

# Hypophosphatemia: an evidence-based approach to its clinical consequences and management

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## SUMMARY

Optimal cellular function is dependent on maintenance of a normal serum phosphorus concentration. Serum phosphorus concentration is affected by several determinants, the most important of which is regulation of phosphorus reabsorption by the kidney. The majority of this reabsorption (80%) occurs in the proximal tubule and is mediated by an isoform of the sodium–phosphate cotransporter (NaPi-II). Parathyroid hormone, via a variety of intracellular signaling cascades leading to NaPi-IIa internalization and downregulation, is the main regulator of renal phosphate reabsorption. Shift of phosphorus from extracellular to intracellular compartments, decreased gastrointestinal absorption, and increased urinary losses, are the primary mechanisms of hypophosphatemia, which affects approximately 2% of hospitalized patients. Hypophosphatemia has been implicated as a cause of rhabdomyolysis, respiratory failure, hemolysis and left ventricular dysfunction. With the exception of ventilated patients, there is little evidence that moderate hypophosphatemia has significant clinical consequences in humans, and aggressive intravenous phosphate replacement is unnecessary. By contrast, patients with severe hypophosphatemia should be treated. Intravenous repletion may be considered, especially for patients who have clinical sequelae of hypophosphatemia.

**KEYWORDS** hemolysis, hypophosphatemia, phosphorus, refeeding, rhabdomyolysis

## REVIEW CRITERIA

We searched a variety of medical literature sources including PubMed, nephrology journals and textbooks, for information on phosphorus homeostasis, clinical consequences of hypophosphatemia, and side effects of parenteral phosphate administration.

## EBM

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## INTRODUCTION

In recent years, numerous studies have evaluated the role of hyperphosphatemia in chronic kidney disease and dialysis patients. Less effort has gone into assessing the clinical significance of hypophosphatemia and scrutinizing its management. Identification of sodium–phosphate cotransporters and regulators of their expression and activity has shed light on the mechanisms of hypophosphatemia in diseases such as hyperparathyroidism, X-linked hypophosphatemia (XLH), autosomal dominant hypophosphatemic rickets and tumor-associated osteomalacia. Hypophosphatemia had previously been linked to rhabdomyolysis, hemolysis, and respiratory and cardiac failure. In spite of the prevalence of hypophosphatemia, these clinical consequences are not commonly encountered.

Severe hypophosphatemia might affect as few as 0.43% of hospitalized patients. Certain populations are likely to include a greater proportion of hypophosphatemic patients—for example, alcoholics (0.9%), septic patients (2.4%), malnourished patients (10.4%), and patients with diabetic ketoacidosis (14.6%). In a retrospective study, severe hypophosphatemia was associated with a fourfold increase in mortality.<sup>1</sup> Evidence for excess morbidity associated with moderate hypophosphatemia is much less definitive. This review critically evaluates the clinical consequences of moderate (1.0–2.5 mg/dl [0.32–0.80 mmol/l]) and severe (<1.0 mg/dl [<0.32 mmol/l]) hypophosphatemia, as well as safety issues regarding rapid correction of a low serum phosphorus concentration.

## PHOSPHATE HOMEOSTASIS

Phosphorus is an essential element. Phosphorus-containing compounds have important roles in cell structure (cell membrane and nucleic acids), cellular metabolism (generation of ATP), regulation of subcellular processes (phosphorylation of key enzymes), and maintenance of acid–base homeostasis (urinary buffering). In the average adult, total body phosphorus content is 700 g,

of which 85% is in bone and teeth, 14% in soft tissues, and only 1% in extracellular fluid. On average, approximately 800–1,400 mg of phosphorus is ingested daily. Normal serum phosphorus concentration is 2.5–4.5 mg/dl (0.80–1.45 mmol/l).<sup>2</sup>

