Hypophosphataemia secondary to oral refeeding syndrome in a patient with long-term alcohol misuse

Clinical record

A 44-year-old homeless man presented voluntarily to hospital for alcoholic detoxification. He lived in a laneway outside a homeless shelter and had previously refused offers of social or medical assistance. Friends assisted him in purchasing the 4–6 L of cask wine (330–500 g alcohol) that he drank each day for over a year. He had not mobilised or eaten adequately for at least 6 months before admission.

On admission, the patient was dehydrated, afebrile and cachectic (weight, 52 kg; body mass index [BMI], 16.0 kg/m^2). Bibasal pulmonary crepitations, non-tender hepatomegaly without ascites, and severe proximal muscle wasting and weakness were evident. Cerebellar signs (truncal ataxia, gross multidirectional nystagmus, dysarthria), mild cognitive loss, moderate sensorimotor neuropathy and decreased vision bilaterally (6/36 with pinhole) were demonstrated.

Haematological and biochemical markers were markedly abnormal and included anaemia (haemoglobin, 108 g/L), leukocytosis (white cell count, 15.6 × 10^9/L), thrombocytopaenia (platelet count, 44 × 10^9/L), hyponatraemia (serum sodium, 110 mmol/L), hypokalaemia (serum potassium, 2.4 mmol/L), hypomagnesaemia (serum magnesium, 0.71 mmol/L), hypoalbuminaemia (serum albumin, 28 g/L) and respiratory alkalosis (pH, 7.65; pCO_2, 22 mmHg, HCO_3^-, 28.1 mEq/L). The serum phosphate level (0.84 mmol/L) was within the reference range (0.80–1.50 mmol/L).

A chest x-ray showed increased interstitial markings in the right lower zone. Sinus tachycardia (101 beats per minute) and prolonged corrected QT interval (524 ms) were present on initial electrocardiography. A cerebral computed tomography scan without contrast was normal.

The patient was managed with intravenous rehydration (0.9% normal saline) and potassium replacement. Empirical antibiotics (intravenous ceftriaxone 1 g daily and oral roxithromycin 300 mg daily) and chest physiotherapy were prescribed for possible pneumonia. The hospital drug and alcohol liaison team managed his alcohol withdrawal with benzodiazepines. His ward diet was supplemented with oral multivitamins and 100 mg intramuscular thiamine daily. Intensive physiotherapy was required to improve his mobility. Following ophthalmic review, intramuscular hydroxocobalamin was prescribed for toxic (alcoholic) optic neuropathy.

On Day 4 of admission, the serum phosphate level was measured again. Normal on admission, it had fallen precipitously to 0.15 mmol/L. Intravenous replacement was prescribed in the form of potassium phosphate (60 mmol potassium, 42 mmol phosphate given over 36 hours in three divided doses). Although oral phosphate was also prescribed in the form of sodium acid phosphate, the patient refused to take this as he disliked the taste.

Serum phosphate levels were initially monitored 12-hourly, then daily, and returned to within the reference range by Day 7. Serum levels of calcium, magnesium, phosphate and potassium on Days 1, 4 and 8 are shown in Box 1 and Box 2.

Over the first week, the patient complained of lower limb myalgia and severe paraesthesiae in the hands. Groin candidiasis, not present on admission, was treated with topical clotrimazole. Severe diarrhoea was associated with refeeding. His mood became labile, although he remained oriented at all times. Sinus tachycardia of up to 122 beats per minute persisted for 1 month, although the corrected QT interval normalised in parallel with electrolyte correction (435 ms on Day 6).

Five weeks after admission, the patient was transferred to a rehabilitation hospital in an attempt to improve his mobility. He was able to walk 30 m with a pick-up frame and one stand-by assistant. His weight had increased to 58.5 kg (BMI, 18.1 kg/m^2) and his mood had improved significantly without pharmacological therapy. ◆

This case describes refeeding syndrome associated with volitional oral nutrition in a patient with chronic alcoholic abuse admitted for detoxification. Refeeding syndrome is an under-recognised and undertreated condition[1-5] of severe, acute electrolyte, fluid-balance and metabolic abnormalities in chronically malnourished patients undergoing renutrition.

Refeeding syndrome was first described in Japanese prisoners during World War II.[6] Since then, it has been described in patients being refed after hunger strikes, starvation after being lost, chronic alcoholism, anorexia nervosa, malignancy, kwashiorkor and marasmus and in obese patients who have had duodenal switch operations.[4,5] Reports conflict over whether it is more common following parenteral[7] or enteral tube[4] nutrition, but descriptions following volitional oral refeeding are less frequent.[2]

In people in a chronically starved state, insulin secretion is reduced in parallel with low carbohydrate intake. Fat catabolism predominates, and free fatty acids and ketone bodies replace glucose as the major energy source. If starvation is severe, body stores of phosphate, potassium and magnesium may be depleted, although serum levels are often maintained.[3-5] With refeeding, there is a shift back to carbohydrate metabolism and an increase in insulin levels. Insulin stimulates the movement of phosphate, potassium and magnesium into the cells, leading to a fall in their serum concentrations.[2] In addition, tissue anabolism increases cellular demand for phosphate, glucose, potassium and water.[1] Hyperphosphaturia may occur with alcoholism,[7,8] and thiamine, required for the intracellular transport of glucose, may be depleted.[9]

The principal biochemical hallmark of refeeding syndrome, as seen in this case, is severe, acute hypophosphataemia that usually occurs within 3–4 days of refeeding.[2,3,10] This is often associated with hypokalaemia, hypomagnesaemia, sodium and fluid retention, thiamine deficiency and hyperglycaemia.

