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REVIEW ARTICLE

Hypophosphataemia Pathophysiology, effects and management on the intensive care unit

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Summary

Routine detection and treatment of hypophosphataemia on the intensive care unit is commonplace. Hypophosphataemia has been associated with a multitude of clinical effects and there are many associations between correction of hypophosphataemia and improvement in symptoms. However, there is no evidence at present to support the routine correction of hypophosphataemia in the absence of clinical symptoms or signs.

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In recent years, the measurement of serum phosphate levels and the treatment of hypophosphataemia have become commonplace, particularly since the advent of parenteral nutrition and the introduction of automated biochemical analysis. There is a growing body of opinion which suggests that routine correction of serum phosphate to within the normal range in patients in the intensive care unit (ICU) is of benefit. This review aims to examine the evidence for this practice as well as considering the likely causes of hypophosphataemia in the ICU and their pathophysiology. The different regimens for phosphate replacement will be compared and their relative safety considered.

Normal phosphate homeostasis

The body of a healthy 70 kg human contains approximately 712 g of phosphorus (28 000 mmol), the majority of which (85%) is stored in bone as hydroxyapatite crystals deposited within the organic matrix. Of the remainder, 14% is stored in soft tissues as phosphate and 1% is found in the blood. The soft tissue phosphate has several roles: as a factor in intermediate metabolism; as a component of genetic material and as a structural component, e.g. phospholipid. Phosphate is the most abundant anion in the cell with a concentration of about 100 $mmol.l^{-1}$. Therefore, the intracellular inorganic phosphate concentration is about 100 times the plasma concentration. Only a small fraction of intracellular phosphate is in the inorganic form, the majority being in intermediary carbohydrates, lipids and proteins. Phosphate found in the blood exists in both organic and inorganic forms with a total plasma concentration of 3.9 $mmol.l^{-1}$. The organic form comprises mainly phospholipids and accounts for approximately two thirds of the total. The inorganic form, comprising the remainder, is the quantity normally measured by standard laboratory tests. This is made up of free inorganic phosphate (85%), which exists as a combination of HPO_4^{2-}, $H_2PO_4^-$ and PO_4^{3-} ions, the ratios of which depend on plasma acid–base balance and protein-bound inorganic phosphate (10%) which forms a complex with calcium, magnesium or sodium (5%).

The normal dietary intake of phosphate is 800–1200 $g.day^{-1}$ in the adult. The homeostasis of phosphate is controlled by parathyroid hormone, 1,25 dihydroxycholecalciferol and calcitonin and involves three main organs: the intestine, the kidneys and bone. Uptake of phosphate occurs along the length of the intestinal tract with the jejunum being the main site of absorption. It is thought that there are two mechanisms. The first is a sodium-dependent active transport mechanism in the proximal intestine [1] which can be blocked by diphosphonates and calcitonin [2] and enhanced by 1,25 dihydroxycholecalciferol. This process is related directly to the intraluminal sodium concentration. The second involves

the passive diffusion of phosphate ions, mainly from the jejunum [3] and ileum [1]. This mechanism is related to the concentration of phosphate so that when dietary intake of phosphate is low, the first mechanism predominates. Gut absorption is affected directly by calcium ions which bind intraluminal phosphate, forming insoluble complexes and thus decreasing the bio-availability of both ions [4]. Phosphate is also excreted into the gastrointestinal tract, mainly in saliva and bile acids [5]. Approximately 60% of this secretion is reabsorbed [6].

The main regulatory organ for phosphate is the kidney. In a normal, healthy human, renal phosphate excretion matches net intestinal absorption, thereby achieving a zero balance. The glomerulus filters 90% of plasma phosphate passively [7]. Reabsorption is an active carrier-mediated process which occurs mainly in the proximal tubule and is influenced by urinary pH [8]. The main regulatory factors are parathyroid hormone (PTH), which decreases tubular reabsorption, and hyperphosphataemia, which, along with respiratory and metabolic acidosis, enhances urinary losses [9, 10].