The serum assay measures inorganic orthophosphates, of which 10% are bound to protein, 5% are complexed with calcium and magnesium, and 85% are  $\text{H}_2\text{PO}_4^-$  and  $\text{HPO}_4^{2-}$ . In theory, there are potentially four species of free orthophosphate that can be measured ( $\text{H}_3\text{PO}_4$ ,  $\text{H}_2\text{PO}_4^-$ ,  $\text{HPO}_4^{2-}$  and  $\text{PO}_4^{3-}$ ), but at physiologic pH,  $\text{H}_3\text{PO}_4$  and  $\text{PO}_4^{3-}$  concentrations are negligible. When dietary phosphorus intake is normal, the serum phosphorus concentration exhibits a circadian rhythm, rapidly decreasing in the early morning, reaching a nadir of  $3.3 \pm 0.3$  mg/dl ( $1.1 \pm 0.1$  mmol/l) at 11:00 h, increasing to a plateau at 16:00 h, and peaking at  $4.6 \pm 0.2$  mg/dl ( $1.5 \pm 0.1$  mmol/l) between 1:00 h and 3:00 h.<sup>3</sup> In plasma, phosphorus circulates in monovalent ( $\text{H}_2\text{PO}_4^-$ ) and divalent ( $\text{HPO}_4^{2-}$ ) forms. At systemic pH, the divalent form predominates. In urine, phosphate is an effective buffer, a function of its relatively high tubular concentration and  $\text{pK}_a$  of 6.8, which is close to the pH of urine under normal conditions.

Maintaining normal phosphorus concentrations is essential for optimal cellular function. The kidney and (to a lesser extent) the small intestine are the main organs that maintain phosphorus homeostasis. A large proportion of dietary phosphate is absorbed from the gastrointestinal tract and excreted in urine. In proximal tubule cells and enterocytes, type II sodium–phosphate cotransporters (NaPi-II) are expressed in the apical membrane; their activity rate limits transepithelial phosphate transport. NaPi-II expression in both cell types is controlled by hormones and metabolic factors in response to homeostatic needs.<sup>4</sup>

Intestinal phosphorus absorption occurs through both cellular and paracellular pathways. Transepithelial phosphate transport across intact intestinal epithelium is driven by an active sodium-dependent process. Compartmental analysis indicates that phosphate entering the cell across the brush border is transported through the cell and sequestered from the intracellular phosphorus pool. The form of phosphorus absorbed is not known, but both luminal pH and ionic strength determine the species available for absorption.<sup>5</sup> A low phosphorus diet and

1,25(OH)<sub>2</sub> vitamin D<sub>3</sub> are the two most important positive regulators of the intestinal isoform (NaPi-IIb). A low phosphorus diet stimulates renal 1 $\alpha$ -hydroxylase, which increases levels of 1,25(OH)<sub>2</sub> vitamin D<sub>3</sub>. Recent studies of transgenic mice demonstrated that adaptation of NaPi-IIb to a low phosphorus diet occurs independently of vitamin D.<sup>6,7</sup>

Metabolic acidosis, estrogen and epidermal growth factor (EGF) enhance expression of NaPi-IIb.<sup>8,9</sup> A novel signaling pathway in regulation of intestinal phosphate transport involves serum and glucocorticoid-inducible kinase 1, and the ubiquitin ligase Nedd4-2. Ubiquitination of target proteins tags them for removal from the cell membrane and for degradation in PROTEASOMES. Serum and glucocorticoid-inducible kinase 1 stimulates phosphate transport, at least in part, by phosphorylating Nedd4-2, thereby inhibiting binding of this ubiquitin ligase to NaPi-IIb.<sup>10</sup> NaPi-IIb is not ubiquitinated and its expression in the membrane is increased.

In the kidney, phosphorus homeostasis is regulated primarily via control of phosphorus reabsorption across the proximal tubule apical membrane. When levels of dietary phosphorus are normal and parathyroid function is intact, about 80% of filtered phosphate is reabsorbed.<sup>5</sup> Low dietary  $\text{P}_i$  intake leads to near complete reabsorption of filtered  $\text{P}_i$ , whereas high dietary  $\text{P}_i$  intake results in decreased proximal tubule  $\text{P}_i$  reabsorption.<sup>11</sup> Three sodium–phosphorus cotransporters are expressed in proximal tubule cells. NaPi-I and NaPi-II are located in the apical membrane, whereas NaPi-III is thought to be expressed in the basolateral membrane, where it functions as a ‘housekeeping’ cotransporter.

There are three isoforms of NaPi-II: a, b and c. NaPi-IIa and NaPi-IIb are electrogenic. NaPi-IIa and NaPi-IIc are expressed exclusively in the brush-border membrane of proximal tubule cells, whereas NaPi-IIb is responsible for intestinal absorption of phosphate. About 70% of proximal tubule phosphate reabsorption is mediated by NaPi-IIa. Parathyroid hormone (PTH) is the primary regulator of phosphate reabsorption in kidney.

