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Phosphate homeostasis in critical care

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Key points

- Serum phosphate is under tight physiological control.
- Hypophosphataemia is common in hospitalized patients, particularly in the critically ill.
- Hypophosphataemia causes multisystem effects if left untreated.
- Phosphate disturbances are often multifactorial.
- Treatment of hyperphosphataemia secondary to rhabdomyolysis or tumour lysis syndrome should be instituted promptly.

Phosphorus plays a critical role in many biological processes, including energy metabolism, cellular signalling, nucleic acid metabolism, membrane integrity, and bone mineralization.[1] Phosphate is an inorganic molecule containing four oxygen atoms and a central phosphorus atom. In its ionic form, phosphate (PO_4^{3-}) is negatively charged, leading it to be an ideal buffer and easily combining with positively charged calcium ions to contribute to hydroxyapatite, the main mineral component of bone, where up to 85% of the body's phosphate stores exist.

Physiology

Phosphorus in the diet is present in inorganic and organic forms. Organic phosphorus is absorbed less freely than inorganic phosphate. Phosphate absorption is highly efficient, with 60–70% of an intestinal load absorbed from a typical diet,[2] occurring mostly in the duodenum and jejunum.

Intestinal absorption occurs both by non-regulated passive transport through the paracellular pathway and regulated active mechanisms[3] via type IIb sodium phosphate co-transporters on the mucosal surfaces. Intracellular transport and export via the basolateral membrane is likely related to movement down the concentration gradient to the relatively low serum concentration.

Three families of sodium/phosphorus (Na/Pi) co-transporters exist. Type I is present in the kidneys and liver, type II in the kidney, small intestine and lung, and type III in most areas of the body.

Plasma phosphorus consists of phospholipids, ester phosphates, and inorganic phosphates. Inorganic phosphates are completely ionized, circulating primarily as hydrogen phosphate $H(PO_4)^{2-}$ or dihydrogen phosphate $H_2(PO_4)^-$ in a ratio of 4:1 at a plasma pH of 7.40.[4]

Phosphate and calcium share an intimate relationship, not least due to the high mineral content of the bone comprising combinations of these molecules. Hydroxyapatite has the formula $Ca_{10}(PO_4)_6(OH)_2$ and provides bone with its compressional strength. Also hydroxyapatite, calcium, and phosphate co-exist in the bone as exchangeable forms of salts, such as $CaHPO_4$ and other amorphous calcium salts. These are in equilibrium with the calcium ions in the extracellular fluids, importantly providing a rapid buffering mechanism to prevent the calcium ion concentration from altering. The calcium ion concentration is therefore under tight control of within a few per cent of the normal level of 1.2 mmol litre^{-1}.

The plasma concentrations of phosphate and calcium are small in proportion to the total body content, but it is these parameters that are under hormonal control (Fig. 1).

Vitamin D3 (cholecalciferol) is a fat-soluble steroid synthesized in the skin, as a result of irradiation of 7-dehydroxycholesterol by ultraviolet rays. It is also present in a similar form in the diet. It is activated by a hepatic enzyme, 25-hydroxylase, placing a hydroxyl group in the 25 position of the vitamin D molecule, resulting in the formation of 25-hydroxycholecalciferol (calcidiol). Further,

