European Journal of Clinical Nutrition (2008) 62, 687–694

0954-3007/08 $30.00
www.nature.com/ejcn

REVIEW

Nutrition in clinical practice—the refeeding syndrome: illustrative cases and guidelines for prevention and treatment

Z Stanga[1,2], A Brunner[1,3], M Leuenberger[2], RF Grimble[3], A Shenkin[4], SP Allison[5] and DN Lobo[5]

[1]*Department of Internal Medicine, University Hospital, Bern, Switzerland;* [2]*Clinical Nutrition Team, Division of Endocrinology, Diabetes and Clinical Nutrition, University Hospital, Bern, Switzerland;* [3]*Institute of Human Nutrition, Faculty of Medicine, Health and Life Sciences, University of Southampton, Southampton, UK;* [4]*Division of Clinical Chemistry, Faculty of Medicine, University of Liverpool, Liverpool, UK and* [5]*Division of Gastrointestinal Surgery, Wolfson Digestive Diseases Centre, Nottingham University Hospitals, Queen's Medical Centre, Nottingham, UK*

The refeeding syndrome is a potentially lethal complication of refeeding in patients who are severely malnourished from whatever cause. Too rapid refeeding, particularly with carbohydrate may precipitate a number of metabolic and pathophysiological complications, which may adversely affect the cardiac, respiratory, haematological, hepatic and neuromuscular systems leading to clinical complications and even death. We aimed to review the development of the refeeding syndrome in a variety of situations and, from this and the literature, devise guidelines to prevent and treat the condition. We report seven cases illustrating different aspects of the refeeding syndrome and the measures used to treat it. The specific complications encountered, their physiological mechanisms, identification of patients at risk, and prevention and treatment are discussed. Each case developed one or more of the features of the refeeding syndrome including deficiencies and low plasma levels of potassium, phosphate, magnesium and thiamine combined with salt and water retention. These responded to specific interventions. In most cases, these abnormalities could have been anticipated and prevented. The main features of the refeeding syndrome are described with a protocol to anticipate, prevent and treat the condition in adults.
European Journal of Clinical Nutrition (2008) **62,** 687–694; doi:10.1038/sj.ejcn.1602854; published online 15 August 2007

Keywords: refeeding syndrome; hypophosphataemia; hypomagnesaemia; thiamine deficiency; nutritional therapy; guidelines

Introduction

The refeeding syndrome was first reported among those released from concentration camps following the Second World War (Burger *et al*., 1948; Schnitker *et al*., 1951). Oral feeding of these grossly malnourished individuals often resulted in fatal diarrhoea, heart failure and neurological complications, including coma and convulsions. Milder symptoms were later reported by Keys *et al*. (1950) during the refeeding of healthy volunteers with a mean weight loss of 23% after starvation.

Severely malnourished patients (Table 1) appear to be at particular risk of developing the refeeding syndrome, whose features (Figure 1) (Travis *et al*., 1971; Craddock *et al*., 1974; O'Connor *et al*., 1977; Patrick, 1977; Heymsfield *et al*., 1978; Weinsier and Krumdieck, 1981; Powers, 1982; Isner *et al*., 1985; Cumming *et al*., 1987; Gustavsson and Eriksson, 1989; Faintuch, 1990; Beumont and Large, 1991; Brooks and Melnik, 1995; Birmingham *et al*., 1996; Marik and Bedigian, 1996; Paula *et al*., 1998; Crook *et al*., 2001; Hadley and Walsh, 2003; Marinella, 2003; Whyte *et al*., 2003; Hearing, 2004; Crook and Panteli, 2005; Kraft *et al*., 2005) include:

- salt and water retention leading to oedema and heart failure, which may be exacerbated by cardiac atrophy,

Correspondence: DN Lobo, Division of Gastrointestinal Surgery, Wolfson Digestive Diseases Centre, Nottingham University Hospitals, Queen's Medical Centre, Nottingham NG7 2UH, UK.
E-mail: dileep.lobo@nottingham.ac.uk
Contributors: ZS: study design, data collection, data interpretation and analysis, preparation of paper and critical review. AB: data collection, data interpretation and analysis, preparation of paper and critical review. ML: data collection and preparation of paper. RFG and AS: data interpretation, preparation of paper and critical review. SPA and DNL: study design, data interpretation and analysis, preparation of paper and critical review.
Received 14 February 2007; revised 17 June 2007; accepted 21 June 2007; published online 15 August 2007

- hypokalaemia due to rapid cellular uptake of potassium as glucose and amino acids are taken up during cellular synthesis of glycogen and protein,
- hypophosphataemia due to increased phosphorylation of glucose,
- rapid depletion of thiamine, a cofactor in glycolysis, leading to Wernicke's encephalopathy and/or cardiomyopathy, and
- hypomagnesaemia due to cellular uptake of this mineral.

