An uncommon cause of hypophosphataemia

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CASE

A woman aged 21 years underwent a diagnostic laparoscopy and appendicectomy for undifferentiated abdominal pain. She re-presented two days later with persistent fever, ongoing abdominal pain, vomiting and anorexia. At admission she was noted to be profoundly hypophosphataemic (0.21 mmol/L) with a normal corrected calcium (2.14 mmol/L). On further questioning, it was revealed the patient had received an iron carboxymaltose infusion two weeks prior from her general practitioner.

The patient's medical history included polycystic ovarian syndrome, as well as chronic urticaria and angioedema, treated with omalizumab monthly.

Renal wasting was found to be the major cause of hypophosphataemia in this case, although poor oral intake and vomiting were the other likely contributors.

Extensive investigations did not reveal a clear cause for this patient's symptoms, and surgical histology showed only minimal appendiceal mucosal inflammation. Despite this, the patient's condition improved with empirical antibiotics and hypophosphataemia management.

QUESTION 1

What are the symptoms of hypophosphataemia?

QUESTION 2

What are the causes of hypophosphataemia?

QUESTION 3

What is the mechanism of iron infusion–induced hypophosphataemia?

QUESTION 4

What are the investigations to consider in hypophosphataemia?

ANSWER 1

Phosphate plays a key role in the energy storage, metabolism and signalling within the cell through phosphorylation. Hypophosphataemia affects multiple body systems, including the haematological, central nervous and cardiopulmonary systems, mineral metabolism as well as skeletal and smooth muscles. Symptoms range from mild irritability, paraesthesia and muscle weakness, to more severe manifestations such as haemolytic anaemia, severe infection, delirium, generalised seizures, cardiac arrythmias, cardiomyopathy, respiratory failure and coma. Symptoms vary depending on the acuity and degree of hypophosphataemia.[1]

ANSWER 2

There are four primary mechanisms by which hypophosphatemia can occur (Table 1):

- redistribution from the extracellular fluid into the intracellular fluid
- inadequate intestinal absorption of phosphate
- increased kidney phosphate excretion[1]
- increased extra-kidney removal.

Hypophosphataemia can also be caused by proximal renal tubular damage, such as that induced by multiple myeloma and certain chemotherapeutic, antiretroviral and anticonvulsant drugs.[1]

ANSWER 3

The proposed mechanism for iron infusion–induced hypophosphataemia is through inhibition of the degradation of fibroblast growth factor-23 (FGF-23), a hormone regulating phosphate metabolism, produced by both osteoclasts and osteoblasts. This in turn reduces phosphate reabsorption in the proximal kidney tubules. Further, FGF-23 also inhibits 1-α-hydroxylase, resulting in lower levels of 1,25-dihydroxyvitamin D3 and reduced intestinal absorption of phosphate.[2–4] Current literature suggests that there is a higher incidence of hypophosphataemia with iron carboxymaltose infusion than with other formulations.[5,6]

It has been shown that the peak onset of hypophosphataemia following iron carboxymaltose infusion is around two weeks post infusion, but can last up to five weeks.[1,7]

ANSWER 4

The clinical history helps to differentiate a true total body phosphate deficiency versus an intracellular phosphate shift.[8] Specific investigations to consider include:[9]

- fractional excretion of phosphate (Figure 1)
- parathyroid hormone
- serum corrected calcium
- 1,25-dihydroxyvitamin D3
- 25-hydroxyvitamin D.

The fractional excretion of phosphate refers to the percentage of filtered phosphate that is actually excreted. Fractional excretion of ≥5% suggests inappropriate renal wasting of phosphate, while fractional excretion <5% suggests appropriate kidney function (with other causes of hypophosphataemia, such as redistribution and reduced intestinal absorption, more likely).

Other relevant investigations for this patient are listed in Table 2.

CASE CONTINUED

The patient had inappropriately high calculated fractional excretion of phosphate (24.4%), as calculated using the formula listed in Figure 1.

$$FEPO_4 = [PO_4\ (Urine) \times Creatinine\ (Serum)]/[PO_4\ (Serum) \times Creatinine\ (Urine)] \times 100$$

Figure 1. Formula for fractional excretion of phosphate
$FEPO_4$, fractional excretion of phosphate; PO_4, phosphate

QUESTION 5

What is the management of hypophosphataemia?