1 Serum electrolyte levels over the first 8 days after admission

Electrolyte	Reference range	Day 1	Day 4	Day 8
Potassium (mmol/L)	3.6–5.1	2.4	3.5	3.9
Calcium (mmol/L) (corrected for serum albumin)	2.25–2.58	2.27	2.60	2.60
Magnesium (mmol/L)	0.74–1.03	0.71	0.69	0.70
Phosphate (mmol/L)	0.80–1.50	0.84	0.15	1.56

Phosphate is the body's major intracellular anion.[4] Daily oral phosphate intake is about 1000–1400 mg, the major sources being meat, poultry, eggs, cereals and dairy products.[4] Wine contains little phosphate.[11] Phosphate is found in phospholipids, nucleic acids, adenosine triphosphate and 2,3-diphosphoglycerate in red blood cells. It is important for intracellular buffering, enzymatic phosphorylation, glucose metabolism, nervous system conduction and leucocyte function. Hypophosphataemia-induced depletion of 2,3-diphosphoglycerate in erythrocytes results in a left shift of the haemoglobin/oxygen dissociation curve, increasing haemoglobin affinity for oxygen and predisposing to local tissue hypoxia.[1,2,4]

However, the clinical manifestations of refeeding syndrome are varied and non-specific (Box 3). Potentially life-threatening sequelae include acute cardiac failure, respiratory failure, Wernicke's encephalopathy, sepsis and acute renal failure. Sudden cardiac death has been reported in two chronically malnourished patients experiencing acute hypophosphataemia after initiation of total parenteral nutrition.[12]

Although non-specific, we believe the constellation of symptoms and signs observed in our patient is typical of refeeding syndrome. Most importantly, acute, severe hypophosphataemia not present on admission was noted 4 days after oral refeeding with a ward diet. The presence of a serum phosphate level of 0.15 mmol/L in our patient represents extreme hypophosphataemia. (The lowest published level we are aware of in a patient who survived is 0.07 mmol/L.[11]) Given the "low normal" value on admission and the patient's risk factors for refeeding syndrome, the serum phosphate level should have been monitored more closely during the first few days of admission.

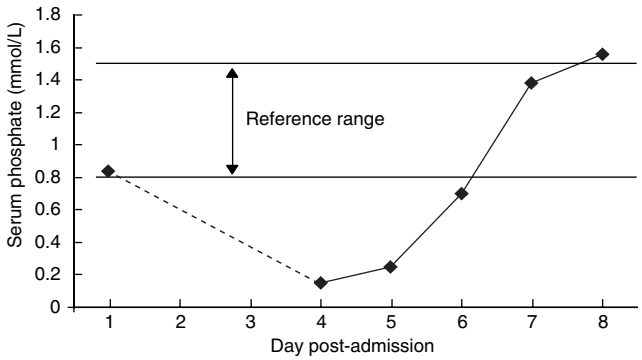
We did consider several differential diagnoses. Although hypophosphataemia is commonly seen in sepsis,[14] clinical and haematological evidence suggested that the patient's respiratory infection had largely resolved by Day 4. Acute respiratory alkalosis may also cause hypophosphataemia,[15] but was unlikely in this case, in view of the normal serum phosphate level on admission. Severe hypokalaemia was already being corrected by intravenous replacement from the day of admission.

The development of paraesthesiae, myalgias, groin candidiasis, diarrhoea and sinus tachycardia (which may have indicated incipient cardiac failure[4,9]) was consistent with the diagnosis of refeeding syndrome.[4] Unfortunately, the creatinine kinase level was not measured to exclude rhabdomyolysis. Cerebellar signs may have been secondary to alcoholic degeneration or mild Wernicke's encephalopathy.

Management of refeeding syndrome includes slowing of caloric intake, correcting electrolyte and metabolic abnormalities, monitoring fluid balance and treating complications. Thiamine and B-complex vitamins should be prescribed prophylactically before refeeding.[4] Interestingly, the early administration of intramuscular thiamine for chronic alcoholism may have protected our patient against Wernicke's encephalopathy secondary to refeeding syndrome.

