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CORE TRAINING FOR DOCTORS

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Management of hypophosphataemia

Introduction

Electrolyte disorders are frequently encountered by doctors working in a variety of hospital specialties. Abnormalities of potassium, sodium and calcium are usually treated promptly owing to the well-recognized consequences of cardiac arrhythmias and altered mental status that develop from delayed treatment, as well as familiarity with their management.

Hypophosphataemia has an incidence of 2–3% in general hospital inpatients. This rises to 30–80% in higher risk populations, including alcoholic patients and septic patients in the intensive care unit (Gaasbeek and Meinders, 2005). Severe hypophosphataemia is associated with increased mortality in septic patients (Shor et al, 2006), respiratory failure (Gravelyn et al, 1988), and can precipitate heart failure (Darsee and Nutter, 1978), but doctors are often uncertain about when and how to initiate phosphate replacement therapy (Hemstreet et al, 2006). This article guides junior doctors through the causes of low serum phosphate and therapeutic approaches to replacement.

Phosphate homeostasis

Phosphate is an essential ion and plays a vital role in many physiological processes. Catabolism of the phosphate bonds in adenosine triphosphate (ATP) yields energy, required for growth and development. Phosphate is also a critical component of cell structures such as the phospholipid bilayer of the cell membrane, nucleic acids and intracellular proteins, as well as forming a crucial element of the bone matrix when bound to hydroxyapatite. In addition, phosphate is involved in the regulation of intracellular enzymatic processes, and plasma and urine acid–base buffering.

In the healthy adult, total body phosphorous content is approximately 700 g, of which 80–85% is contained within the bony skeleton. Some phosphate (14–19%) is bound in skeletal muscle and the viscera, with the remaining phosphate (0.1–1%) free in extracellular fluid. On average, a healthy adult ingests 900–1400 mg of phosphate daily through his/her diet (Gaasbeek and Meinders, 2005).

Neutral phosphate balance is maintained through tight homeostatic control of intestinal absorption in the jejunum, renal tubular excretion and reabsorption, bone remodelling and redistribution between the intracellular and extracellular fluids. This is largely achieved through a complex interplay of multiple regulators of phosphate homeostasis. One of these is vitamin D, which in its active form encourages intestinal absorption of phosphate and maintains bone mineral content.

Conversely, parathyroid hormone is responsible for bone remodelling and thus mobilizes phosphate stores from bone into the extracellular space. More recently, phosphatonins have also been identified as having a key role in the regulation of phosphate homeostasis and balance. These include bone-derived fibroblast growth factor-23 which stimulates fractional excretion of phosphate from the renal tubules in the presence of its co-receptor complex Klotho, as seen in patients with inherited hypophosphataemic rickets (Lee and Weber, 2010).

Measuring serum phosphate

Total plasma phosphate is a combination of both organic and inorganic phosphate compounds. The normal concentration is approximately 3.9 mmol/litre. Since organic phosphate is stored in intermediary substrates its concentration is difficult to measure. Serum assays performed

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in clinical laboratories typically only measure inorganic phosphate concentration, for which the normal range is 0.84–1.45 mmol/litre.

Some care is necessary with the interpretation of serum phosphate results. Concentrations fall transiently after high carbohydrate meals, and substantial diurnal variation exists (Subramanian and Khardori, 2000). Measurements should therefore be acquired at equivalent times each day, before eating, to minimize this variation. Furthermore, as a result of the assay technique, serum phosphate concentration can be a poor indicator of total body phosphate. Despite these limitations, in clinical practice, pragmatic definitions of hypophosphataemia are: mild (serum concentrations of 0.65–0.84 mmol/litre), moderate (0.32–0.64 mmol/litre) or severe (<0.32 mmol/litre).

Investigating hypophosphataemia

Thorough clinical history and examination and a review of the drug chart for medications that alter serum phosphate levels are helpful when looking for the cause of hypophosphataemia. It is good practice to interpret serum phosphate alongside calcium and magnesium levels as similar regulatory pathways are involved in their homeostasis. Low serum phosphate with high serum calcium can suggest primary hyperparathyroidism while both low serum calcium and phosphate levels can indicate low vitamin D levels. Measuring parathyroid hormone and vitamin D levels are thus helpful if serum calcium levels are deranged. Other electrolytes can also point to a cause for hypophosphataemia as low magnesium levels can indicate general malnutrition states, while low potassium levels with hypophosphataemia are found in diabetic ketoacidosis and refeeding syndrome.