Table 1 Some groups of malnourished patients at particular risk of developing the refeeding syndrome

Unintentional weight loss
Loss of >5% of body weight in 1 month
Loss of >7.5% of body weight in 3 months
Loss of >10% of body weight in 6 months
Low nutrient intake
Patients starved for >7 days
Prolonged hypocaloric feeding or fasting
Chronic swallowing problems and other neurological disorders
Anorexia nervosa
Chronic alcoholism
Depression in the elderly
Patients with cancer
Chronic infectious diseases (AIDS, tuberculosis)
During convalescence from catabolic illness
Postoperative patients
Diabetic hyperosmolar states
Morbid obesity with profound weight loss
Homelessness, social deprivation
Idiosyncratic/eccentric diets
Hunger strikers
Increased nutrient losses/decreased nutrient absorption
Significant vomiting and/or diarrhoea
Dysfunction or inflammation of the gastrointestinal tract
Chronic pancreatitis
Chronic antacid users (these bind minerals)
Chronic high-dose diuretic users
After bariatric surgery

In severe nutritional depletion, atrophy of the gut mucosa and impairment of pancreatic function may predispose to severe diarrhoea following oral or enteral refeeding, precipitating further electrolyte and mineral imbalance.

It is difficult to give a precise definition for the refeeding syndrome, since many otherwise well nourished patients, refed after only a few days starvation, will show a modest change in biochemical values, for example a fall in serum potassium and phosphate concentrations, without displaying any symptoms. There is a spectrum or gradation in the features of this condition from such asymptomatic cases to those with severe malnutrition who are at risk of overt and even life-threatening symptoms. The cutoff point at which the 'refeeding syndrome' can be said to be present is, therefore, somewhat arbitrary. We have taken the view that the full-blown syndrome should be defined by the presence of symptoms, but that biochemical changes of sufficient degree to pose a potential risk should be acted upon without delay in order to prevent the clinical features developing. Perhaps, we should adopt the terms 'symptomatic refeeding syndrome' and 'potential or biochemical refeeding syndrome'.

We report seven cases illustrating various aspects of this syndrome and, on the basis of these cases and a review of the

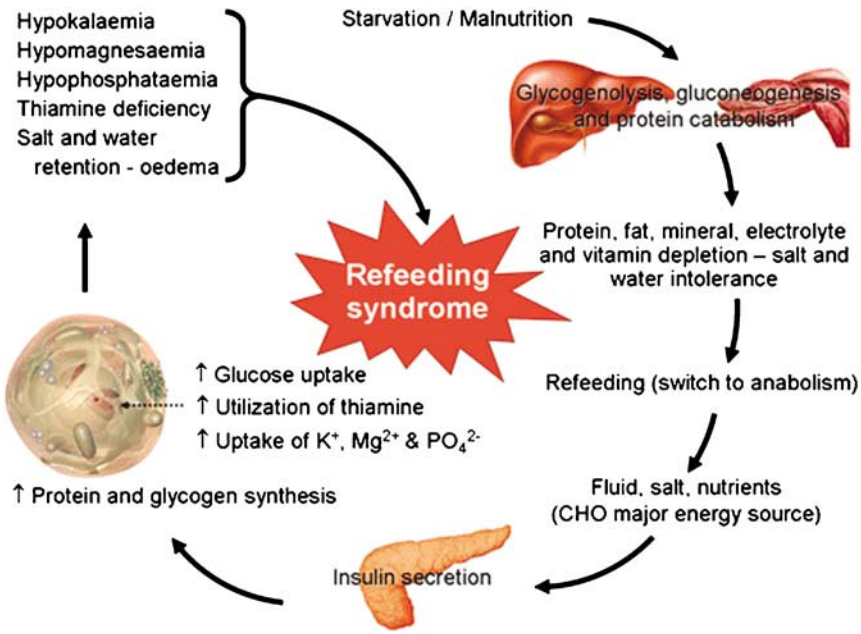

Figure 1 Pathogenesis and features of the refeeding syndrome.

literature, propose a refeeding regimen in adults to avoid this complication.

