CLINICAL REVIEW

Refeeding syndrome: what it is, and how to prevent and treat it

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Refeeding syndrome is a well described but often forgotten condition. No randomised controlled trials of treatment have been published, although there are guidelines that use best available evidence for managing the condition. In 2006 a guideline was published by the National Institute for Health and Clinical Excellence (NICE) in England and Wales. Yet because clinicians are often not aware of the problem, refeeding syndrome still occurs.[1]

This review aims to raise awareness of refeeding syndrome and discuss prevention and treatment. The available literature mostly comprises weaker (level 3 and 4) evidence, including cohort studies, case series, and consensus expert opinion.[2] Our article also draws attention to the NICE guidelines on nutritional support in adults, with particular reference to the new recommendations for best practice in refeeding syndrome.[3] These recommendations differ in parts from—and we believe improve on—previous guidelines, such as those of the Parenteral and Enteral Nutrition Group of the British Dietetic Association (box 1).[4]

What is refeeding syndrome?

Refeeding syndrome can be defined as the potentially fatal shifts in fluids and electrolytes that may occur in malnourished patients receiving artificial refeeding (whether enterally or parenterally[5]). These shifts result from hormonal and metabolic changes and may cause serious clinical complications. The hallmark biochemical feature of refeeding syndrome is hypophosphataemia. However, the syndrome is complex and may also feature abnormal sodium and fluid balance; changes in glucose, protein, and fat metabolism; thiamine deficiency; hypokalaemia; and hypomagnesaemia.[1 6]

How common is refeeding syndrome?

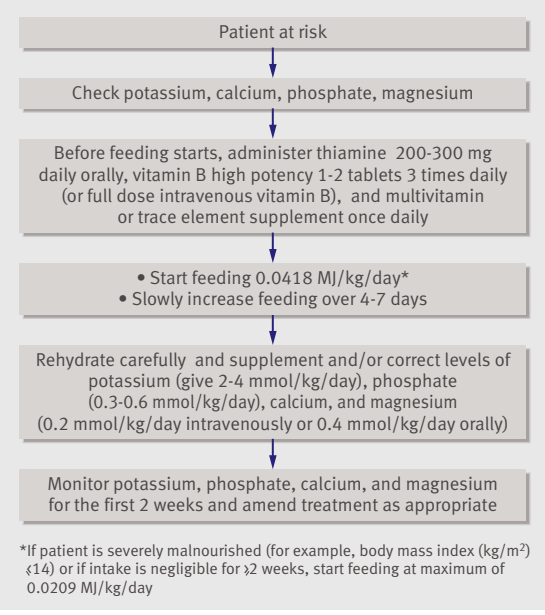
The true incidence of refeeding syndrome is unknown—partly owing to the lack of a universally accepted definition. In a study of 10 197 hospitalised patients the incidence of severe hypophosphataemia was 0.43%, with malnutrition being one of the strongest risk factors.[7] Studies report a 100% incidence of hypophosphataemia in patients receiving total parenteral nutrition solutions that do not contain phosphorus. When solutions containing phosphate are used, the incidence can decrease to 18%.[8]

Several prospective and retrospective cohort studies of hyperalimentation in intensive care units have documented the occurrence of refeeding syndrome.[6 9] In a well designed prospective cohort study of a heterogeneous group of patients in intensive care units, 34% of patients experienced hypophosphataemia soon after feeding was started (mean (standard deviation) 1.9 (1.1) days).[10] Many case reports have highlighted the potentially fatal nature of the condition.[11 12] However, it is often not recognised or maybe inappropriately treated, especially on general wards.[1 6]

How does refeeding syndrome develop?

Prolonged fasting

The underlying causative factor of refeeding syndrome is the metabolic and hormonal changes caused by rapid



Guidelines for management. Adapted from the guidelines of NICE[3] and the British Association of Parenteral and Enteral Nutrition[4]

A web extra box (box A) about the complications of refeeding syndrome and their underlying mechanisms is on bmj.com

Box 1 Why use the NICE guidelines on refeeding syndrome?