ANSWER 5

The management of hypophosphataemia depends on the severity, chronicity and cause. In the case of iron infusion–induced hypophosphataemia, phosphate replacement remains key. Mild-to-moderate hypophosphataemia (serum phosphate >0.3 mmol/L) can be managed with oral replacement therapy. Patients with acute severe hypophosphataemia (<0.3 mmol/L) should be managed with intravenous replacement therapy initially, with subsequent transition to oral replacement once serum phosphate

Table 1. Common causes of hypophosphataemia

Redistribution from the extracellular fluid into the intracellular fluid	Inadequate intestinal absorption of phosphate	Increased kidney phosphate excretion	Increased extra-kidney removal
• Glucose intravenous infusion • Diabetic ketoacidosis • Acute respiratory alkalosis • Refeeding syndrome	• Use of phosphate binders	• Primary hyperparathyroidism • Parathyroid hormone–related protein-dependent hypercalcaemia of malignancy • Intrinsic renal disease (eg Fanconi syndrome) • Drugs/toxins (eg ethanol, acetazolamide, heavy metals, cisplatin, foscarnet)	• Haemodialysis

Table 2. Relevant investigations at initial presentation and re-admission

Investigations	Value at initial presentation	Value at re-admission	Reference range
Serum phosphate	**0.38 mmol/L**	**0.21 mmol/L**	0.75–1.5 mmol/L
Corrected calcium	2.15 mmol/L	2.14 mmol/L	2.1–2.6 mmol/L
Parathyroid hormone	N/A	6.3 pmol/L	1–7 pmol/L
25-hydroxyvitamin D	N/A	57 nmol/L	50–150 nmol/L
1,25 dihydroxyvitamin D	N/A	52 pmol/L	48–190 pmol/L
Serum creatinine	75 µmol/L	68 µmol/L	45–90 µmol/L
Estimated glomerular filtration rate	>90 mL/min/1.73m^2	>90 mL/min/1.73m^2	>60 mL/min/1.73m^2
Urine phosphate	N/A	10 mmol/L	N/A
Urine creatinine	N/A	4.9 mmol/L	N/A
Calculated fractional excretion of phosphate	N/A	**24.4%**	<5%
C-reactive protein	**58**	**218**	<5

N/A, not applicable

Table 3. Phosphate trend pre- and post-iron infusion

	Six days pre-iron infusion	Two weeks post-iron infusion	Ten days post-admission (and phosphate replacement)	One month post-hospitalisation
Serum phosphate (mmol/L)	0.8 mmol/L	**0.21 mmol/L**	0.95 mmol/L	1.1 mmol/L
[Reference range]	[0.8–1.5 mmol/L, at external pathology]	[0.75–1.5 mmol/L]	[0.75–1.5 mmol/L]	[0.8–1.5 mmol/L, at external pathology]

is >0.5 mmol/L. It is important to consider the amount of elemental phosphate administered in the phosphate supplement. During intravenous replacement, it is imperative to monitor for side effects including hypocalcaemia, kidney injury (due to heterotopic calcification) and arrhythmias. If the 25-hydroxy or 1,25-dihydroxyvitamin D levels are low, replacement with cholecalciferol and calcitriol, respectively, can also help improve phosphate levels by increasing intestinal absorption.[4]

CASE CONTINUED

The patient received intravenous phosphate replacement, followed by regular oral replacement. This was administered in divided doses to minimise side effects such as diarrhoea. Oral phosphate replacement was ceased after several weeks of stable phosphate levels. Her phosphate trend at baseline, post-iron infusion and after phosphate replacement is shown in Table 3.

Key points

- Severe hypophosphataemia is an infrequent but potentially serious complication of iron infusion, especially iron carboxymaltose. This is significant given the increasing frequency of iron carboxymaltose infusions administered in general practice.
- Symptoms can mimic those of iron deficiency or infection and specific investigations are required to confirm the diagnosis.
- Severe hypophosphataemia requires initial intravenous replacement followed by oral supplementation for several weeks.

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