Case reports

Case 1: hunger striker

Protesting against a deportation order, a 27-year-old asylum seeker, with no previous medical history, went on hunger strike over a period of 4 months, refusing all nourishment apart from tea and coffee with sugar. At this time, he was admitted to hospital and, over the subsequent 2 weeks, lost a further 10 kg in weight (to 49 kg, body mass index (BMI) 14.7 kg/m^2). He became progressively weaker, more inactive and apathetic. At this point, he was treated by enteral and parenteral nutrition with a total intake of 6.7 MJ/day (1600 kcal/day). He was also given a daily infusion of 500 ml 0.9% saline with 20 mmol KCl and vitamins and trace elements according to the dietary reference intakes (DRI) (Food and Nutrition Board, 2005) (Supradyn one tablet/day: 100% of DRI). After 3 days, his condition had deteriorated. He had gained 5 kg in weight, due to salt and water retention, and developed hypokalaemia (2.8 mmol/l, normal range: 3.5–4.7 mmol/l), hypomagnesaemia (0.49 mmol/l, normal range: 0.7–1.0 mmol/l) and hypophosphataemia (0.05 mmol/l, normal range: 0.74–1.55 mmol/l). He showed neurological symptoms and signs with vertigo and vertical nystagmus. Artificial nutritional support was discontinued; a single dose of thiamine 200 mg was given intravenously (i.v.) and potassium phosphate 40 mmol was infused daily for 3 days. He also received a single i.v. dose of magnesium sulphate 20 mmol. After 3 days his electrolyte and mineral concentrations had risen into the normal range (K^+ 4.2 mmol/l, Mg^{2+} 0.77 mmol/l and PO_4^{2-} 1.16 mmol/l). Three days later, oral nutrition (6.7 MJ/day (1600 kcal/day)) was started and micronutrients were given i.v. according to the DRI (one ampoule each of Soluvit, Vitalipid and Addamel). After 37 days, his vertigo resolved. His mood and physical strength gradually improved and he was discharged after 57 days in hospital with a weight of 64.4 kg (gain of 15.4 kg) and a BMI of 19.2 kg/m^2. Unfortunately, the vertical nystagmus continued, preventing him from reading or watching television.

Key points. This case illustrates the vulnerability of patients with extreme weight loss and a very low BMI to the refeeding syndrome. The rapid falls in potassium, magnesium and phosphate within 24–48 h without adequate supplements were typical, although his main neurological sequelae were due mainly to Wernicke's encephalopathy from acute thiamine deficiency. Thiamine is not stored in appreciable amounts, so that any acceleration of carbohydrate metabolism—for which it is a cofactor—may precipitate acute deficiency. In such cases, this should always be anticipated by giving prophylactic thiamine at a dose of 200–300 mg i.v. daily, with the first dose being given 30 min before refeeding.

The incidence of some form of the refeeding syndrome in severely malnourished patients started on artificial feeding is approximately 50%, with half of these developing the syndrome within 3 days of starting treatment (Hernandez-Aranda *et al*., 1997).

Case 2: anorexia nervosa

A 40-year-old woman with long standing anorexia had suffered several complications of the condition in the past, including electrolyte disorders, arrhythmias, amenorrhoea, osteoporosis, depression and progressive social isolation. Before admission, she had lost further weight to 40 kg (BMI 13.5 kg/m^2). While admission was being contemplated, she resumed eating several large meals a day, precipitating the refeeding syndrome. On admission, she had ankle oedema and hypotension (95/70 mm Hg). Serum concentrations of phosphate, magnesium and potassium were low and the electrocardiogram (ECG) showed sinus bradycardia (51 b.p.m.) and a prolonged QT interval (490 ms). Within 4 h of admission and continuation of oral nutrition and, despite oral supplements of vitamins and electrolytes, she developed muscle weakness and drowsiness. The ECG showed short runs of ventricular tachycardia. i.v. supplementation of electrolytes and minerals was started and the serum electrolyte concentrations returned to normal within 2 days, with resolution of the muscle weakness and the ventricular tachycardia. However, the QT interval remained prolonged at 460 ms.

Key points. Severe anorexia nervosa with a very low BMI is a common cause of the refeeding syndrome in hospital practice. In this case, refeeding was begun by the patient herself and was continued after hospital admission.

In severe and prolonged malnutrition, there may be cardiac atrophy as well as electrolyte abnormalities, including sinus bradycardia and a prolonged QT interval (Heymsfield *et al*., 1978; Powers, 1982). These changes make the heart more vulnerable to hypophosphataemia and hypokalaemia with ventricular arrhythmias and sudden death (Isner *et al*., 1985; Beumont and Large, 1991), especially, if the QT interval exceeds 470 ms (Cooke *et al*., 1994). It should also be remembered that the concomitant abuse of diuretics, laxatives and alcohol by anorectic patients may exacerbate electrolyte and vitamin deficiencies. It is, therefore, important to be alert to the danger of the refeeding syndrome in patients with these problems.