- The guidelines are the most recent comprehensive review of the literature on refeeding syndrome
- The guideline development group was strongly multidisciplinary with wide ranging consultation with both professional and patient stakeholders
- The guidelines clearly identified points of good practice and areas for further research
- The new guidelines give explicit clinical criteria for patients "at risk" and "highly at risk" of developing refeeding syndrome, enabling better identification and prevention
- For patients with electrolyte deficits the new guidelines recommend immediate start of nutritional support at a lower rate, rather than waiting till the electrolyte imbalance has been corrected (as was recommended by previous guidelines), thus potentially avoiding further nutritional deterioration in patients

refeeding, whether enteral or parenteral. The net result of metabolic and hormonal changes in early starvation is that the body switches from using carbohydrate to using fat and protein as the main source of energy, and the basal metabolic rate decreases by as much as 20-25%.[13]

During prolonged fasting, hormonal and metabolic changes are aimed at preventing protein and muscle breakdown. Muscle and other tissues decrease their use of ketone bodies and use fatty acids as the main energy source. This results in an increase in blood levels of ketone bodies, stimulating the brain to switch from glucose to ketone bodies as its main energy source. The liver decreases its rate of gluconeogenesis, thus preserving muscle protein. During the period of prolonged starvation, several intracellular minerals become severely depleted. However, serum concentrations of these minerals (including phosphate) may remain normal. This is because these minerals are mainly in the intracellular compartment, which contracts during starvation. In addition, there is a reduction in renal excretion.

Refeeding

During refeeding, glycaemia leads to increased insulin and decreased secretion of glucagon. Insulin stimulates glycogen, fat, and protein synthesis. This process requires minerals such as phosphate and magnesium and cofactors such as thiamine. Insulin stimulates the absorption of potassium into the cells through the sodium-potassium ATPase symporter, which also transports glucose into the cells. Magnesium and phosphate are also taken up into the cells. Water follows by osmosis. These processes result in a decrease in the serum levels of phosphate, potassium, and magnesium, all of which are already depleted. The clinical features of the refeeding syndrome occur as a result of the functional deficits of these electrolytes and the rapid change in basal metabolic rate.

Box 2 Patients at high risk of refeeding syndrome [1 3 4]

- Patients with anorexia nervosa
- Patients with chronic alcoholism
- Oncology patients
- Postoperative patients
- Elderly patients (comorbidities, decreased physiological reserve)
- Patients with uncontrolled diabetes mellitus (electrolyte depletion, diuresis)
- Patients with chronic malnutrition:
  - -Marasmus
  - -Prolonged fasting or low energy diet
  - -Morbid obesity with profound weight loss
  - - High stress patient unfed for >7 days
  - -Malabsorptive syndrome (such as inflammatory bowel disease, chronic pancreatitis, cystic fibrosis, short bowel syndrome)
- Long term users of antacids (magnesium and aluminium salts bind phosphate)
- Long term users of diuretics (loss of electrolytes)

What electrolytes and minerals are involved in the pathogenesis?

Phosphorus

Phosphorus is predominantly an intracellular mineral. It is essential for all intracellular processes and for the structural integrity of cell membranes. In addition, many enzymes and second messengers are activated by phosphate binding. Importantly it is also required for energy storage in the form of adenosine triphosphate (ATP). It regulates the affinity of haemoglobin for oxygen and thus regulates oxygen delivery to tissues. It is also important in the renal acid-base buffer system.

In refeeding syndrome, chronic whole body depletion of phosphorus occurs. Also, the insulin surge causes a greatly increased uptake and use of phosphate in the cells. These changes lead to a deficit in intracellular as well as extracellular phosphorus. In this environment, even small decreases in serum phosphorus may lead to widespread dysfunction of cellular processes affecting almost every physiological system (see box A on bmj.com).[14]

Potassium

Potassium, the major intracellular cation, is also depleted in undernutrition. Again, serum concentration may remain normal. With the change to anabolism on refeeding, potassium is taken up into cells as they increase in volume and number and as a direct result of insulin secretion. This results in severe hypokalaemia. This causes derangements in the electrochemical membrane potential, resulting in, for example, arrhythmias and cardiac arrest.

Magnesium

Magnesium, another predominantly intracellular cation, is an important cofactor in most enzyme systems, including oxidative phosphorylation and ATP production. It is also necessary for the structural integrity of DNA, RNA, and ribosomes. In addition, it affects membrane potential, and deficiency can lead to cardiac dysfunction and neuromuscular complications.[18]

Glucose

Glucose intake after a period of starvation suppresses gluconeogenesis through the release of insulin.