Hormonal (PTH and atrial natriuretic peptide) and nonhormonal (nitric oxide) factors activate intracellular signaling cascades leading to internalization of NaPi-IIa. Internalization occurs via CLATHRIN-coated structures, early endosomes and, subsequently, lysosomal degradation of

## GLOSSARY

### PKa

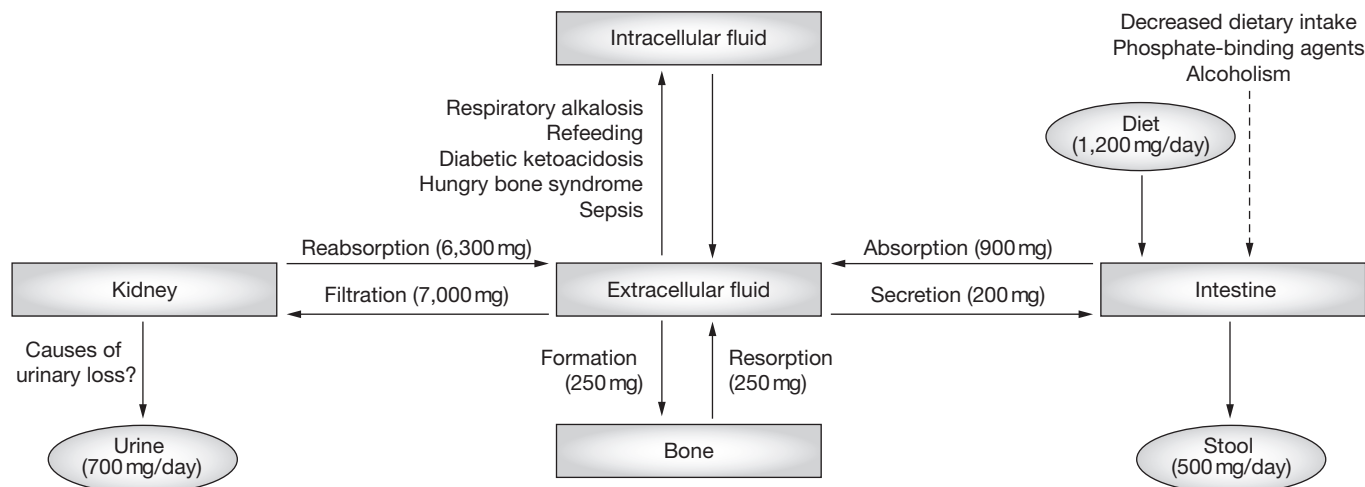
The negative logarithm of the dissociation constant, which represents the tendency of a substance to reversibly separate into smaller constituents

### PROTEASOMES

The protease part of the ubiquitin system, which is the proteolytic system in eukaryotic cells that degrades polyubiquitylated proteins

### CLATHRIN

A primary protein constituent of the ‘coats’ of endocytic vesicles that can bind specific membrane receptors



**Figure 1** Phosphate fluxes and causes of hypophosphatemia. Decreased intake (e.g. as an effect of phosphate-binding agents), redistribution (e.g. into the intracellular compartment in response to respiratory alkalosis) and increased excretion (e.g. in the urine) of phosphorus are the mechanisms underlying hypophosphatemia.

**GLOSSARY**

**PHOSPHATONINS**

Hormones that regulate phosphate metabolism (e.g. fibroblast growth factor 23 and frizzled-related protein 4)

NaPi-IIa. In renal proximal tubule cells, PTH binding to apical receptors activates protein kinase C (PKC), and binding to basolateral PTH receptors activates both PKC and cyclic AMP/protein kinase A (PKA) pathways. The exact steps involved in internalization of NaPi-IIa after PKA and PKC activation are not clear; however, mitogen-activated protein (MAP) kinase (extracellular receptor kinase ERK1/2) might be involved. ERK1/2 inhibition prevents PTH-induced internalization of NaPi-IIa, and also completely or partially prevents NaPi-IIa down-regulation upon pharmacologic activation of PKA and PKC, respectively. This mechanism indicates that the PKA and PKC pathways converge, at least partially, at the level of ERK1/2.<sup>12</sup>