Case 3: post-bariatric surgery for obesity

A 30-year-old woman underwent gastric bypass surgery for severe obesity (BMI 60.9 kg/m^2). She lost 35 kg (BMI 48.4 kg/m^2) in the first 4 months after the operation. For 2 weeks before admission, she had felt unwell with vomiting after food and had been unable to ingest anything more than sips of liquid. On admission, she appeared to be salt and water

depleted with a blood pressure of 110/70 mm Hg and a pulse rate of 110 b.p.m. Serum concentrations of phosphate and potassium were normal, but concentrations of folate (10.2 nmol/l, normal: >12.2 nmol/l) and iron (5 μmol/l, normal range: 6–30 μmol/l) were low. In the first 24 h of hospitalization, 2.5 l of i.v. 0.9% saline and a standard nasogastric feed (4.2 MJ/day (Isosource: 1000 kcal/day, K^+ 35 mmol, PO_4^{2-} 24 mmol)) were prescribed. Folate and iron supplements were given orally (Folvite 1 mg/day and Ferrum Hausmann 200 mg Fe (II)/day). Within 10 h, she developed tachypnoea, orthopnoea and dependent oedema. Her pulse rate rose to 128 b.p.m. and blood pressure fell to 85/55 mm Hg. Chest X-ray shows pulmonary oedema and cardiomegaly. Biochemical screen showed hypokalaemia (2.2 mmol/l), hypophosphataemia (0.68 mmol/l) and lactic acidosis. Thiamine deficiency was not considered. There was only limited improvement with diuretics, oxygen and K^+ and PO_4^{2-} supplementation. On the following day, she was seen by the nutrition support team and prescribed thiamine i.v. (300 mg/day) and an enteral feed (6.3 MJ/day (1500 kcal/day)). Within 4 h of thiamine administration her heart failure began to improve and acidosis to resolve. Supplements were continued for 7 days and after 2 weeks she had recovered and was discharged.

Key points. Despite continuing obesity, this patient had lost a large amount of weight over a short period and, additionally, had developed vomiting with gastrointestinal dysfunction, thereby increasing her vulnerability to micronutrient deficiencies and the refeeding syndrome. In contrast to Case 1 (dry beriberi), this patient showed classical features of heart failure secondary to thiamine deficiency (wet beriberi), proven also by her rapid response to thiamine supplementation. The possibility of beriberi as a cause of heart failure and adequate thiamine supplementation (Rolfe, 1994; Betrosian *et al*., 2004) should be considered in all high-risk patients, including those with malabsorption, malnutrition, malignancy or chronic alcohol abuse.

Case 4: malnutrition in an extreme vegetarian

A 52-year-old man with a schizoaffective disorder underwent a pancreaticoduodenectomy for a carcinoid tumour of the duodenum. Following surgery, he became an extreme vegetarian, eating only apples. Over the next 3 years, he lost half his body weight, ending up weighing only 30 kg (BMI 13.8 kg/m^2). On admission, his serum levels of potassium (3.3 mmol/l), iron (3 μmol/l), vitamin B12 (96 pmol/l, normal range: 150–670 pmol/l) and albumin (23 g/l) were all low. He was started on 1250 ml/day (180 g carbohydrate, 10 g nitrogen, K^+ 47 mmol, Mg^{2+} 5.3 mmol and PO_4^{2-} 20 mmol) of parenteral nutrition. In addition, he was given an i.v. infusion of 250 ml/day of 0.9% saline along with oral vitamin supplements (Supradyn two tablets/day: 200% of DRI) and iron (Ferrum Hausmann 200 mg Fe (II)/day). After 48 h, he had dependent oedema, ascites, dyspnoea and sinus tachycardia (128 b.p.m.). There were falls in serum K^+ (2.2 mmol/l), PO_4^{2-} (0.53 mmol/l) and Mg^{2+} (0.61 mmol/l), which were corrected with i.v. supplements (PO_4^{2-} 20 mmol/day, K^+ 40 mmol/day, Mg^{2+} 10 mmol/day, iron 100 mg/day and a single dose of thiamine 100 mg). Vitamins and trace elements were administered i.v. according to their DRIs (one ampoule each of Soluvit, Vitalipid and Addamel).

It subsequently transpired that the patient had been secretly taking 4 l of distilled water and 15 apples daily, which he had delivered to him in hospital. This may have contributed to the severity of the biochemical and clinical changes. After a period of intense psychotherapy, he resumed a balanced diet and was discharged after 5 weeks, having gained 4.6 kg.

Key points. This patient not only suffered from malnutrition due to the extreme eccentricity of his diet, but also due to malabsorption from his previous surgery. The combination of salt and water retention and biochemical changes should be anticipated in vulnerable patients. Salt and water intake should be limited and appropriate supplements given. Macronutrient intake should be started at 30% of requirements and built up slowly over 5–7 days, calculated on the basis of the patient's actual, not ideal, body weight.