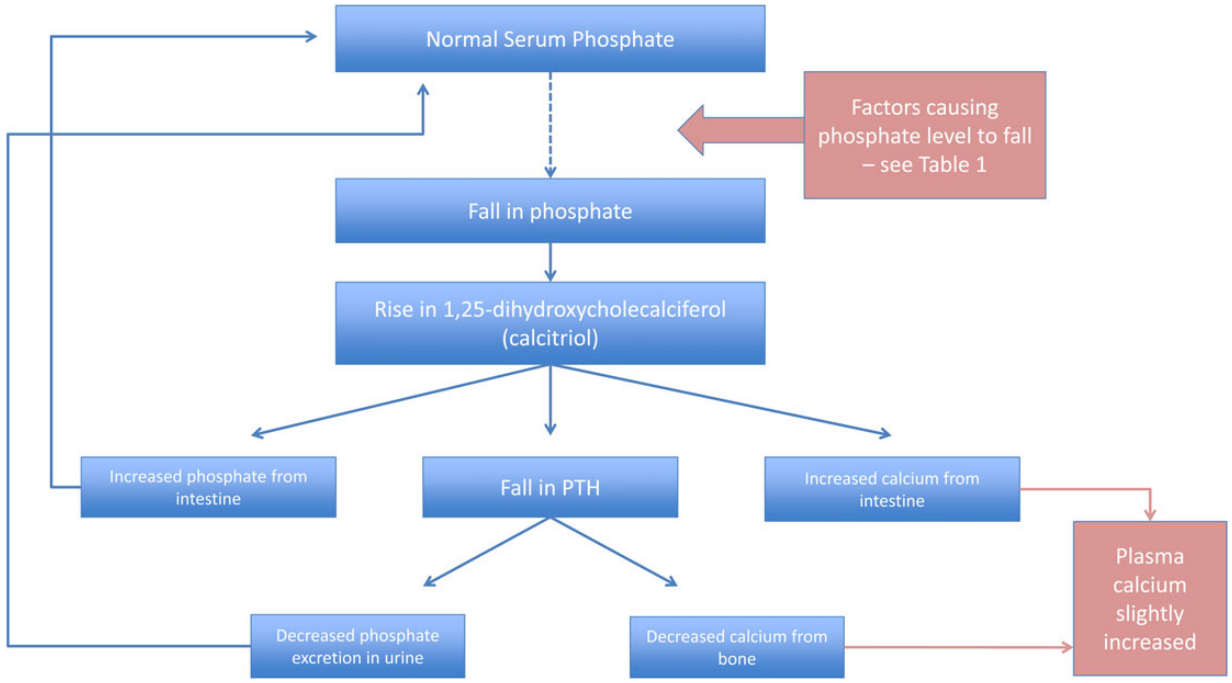

Fig 1 Hormonal control of phosphate. PTH, parathyroid hormone.

conversion to its most active form, 1,25-dihydroxycholecalciferol (calcitriol), occurs in the proximal tubules of the kidneys with negative feedback at each stage by 25-hydroxycholecalciferol, and parathyroid hormone, respectively. Hypophosphataemia also encourages the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol.

1,25-Dihydroxycholecalciferol raises calcium and phosphate levels by increasing gut absorption. Here, the type IIb sodium phosphate co-transporter appears to be regulated at the membrane level by 1,25-dihydroxcholecalciferol, but not at a transcriptional level. 1,25-Dihydroxycholecalciferol also increases activity of the osteoblasts, laying down calcium into the bone matrix and increases calcium and phosphate reabsorption by the epithelial cells of the renal tubules.

Parathyroid hormone is released in response to changes in calcium concentration but also acts on phosphate. As parathyroid levels increase, the bone releases calcium and phosphate-containing minerals into the circulation. Parathyroid hormone also has a direct effect on the kidney to increase tubular reabsorption of calcium, but also to decrease the phosphate reabsorption by acting on the proximal tubules. The net effect is that phosphate levels decrease in response to parathyroid hormone. Parathyroid hormone also promotes formation in the kidneys of 1,25-dihydroxycholecalciferol, therefore enhancing the absorption of calcium and phosphate from the gastrointestinal (GI) tract.

Phosphate is completely reabsorbed by the kidney when the plasma concentration is below 1 mmol litre^{-1} with none lost to the urine. Above this critical concentration, phosphate loss is proportional to the concentration present.

Hypophosphataemia

Up to 5% of hospitalized patients may have low serum phosphate concentrations <0.8 mmol litre^{-1}, but this is more common in critically ill patients.[5] One study of 2730 critically ill patients in Australia reported an incidence as high as 26%.[6] Profound hypophosphataemia (<0.32 mmol litre^{-1}), which can lead to physiological disturbances, is much less common however.

There are four mechanisms by which hypophosphataemia can occur:

(i) redistribution,
(ii) decreased absorption,
(iii) increased renal loss,
(iv) renal replacement therapies.

Critical care patients and those undergoing surgery commonly have multiple risk factors that may lower phosphate levels. This is particularly true for major surgery, such as cardiac surgery and abdominal aortic surgery.[7] After major hepatic surgery, hypophosphataemia is extremely frequent.[7] Internal redistribution is the most common cause in these physiologically stressed patients. Glycolysis causes an increase in the phosphorylated compounds in the liver and skeletal muscle, the source of which is the inorganic phosphate in extracellular fluid. The use of insulin, or stimulation of increased endogenous insulin secretion, will cause a decrease in serum phosphate levels by moving phosphate intracellularly along with glucose. Epinephrine, glucagon, and other hormones also produce this effect by a similar mechanism (Table 1). This can become more problematic in patients with underlying phosphate depletion—such as those who are fasted for prolonged periods, malnourished due to chronic alcohol intake, or anorexia nervosa. During the anabolic period, after re-feeding, there is an influx of phosphate into the cells which can lead to a severe hypophosphataemia. This is the primary manifestation of the 're-feeding syndrome'.