If the cause of hypophosphataemia is still unclear, urine samples can be used to quantify renal losses. Renal phosphate excretion can be measured through either 24-hour urine collection or through calculation of the fractional excretion of filtered phosphate from a random urine sample. Normal fractional excretion of phosphate varies between 5 and 20% but in low phosphate states a level above 5% indicates a renal cause (Assadi, 2010).

Causes of hypophosphataemia

Hypophosphataemia can be caused by three mechanisms: reduced intestinal absorption, internal redistribution, or increased renal excretion (*Table 1*).

Decreased intake and reduced intestinal absorption

The normal human diet is abundant in phosphate-rich foods but hypophosphataemia can arise in cases of severe and prolonged malnutrition. It is important to be alert in patients with diarrhoea and vomiting, nasogastric suctioning, or those using phosphate-binding antacids that can reduce absorption of vitamin D and phosphate. Alcoholics are particularly at risk because of their chronic malnutrition, chronic diarrhoea, use of phosphate-binding antacids to treat gastritis, and risk of refeeding syndrome (Amanzadeh and Reilly, 2006).

Vitamin D is important in promoting phosphate uptake from the gut and deficiency is found in individuals with poor diet (lack of fish and dairy products) and low sunlight exposure. Several medications reduce vitamin D levels through their induction of cytochrome P450 enzymes which metabolize vitamin D, particularly phenytoin and phenobarbital, but also other CYP450-inducing agents including carbamazepine, isonizaid and rifampicin (Liamis et al, 2010).

Internal redistribution

Internal redistribution is the most common cause of hypophosphataemia, and in most cases results from an acute shift of phosphate from the extracellular to the intracellular compartment. Insulin causes uptake of glucose and phosphate ions into cells, principally skeletal muscle and the liver, resulting in an apparent low serum phosphate level. This frequently causes hypophosphataemia in patients who are treated in hospital for diabetic ketoacidosis with intravenous insulin. Similarly, insulin release during refeeding syndrome causes influx of phosphate into cells when glucose

Table 1. Causes of hypophosphataemia

Decreased intake and reduced intestinal absorption	Malnutrition	
	Alcohol misuse	
	Vitamin D deficiency	Nutritional deficiency
		Secondary to cytochrome P450-inducing medications
	Diarrhoea and vomiting	
	Nasogastric suctioning	
	Phosphate binding antacids	
Internal redistribution	Glucose and insulin co-administration (during diabetic emergencies)	
	Refeeding syndrome	
	Respiratory alkalosis (including salicylate poisoning)	
	Sepsis	
	Malignancy	
	Severe burns	
	Rapid cell uptake/proliferation (leukaemia, hungry bone syndrome, erythropoietin)	
Increased renal excretion or artificial clearance	Hyperparathyroidism	
	Fanconi's syndrome	
	X-linked hypophosphataemic rickets	
	Autosomal dominant hypophosphataemic rickets	
	Drugs (diuretics, bisphosphonates, glucocorticoids, aminoglycosides, anti-cancer drugs, some antiretrovirals and antibiotics)	
	Metabolic acidosis	
	Oncogenic osteomalacia	
	Haemodialysis	

is reintroduced to the body following a prolonged period of malnourishment (Marinella, 2005).

Other causes of redistribution include respiratory alkalosis, sepsis, burns, and rapid cell turnover. Hyperventilation causes a fall in carbon dioxide concentrations and a subsequent rise in intracellular pH. This stimulates glycolysis and phosphofructokinase activity, increasing the formation of phosphorylated compounds, causing a shift of phosphate away from the extracellular fluid and into cells. The mechanism of hypophosphataemia secondary to sepsis is unclear but it is thought that hyperventilation, increased uptake by leucocytes and an intracellular shift induced by inflammatory cytokines all contribute (Geerse et al, 2010). Phosphate redistribution can also occur 2–10 days after severe burns, and although the exact mechanism remains incompletely understood, it has been suggested that phosphate loss occurs through the skin (Berger et al, 1997).

Finally, rapid cell turnover as a result of malignancy and hungry bone syndrome can lower serum phosphate levels through rapid cellular turnover and increased phosphate uptake into cells. Clinicians should also be aware that, in exceptional circumstances, administration of exogenous hormones, such as erythropoeisis-stimulating agents, can exacerbate hypophosphataemia when factors favouring low serum phosphate are present.

