these patients (Marik and Bedigian, 1996).

The National Institute of Clinical Excellence highlighted the importance of recognizing and preventing the occurrence of refeeding syndrome in malnourished patients because of its potentially fatal outcome (National Institute of Clinical Excellence, 2006). This article reviews the mechanisms leading to refeeding syndrome and its clinical consequences, highlights groups at risk of refeeding syndrome and outlines an approach to management.

Pathophysiology of refeeding syndrome

During starvation, reduced carbohydrate intake leads to a fall in insulin levels and a rise in glucagon levels. The body switches from using carbohydrate to protein and then fat stores as its main energy source; this catabolic state leads to a reduction in lean body mass (Crook et al, 2001). During this time, intracellular stores of phosphate, magnesium and potassium become depleted, although it is important to recognize that serum concentrations of these electrolytes can remain normal during starvation as a result of contraction of the intracellular compartment and reduced renal excretion (Mehanna et al, 2008). Therefore, normal blood electrolytes before feeding a malnourished patient do not preclude that patient from the risk of developing refeeding syndrome.

When feeding is re-introduced, the resultant glucose load stimulates the secretion of insulin and the body switches from fat to carbohydrate as the principal energy source (Crook et al, 2001). Insulin stimulates the uptake of potassium, magnesium and phosphate into cells, and promotes the anabolic production of glycogen, fat and protein; these anabolic processes require phosphate and magnesium, as well as thiamine, leading to depletion of body stores and serum levels (Mehanna et al, 2008). These rapid electrolyte shifts, and the resultant osmotic fluid shifts, may lead to a number of clinical complications of the refeeding syndrome, which are outlined below. However, it is important to recognize that the refeeding syndrome can often be asymptomatic and manifested solely by changes serum electrolyte levels; therefore, vigilance for its occurrence is of the utmost importance, so that prompt management can prevent clinical symptoms developing.

Hypophosphataemia

Hypophosphataemia is one of the predominant features of refeeding syndrome. Phosphate has a number of important physiological processes; for example, it is a structural component of the phospholipid cell membrane, nucleic acids and nucleoproteins and, functionally, it is central to regulating enzymatic action through protein phosphorylation (Crook et al, 2001). Phosphate is also required for many intracellular pathways such as oxidative phosphorylation and glycolysis. Glycolysis produces adenosine triphosphate or ATP, which provides energy to the cells, and 2,3-diphosphoglycerate (another byproduct of glycolysis) modulates the oxygen dissociation curve. Nerve conduction also requires phosphate. Finally, phosphate plays a role in white blood cell function (Craddock et al, 1974).

Given the crucial physiological functions of phosphate, hypophosphataemia can affect the body in a number of ways:

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The cardiovascular system

Starvation is thought to result in cardiac myocyte ATP depletion resulting in impaired cardiac contractility (O'Connor et al, 1977). This, in association with fluid shifts, can result in cardiac failure. Hypophosphataemia is also associated with cardiac arrhythmias (Venditti et al, 1987).

The nervous system

A number of neurological consequences of hypophosphataemia have been described including delirium, seizures and paraesthesia (Crook et al, 2001). Hypophosphataemia has also been reported to mimic Guillain–Barré syndrome necessitating ventilatory support (Sebastian et al, 2008).

The musculoskeletal system

Hypophosphataemia can result in myopathy (Ravid and Robson, 1976) and, when severe, has been associated with rhabdomyolysis (Knochel, 1977). Difficulty in weaning patients from mechanical ventilatory support may also occur as a result of the refeeding syndrome (Gariballa, 2008), while diaphragmatic contractility has been shown to improve following correction of hypophosphataemia (Aubier et al, 1985).

The haematological system

As previously discussed, phosphate is required for glycolysis. 2,3-diphosphoglycerate is a by-product of glycolysis and therefore hypophosphataemia results in a reduction in the erythrocyte concentration of 2,3-diphosphoglycerate. This, in turn, results in a shift of the cellular oxygen-dissociation curve to the left, enhancing haemoglobin affinity for oxygen and leading to tissue hypoxia (Larsen et al, 1996).