Insulin enhances proximal tubule P<sub>i</sub> reabsorption by stimulating brush-border membrane Na–P<sub>i</sub> cotransport, and prevents the phosphaturic action of PTH. Growth hormone stimulates proximal tubule Na–P<sub>i</sub> cotransport, an effect that is partially mediated by insulin-like growth factor 1 (IGF1). EGF stimulates P<sub>i</sub> reabsorption in perfused proximal tubules, but inhibits P<sub>i</sub> transport in opossum kidney cells. Thyroid hormone increases proximal tubule P<sub>i</sub> reabsorption by specifically enhancing brush-border membrane Na–P<sub>i</sub> cotransport. Calcitonin and glucocorticoids inhibit proximal tubule brush-border reabsorption.<sup>11</sup>

Several PHOSPHATONINS—including fibroblast growth factor 23 (FGF23), frizzled-related protein 4 (FRP4) and matrix extracellular

phosphoglycoprotein (MEPE)—associated with different pathophysiological states of renal phosphate handling, also influence apical expression of NaPi-IIa.<sup>13</sup> Reduced or increased phosphate intake results in increased or decreased expression of NaPi-IIa, respectively.

**MECHANISMS OF HYPOPHOSPHATEMIA**

Serum phosphorus concentration is determined by several factors (Figure 1). Dietary phosphorus intake, stage of growth and time of day contribute to the variability of fasting serum phosphorus concentrations. Hypophosphatemia is observed in approximately 2% of hospitalized patients,<sup>14</sup> and can be related to decreased intestinal absorption of phosphorus, redistribution of phosphorus from the extracellular to the intracellular compartment, increased loss of phosphorus through the kidneys, or any combination of these processes.<sup>2</sup> The most common manifestation of hypophosphatemia in hospitalized patients is secondary to redistribution of phosphorus as a result of respiratory alkalosis.

**Decreased intake of phosphorus**

It is rare for decreased dietary intake alone to cause hypophosphatemia, probably because renal phosphate reabsorption is enhanced to compensate for decreased intake. On the other hand, malabsorption and phosphate binders can decrease intestinal phosphate absorption and result in hypophosphatemia.<sup>15,16</sup> In a study of normal human volunteers it took

approximately 3 months for the combination of a low phosphorus diet and antacids to reduce serum phosphorus concentration to 1.0 mg/dl (0.3 mmol/l).<sup>17</sup>

### Redistribution of phosphorus

Hypophosphatemia secondary to phosphorus redistribution is commonly caused by respiratory alkalosis and refeeding of malnourished patients. Acute respiratory alkalosis and metabolic alkalosis decrease serum phosphorus concentration. The reduction is much greater in respiratory alkalosis than in metabolic alkalosis of comparable severity.<sup>18,19</sup> During respiratory alkalosis, intracellular CO<sub>2</sub> decreases, causing intracellular pH to rise. This mechanism stimulates the glycolytic pathway, specifically phosphofructokinase, a key rate-limiting enzyme of glycolysis. Production of sugar phosphates is enhanced, which in turn induces intracellular phosphorus entry, thus decreasing serum phosphorus concentration.<sup>5</sup>

Respiratory alkalosis enhances phosphorus uptake by muscle. The kidney responds by increasing phosphate reabsorption, independent of serum phosphorus concentration and becomes refractory to the phosphaturic effect of PTH. This refractoriness is due to decreased pCO<sub>2</sub> rather than to the concomitant extracellular alkalosis.<sup>19</sup> Hypophosphatemia is also associated with other medical conditions of which hyperventilation is a feature, such as sepsis, heat stroke and hepatic coma.<sup>20–22</sup>

One of the earliest reports of refeeding syndrome was in starved Japanese prisoners of war.<sup>23</sup> Patients with anorexia nervosa, and those subject to prolonged fasting or parenteral or enteral feeding after major surgery, are well recognized modern counterparts of the starved prisoners. The proposed mechanism of hypophosphatemia in these patients is increased insulin release that causes an intracellular shift in distribution of phosphorus. Enhanced synthesis of ATP, 2,3-diphosphoglycerate (DPG) and creatine phosphokinase (CPK) might contribute to the hypophosphatemia associated with refeeding syndrome.<sup>24</sup> Early studies in dogs and humans showed that the serum phosphorus concentrations of normal dogs and men drop after ingestion or infusion of glucose. Fiske was the first to call attention to this relationship between carbohydrates and serum phosphorus concentration.<sup>25</sup> Sokhey found that the decrease in urinary phosphate excretion after

infusion of glucose was almost as great as that induced by insulin.<sup>26</sup> Glucose injections in dogs made diabetic by pancreatectomy did not cause serum phosphorus concentration to change unless insulin was coinjected.<sup>27</sup> In the same study of a series of hepatectomized animals, hypophosphatemia after glucose infusion was observed, but not in animals from which all striated muscle had been removed. The investigators concluded that the site of phosphorus sequestration is muscle.