Increased renal excretion or artificial clearance

Inherited and acquired disorders of the renal tubules are well-recognized causes of serum hypophosphataemia through increased phosphate clearance. Serum phosphate levels vary in hyperparathyroidism, depending on the classification. In primary hyperparathyroidism, there is reduced renal reabsorption of phosphate causing low serum phosphate levels. In secondary hyperparathyroidism serum phosphate levels may vary depending on the cause, but tend towards high values in renal insufficiency and low values in vitamin D deficiency, while tertiary hyperparathyroidism is usually associated with hyperphosphataemia. Other acquired causes of hypophosphataemia include metabolic acidosis and oncogenic osteomalacia, a rare paraneoplastic cause of hypophosphataemia characterized by high alkaline phosphatase and low vitamin D levels.

There are several inherited causes of increased renal excretion, of which X-linked hypophosphataemic rickets is the most common, causing 80% of cases. It results in hypophosphataemia and low levels of vitamin D_3, and is caused by a mutation in the PHEX protein which normally acts to inhibit phosphate excretion. Other hereditary causes include autosomal dominant hypophosphataemic rickets, caused by a mutation in fibroblast growth factor-23.

Several drugs cause increased renal excretion of phosphate, including diuretics, chemotherapeutic agents, antivirals and some anticonvulsants and antibiotics. Of the diuretics, carbonic anhydrase inhibitors (such as acetazolamide) are the most potent phosphaturic drugs as a result of their inhibition of phosphate reabsorption in the proximal tubule where most phosphate reabsorption occurs. Thiazides also lower phosphate levels, as a result of their inhibition of distal tubule phosphate resorption, while loop diuretics have minimal phosphaturic activity. Antiretrovirals such as tenofovir or adefovir can also cause a significant fall in phosphate levels by increasing fractional urinary excretion of phosphate.

Rarer recognized causes include valproate, tetracycline and aminoglycosides. Several medications cause Fanconi's syndrome, characterized by impaired proximal tubular reabsorption of bicarbonate, phosphate, glucose and amino acids. Chemotherapeutic agents, including ifosfamide, are the most well-recognized causes of drug-induced Fanconi's syndrome. Finally, although hypophosphataemia is unusual in patients with a normal diet on standard haemodialysis, it can occur during long hours quotidian haemodialysis, and may be associated with a higher incidence of respiratory failure (Demirjian et al, 2011).

Clinical features of hypophosphataemia are non-specific and often related to the cause and duration of hypophosphataemia (*Table 2*). Many patients are asymptomatic but hypophosphataemia can cause musculoskeletal, cardiovascular and pulmonary symptoms.

Musculoskeletal symptoms are the most common complaint of patients with hypophosphataemia, and patients with acute phosphate deficiency can complain of muscle pain and weakness, although many are asymptomatic. Chronic phosphate deficiency in alcoholic patients and malnourished patients is known to cause more pronounced weakness, proximal myopathy and bone pain. An acute-on-chronic deficiency can precipitate rhabdomyolysis, shown by a rise in creatine kinase levels. Chronic phosphate deficiency can also cause hypophosphataemic osteomalacia with proximal muscle weakness and bone pain associated with a raised alkaline phosphatase level.

Hypophosphataemia can cause respiratory insufficiency with diaphragmatic weakness as a result of low ATP levels and reduced muscle contractility (Aubier et al, 1985). It can precipitate or worsen respiratory failure and, in ventilated patients, diminish the ability to wean patients off ventilation. Correcting low phosphate levels improves respiratory function and symptoms (Gravelyn et al, 1988).

Severe hypophosphataemia may cause reduced myocyte contractility (Fuller et al, 1978), manifesting clinically as acute heart failure or a propensity to ventricular ectopic activity (Darsee and Nutter, 1978). Hypophosphataemia is also a significant predictor of ventricular tachycardia following myocardial infarction (Ognibene et al, 1994).

Table 2. Clinical features of hypophosphataemia

Musculoskeletal	Myalgia
	Muscle weakness
	Osteomalacia
	Rhabdomyolysis
Pulmonary	Respiratory failure
	Decreased peripheral oxygen delivery
Cardiovascular	Acute heart failure
	Ventricular ectopics
	Ventricular tachycardia post myocardial infarction
Others	Paraesthesia and tremor
	Haemolysis
	Leucocyte dysfunction

Furthermore, there have been several case reports of hypophosphataemia inducing neurological symptoms including paraesthesia and tremor (Lotz et al, 1968). Hypophosphataemia is associated with erythrocyte and leucocyte dysfunction. Low serum phosphate causes a reduction in erythrocyte intracellular ATP levels required to maintain erythrocyte membrane viability resulting in haemolysis, and in leucocytes is thought to impair chemotaxis and function (Craddock et al, 1974).