In the hypophosphataemic state, low serum phosphate is the most potent regulator of phosphate conservation, acting by extending tubular reabsorption to cover the whole nephron and desensitising the nephron to the effects of PTH [11]. In addition to its effects on the gut, the vitamin D metabolite 1,25 dihydroxycholecalciferol enhances bone reabsorption to mobilise phosphate in a PTH-independent manner [12].

Physiological functions of phosphate

Phosphate has multiple physiological functions:

1 It is the source of the high-energy phosphate bonds of adenosine triphosphate (ATP). Adenosine triphosphate fuels a wide range of processes including muscle contractility, neuronal transmission and electrolyte transport.

2 It is a vital component of many intracellular compounds including phospholipids, nucleic acids, nucleoproteins and enzymatic cofactors such as nicotinamide diphosphate.

3 It has an important role as an intracellular messenger (e.g. cyclic adenosine monophosphate and cyclic guanosine monophosphate).

4 It has a crucial role as a component of 2,3-diphosphoglycerate in the supply of oxygen to the tissues.

5 It is an essential regulator of enzymes in the glycolytic pathway.

6 It acts as a buffer for the maintenance of plasma and urinary pH.

7 It has a role in many functions of the immune system and the coagulation cascade.

Routine laboratory measurement estimates the serum level of the element phosphorus by the phosphomolybdate ultraviolet assay. This test has a within-run precision of about 1.5% [13]. In the body, phosphorus exists mainly as phosphate and this term is therefore used.

What is hypophosphataemia?

The normal range for inorganic serum phosphate is generally quoted as $0.8–1.3\,\text{mmol.l}^{-1}$. Hypophosphataemia is usually subdivided into two categories. Moderate hypophosphataemia is arbitrarily defined as $0.32–0.65\,\text{mmol.l}^{-1}$ and severe hypophosphataemia as less than $0.32\,\text{mmol.l}^{-1}$ [14]. The incidence of moderate hypophosphataemia in hospitalised patients has been reported to range from 2.5 to 3.1% [15] and the incidence of severe hypophosphataemia ranges from 0.24 to 0.42% [16]. A study of patients admitted to a respiratory intensive care unit reported an incidence of moderate hypophosphataemia of 17%. Patients with chronic obstructive airways disease who are not in an ICU have an incidence of hypophosphataemia (defined in the study as phosphate $< 0.64\,\text{mmol.l}^{-1}$) of 8.8% [17]. The incidence of moderate hypophosphataemia is much higher in critically ill patients, having been reported to be as high as 28% [18] and it is frequently noted in patients with severe trauma [19].

The correlation between serum phosphate concentrations and symptoms is less than clear [14]. Hypophosphataemia does not necessarily indicate phosphorus depletion. Muscle phosphate concentration has been found to be related more to chronic nutritional state than to acute changes in serum phosphate. Serum phosphate concentrations as low as $0.3\,\text{mmol.l}^{-1}$ have been seen with normal muscle phosphate content in patients recovering from acute trauma. This difficulty in interpreting phosphate levels is compounded by the normal diurnal variation in plasma phosphate (a swing of as much as $0.17\,\text{mmol.l}^{-1}$ with a peak at 11.00 a.m.) [20] and the uncertainty as to whether this applies to the ICU patient.

Despite these problems, serum phosphate is the most readily available and widely used measure of body phosphate stores. Many correlations have been drawn between the correction of hypophosphataemia and improvement in the clinical effects to be described.

Causes of hypophosphataemia in the ICU

The causes of hypophosphataemia can be subdivided into three categories.

Inadequate intake

Patients on the ICU may have reduced intake of phosphate for a number of reasons. They may be chronically malnourished as a result of their pre-admission state of health.

When they are fed, they may receive a phosphate-depleted feed, especially if they are being fed by the parenteral route. When total parenteral nutrition (TPN) was first introduced, the source of phosphate used was the hydrolysates of proteins such as casein which contain small amounts of a variety of minerals. With the introduction of synthetic amino acid solutions came multiple case reports of TPN-induced hypophosphataemia. These reports were mainly from North America where the protein source was synthetic amino acids and the energy source was glucose. In Europe, phosphate continued to be inadvertently provided from both the old protein source and the phospholipids found in the fat emulsions used as the energy source.