Patients with hyperglycaemia, and subsequent osmotic diuresis (and therefore loss of phosphate in the urine) who are treated with insulin, are at risk of hypophosphataemia, and this should be monitored closely and corrected as necessary.

Another redistributive cause of hypophosphataemia is respiratory alkalosis.[8] Extracellular decreases in carbon dioxide will result

Table 1 Causes of hypophosphataemia

Internal redistribution	
Hormonal triggers	Insulin, glucagon, epinephrine, dopamine
Drugs	Carbohydrate infusions, β-2 agonists, steroids, xanthine derivatives
Respiratory alkalosis	Mechanical ventilation, sepsis, alcohol withdrawal, hepatic coma, anxiety, salicylate overdose
Glucose shifts	Treatment of DKA, re-feeding after malnutrition
Rapid cell uptake/proliferation	Hungry bone syndrome (post-parathyroidectomy), acute leukaemia
Renal losses	
Drugs	Diuretics including acetazolomide and metolazone
	Tenofovir
	Imatinib
	Glucocorticoid/mineralocorticoid therapy
Acute volume expansion	
Hyperparathyroidism—primary and secondary	
Renal transplantation	
Fanconi syndrome	
Primary renal phosphate wasting	X-linked hypophosphataemic rickets
	Autosomal-dominant hypophosphataemic rickets
	Tumour-induced osteomalacia
Decreased intestinal absorption	
Poor phosphate diet and/or malabsorption	
Phosphate binding antacids	
Steatorrhoea or chronic diarrhoea	
Vitamin D deficiency or resistance	
Renal replacement therapy	

in a similar change within the cell. Elevated pH stimulates glycolysis leading to hypophosphataemia. Respiratory alkalosis may be the precipitating factor in the hypophosphataemia-induced acute rhabdomyolysis that can occur in alcoholic patients; however, the underlying hypophosphataemia may initially be masked by the release of phosphate from injured muscle cells.

Post-parathyroidectomy and sometimes with thyroidectomy, there can be a rapid deposit of calcium and phosphate into the bone, the 'hungry bone syndrome' in those previously osteopenic, which can be symptomatic.

Poor oral intake alone is rarely a sole cause for hypophosphataemia due to the high efficiency of the gut to absorb dietary phosphate and up to 100% renal reabsorption. It can become more of a problem in conditions associated with GI phosphate loss however, such as chronic diarrhoea, vomiting, or the use of aluminium or magnesium containing antacids or other phosphate binding drugs. GI effects are worsened in those with concomitant vitamin D deficiency.

Renal loss of phosphate has a number of causes, most commonly due to the use of diuretic therapy (Table 1). Acute volume expansion can also cause phosphate to decrease due to diminished proximal sodium reabsorption on which phosphate transport closely depends.

Renal replacement therapy is a common cause of hypophosphataemia in the critically ill patient due to loss with effluent waste. Replacement in this situation is important to prevent physiological consequences of hypophosphataemia due to rapid changes in serum concentrations.

Hyperphosphataemia

Hyperphosphataemia can also be attributed to four different mechanisms:

(i) acute phosphate load,
(ii) cellular shift,
(iii) decreased renal clearance,
(iv) pseudohyperphosphataemia.

Acute phosphate load can be divided into exogenous and endogenous. Exogenous load is uncommon, but has been seen in patients using phosphate-containing laxatives,[9] which can lead to acute phosphate nephropathy, and those taking high-dose fosphenytoin for the treatment of seizures. These are usually in association with volume contraction (diarrhoea), renal impairment, or both.

Endogenous load is seen more frequently, in tumour lysis syndrome and rhabdomyolysis. Tumour lysis syndrome is commonly caused by chemotherapeutic agents in patients with large tumour burden and rapid cell turnover, such as non-Hodgkins or Burkitt's lymphoma, but can also occur spontaneously in the course of these disease processes. Cell turnover releases potassium, phosphate, purines, and proteins, the latter two of which can be converted to uric acid and urea, respectively, and cause hyperuricaemia. The need for urgent renal replacement therapy may be required as the kidney is overwhelmed with cell components. In rhabdomyolysis, the severity of hyperphosphataemia and hypocalcaemia may be increased if haem pigment-induced acute kidney injury ensues.[10]

Acute cellular shifts of phosphate are far less common but can be seen in diabetic ketoacidosis, with severe hyperglycaemia alone, and in lactic acidosis. All types of metabolic acidosis reduce the glycolysis rate and therefore the phosphate taken up into cells. Lactic acidosis is associated with cell death and subsequent release of intracellular phosphate. Consequently, hypophosphataemia can then be seen when these conditions are treated.