Case 5: chronic alcoholism

A 62-year-old man presented to the orthopaedic clinic with a proximal femoral fracture. He had been drinking 750 ml of wine daily (56 U alcohol/week) for the last 8 years and was found to have early signs of dementia, malnutrition (BMI 17.9 kg/m^2) and osteoporosis. On admission to the orthopaedic ward for femoral surgery, a multivitamin tablet (Supradyn: 100% DRI) was prescribed and, postoperatively, he was given high-energy drinks (Ensure Plus: 2 × 200 ml/day, 2.5 MJ/day (600 kcal/day)). On the second postoperative (p.o.) day, he developed ophthalmoplegia, diplopia and hypotension. Investigations confirmed thiamine deficiency (erythrocyte thiamine pyrophosphate concentration 19 nmol/l, normal range: 66–200 nmol/l) as well as hypomagnesaemia (0.62 mmol/l). Thiamine (200 mg/day for 5 days) and magnesium supplements (20 mmol/day for 3 days) were given i.v. The hypotension resolved 3 h after the first dose, and after 12 h, there was improvement in his neurological symptoms, which had resolved completely by the time of his discharge 1 month later.

Key points. This case illustrates the importance of giving i.v. thiamine prophylactically to all alcoholic patients (200 mg i.v. on the first day, then 300 mg p.o. for 5 days) undergoing hospital treatment, especially when this is accompanied by nutritional support. Oral multivitamin supplements are inadequate to prevent critical falls in thiamine levels with refeeding. K^+, PO_4^{2-} and Mg^{2+} levels should also be monitored and supplemented appropriately.

Case 6: chronic diarrhoea and coeliac disease
A 65-year-old man with a 15-year history of coeliac disease who was being treated with steroids and a gluten-free diet presented with fatigue and increased thirst for the last month. For 2 months before admission, he had suffered from watery diarrhoea (15–20 stools daily) and weight loss of 12 kg. On admission, he appeared dehydrated and malnourished (BMI 17.5 kg/m^2). Investigations showed *Clostridium difficile* in the stool, anaemia (Hb 9.1 g/dl) and hypoalbuminaemia (serum albumin 26 g/l). Hypokalaemia was present (2.4 mmol/l), but magnesium and phosphate concentrations were normal. After restoration of salt, water and potassium balance, parenteral nutrition (2500 ml/day, 360 g carbohydrate, 20 g nitrogen) was begun. *Clostridium difficile* infection was treated with metronidazole. After 3 days, his diarrhoea had improved, but his weight had increased by 4 kg (reflecting salt and water gain), with peripheral oedema and pleural effusions. He developed severe hypophosphataemia and hypokalaemia, but the serum magnesium was at the lower limit of normal. This was accompanied by generalized muscle weakness, thrombocytopaenia and gastrointestinal bleeding. Folate concentrations were normal (16.1 nmol/l). Following fluid restriction, temporary withdrawal of parenteral nutrition, i.v. phosphate supplements (20 mmol/day for 4 days), and transfusion with blood, platelets and fresh frozen plasma, these problems resolved and the patient recovered fully after 2 weeks.

Key points. Fluid, electrolyte and mineral loss from diarrhoea exacerbated the risk, due to malnutrition, of developing the refeeding syndrome, especially when parenteral nutrition was given in full amount immediately rather than being introduced slowly. Steroid treatment may also have added to negative nitrogen balance and potassium depletion. The development of muscle weakness, cardiac decompensation, thrombocytopaenia and gastrointestinal bleeding in this case could all be explained by phosphate depletion, although folate, selenium, magnesium and thiamine deficiency can develop in patients with coeliac disease and diarrhoea. These should, therefore, be monitored carefully. Hypophosphataemia can develop rapidly (within 3–4 days) and should be prevented by prophylactic supplements.

Case 7: cancer
A 49-year-old man with oesophageal cancer developed dysphagia, leading to weight loss (11 kg in 6 weeks) and malnutrition (BMI 16.3 kg/m^2). Investigations showed anaemia (Hb 8.7 g/dl), hypoalbuminaemia (serum albumin 27 g/l), hypokalaemia (2.2 mmol/l) and a prolonged prothrombin time. A percutaneous endoscopic gastrostomy was inserted, and enteral feeding initiated at 4.2 MJ/day (Survimed, 1000 kcal/day), increasing by 1.0 MJ (250 kcal) daily up to 8.4 MJ/day (Survimed: 2000 kcal/day, micronutrients: 100% DRI). Moreover, vitamins and trace elements were supplemented with a multivitamin product (Supradyn one tablet/day: 100% of DRI). Radiotherapy and chemotherapy were begun. After 4 days, the patient complained of numbness and paraesthesiae in the hands and feet as well as abdominal cramps. Biochemical investigations showed classical features of the refeeding syndrome; with hypokalaemia (2.1 mmol/l), hypophosphataemia (0.43 mmol/l) and hypomagnesaemia (0.43 mmol/l). Following i.v. supplementation with K^+ (60 mmol/day for 3 days), PO_4^{2-} and Mg^{2+} (20 mmol/day of each for 3 days), the symptoms resolved.