Although it may be difficult to provide phosphate-depleted enteral feed, gut absorption of phosphate may be reduced. It is known that chemical binding of certain elements (e.g. aluminium and magnesium) to phosphate in the gut produces insoluble complexes, thus lowering the bio-availability of phosphate [21]. Sucralfate is an aluminium-sulphate glucose complex frequently used in the ICU for ulcer prophylaxis. It contains $\approx 18\%$ aluminium by weight. There have been case reports relating the treatment of hyperphosphataemia induced by renal failure with sucralfate and sucralfate-induced hypophosphataemia [22]. However, a study of long-term sucralfate use in non-ICU patients (1 g four times daily for more than 8 weeks as ulcer prophylaxis) failed to demonstrate any significant reduction in serum phosphate [23].

Malabsorption is also seen with aluminium- and magnesium-based antacids but usually only with prolonged use [21]. Diseases that greatly limit the absorptive capacity of the small bowel, such as Crohn's disease, short bowel syndrome and radiation enteritis, may also produce hypophosphataemia.

Redistribution of phosphate into cells

Patients receiving parenteral nutrition are frequently total body phosphate depleted before therapy begins. A chronically malnourished patient is often in a catabolic state which is associated with muscle breakdown and the subsequent loss of intracellular phosphate. Serum phosphate remains relatively normal against a background of elevated urinary losses, leading to total body depletion [14]. Clearly, this loss cannot be predicted just by measuring serum phosphate. When parenteral nutrition is started, the patient receives a high glucose load. This promotes an anabolic state mediated in part by insulin release. The resultant increase in intracellular phosphate requirements due to rapid acceleration of glucose phosphorylation unmasks a state of severe intracellular phosphate depletion and produces serum hypophosphataemia.

Drugs have also been implicated in altering the distribution of phosphate. Catecholamines have been reported to produce an intracellular shift of phosphate, probably via beta-adrenergic receptor mediated stimulation of phosphate uptake [24]. Infusion of adrenaline within the range seen on the ICU appears to produce a dose-dependent reduction in serum phosphate [25]. One paper reported the reduction to be only transient with plasma phosphate returning to pretreatment levels despite continued infusion for 180 min [26]. Similarly, hypophosphataemia has been reported following procedures associated with high endogenous catecholamine release, e.g. trauma and burns. Beta-adrenergic receptor agonists also appear to produce reductions in serum phosphate levels. In one study a single intravenous dose of terbutaline 12 μg produced a decrease in serum phosphate of 0.22 mmol.l^{-1} after 180 min [27]. There have been clinical reports of the development of hypophosphataemia during the treatment of acute asthma, although the clinical significance of these findings is unknown.

Development of alkalosis, of either metabolic or respiratory origins, will also produce hypophosphataemia, probably due to an intracellular shift of phosphate [28]. In particular, the use of bicarbonate in the treatment of drug overdose may significantly decrease plasma phosphate concentrations.

Loss of phosphate from the body

Various drugs used in the ICU setting promote increased urinary phosphate losses. Acetazolamide is the most effective phosphaturic diuretic. This may be related to its ability to increase urinary bicarbonate excretion and hence alter urinary pH. Loop diuretics such as frusemide and bumetanide have minimal effect on phosphate excretion because little occurs in the loop of Henle. However, frusemide does have a weak carbonic anhydrase activity [29] and therefore has a weak phosphaturic effect. Frusemide in a single dose has also been shown to reduce the renal threshold for phosphate excretion in patients with chronic obstructive airways disease. Thiazide diuretics also have only a weak phosphaturic effect related to their inhibition of carbonic anhydrase [30]. Case reports of clinically significant hypophosphataemia following thiazide administration usually involve patients with other causes of hypophosphataemia [31]. Of the other drugs with a diuretic effect, both metolazone and mannitol have only very weak phosphaturic effects. Of greater clinical significance is the interference of mannitol with the assay of serum phosphate leading to falsely low estimates [32].

Increased urinary losses and a reduction in the renal threshold for phosphate are seen in patients on theophylline. This effect is seen in both healthy volunteers and in patients with chronic obstructive airways disease, although the effect has not been seen in asthmatic children [33].