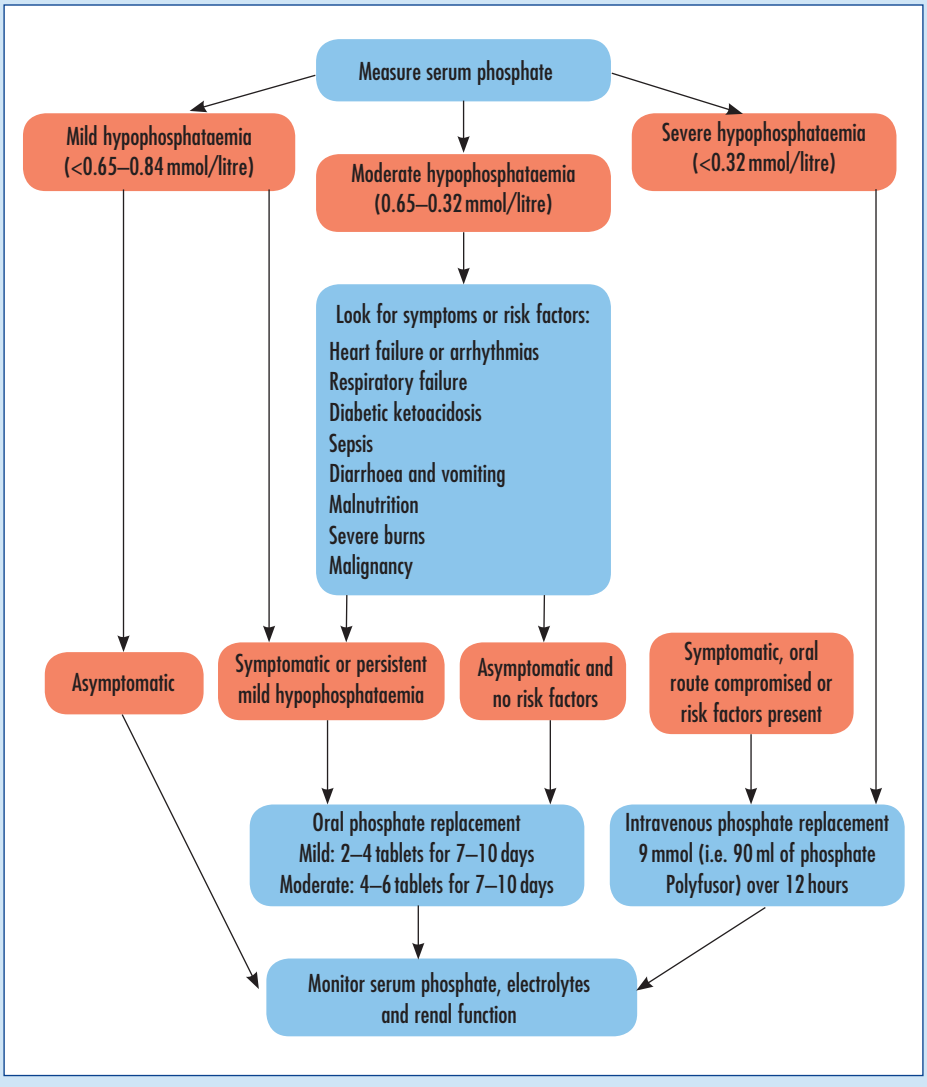
Treating hypophosphataemia

Initiation of phosphate replacement therapy must be carefully considered, as not all cases require treatment. It is important to establish the underlying cause and whether the patient is symptomatic (*Figure 1*).

Mild hypophosphataemia

Asymptomatic and ambulatory patients with mild hypophosphataemia do not usually require phosphate replacement therapy, as the cause is often self-limiting. However, if the patient persistently remains hypophosphataemic or develops any symptoms related to low serum phosphate levels, oral replacement should be considered. This can easily be administered as cow's milk unless there is intolerance to dairy products. In this instance consider replacing phosphate orally with two to four tablets of Phosphate-Sandoz 500 mg tablets, each containing 16 mmol phosphate, to provide 15 mg/kg of elemental phosphorous daily, given as equal divided doses to minimize the risk of adverse gastrointestinal effects (Shiber and Mattu, 2002).