Patients with acute or chronic kidney disease develop hyperphosphataemia primarily due to a decrease in glomerular filtration rate. To some extent, this can initially be maintained by suppression of the sodium–phosphate co-transporters in the luminal membrane of the proximal tubules, but below filtration rates of 20–25ml min^{-1}, phosphate reabsorption is thought to be maximally suppressed, and inevitably leads to an increase

Table 2 Causes of hyperphosphataemia

Acute phosphate load	Tumour lysis syndrome Rhabdomyolysis Exogenous phosphate, for example, sodium phosphate laxative, fosphenytoin
Cellular shift	Metabolic acidosis
Decreased renal clearance	Acute or chronic kidney disease Increased tubular reabsorption • Hypoparathyroidism or pseudohypoparathyroidism • Bisphosphonates • Vitamin D toxicity • Acromegaly • Familial tumoural calcinosis
Pseudophyperphosphataemia	Endogenous • Hyperglobulinaemia • Hyperlipidiaemia • Haemolysis • Hyperbilirubinaemia Exogenous • Amphotericin B • Heparin • Tissue plasminogen activator

Table 3 Adverse clinical effects of severe hypophosphataemia

Respiratory
Acute respiratory failure
Impaired diaphragmatic contractility
Failure to wean from mechanical ventilation
Cardiovascular
Decreased myocardial contractility, decreased stroke volume
Increased inotropic requirement
Arrhythmias
Metabolic
Insulin resistance
Depletion of 2,3 DPG–oxygen dissociation curve shifts to left
Neurological
Delirium
Seizures
Coma
Gastrointestinal
Dysphagia
Ileus
Haematological
Haemolysis
Leucocyte dysfunction—impaired phagocytosis and granulocyte chemotaxis
Musculoskeletal
Weakness
Myalgia

in plasma levels due to ongoing absorption via the gut. Dysfunctional kidneys are unable to efficiently form 1,25-dihydroxycholecalciferol, leading to a secondary hyperparathyroidism. Additionally, hyperphosphataemia can independently contribute to cardiac causes of death through increased myocardial and vascular calcification, and microcirculatory complications[11] in patients with chronic renal failure.

Other causes of decreased renal clearance of phosphate secondary to increased proximal tubular reabsorption can be seen in Table 2.

A pseudohyperphosphataemia can occur due to interference with laboratory analysis in conditions such as hyperglobulinaemia, hyperlipidaemia, hyperbilirubinaemia, and haemolysis. Some drugs can also cause this falsely raised laboratory result, such as amphotericin B and heparin. Values for phosphate should be determined using alternative techniques in these cases.

Consequences of disordered phosphate

As previously discussed, the causes of hypophosphataemia in the critically ill are multifactorial. A combination of sepsis, trauma (in particular, burns and head trauma), acid–base disorders, glucose/insulin therapy, catecholamines, and diuretic use mean that patients in critical care are at much higher risk of hypophosphataemia with higher associated mortality. It is unclear however whether hypophosphataemia contributes directly to this mortality increase, or is a marker of illness severity (Table 3).[7]

Symptomatic hypophosphataemia usually occurs when the phosphate level is lower than 0.32 mmol litre^{-1}.[8]

Symptoms can often be explained due to complications of impaired metabolism—in particular, muscle dysfunction, presenting with acute respiratory failure, failure to wean from ventilation, decreased myocardial contractility with increased inotropic requirement, or with skeletal muscle weakness and rhabdomyolysis. Rhabdomyolysis is more common in those with pre-existing myopathy, e.g. chronic alcoholism, where subsequent hypophosphataemia may precipitate rhabdomyolysis.

Another major cause of symptomatic hypophosphataemia is depletion of 2,3 diphosphoglycerate.[8] This causes a shift of the oxygen dissociation curve to the left, affecting oxygen delivery to tissues, and in those with chronic lung disease, this effect may be even more marked. Cardiac arrhythmias, both supraventricular and ventricular in origin, can occur alongside this.