One study demonstrated a 0.15 mmol.l^{-1} decrease in plasma phosphate 90 min after a 5 mg.kg^{-1} dose given orally [34]. In moderate or massive overdose, theophylline may result in hypophosphataemia due to elevated circulating catecholamine levels. Glucocorticoids but not mineralocorticoids increase urinary phosphate loss by reducing the rate of uptake of phosphate by the carrier system of the proximal tubule [35]. This increased loss is not sustained with chronic use of glucocorticoids and has not been seen by all investigators. Dopamine in doses of 0.25–8 μg.kg^{-1}.min^{-1} has been shown to have a phosphaturic effect both in healthy volunteers and in patients with renal failure [36].

Acute paracetamol overdose produces severe hypophosphataemia in $\approx$ 40% of patients [37]. In these patients serum phosphate correlates with renal threshold phosphate concentration implying that renal losses rather than intracellular redistribution is the cause. With amino acid containing parenteral feeds there is increased urinary excretion of amino acids with concurrent elevated urinary phosphate losses. Some causes of hypophosphataemia involve more than one of the above mechanisms. The recovery phase of severe burns is a case in point. Patients with extensive third degree burns retain large quantities of salt and water. As healing progresses, the retained salt and water are mobilised and excreted by the kidney. Accompanying this diuresis is a sizeable loss of phosphate. Simultaneously, the patient becomes anabolic with rapid cellular uptake of phosphate. Patients with diabetes mellitus who are well controlled generally have no disturbance of phosphate metabolism [38]. However, those developing glycosuria, ketonuria and polyuria almost always lose phosphate into the urine. Acidosis causes breakdown of intracellular components with subsequent loss of phosphate. Coexistent glycosuria, ketonuria and polyuria augment the phosphaturia [39, 40]. A state of glucose intolerance has been shown to exist in hypophosphataemic patients; this appears to be mediated primarily by changes in tissue sensitivity to insulin [41]. During the treatment of uncontrolled diabetes, exogenous insulin administration promotes an anabolic state similar to that described above for parenteral nutrition.

Chronic alcoholic patients admitted to the ICU have many reasons for hypophosphataemia. Obvious causes include poor nutritional status, the use of antacids, diarrhoea and vomiting. However, hypomagnesaemia and hypocalcaemia, both of which are present in the chronic alcoholic, predispose to hypophosphataemia. Also, repeated episodes of ketoacidosis occurring as a direct consequence of an inadequate diet may lead to damage of intracellular components and phosphate loss similar to that seen in diabetic ketoacidosis [41–44].

Other causes of hypophosphataemia encountered on the ICU include recovery from hypothermia, haemodialysis, salicylate poisoning and gram negative bacteraemia, in which the hypophosphataemia results from a combination of prior phosphate depletion, transcellular shifts caused by glucose, insulin and catecholamine infusions and increased anaerobic glycolysis.

Effects of hypophosphataemia

Respiratory effects

Respiratory failure requiring mechanical ventilation has been reported to occur with hypophosphataemia. This is due to a decrease in high energy substrate availability at the cellular level leading to respiratory muscle dysfunction [45]. It has been found that correction of moderate hypophosphataemia significantly improves diaphragmatic function in patients with acute respiratory failure. The administration of phosphate in one study over a 4-h period was associated with an improvement in diaphragmatic function which was apparent immediately, suggesting immediate benefits with phosphate repletion. In patients with severe hypophosphataemia, failure to wean from mechanical ventilation until repletion of phosphorus has been demonstrated [46, 47].

A further effect of hypophosphataemia on respiratory function is its influence on the equilibrium between oxygen and haemoglobin. Erythrocyte concentrations of inorganic phosphate are proportional to plasma concentrations and arise from free diffusion of the ion across the cell membrane. Therefore, phosphate diffuses out of the cell during hypophosphataemia and the resulting intracellular depletion of phosphate serves to inhibit glycolysis and activate adenosine 5′-monophosphate deaminase. This may result in loss of 2,3-diphosphoglycerate (DPG) with a subsequent left shift of the oxygen dissociation curve [48]. *In vitro* studies of the effects of phosphate on the oxygen dissociation curve show that the addition of phosphate produces a right shift. This appears to be produced by two different mechanisms. There is a direct action not mediated by DPG that is immediate and there is also a delayed increase in intracellular 2,3-DPG. This *in vitro* work is supported by the demonstration of an increase in the P 50 of keto-acidotic patients when phosphate was administered, i.e. a right shift of the oxygen dissociation curve producing improved tissue oxygenation [49].