Figure 1. Practical guide to phosphate replacement, taking into account the baseline serum concentration and presence of symptoms or risk factors. In the most severe cases or if symptomatic, phosphate replacement should always be considered as shown.



Moderate hypophosphataemia

Oral replacement of phosphate in asymptomatic patients with moderate hypophosphataemia is the safest method of restoring a normal serum phosphate. There are no data that identify any significant harm caused by administering oral preparations in this group of patients. A suggested protocol is four to six tablets of a preparation such as Phosphate-Sandoz 500 mg tablets in divided daily doses not exceeding 3 g per day for 7–10 days (Brunelli and Goldfarb, 2007). However, patients receiving oral replacement therapy must be warned about the common side effect of diarrhoea and doses can be reduced if this occurs. During repletion, daily monitoring of serum phosphate is required to guide the clinician and tailor therapy to the individual response.

If patients are overtly symptomatic or bed-bound, the enteral route is not considered sufficient, as symptom relief cannot be achieved at an acceptable rate. In this instance, parenteral phosphate replacement therapy may be considered, as if treating a severe case of hypophosphataemia.

Severe hypophosphataemia

Patients with severe hypophosphataemia are rarely asymptomatic, and thus require more aggressive phosphate replacement. The intravenous route is preferred as it rapidly corrects the deficit and consequently reduces symptom burden.

For many years, the gold-standard regimen has been that described by Vannatta et al (1983). This regimen slowly and safely replaces phosphate by infusing 90 ml of phosphate Polyfusor over 12 hours. This achieves a total replacement of 9 mmol of phosphate and can be repeated as required. It should be noted that phosphate Polyfusor is commonly manufactured as a 500 ml preparation, and care should be taken to only deliver 90 ml per infusion. The primary advantage of following this cautious regimen is that cardiac monitoring is not required during the infusion phase, and so it can be performed safely on a general inpatient ward. However, the proportion of hypophosphataemic patients that achieved a normal serum phosphate level after 24 hours in Vannatta's study was only 58%. A minority of patients require repeated infusions with the risks associated with intravenous cannulae (Brunelli and Goldfarb, 2007).

More recently, there has been interest in using more aggressive replacement. This has centred mainly on critically ill patients in intensive care settings, with access to cardiac monitoring. Several regimens have been proposed, most using a weight and serum phosphate-based algorithm (Charron et al, 2003). Use of these regimens has resulted in a 29% increase in the number of patients achieving normal phosphate levels following infusion when compared to the Vannatta regimen (Taylor et al, 2004). However, aggressive phosphate replacement is not without risk. Excessive intravenous phosphate replacement can lead to further electrolyte disturbances and their clinical consequences, including cardiac arrhythmias associated with hyperkalaemia, hypocalcaemic tetany, hyperphosphataemia, renal failure and acidosis. Therefore, the authors recommend that severely hypophosphataemic patients in the intensive care or high dependency setting should be treated with the established Vannatta protocol.

Conclusions

Hypophosphataemia is a common electrolyte disturbance, and may be dangerous. Its underlying cause should always be investigated, and those causes associated with transient hypophosphataemia may be appropriately managed expectantly. If severe hypophosphataemia is encountered or the patient is symptomatic, phosphate replacement therapy can be considered. Junior doctors should be familiar with the oral and intravenous preparations of phosphate replacement available, and be able to follow appropriate dosing regimens with awareness of potential adverse effects. BJHM

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KEY POINTS

- Hypophosphataemia is common and associated with significant morbidity and mortality.
- Junior doctors are frequently unfamiliar with the indications for and modes of its treatment.
- Oral phosphate replacement is advised in the symptomatic mildly hypophosphataemic or moderately hypophosphataemic patient.
- Intravenous phosphate replacement should be initiated in the symptomatic moderately hypophosphataemic or severely hypophosphataemic patient.
- Intravenous phosphate is often supplied in large volumes.
- Rapid intravenous infusion (>90 ml/12 hours) is hazardous and should only be undertaken in a monitored environment.

TOP TIPS

- Always measure baseline serum phosphate concentrations in patients who may be at risk.
- Assess for presence of symptoms and risk factors.
- Replace phosphate via the enteral route first, unless the patient is very symptomatic or severely deplete.
- Be vigilant to the rate and volume of intravenous replacement.
- Always re-evaluate serum phosphate concentration and the patient's clinical status after replacement.
- Do not rely exclusively on the *British National Formulary* for a guide to phosphate replacement.