Haematological effects of hypophosphataemia seen in the critically ill are those of haemolysis and leucocyte dysfunction—impaired phagocytosis and granulocte chemotaxis. Dysfunction in leucocytes explains the higher incidence of Gram-negative sepsis in hypophosphataemic patients.[8]

Insulin resistance and ileus are common features seen in the critically ill and postoperative patient group, and can be caused by or contributed to by hypophosphataemia. Altered mental status, delirium, seizures, and coma, have most often been described in the course of refeeding. Hypophosphataemia can also lead to both peripheral and central neuropathies.[8]

Hypocalcaemia and tetany may occur with rapid increases in plasma phosphate due to deposition of calcium into soft tissues. Severe hyperphosphataemia with symptomatic hypocalcaemia can be life threatening, not least because of the negative inotropic effects on the myocardium. Therefore, haemodialysis is often indicated in these patients, particularly in those with pre-existing impaired renal function.

Treatment

Hypophosphataemia does not always necessitate replacement therapy,[8] as this depends on the body's overall phosphate status. Degrees of severity of hypophosphataemia may lead to either enteral or parenteral replacement.

A serum phosphate level below 0.64 mmol litre^{-1} (2 mg dl^{-1}) in asymptomatic patients warrants enteral replacement, in patients who are reliably absorbing feed and have adequate vitamin D stores. Enteral phosphate replacement is given in the form of Phosphate Sandoz® effervescent tablets. Each tablet contains

PO_4^{3-} 16.1 mmol, Na^+ 20.4 mmol, and K^+ 3.1 mmol. The usual adult dose is up to 6 tablets daily (dissolved in water) in divided doses, to produce a solution that can be given safely via feeding tubes. Tablets should not be taken with aluminium, calcium, or magnesium salts as these will bind phosphate and reduce absorption.

Parenteral phosphate replacement is indicated if the patient has severe hypophosphataemia (<0.32 mmol litre^{-1}) or is symptomatic. It may also be considered for patients unlikely to absorb oral agents. A commonly used treatment is the Phosphate Polyfusor®, a solution containing 50 mmol PO_4^{3-}, 9.5 mmol K^+, and 81 mmol Na^+ in 500 ml, given over 24 h via a central venous catheter. This preparation should be infused alone, via a dedicated port of a central line, and if given peripherally should have a dedicated cannula. Peripherally, the ideal is to reduce the rate of infusion due to risk of pain and phlebitis at the injection site, but with close monitoring could be given at the same rate as the central dose.

Caution should be taken in those with renal impairment, as in this particular group, the risk of iatrogenic hyperphosphataemia is significant. Phosphate replacement may exacerbate hypocalcaemia and can cause metastatic soft tissue calcification. At least, daily monitoring is necessary for those having treatment to reduce the risk of hyperphosphataemia. Calcium should be corrected before administration of phosphate replacement.

Phosphate Sandoz® and Phosphate Polyfusor® contain a relatively high dose of sodium which may be unsuitable for some patients requiring phosphate replacement.

Another common replacement regimen includes that of i.v. potassium phosphates. Products can be a combination of monobasic potassium phosphate and dibasic potassium phosphate. They must be diluted before use in either 0.9% sodium chloride or 5% glucose to a minimum volume of 100 ml, and given at a rate of no greater than 20 mmol of phosphate per hour preferably via a central line. This avoids administrations of high-sodium content fluid, and in patients requiring potassium replacement and phosphate, can be very useful. Dose should be titrated against plasma phosphate and potassium levels regularly to avoid hyperphosphataemia and hyperkalaemia.

Alternatively, potassium acid phosphate (potassium dihydrogen phosphate) with a neat concentration of 1 mmol ml^{-1} each of potassium and phosphate can be used. Other alternatives such as Glycophos® (20 mmol phosphate, 40 mmol sodium in 20 ml solution) or Addiphos® (40 mmol phosphate, 30 mmol potassium, and 30 mmol sodium in 20 ml solution) can be added to i.v. fluids including TPN.

Hyperphosphataemia should be treated by correction of the underlying cause. In the case of rapid cell turnover or rhabdomyolysis, renal replacement therapy may be indicated and should be instituted promptly.

Summary

Phosphate disturbances in critically ill patients are relatively common, often multifactorial, and can occasionally have catastrophic consequences if not monitored and treated appropriately. Transient changes may be left without intervention due to rapid movement between intracellular and extracellular spaces if the patient remains asymptomatic. Correction of phosphate disturbances should be done carefully with close monitoring, regular review, and a thorough knowledge of the pharmacology and physiology and an understanding of the potential pitfalls of standard laboratory monitoring.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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