Box 3 Criteria from the guidelines of the National Institute for Health and Clinical Excellence for identifying patients at high risk of refeeding problems (level D recommendations*)[3]

Either the patient has one or more of the following:

- Body mass index (kg/m^2) ‹16
- Unintentional weight loss ›15% in the past three to six months
- Little or no nutritional intake for ›10 days
- Low levels of potassium, phosphate, or magnesium before feeding

Or the patient has two or more of the following:

- Body mass index ‹18.5
- Unintentional weight loss ›10% in the past three to six months
- Little or no nutritional intake for ›5 days
- History of alcohol misuse or drugs, including insulin, chemotherapy, antacids, or diuretics

*Recommendations derived from low grade evidence—mainly cohort and case series studies—and from consensus expert opinion

Excessive administration may therefore lead to hyperglycaemia and its sequelae of osmotic diuresis, dehydration, metabolic acidosis, and ketoacidosis. Excess glucose also leads to lipogenesis (again as a result of insulin stimulation), which may cause fatty liver, increased carbon dioxide production, hypercapnoea, and respiratory failure.[15]

Vitamin deficiency

Although all vitamin deficiencies may occur at variable rates with inadequate intake, thiamine is of most importance in complications of refeeding. Thiamine is an essential coenzyme in carbohydrate metabolism. Its deficiency result in Wernicke's encephalopathy (ocular abnormalities, ataxia, confusional state, hypothermia, coma) or Korsakoff's syndrome (retrograde and anterograde amnesia, confabulation).[19]

Sodium, nitrogen, and fluid

Changes in carbohydrate metabolism have a profound effect on sodium and water balance. The introduction of carbohydrate to a diet leads to a rapid decrease in renal excretion of sodium and water.[20] If fluid repletion is then instituted to maintain a normal urine output, patients may rapidly develop fluid overload. This can lead to congestive cardiac failure, pulmonary oedema, and cardiac arrhythmia.

Recommendation for phosphate and magnesium supplementation[3 4 6 13]

Mineral	Dose
Phosphate	
Maintenance requirement	0.3-0.6 mmol/kg/day orally
Mild hypophosphataemia (0.6-0.85 mmol/l)	0.3-0.6 mmol/kg/day orally
Moderate hypophosphataemia (0.3-0.6 mmol/l)	9 mmol infused into peripheral vein over 12 hours
Severe hypophosphataemia (‹0.3 mmol/l)	18 mmol infused into peripheral vein over 12 hours
Magnesium	
Maintenance requirement	0.2 mmol/kg/day intravenously (or 0.4 mmol/kg/day orally)
Mild to moderate hypomagnesaemia (0.5-0.7 mmol/l)	Initially 0.5 mmol/kg/day over 24 hours intravenously, then 0.25 mmol/kg/day for 5 days intravenously
Severe hypomagnesaemia (‹0.5 mmol/l)	24 mmol over 6 hours intravenously, then as for mild to moderate hypomagnesaemia (above)

How can refeeding syndrome be prevented?

Identification of high risk patients is crucial (boxes 2 and 3).[3 4] Any patient with negligible food intake for more than five days is at risk of developing refeeding problems. Patients may be malnourished as a result of reduced intake (for example, owing to dysphagia, anorexia nervosa, depression, alcoholism); reduced absorption of nutrition (as in, for example, inflammatory bowel disease, coeliac disease); or increased metabolic demands (for example, in cancer, surgery). High risk patients include those who have been chronically undernourished, especially those who also have diminished physiological reserve. Patients with dysphagia (for example, as a result of stroke) in particular may be at high risk.

The figure summarises how to prevent and treat refeeding syndrome. To ensure adequate prevention, the NICE guidelines recommend a thorough nutritional assessment before refeeding is started.[3] Recent weight change over time, nutrition, alcohol intake, and social and psychological problems should all be ascertained. Plasma electrolytes (especially phosphate, sodium, potassium, and magnesium) and glucose should be measured at baseline before feeding and any deficiencies corrected during feeding with close monitoring.[3]

The NICE guidelines recommend that refeeding is started at no more than 50% of energy requirements in "patients who have eaten little or nothing for more than 5 days." The rate can then be increased if no refeeding problems are detected on clinical and biochemical monitoring (level D recommendation—see box 3).

