Hypophosphataemia

References

Ranges for serum phosphate vary among laboratories. The normal range in adults is generally considered to be 0.8-1.5 mmol/L [1]. The normal range in children is age-related. The Royal College of Paediatrics and Child Health quotes this as 1.3-2.6 mmol/L (<1 year) and 0.9-1.8 mmol/L (1-16 years) [2].

Significant hypophosphataemia (below 0.4 mmol/L) may occur due to redistribution into cells, renal losses or decreased intake. Patients with low phosphate often also have other electrolyte deficiencies [3].

A normal diet contains plenty of phosphate, as it is present in all living organisms. Normal dietary intake varies according to age and other physiological factors (eg, pregnancy). The recommended daily intake for children aged 1 year is 460 mg whilst for a 50-year-old adult it is 700 mg. Phosphate is absorbed in the intestinal tract [4]. Normally the majority of this is reabsorbed by the renal tubular cells. Vitamin D increases uptake, and homeostasis in terms of bone content of phosphate and renal excretion is controlled by vitamin D, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23) [5].

Aetiology

- **Inadequate intake:**
  - Poor intake may be due to poor diet, including eating disorders such as anorexia nervosa, difficulty with chewing and swallowing, and alcohol dependency.
  - Malnutrition due to malabsorption or persistent vomiting.
  - The severely ill patient is most at risk when they start to recover and move from a catabolic state to an anabolic state.
  - Vitamin D deficiency.
  - Gut phosphate binders - eg, aluminium hydroxide.

- **Increased renal excretion:**
  - Hyperparathyroidism: PTH reduces reabsorption by the proximal renal tubule.
  - High salt load causes reduced reabsorption of sodium by the proximal tubule but also reduced phosphate reabsorption.
  - Vitamin D deficiency, including hypophosphataemic rickets.
  - Renal tubular disorders, including Fanconi's syndrome, Dent's disease.
  - Hypophosphataemia is common after renal transplantation, especially after long periods of dialysis.
  - Drugs causing renal phosphate leak, including aminoglycosides, cisplatin and tenofovir.
  - Heavy metal poisoning and paraproteinaemias by impairing renal tubule function.
  - Oncogenic osteomalacia is a paraneoplastic syndrome of osteomalacia, hypophosphataemia, renal phosphate loss, bone pain, and muscle weakness. It is caused by excessive synthesis and secretion of FGF23, a phosphaturic hormone that is normally produced by osteocytes [6]. Several tumours can cause this but most are benign tumours of mesenchymal origin.

- **Move from extracellular to intracellular compartment:**
  - Treatment of diabetic ketoacidosis (insulin drives phosphate into cells).
  - Refeeding syndrome - carbohydrate refeeding after fasting. Other risks of refeeding include low potassium, low magnesium, low calcium and abnormal glucose metabolism [1].
  - Acute respiratory alkalosis.
  - The hungry bone syndrome (increased uptake by bone matrix) which occurs after parathyroidectomy [7].
  - Leukaemia or lymphomas.

Epidemiology

- Hypophosphataemia is rare in the general population but relatively common in hospitalised patients (2.2-3.1%) and higher still in those on intensive care units (45% of all hospitalised patients), those with sepsis (65-80%), those with chronic alcohol dependency (30-40%), those with major trauma (56-75%) and those with chronic obstructive pulmonary disease (20%) [8, 9, 10].
- Hypophosphataemia is more likely in alcohol dependency, diabetic ketoacidosis, burns and sepsis. It is a feature of X-linked hypophosphataemic rickets. This is rare, occurring in 1 in 20,000 live births [6].
- In adolescents it is often due to eating disorders but in older people it tends to be associated with alcohol dependency, malignancy or vitamin D deficiency.

Presentation

- Chronic or mild hypophosphataemia may be asymptomatic (phosphate levels 0.6-0.8 mmol/L) [8]. Most patients with hypophosphataemia have no specific symptoms or perhaps fatigue.
- Muscle weakness (diaphragmatic, cardiac and skeletal), bone pain, rhabdomyolysis, and altered mental status (confusion, hallucinations) are the most common presenting features.
Severe acute hypophosphataemia (level <0.3 mmol/L) may present with disorientation, seizures, focal neurological deficits, congestive heart failure, and muscle pain.

Syndromes of chronic phosphate loss usually present with bone pain, muscular weakness and skeletal disorders.

Markedly low phosphate with bone pain and excessive phosphate loss in urine in an adult suggests an oncogenic osteomalacia.

Examination

- There are usually no physical signs.
- If hypophosphataemia starts in childhood, there is usually short stature and perhaps bowed legs from rickets.
- In adults, firm palpation of bones may show tenderness.
- Hepatomegaly may indicate chronic alcohol dependency or underlying malignancy.

Investigations

- Calcium, phosphate, magnesium, plasma proteins - in the presence of low phosphate:
  - High calcium suggests hyperparathyroidism.
  - Low calcium suggests lack of vitamin D or malabsorption, or hungry bone syndrome.
  - Low magnesium suggests dietary deficiency.
  - Consider paraproteinaemia if high globulins, severe hypophosphataemia with suspicious features such as anaemia, bone pain, renal dysfunctions or hypercalcaemia.