Key points. In a study on malnourished cancer patients started on artificial nutritional support, the incidence of the refeeding syndrome, based on a phosphate concentration <0.41 mmol/l, was found to be 24.5%, and was even more frequent with enteral (37.5%) than with parenteral (18.5%) nutrition (Gonzalez Avila *et al*., 1996). In that study, 61.5% of patients who developed the refeeding syndrome did so within 72 h of starting feeding.

Discussion

The seven cases illustrate the many contexts in which the refeeding syndrome may occur and highlight the rapidity of its onset, which may be within hours of commencing refeeding. Common factors include the severity of the underlying malnutrition, overaggressive nutritional support in the early stages without adequate supplements of phosphate, thiamine, potassium and magnesium, and associated conditions that exacerbate micronutrient, electrolyte and mineral deficiencies, for example alcoholism, gastrointestinal disorders and poor or eccentric diets.

Although phosphate is just one of the components affected, hypophosphataemia has far reaching consequences on the functioning of various organ systems. During starvation, phosphate and potassium are lost from the cell in proportion to the breakdown of glycogen and protein, potassium being the main intracellular cation balancing the negative charges on proteins. There is, therefore, no clinical deficiency of these electrolytes until catabolism is abruptly reversed and resynthesis of glycogen and protein begins, creating a sudden demand for inorganic phosphate for phosphorylation and adenosine triphosphate (ATP) synthesis and for potassium to balance the negative charges on protein and glycogen. Magnesium, being involved in ATP synthesis, is also taken up by the cells. Upon the introduction of carbohydrate, insulin is released into the blood stream and there is a shift of metabolism from fat to carbohydrate. Acute thiamine deficiency may be precipitated, especially in patients suffering from chronic alcoholism, since diminished thiamine reserves are rapidly used up, as carbohydrate metabolism is accelerated. Excessive infusion of glucose may also cause hyperglycaemia leading to osmotic diuresis, dehydratation and hyperosmolar nonketotic coma (Crook *et al*., 2001). The production of fat

Table 2 Ideal timing of interventions in patients at risk of the refeeding syndrome (adapted from World Health Organization, 1999)

Early treatment			*Rehabilitation*
Days 1–3	*Days 4–6*	*Days 7–10*	*Days > 10*
Resuscitation	*Repair of metabolic derangements*		*Repletion of tissue*
Treat to prevent ● Hypoglycaemia ● Hypothermia ● Dehydration Anticipate salt and water intolerance and mineral and micronutrient deficiencies. Give prophylactic supplements (for example, thiamine)	Monitor and treat any fluid, electrolyte, mineral and micronutrient imbalances that may develop		Continue mineral and micronutrient supplements as required
Treat underlying disease (for example, infection). Commence feeding at 30% of requirements, increasing cautiously		Increase feeding to replete lost tissue	Prepare for discharge

Table 3 Refeeding guidelines—for prevention and treatment of the refeeding syndrome in adult patients at risk

General recommendations

Raise awareness within all health care personnel

- Be aware of patients at risk
- Provide adequate assessment, interdisciplinary care plans, and follow up
- Appreciate that risks apply whether patients are fed by the oral, enteral or parenteral route
- Carefully restore circulatory volume: monitor pulse rate and fluid balance
- Energy intake should be instituted carefully and gradually increased over 4–10 days
- Empirical supplementation of the electrolytes and vitamins can be started before feeding is initiated

Days 1–3

1. Energy (by all routes): start at 42 kJ/kg/day (10 kcal/kg/day) and slow increase to 63 kJ/kg/day (15 kcal/kg/day); 50–60% carbohydrates, 30–40% fat, and 15–20% protein.
2. Electrolytes: measure serum concentrations basally, 4–6 h later, and daily during feeding (see below).
   Supplement prophylactically (unless pre-feeding plasma levels are high), in most cases by the intravenous route initially. Amounts depend on patient size and plasma concentrations, but usual daily requirements are:
   - Phosphate 0.5–0.8 mmol/kg/day
   - Potassium 1–3 mmol/kg/day
   - Magnesium 0.3–0.4 mmol/kg/day. Levels should be monitored frequently and supplements increased if necessary.
3. Fluid: restrict to sufficient to maintain renal function, to replace deficits or losses, and avoid weight gain, that is achieve zero balance. Patients usually need 20–30 ml/kg/day.
4. Salt: restrict sodium to <1 mmol/kg/day. If oedema develops, restrict further.
5. Minerals and trace elements: 100% DRI. Iron should not be supplemented in the first week.
6. Vitamins 200% DRI. Give 200–300 mg thiamine i.v. at least 30 min before feeding, and 200–300 mg daily i.v. or orally till day 3.
7. Monitor daily
   - Body weight (fluid balance).
   - Clinical examination: oedema, blood pressure, pulse rate, cardiovascular and respiratory systems.
   - Biochemistry: phosphate, magnesium, potassium, sodium, calcium, glucose, urea, creatinine, (thiamine).
   - Preferably ECG-monitoring in severe cases.