Cellular sequestration of phosphorus and hypophosphatemia are also observed in leukemia patients with rapidly replicating tumor cells, following hematopoietic reconstitution after allogeneic peripheral blood stem cell transplantation, and after parathyroidectomy (the so-called 'hungry bone syndrome').<sup>28–30</sup> Intracellular shifts of phosphorus secondary to correction of respiratory acidosis can result in hypophosphatemia after institution of mechanical ventilation in chronic obstructive pulmonary disease (COPD) patients.<sup>31</sup> This hypophosphatemia occurs upon correction to normal pH.

### Increased urinary excretion of phosphorus

Enhanced urinary excretion of phosphate occurs in patients with primary hyperparathyroidism, as well as in those with secondary hyperparathyroidism associated with hypocalcemia and intact renal function. PTH signal transduction via cAMP-dependent and cAMP-independent pathways promotes internalization of NaPi-IIa cotransporters from the cell membrane and their subsequent degradation. This process decreases Na–Pi cotransport activity.<sup>32</sup> The amino-terminal region of PTH-related protein has significant homology with that of PTH. As such, both substances have a similar effect on excretion of urinary phosphorus and nephrogenous cAMP *in vivo*, and on sodium-dependent phosphate transport in brush-border membrane vesicles *in vitro*.<sup>33</sup>

Hypophosphatemia associated with primary hyperparathyroidism is usually of moderate severity; increased urinary phosphate excretion is balanced by mobilization of phosphate from bone and enhanced intestinal absorption. Serum phosphorus concentrations are seldom less than 2.0 mg/dl (0.6 mmol/l) unless patients' phosphorus intake is low or they simultaneously ingest phosphate-binding antacids.<sup>34</sup>

Impaired reabsorption of phosphate by proximal tubules and subsequent hypophosphatemia can

### GLOSSARY

pCO<sub>2</sub>  
Partial pressure of carbon dioxide



and low serum phosphorus concentrations. Osteomalacic muscle weakness is not myopathic; rather, it is due to nonspecific atrophy probably caused by disuse and malnutrition, especially in states of nutritional deficiency.<sup>57</sup> The small number of case reports and coexistent metabolic abnormalities that have been implicated as etiologies of rhabdomyolysis make it difficult to establish a strong cause-and-effect relationship between hypophosphatemia and rhabdomyolysis in any individual patient. Most case report patients have had moderate hypophosphatemia. It seems likely that moderate and severe hypophosphatemia are frequently associated with mild subclinical rhabdomyolysis that infrequently results in clinical sequelae.

### Hemolysis

Hypophosphatemia can alter red cell glycolytic intermediates and oxygen transport. These alterations include markedly reducing levels of erythrocyte ATP and 2,3-DPG, which enhances the affinity of oxygen for hemoglobin (reflected as a drop in  $p_{50}$ ). The fall in ATP decreases red cell hexokinase activity and increases phosphofructokinase activity. As a result, erythrocyte concentrations of glucose-6-phosphate and fructose-6-phosphate are reduced, and more triose phosphates accumulate.<sup>58,59</sup> ATP is required for maintenance of erythrocyte biconcavity and viability in the circulation.<sup>60,61</sup> ATP depletion has been associated with decreased cell membrane deformability and life span,<sup>62</sup> but there have been few human case reports of hypophosphatemia associated with hemolytic anemia (phosphorus concentration  $\leq 1.7$  mg/dl [0.54 mmol/l]).<sup>63–66</sup> In these few cases, serum phosphorus concentration was either rapidly falling (refeeding) or severely depressed ( $\leq 0.2$  mg/dl [0.06 mmol/l]).