- Renal function and electrolytes: renal tubular disease or extra renal causes commonly cause electrolyte disturbance.
- Liver function tests (LFTs): may show elevated alkaline phosphatase in chronic hypophosphataemia due to osteomalacia. They may also indicate chronic alcohol dependency.
- PTH and vitamin D levels.
- If respiratory alkalosis is considered, arterial blood gases are required.
- If renal loss is considered, fasting morning urine for phosphate content, along with blood sample.
- If Fanconi’s syndrome is considered, obtain plasma bicarbonate and urate and test urine for glucose and amino acids. A full Fanconi’s syndrome consists of renal glycosuria, aminoaciduria, renal tubular acidosis, low blood urate due to high urinary loss, and excessive urinary loss of phosphate.
- If a hereditary cause is suspected, genetic testing may be necessary.
- X-rays can help evaluate osteopenia, osteomalacia, or hyperparathyroidism. Looser zones suggest osteomalacia. Erosions of the distal phalanges and clavicles and circular punched-out lesions in the long bones are typical of primary hyperparathyroidism.
- Bone scintigraphy may demonstrate increased uptake at multiple areas in cases of severe osteomalacia.
- Ultrasound of the neck may help identify enlarged parathyroid glands but technetium \(^{99m}\text{Tc}\) scanning can be more accurate and easier to locate ectopic glands.
- Dual-energy X-ray absorptiometry (DXA) bone density scan: chronic phosphate deficiency will cause loss of bone density.
- If X-rays are inconclusive, bone biopsy may be required.

Management

Mild hypophosphataemia often resolves without treatment but severe hypophosphataemia may cause diaphragmatic weakness requiring artificial ventilation.

- Treatment is dependent upon cause, severity and duration.
- There are no national guidelines for the treatment of acute hypophosphataemia.
- Treatment should address the underlying cause where possible.
- Patients should be referred to a specialist if:
  - The cause is uncertain.
  - Hypophosphataemia is chronic or severe (phosphate <0.3 mmol/L).
  - They are symptomatic.
  - There is short stature or there are skeletal deformities consistent with rickets.
  - There is a family history of skeletal deformities or hypophosphataemia.

- Phosphate supplements:
  - Phosphate supplements should be given where hypophosphataemia may be anticipated, as in refeeding after anorexia, starvation or alcohol dependency.
  - Usually oral phosphate is well tolerated although very high doses may cause diarrhoea.
  - Where there is an acute situation or lack of intestinal function, parenteral phosphate may be used but this is much more dangerous and requires monitoring of calcium, phosphate and electrolyte levels every six hours as response is unpredictable. There is no consensus on the level at which parenteral phosphate should be introduced, but there is universal agreement that it should be introduced when serum phosphate levels are under 0.3 mmol/L. The risk is severe hypocalcaemia which may be life-threatening, or over-treatment resulting in hyperphosphataemia and hyperkalaemia. Patients with poor renal function are at higher risk from intravenous treatment.

- In coeliac disease or Crohn’s disease the underlying disease should be treated but vitamin D supplements may be required.
- Oral phosphate supplements may be beneficial in genetic disorders that lead to urinary phosphate loss although they do not correct the underlying abnormality. Monitor blood calcium and phosphate, bone density and growth.
- In oncogenic osteomalacia, phosphate supplements are useful until the tumour has been identified and removed.
- Vitamin D deficiency is usually treated with oral vitamin D but in severe renal disease the kidneys may be unable to convert hepatic 24 hydroxyvitamin D3 to 1,25 dihydroxyvitamin D3 and so this form may need to be given.
Hyperparathyroidism requires identification and removal of the offending tumour.
Problems such as alcohol dependency and eating disorders require appropriate intervention.
Congenital phosphate wasting syndromes require long-term supplementation.
To reduce the risk of hypophosphataemia, patients having renal transplantation may be considered for parathyroidectomy before transplant surgery, or more recently the calcimimetic agent cinacalcet has been shown to improve phosphate levels[14].
Patients with diabetic ketoacidosis are at high risk of developing hypophosphataemia. This is mostly mild and asymptomatic and studies suggest that parenteral phosphate does not improve clinical outcome. However, severe hypophosphataemia (0.5 mmol/L or less) warrants parenteral treatment[15].

Complications
- Acute hypophosphataemia can produce seizures, delirium, coma, or focal neurological findings.
- There may be heart failure, rhabdomyolysis, acute haemolysis, leukocyte dysfunction, and abnormal LFTs.
- Heart failure, rhabdomyolysis, and haemolysis can produce acute kidney injury.
- Leukocyte dysfunction increases susceptibility to infection.
- They can also exhibit platelet dysfunction, glucose intolerance, and metabolic acidosis.
- Chronic hypophosphataemia due to phosphate loss causes mostly bone pathology.
- In children, rickets leads to short stature and bony deformities with abnormal bone mineralisation.
- Adults may develop osteomalacia with severe bone pain and fractures.

Prognosis
- Correction of acute hypophosphataemia tends to leave no long-term complications but failure to recognise and treat an acute, severe situation can lead to fatality.
- X-linked hypophosphataemia rickets and vitamin D-resistant rickets are only incompletely treatable and result in lifelong skeletal deformities.
- Whether hypophosphataemia itself increases mortality is difficult to ascertain, as many of the patients are critically unwell from the cause of the low phosphate. Prospective and retrospective studies have reported a 2- to 4-fold increase in mortality in hospitalised patients with severe hypophosphataemia, due to its effects on respiratory and cardiovascular stability[11].

Prevention
Those at high risk, such as renal dialysis and transplant patients, those with eating disorders, and patients who have just had parathyroidectomy, should be monitored and given appropriate oral or parenteral supplementation if required.

Further reading & references
- Hypophosphatemic Rickets, X-linked Dominant, XLHR; Online Mendelian Inheritance in Man (OMIM)
- Hypophosphatemic Rickets, Autosomal Dominant, ADHR; Online Mendelian Inheritance in Man (OMIM)
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