Cardiovascular effects

Hypophosphataemia is thought to produce reversible myocardial dysfunction and may also induce an impaired response to vasopressor agents. One of the first reports of myocardial dysfunction induced by hypophosphataemia was published in 1977 [50]. Seven critically ill patients with serum phosphate levels of less than 0.64 mmol.l^{-1}

were studied. Direct systemic arterial pressure and thermodilution cardiac output were measured before and after the infusion of a solution of potassium phosphate salts. It was shown that the return of serum phosphate to normal was associated with an increase in stroke work that averaged 44%. More recently, the administration of phosphate to a group of hypophosphataemic surgical intensive care patients over a 30-min period was associated with a mean increase in cardiac index of 18% [51]. In both cases phosphate was administered in a small fluid volume and there was no change in central venous pressure or pulmonary capillary wedge pressure during the course of the study. Additionally, there appears to be an association between hypophosphataemia and ventricular dysrhythmias. In a group of 111 patients who had suffered a myocardial infarction and were admitted to a coronary care unit, low serum phosphate was found to be a significant predictor of ventricular tachycardia [52]. Phosphate administration in patients with severe hypophosphataemia, ventricular arrhythmia and no evidence of cardiac disease has been reported to improve or reverse the arrhythmia [53].

Neurological effects

A variety of central and peripheral neurological manifestations of hypophosphataemia have been described. Paraesthesia and tremors have been reported with severe hypophosphataemia and have been shown to resolve with phosphate administration [54]. A severe neuropathy which resembles Guillain–Barré syndrome has been reported in patients with a serum phosphate of less that $0.2\,\text{mmol.l}^{-1}$. A selective slowing of conduction in peripheral nerve fibres has been demonstrated in patients with a phosphate responsive neuropathy [55]. Severe hypophosphataemia has also been associated with seizures and coma. In a report of three cases, hypophosphataemia coincided with a high rate of glucose and water administration. All three patients had other reasons to be comatose, namely liver disease (two cases) and hypothermia (one case). Only two of the three patients showed an improvement in neurological status with phosphate therapy [56]. There has also been a report of severe hypophosphataemia mimicking Wernicke's encephalopathy in an alcoholic patient not admitted to the ICU [57].

Muscular effects

Hypophosphataemia can reduce the strength of skeletal muscle producing symptomatic muscle weakness. A myopathy has been described that mainly affects the proximal muscles and which may be severe enough to produce immobility or pain on motion [14]. A more malignant myopathy associated with rhabdomyolysis and elevated serum creatine phosphokinase concentrations has also been described. However, the role of hypophosphataemia in patients with critical illness myopathy is questionable because patients have developed the disorder in spite of normal serum phosphate concentrations [14, 16].

Haematological effects

In addition to its effects on the ability of haemoglobin to carry oxygen, severe hypophosphataemia also increases the fragility of red cells [48]. This is due to impairment of ATP-dependent processes that are responsible for the maintenance of the shape and deformability of red blood cells. Haemolytic anaemia has been reported to occur in severe hypophosphataemia. All other blood cell lines are affected by hypophosphataemia, although studies demonstrating reduced chemotaxis, phagocytosis and bacterial killing by white cells, as well as reduced platelet function, have only been carried out in dogs [58].

Treatment of hypophosphataemia

Phosphate therapy by the intravenous route is not without complications. High dose, rapid infusions of phosphate have been associated with hyperphosphataemia, hypotension, hypocalcaemia and associated tetany, renal failure and electrocardiographic abnormalities. Phosphate therapy should only be undertaken with extreme caution in patients with renal failure. These complications are based on a handful of case reports involving large doses (e.g. 344 mmol) of phosphate given at excessive rates ($50\,\text{mmol.h}^{-1}$) [59–61]. The type of phosphate preparation is also important and it should be remembered that potassium-containing preparations will cause hyperkalaemia if infused rapidly at high dose.