Hypophosphataemia can lead to haemolysis as a result of a reduction in red blood cell ATP concentration which, in turn, can make the cells more rigid and more prone to destruction (Feo and Mohandas, 1977). Leukocyte dysfunction has also been reported in association with hypophosphataemia (Craddock et al, 1974) since ATP is required for phagocytosis and chemotaxis. Thus, hypophosphataemia may result in increased susceptibility to infection.

Hypomagnesaemia

The mechanism of hypomagnesaemia in refeeding syndrome is multifactorial; it relates in part to the movement of magnesium into cells on carbohydrate refeeding and may be confounded by poor dietary intake of magnesium (Solomon and Kirby, 1990; Crook et al, 2001). Magnesium is another intracellular cation that serves as a cofactor for a number of cellular enzymes and is important for maintenance of membrane potential. Hypomagnesaemia affects the heart, resulting in electrocardiogram abnormalities, including widening of the QRS complex, peaked T waves, prolongation of the PR interval, T wave inversion and the appearance of U waves; severe ventricular arrhythmias such as torsades de pointes may also result. Hypocalcaemia often occurs in severe hypomagnesaemia and is related to the severity of magnesium depletion. The neuromuscular consequences of this include seizures and carpopedal spasm (Abbott and Rude, 1993).

Hypokalaemia

Potassium is the most abundant intracellular cation, and is involved in determining the cellular action potential. As mentioned above, the release of insulin during refeeding results in increased movement of potassium into the cells. While mild hypokalaemia may be asymptomatic, severe hypokalaemia can lead to generalized weakness and occasionally paralysis. Hypokalaemia may also precipitate cardiac arrhythmias and sudden death.

Glucose

Refeeding, and the subsequent release of insulin, leads to suppression of gluconeogenesis. Once this has occurred, further infusion of glucose may result in hyperglycaemia, which may lead to hyperosmolar non-ketotic acidosis or ketoacidosis (Crook et al, 2001). Insulin can also induce glucose conversion to fat (lipogenesis), which may in turn cause hypertriglyceridaemia, fatty liver and/or hypercapnoea and respiratory failure (Klein et al, 1998; Crook et al, 2001).

Fluid balance

Refeeding causes sodium and water retention (Veverbrants and Arky, 1969). The resultant increase in the extracellular compartment, as well as the use of intravenous fluids, may precipitate oedema and cardiac failure.

Thiamine deficiency

Starvation results in a number of vitamin deficiencies, including thiamine, which is an essential cofactor involved in carbohydrate metabolism, but is not stored in substantial amounts. Thus, as refeeding occurs, residual stores are quickly depleted. Thiamine deficiency can be estimated by measuring erythrocyte transketolase activity or blood thiamine concentrations directly (Talwar et al. 2000). However, these tests are of no clinical utility in the context of refeeding syndrome, not least because they are rarely available in the emergency setting, and a pragmatic approach of thiamine supplementation before refeeding should be adopted in patients at risk of developing refeeding syndrome.

Thiamine deficiency may result in Wernicke's encephalopathy, although the classical triad of confusion, ataxia and ophthalmoplegia is not always seen; recent criteria for diagnosis require two or more of the following: dietary deficiency, oculomotor abnormalities, cerebellar dysfunction and altered mental state (Caine et al, 1997). If it is not adequately treated, Korsakoff's syndrome may result, which is characterized by short-term memory loss and confabulation.

Prevention and treatment of refeeding syndrome

It is important to remember that refeeding syndrome not only occurs with the use of parenteral nutrition, but can also occur with enteral nutrition; moreover, it has been reported with volitional oral intake of an unsupplemented diet (Sebastian et al, 2008) and may also occur following the administration of intravenous dextrose solutions.

Central to the management of refeeding syndrome is the recognition of those patient groups that may be at risk; this includes patients with malnutrition, which may arise for a variety of reasons, such as impaired nutrient absorption (e.g. inflammatory bowel disease, extensive intestinal resection or patients who have undergone surgery for obesity), increased catabolism (e.g. inflammatory processes or cancer) and/or reduced intake (e.g. anorexia nervosa, dysphagia) (Mehanna et al, 2008).