Days 4–6

1. Energy (by all routes): 63–84 kJ/kg/day (15–20 kcal/kg/day); 50–60% carbohydrates, 30–40% fat, and 15–20% protein.
2. Electrolytes: continue supplementation as above, giving more or less according to plasma concentrations. If the refeeding syndrome is already established, aim to restore normal levels. If
   - PO_4^{2-} <0.6 mmol/l—give 30–50 mmol phosphate (eg. Phosphates Polyfusor) i.v. over 12 h.
   - Mg^{2+} <0.5 mmol/l—give 24 mmol $MgSO_4$ i.v. over 12 h.
   - K^{+} <3.5 mmol/l—give >20–40 mmol KCl i.v. over 4 h.

   Remeasure and repeat if necessary.
3. Minerals and vitamins: as for days 1–3.
4. Fluid: depending on hydration, weight change and losses. Patients usually need 25–30 ml/kg/day.
5. Monitor daily: as for days 1–3.

Days 7–10

1. Energy (by all routes): 84–132 kJ/kg/day (20–30 kcal/kg/day); 50–60% carbohydrates, 30–40% fat, and 15–20% protein.
2. Electrolytes, minerals and vitamins: as above. Iron should be supplemented from day 7 onwards

Table 3 *Continued*

3. Fluid: to maintain zero balance. Approximately 30 ml/kg/day
4. Monitor
- Body weight and biochemistry: twice weekly
- Clinical examination: daily

Abbreviations: DRI, dietary reference intakes; ECG, electrocardiogram; i.v., intravenous.

from glucose due to lipogenesis can result in hypertriglyceridaemia and/or a fatty liver (Crook *et al*., 2001).

From a study of these cases, the published literature (Faintuch, 1990; Brooks and Melnik, 1995; Marik and Bedigian, 1996; Crook *et al*., 2001; Marinella, 2003; Hearing, 2004; Kraft *et al*., 2005) and recent guidelines on nutritional support (World Health Organisation, 1999; World Health Organisation, 2004; National Collaborating Centre for Acute Care, 2006), it is possible to suggest a protocol for the prevention and treatment of the refeeding syndrome (Tables 2 and 3) in which it is important to:

- always be aware of the circumstances in which the syndrome is likely to develop,
- refeed slowly and build up the macronutrient content of the feed over several days,
- monitor the patient frequently,
- anticipate the additional requirements, particularly of phosphate, potassium, magnesium and thiamine, and
- minimize salt intake, unless the patient is salt depleted.

Fluid intake should also be minimized to that required to replace any deficit or to allow normal renal function. In a small, thin patient this may be as little as 1000–1200 ml/day. The present cases emphasize the need for:

- thorough initial screening of such patients,
- very cautious and slow introduction of refeeding,
- anticipation of the problem with i.v. supplements,
- careful and frequent monitoring in the early stages, and
- early recognition and treatment of the condition if it develops.

Although there are no internationally validated guidelines for the treatment of the refeeding syndrome, on the basis of the published literature and expert opinion, we make the following recommendations for the prevention and management of the refeeding syndrome in adults (Table 3).

Acknowledgements

AB has been supported by grants from the Swiss Foundation for Nutrition Research and the Swiss Society for Internal Medicine.

Conflict of interest

None of the authors has a conflict of interest to declare.

Ethics committee approval

None required.

References

Betrosian AP, Thireos E, Toutouzas K, Zabaras P, Papadimitriou K, Sevastos N (2004). Occidental beriberi and sudden death. *Am J Med Sci* **327**, 250–252.

Beumont PJ, Large M (1991). Hypophosphataemia, delirium and cardiac arrhythmia in anorexia nervosa. *Med J Aust* **155**, 519–522.

Birmingham CL, Alothman AF, Goldner EM (1996). Anorexia nervosa: refeeding and hypophosphatemia. *Int J Eat Disord* **20**, 211–213.

Brooks MJ, Melnik G (1995). The refeeding syndrome: an approach to understanding its complications and preventing its occurrence. *Pharmacotherapy* **15**, 713–726.

Burger GCE, Drummond JC, Sandstead HR (1948). *Malnutrition and Starvation in Western Netherlands, September 1944 - July 1945*. General State Printing Office: The Hague.

Cooke RA, Chambers JB, Singh R, Todd GJ, Smeeton NC, Treasure J *et al*. (1994). QT interval in anorexia nervosa. *Br Heart J* **72**, 69–73.

Craddock PR, Yawata Y, VanSanten L, Gilberstadt S, Silvis S, Jacob HS (1974). Acquired phagocyte dysfunction. A complication of the hypophosphatemia of parenteral hyperalimentation. *N Engl J Med* **290**, 1403–1407.

Crook MA, Hally V, Panteli JV (2001). The importance of the refeeding syndrome. *Nutrition* **17**, 632–637.