For patients at high risk of developing refeeding syndrome, nutritional repletion of energy should be started slowly (maximum 0.042 MJ/kg/24 hours) and should be tailored to each patient. It can then be increased to meet or exceed full needs over four to seven days. In patients who are very malnourished (body mass index ≤14 or a negligible intake for two weeks or more), the NICE guidelines recommend that refeeding should start at a maximum of 0.021 MJ/kg/24 hours, with cardiac monitoring owing to the risk of cardiac arrhythmias (level D recommendation).[3] This explicit specification of the rate of refeeding in severely malnourished patients should help avoid complications arising from rapid refeeding and is an improvement on previous guidelines.[4] The NICE guidelines also state that correcting electrolyte and fluid imbalances before feeding is not necessary and that this should be done along with feeding. This is a change from previous guidelines[4] and potentially avoids prolongation of malnourishment and its effects on patients.

All guidelines recommend that vitamin supplementation should be started immediately, before and for the first 10 days of refeeding. Circulatory volume should also be restored. Oral, enteral, or intravenous supplements of the potassium, phosphate, calcium, and magnesium should be given unless blood levels are high before refeeding. Good quality studies on the exact levels of supplementation are lacking, however,

SUMMARY POINTS

Refeeding syndrome is a potentially fatal condition, caused by rapid initiation of refeeding after a period of undernutrition

It is characterised by hypophosphataemia, associated with fluid and electrolyte shifts and metabolic and clinical complications

Awareness of refeeding syndrome and identification of patients at risk is crucial as the condition is preventable and the metabolic complications are avoidable

Patients at high risk include chronically undernourished patients and those who have had little or no energy intake for more than 10 days

Refeeding should be started at a low level of energy replacement. Vitamin supplementation should also be started with refeeding and continued for at least 10 days

Correction of electrolyte and fluid imbalances before feeding is not necessary; it should be done alongside feeding

and so the required levels of these supplements cited by NICE (figure) are only level D recommendations.[3]

Electrolyte levels should be measured once daily for one week, and at least three times in the following week. Urinary electrolytes could also be checked to help assess body losses and to guide replacement.

How can refeeding syndrome be detected and treated?

Refeeding syndrome is detected by considering the possibility of its existence and by using the simple biochemical investigations described above. If the syndrome is detected, the rate of feeding should be slowed down and essential electrolytes should be replenished. The hospital specialist dietetics team should be involved.

The best method for electrolyte repletion has not yet been determined. Hypophosphataemia, hypomagnesaemia, and hypokalaemia in hospitalised patients are ideally treated with intravenous supplementation (table), but this is not without risks. A prospective comparative cohort study of 27 patients with severe hypophosphataemia showed the safety of administering 15-30 mmol phosphate over three hours via a central venous catheter in an intensive care unit.[16] However, the researchers reported the need for repeated doses in most patients. Terlevich et al reported efficacy of 50 mmol phosphate infused into a peripheral vein over 24 hours in 30 patients with no pre-existing renal dysfunction on general wards.[17] Further infusions may be required and so careful monitoring of blood levels is required. Caution is needed in patients with existing renal impairment, hypocalcaemia (which may worsen), or hypercalcaemia (which may result in metastatic calcification).

Fluid repletion should be carefully controlled to avoid fluid overload as described earlier. Sodium administration should be limited to the replacement of losses. In patients at high risk of cardiac decompensation, central venous pressure and cardiac rhythm monitoring should be considered.

Conclusion

Adherence to the NICE guidelines for preventing and treating refeeding syndrome (boxes 2 and 3) should reduce the incidence and associated complications of the syndrome. Further research is needed to determine the true incidence of refeeding syndrome and to ascertain the best management protocols.

AREAS FOR FUTURE RESEARCH

- Formulation of consensus definitions and outcomes for reporting studies on nutrition
- Large multicentre studies concentrating on homogeneous, well defined study samples
- High quality trials to identify the best replacement and treatment regimens for phosphate and other minerals for refeeding syndrome

SOURCES AND SELECTION CRITERIA

We used the terms "refeeding", "syndrome", and "hypophosphataemia" to search the databases Medline, Embase, PubMed, Cochrane, CINAHL, and AMED (Allied and Complementary Medicine Database), as well as cross checking with reference lists, textbooks, and personal reference lists. We assessed the 151 identified papers for relevance. We assessed the quality of evidence in original articles according to guidelines published on the Evidence-Based On-Call website.[2]

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