A study of 500 patients admitted to a variety of specialties in a single UK teaching hospital found the overall prevalence of malnutrition on admission was 40%; of equal concern was the finding that 78% of these patients went on to lose further weight during their hospital stay (McWhirter and Pennington, 1994).

It appears that the prevalence of malnutrition remains a concern throughout the UK, since the British Association of Parenteral and Enteral Nutrition found that 28% of a sample of over 5000 inpatients from 130 hospitals were at risk of malnutrition (Russell and Elia, 2009). In this survey, malnutrition was common across all patient ages and all diagnostic categories, but was particularly common in patients with gastrointestinal or neurological conditions.

Patients with anorexia nervosa at risk of refeeding syndrome warrant mention, not only because associated laxative or diuretic abuse can augment any electrolyte abnormalities, but also because they can pose a difficult management problem for general physicians on hospital wards, and it is important to ensure continued psychiatric support if admission to a medical unit is required.

Screening

Given the high prevalence of malnutrition, National Institute of Clinical Excellence recommend that all patients should be screened for malnutrition on admission to hospital (National Institute of Clinical Excellence, 2006). Screening should allow the establishment of pathways of care for malnourished patients, including referral to dietetic services if required. Screening tools need to be easy and quick to use, and have good reproducibility and validity. A number of nutritional screening tools have been developed; the Subjective Global Assessment (SGA), for example, can be administered at the bedside and allows a subjective assessment of an individual's nutritional status based on history (including weight loss, change in dietary intake, presence of gastrointestinal symptoms, functional capacity) and examination findings (including muscle wasting, subcutaneous fat loss, presence of oedema or ascites) (Detsky et al, 1987).

The Malnutrition Universal Screening Tool (MUST) is a simple and validated tool that has been developed by the British Association of Parenteral and Enteral Nutrition to screen for malnutrition and is calculated on the basis of body mass index, the percentage of unintentional weight loss over a 3–6-month period and whether or not the patient has had, or is likely to have, no nutritional intake for more than 5 days (Elia, 2003). While screening tools such as MUST or SGA facilitate the identification of patients who are already malnourished or are at risk of malnutrition, additional criteria based on electrolyte parameters and confounding risk factors, such as alcohol use or medications that may lead to electrolyte imbalance (e.g. diuretics or phosphate binding antacids), allow further determination of those patients at high risk of developing refeeding syndrome (*Table 1*).

Management

Since there have been no published randomized controlled studies evaluating the management of refeeding syndrome, National Institute of Health and Clinical Excellence recommendations are based, at best, on cohort studies. For patients with minimal nutritional intake for more than 5 days, nutrition support should be introduced at a maximum of 50% of total energy requirements for the first 48 hours, increasing gradually to meet nutritional requirements only if no refeeding problems are identified. Requirements for fluid, electrolytes, vitamins, minerals and trace elements should be met from day 1 of feeding (National Institute of Clinical Excellence, 2006).

For patients at high risk of refeeding syndrome (*Table 1*), National Institute of Health and Clinical Excellence recommend that nutrition support should be started at 10 kcal/kg/day and that this should be gradually increased

Table 1. Criteria for determining people at high risk of refeeding syndrome

One or more of the following:	Body mass index less than 16 kg/m^2
	Unintentional weight loss of 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 before feeding
Or two or more of the following:	Body mass index less than 18.5 kg/m^2
	Unintentional weight loss of 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

From National Institute for Clinical Excellence (2006)

over 4–7 days with close monitoring of the patient. In extreme cases (e.g. body mass index less than 14 kg/m^2), initiation of feeding at 5 kcal/kg/day should be considered, and these patients may need to be managed in an environment with facilities for cardiac monitoring, such as a high dependency unit. The latter may also be necessary for any patient with a cardiac rhythm abnormality or severe electrolyte disturbance, and it is important to ensure that fluid balance is closely monitored and effectively managed.