Crook MA, Panteli JV (2005). The refeeding syndrome and hypophosphataemia in the elderly. *J Intern Med* **257**, 397–398.

Cumming AD, Farquhar JR, Bouchier IA (1987). Refeeding hypophosphataemia in anorexia nervosa and alcoholism. *BMJ* **295**, 490–491.

Faintuch J (1990). The refeeding syndrome: a review. *J Parenter Enteral Nutr* **14**, 667–668.

Food and Nutrition Board, Institute of Medicine of the National Academies (2005). Dietary Reference Intakes Table – The Complete Set. http://www.iom.edu/?id = 21377.

Gonzalez Avila G, Fajardo Rodriguez A, Gonzalez Figueroa E (1996). The incidence of the refeeding syndrome in cancer patients who receive artificial nutritional treatment. *Nutr Hosp* **11**, 98–101.

Gustavsson CG, Eriksson L (1989). Acute respiratory failure in anorexia nervosa with hypophosphataemia. *J Intern Med* **225**, 63–64.

Hadley SJ, Walsh BT (2003). Gastrointestinal disturbances in anorexia nervosa and bulimia nervosa. *Curr Drug Targets C N S Neurol Disord* **2**, 1–9.

Hearing SD (2004). Refeeding syndrome. *BMJ* **328**, 908–909.

Hernandez-Aranda JC, Gallo-Chico B, Luna-Cruz ML, Rayon-Gonzalez MI, Flores-Ramirez LA, Ramos Munoz R *et al*. (1997). Malnutrition and total parenteral nutrition: a cohort study to determine the incidence of refeeding syndrome. *Rev Gastroenterol Mex* **62**, 260–265.

Heymsfield SB, Bethel RA, Ansley JD, Gibbs DM, Felner JM, Nutter DO (1978). Cardiac abnormalities in cachectic patients before and during nutritional repletion. *Am Heart J* **95**, 584–594.

Isner JM, Roberts WC, Heymsfield SB, Yager J (1985). Anorexia nervosa and sudden death. *Ann Intern Med* **102**, 49–52.

Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HF (1950). *The Biology of Human Starvation*. University of Minnesota Press: Minneapolis.

Kraft MD, Btaiche IF, Sacks GS (2005). Review of the refeeding syndrome. *Nutr Clin Pract* **20**, 625–633.

Marik PE, Bedigian MK (1996). Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. *Arch Surg* **131**, 1043–1047.

Marinella MA (2003). The refeeding syndrome and hypophosphatemia. *Nutr Rev* **61**, 320–323.

National Collaborating Centre for Acute Care (2006). *Nutrition Support in Adults: Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition*. National Collaborating Centre for Acute Care: London. (http://www.rcseng.ac.uk/publications/docs/nutrition_support_guidelines.html).

O'Connor LR, Wheeler WS, Bethune JE (1977). Effect of hypophosphatemia on myocardial performance in man. *N Engl J Med* **297**, 901–903.

Patrick J (1977). Death during recovery from severe malnutrition and its possible relationship to sodium pump activity in the leucocyte. *BMJ* **1**, 1051–1054.

Paula FJ, Plens AE, Foss MC (1998). Effects of hypophosphatemia on glucose tolerance and insulin secretion. *Horm Metab Res* **30**, 281–284.

Powers PS (1982). Heart failure during treatment of anorexia nervosa. *Am J Psychiatry* **139**, 1167–1170.

Rolfe M (1994). Beri-beri: 'Endemic amongst urban Gambians'. *Afr Health* **16**, 22–23.

Schnitker MA, Mattman PE, Bliss TL (1951). A clinical study of malnutrition in Japanese prisoners of war. *Ann Intern Med* **35**, 69–96.

Travis SF, Sugerman HJ, Ruberg RL, Dudrick SJ, Delivoria-Papadopoulos M, Miller LD *et al*. (1971). Alterations of red-cell glycolytic intermediates and oxygen transport as a consequence of hypophosphatemia in patients receiving intravenous hyperalimentation. *N Engl J Med* **285**, 763–768.

Weinsier RL, Krumdieck CL (1981). Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. *Am J Clin Nutr* **34**, 393–399.

Whyte E, Jefferson P, Ball DR (2003). Anorexia nervosa and the refeeding syndrome. *Anaesthesia* **58**, 1025–1026.

World Health Organisation (1999). *Management of Severe Malnutrition: A Manual for Physicians and Other Senior Health Workers*. World Health Organisation: Geneva. (http://www.who.int/nutrition/publications/en/manage_severe_malnutrition_eng.pdf).

World Health Organisation (2004). *Severe Malnutrition: Report of a Consultation to Review Current Literature*. World Health Organisation: Geneva. (http://www.who.int/nutrition/publications/Lit_review_report.pdf).