Ideally, patients at risk of developing refeeding syndrome should be identified and a prophylactic low-caloric low-carbohydrate dietary regimen implemented.[3] Initially, 85 kJ per kilogram of body weight per day, with a generous protein allowance (1.2–1.5 g protein per kilogram of body weight per day), has been suggested.[4,13] Caloric intake can then be gradually increased over the following 1–2 weeks, ensuring that clinical and biochemical parameters are closely monitored.[4,12,13] It is important to note that most current recommendations are based on parenteral or enteral tube nutrition. Protocols are not well developed for volitional oral refeeding. However, "slow" refeeding in these patients could be

2 Serum phosphate levels over the first 8 days after admission*



* Dotted line indicates the direction of change only (no data were available for Days 2 and 3). ◆

3 Clinical features of refeeding syndrome[4]

Clinical feature	Possible mechanisms
Cardiovascular	
Acute cardiac failure	Fluid retention (secondary to carbohydrate intake[1,2,4] and hyperinsulinaemia[9]), arrhythmias, cardiomyopathy[1,2,4]
Arrhythmias, sudden cardiac death[3,12]	Electrolyte disturbance[1,2]
Respiratory	
Respiratory failure	Diaphragmatic myopathy[2,8]
Neurological	
Seizures, paraesthesiae	Electrolyte and/or metabolic disturbance,[1,4] cellular hypoxia secondary to reduced 2,3-DPG and ATP
Wernicke's encephalopathy	Thiamine deficiency[1,2,13]
Gastrointestinal	
Diarrhoea or constipation	Electrolyte and/or metabolic disturbance,[4] intestinal atrophy following malnutrition[13]
Haematological	
Sepsis	Leukocyte dysfunction, hyperglycaemia, acid–base disturbance[1,4]
Haemorrhage	Thrombocytopaenia,[2,9] platelet dysfunction[9]
Haemolytic anaemia	Depletion of erythrocyte ATP, resulting in increased cell membrane rigidity[1]
Metabolic	
Hyperglycaemia[4]	Glucose ingestion[4]
Acid–base disturbance[1,4]	Impaired phosphate renal buffering[2,12]
Renal	
Acute tubular necrosis	Rhabdomyolysis[4]
Musculoskeletal	
Myopathy	Depletion of muscle ATP,[1,9] electrolyte disturbance[1]
Rhabdomyolysis	Impaired production of phospholipid cell membranes causes sarcolemma dysfunction[1,2]

ATP = adenosine triphosphate. DPG = diphosphoglycerate.◆

Lessons from practice

- Refeeding syndrome is a potentially lethal condition in chronically malnourished patients undergoing renutrition. The syndrome is under-recognised and undertreated.
- Electrolyte levels should initially be monitored daily in at-risk patients, as acute, profound hypophosphataemia may develop even in asymptomatic patients.
- Regimens for volitional oral refeeding are not well developed, but a prophylactic low-caloric (85 kJ per kilogram of body weight per day), low-carbohydrate diet has been advised.
- Prophylactic thiamine, phosphate and potassium supplementation is often required for at-risk patients.p
- Patients with serum phosphate levels below 0.3–0.5 mmol/L or symptoms of hypophosphataemia require intravenous phosphate replacement. ◆

achieved by providing a similar low daily caloric intake with reduced food portions. Ideally, an experienced dietitian should be consulted.[4] In our case, a dietitian was not available on site, and, given the prompt correction of electrolyte abnormalities and absence of acute cardiac failure, no change to diet was made.

Levels of serum electrolytes, urea and creatinine should be monitored at least daily in the acute phase. Prophylactic phosphate and potassium supplementation is often required at the time of refeeding in high-risk patients. Phosphate replacement is recommended if serum levels are below 0.3–0.5 mmol/L[3,4,10] or if the patient is symptomatic. As oral replacement at these levels is often inadequate, intravenous replacement is advised.[7,10] Complications of overzealous intravenous phosphate replacement may include hyperphosphataemia, hypocalcaemia, tetany, hypotension, hyperkalaemia, hypernatraemia, renal failure and metastatic calcification.[2,10] Although successful intravenous regimens based on patient weight and serum phosphate levels in intensive care settings have been described,[15] these are often complicated and impractical for ward patients.

Terlevich et al[10] described the use of 50 mmol intravenous phosphate over 24 hours in 30 ward patients with refeeding syndrome and normal renal function. Twenty-eight patients safely achieved a serum phosphate level above 0.5 mmol/L within 72 hours. We used 42 mmol intravenous phosphate over 36 hours to normalise serum levels in our patient. While less aggressive than the protocol described by Terlevich et al, it was deemed sufficient given that the patient was largely asymptomatic and that serum phosphate levels were improving. Intravenous phosphate was dispensed on site in 14 mmol aliquots, and prescribing this amount over 12 hours simplified the dosing regimen.

Clinical diagnosis of refeeding syndrome requires a high index of suspicion.[1] Its hallmark of acute, severe hypophosphataemia in chronically malnourished patients after refeeding may occur even in patients who are largely asymptomatic and orally fed. Prevention of morbidity and, in some cases, death requires careful management of diet, vitamin intake and electrolyte and fluid balance.

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