Stanga et al (2007) reported on the management of seven patients at high risk of refeeding syndrome; their recommendations included initiating feeding at 10 kcal/kg/day on days 1–3 and increased to 15 kcal/kg/day slowly, with electrolytes being measured 4–6-hourly on initiation of feeding and daily thereafter. All patients at risk of refeeding syndrome should receive oral thiamine and an oral vitamin B complex preparation such as vitamin B compound strong (vitamin B co strong) at least 30 minutes before feeding is started; these supplements should be continued for a minimum of 10 days thereafter. For patients who cannot take these medications orally, an intravenous vitamin B preparation (Pabrinex) should be administered instead. Malnourished patients are also at risk of other vitamin and micronutrient deficiencies, and it is important to assess blood levels and ensure adequate replenishment with appropriate vitamin and trace element supplements.

As highlighted by Stanga and colleagues (2007), blood tests (electrolytes including sodium, urea, creatinine, phosphate, calcium, magnesium, potassium and glucose) should be checked before initiation of nutritional support and monitored at least daily for the first week. National Institute of Health and Clinical Excellence recommend supplementation of phosphate (0.3–0.6 mmol/kg/day), potassium (2–4 mmol/kg/day) and magnesium (intravenous (0.2 mmol/kg/day), enteral or oral route (0.4 mmol/kg/day)) unless pre-feeding levels are high, and their guidelines advocate the correction of electrolytes while feeding, rather than delaying nutritional support while electrolytes are given.

Oral supplementation of phosphate can be inadequate and poorly tolerated by patients since it can induce diarrhoea; many therefore recommend intravenous supplementation (Hearing, 2004). Traditionally, intravenous phosphate replacement required complicated infusion regimens based on body weight and multiple blood tests. However, a study of 30 patients with refeeding syndrome requiring phosphate infusions (defined as having a plasma phosphate concentration of less than 0.50 mmol/litre) demonstrated that 50 mmol of phosphate (phosphate polyfusor, Fresenius Kabi, Warrington) was both safe and effective, although some patients required repeated infusions (Terlevich et al, 2003). An important feature of this study to note is that all patients were treated on general medical or surgical wards and did not require admission to a high dependency unit.

Oral magnesium supplements, like oral phosphate supplements, can be problematic by inducing diarrhoea and intravenous replacement is often required. However, there are limited data on the appropriate route and rate of electrolyte replacement in the setting of refeeding syndrome, and hospital protocols should guide clinicians on correction levels, based on National Institute of Clinical Excellence (2006) recommendations.

There is clear evidence that metabolic complications of refeeding occur less often following the initiation of both enteral (Powers et al, 1986) or parenteral (Fettes and Lough, 2000) nutrition, if patients are managed by a multidisciplinary nutrition support team. Despite this, in 2005 less than half of all hospitals were found to have a nutrition support team in place (British Artificial Nutrition Survey, 2006). These issues have been recognized by National Institute of Health and Clinical Excellence, who now clearly advocate the institution of multidisciplinary nutrition support teams – in order to ensure the safe and effective provision of nutritional support – throughout all acute hospital trusts (National Institute of Clinical Excellence, 2006).

Conclusions

Refeeding syndrome is associated with significant morbidity and mortality, yet it is preventable if anticipated. The key to its treatment is therefore recognition of those at risk. Non-specialist physicians and surgeons may not appreciate the importance of refeeding syndrome, nor have a comprehensive understanding of those patients most at risk. Studies are warranted to provide better evidence for the management of refeeding syndrome in all clinical settings. Nutrition support teams have an important role, not only by treating patients at risk of refeeding syndrome, but also in the education of medical and nursing staff and increasing awareness of National Institute of Health and Clinical Excellence guidelines on nutritional support throughout all hospital wards. **BJHM**

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Conflict of interest: none.

KEY POINTS

- Refeeding syndrome is preventable but remains under-recognized in hospital patients.
- It occurs when feeding (oral, enteral or parenteral) is introduced following a period of starvation.
- Multiple electrolyte and metabolic derangements can occur which can be fatal.
- The key to managing refeeding syndrome is recognition of those at risk.
- The National Institute for Health and Clinical Excellence has published guidelines on nutritional support in adults, which include the management of patients at risk of refeeding syndrome.
- Nutrition support teams have a role in the education of medical staff on the management of refeeding syndrome.

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