Various regimens aimed at avoiding these side-effects have been described, two of which will be considered. Vannatta *et al.* described a phosphate therapy regimen for patients with severe hypophosphataemia, normokalaemia, intact renal function and multiple causes of phosphate depletion [62]. The authors concluded that it is safe to infuse $0.32\,\text{mmol.kg}^{-1}$ of phosphate over a 12-h period. If this fails to increase the serum phosphate concentration by more than $0.2\,\text{mmol.l}^{-1}$ after 6 h, then a higher dose, i.e. $0.4–0.5\,\text{mmol.kg}^{-1}$ can be given, also over 12 h. This higher dose was only given to one of their patients. During infusion of phosphate, serum calcium, potassium and phosphate levels were measured regularly and the infusion rate was adjusted accordingly. No patient suffered any side-effects of the infusion. However, the responses of individual serum phosphate levels were variable. A normal plasma phosphate level was achieved in all patients within 36 h. More recently, a regimen for replacement in patients with moderate hypophosphataemia has been described [63] which uses higher doses than those used by Vannatta

et al. The study examined 11 patients on a surgical ICU who had recently undergone a variety of major surgical procedures. All patients had a serum phosphate level of 0.37–0.65 mmol.l^{-1} on entering the study. The regimen involved administration of sodium phosphate 15 mmol (potassium phosphate if potassium < 3.5 mmol.l^{-1}) in 100 ml 0.9% saline over 2 h. Phosphate levels were measured immediately after infusion (i.e. peak concentration) and at 6 h after infusion (i.e. after redistribution). If at 6 h the serum phosphate remained below 0.65 mmol.l^{-1}, a further 15 mmol dose was given. If at 6 h the serum phosphate level was greater than 0.65 mmol.l^{-1}, then it was checked at 18 and 24 h. Repeat phosphate was only administered if the serum level decreased below 0.65 mmol.l^{-1} during this time. The maximum dose in any 24-h period was 45 mmol or three doses. Reasons for terminating the protocol in any patient included biochemical or clinical evidence of hypocalcaemia, reduced urine output and high peak plasma phosphate concentration or phosphate–calcium product. Eight of the 11 patients were corrected to normophosphataemia with a single dose, two patients required one further dose and the last patient required the full 45 mmol dose. No patient suffered from significant adverse side-effects. A further study of the correction of severe hypophosphataemia in patients with septicaemic shock concluded that administration of 20 mmol of glucose phosphate over 30 min was safe and had beneficial haemodynamic effects [64].

It is apparent from the above discussion that severe hypophosphataemia is associated with a number of neuromuscular and cardiovascular sequelae and that phosphate supplementation leads to improved symptoms and clinical parameters. Likewise, moderate hypophosphataemia appears to have a role in impaired diaphragmatic contractility, insulin resistance and ventricular arrhythmias. Hypophosphataemia in the ICU is multifactorial so that factors such as catecholamine infusion or drug treatment of asthma, which on their own are of doubtful significance, become integral in the larger clinical picture of a malnourished patient on TPN with an insulin infusion requiring intermittent frusemide to support urine output. Evidence for the routine correction of hypophosphataemia in the absence of any of the described clinical sequelae is lacking, although lack of evidence does not imply absence of effect. What is needed is a trial or a series of double blind, controlled trials that demonstrate an improved clinical outcome with phosphate therapy. In the absence of such studies, routine phosphate therapy or 'treatment of the numbers' cannot be recommended. However, it is not possible to stop the current widespread practice of phosphate therapy in many ICUs simply because of the absence of well-conducted studies. The emphasis should therefore be directed towards identifying risk factors for hypophosphataemia and correcting the aetiological factors when possible. All patients have a daily requirement for phosphate and this should be provided.

Whilst two regimens for phosphate therapy have been described here there is no evidence to suggest an improved outcome with a higher infusion rate or more rapid correction. The frequent assessment of potassium, calcium, magnesium and phosphate is essential for correct monitoring of the effects of the infusion and the rate and dose of the infusion should therefore be tailored to the results of such measurements.

In summary, further properly designed trials are essential before routine correction of plasma phosphate levels can be recommended on the ICU.

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