### Leukocyte dysfunction

Hypophosphatemia can also reduce the ATP content of leukocytes and ameliorate neutrophil phagocytosis, intracellular killing, consumption of oxygen and generation of superoxide during phagocytosis.<sup>67,68</sup> The high rate of sepsis during hyperalimentation might result, in part, from acquired dysfunctions in leukocyte chemotaxis and phagocytosis, secondary to hypophosphatemia. That these *in vitro* studies are relevant to hyperalimentation-associated hypophosphatemia has been indicated by observation of a 44-year-old woman. In this patient with assumed occult malignancy, development of

hypophosphatemia (serum phosphorus concentration of 2.0 mg/dl [0.6 mmol/l]) 2 days after hyperalimentation was accompanied by pneumonia and empyema. Leukocyte studies revealed diminished ATP levels (to roughly half normal) and impaired chemotaxis. Incubation with phosphate and adenosine reversed these changes. After termination of hyperalimentation and phosphate supplements, serum phosphorus concentration, leukocyte ATP and leukocyte chemotaxis rapidly returned to normal and pneumonia and empyema were resolved.<sup>67</sup>

In another study, the relationship between serum phosphorus concentration and intracellular concentrations of inorganic phosphorus and ATP in red blood cells, leukocytes and platelets of patients with hypophosphatemia secondary to vitamin-D-resistant rickets was studied. Six patients with low serum phosphorus concentrations ( $< 3.1$  mg/dl [1 mmol/l]) were included. Intracellular ATP levels were maintained within normal range, even though plasma and intracellular phosphorus concentrations were low.<sup>69</sup> So, although there is good evidence from animal models that hypophosphatemia impairs leukocyte function, there is no compelling data in animals or humans that this impairment is associated with an increased risk of infection.

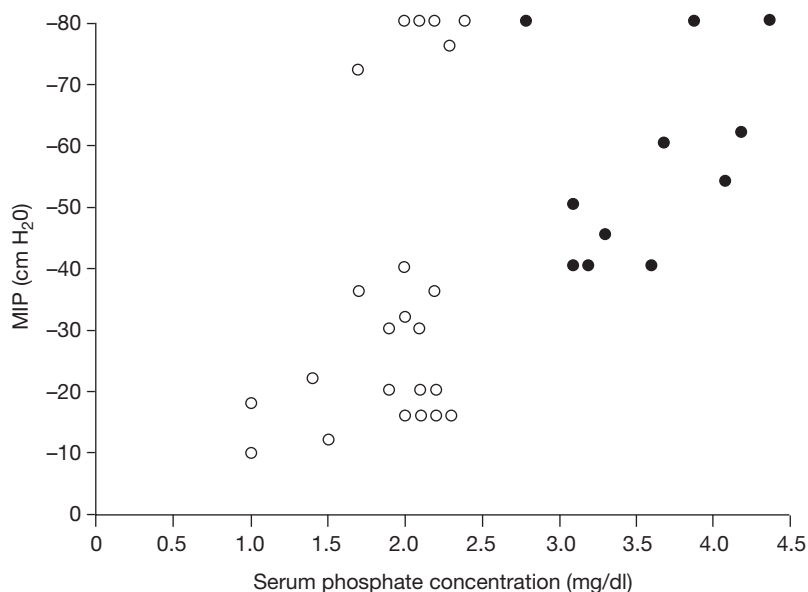
### Respiratory failure

Hypophosphatemia might cause respiratory failure. In one study, maximal inspiratory and expiratory pressures of hospitalized patients with serum phosphate concentrations less than 2.5 mg/dl (0.8 mmol/l) were measured at the bedside. These measurements were repeated daily during phosphate repletion until serum phosphorus concentration reached the normal range. In most hypophosphatemic patients—but no normophosphatemic patients—respiratory muscle weakness (defined as low maximal inspiratory pressure or low maximal expiratory pressure) was detected. Respiratory muscle strength improved after phosphate repletion. The mean serum phosphorus concentration of these 23 patients was  $1.9 \pm 0.4$  mg/dl ( $0.61 \pm 0.13$  mmol/l). Twelve patients had a serum phosphorus concentration of up to 2.0 mg/dl (0.64 mmol/l) and four had a serum phosphorus concentration between 1.0 and 1.5 mg/dl (0.3–0.5 mmol/l). There was a correlation between the decrease in maximal inspiratory pressures and the severity of hypophosphatemia (Figure 2).<sup>70</sup>

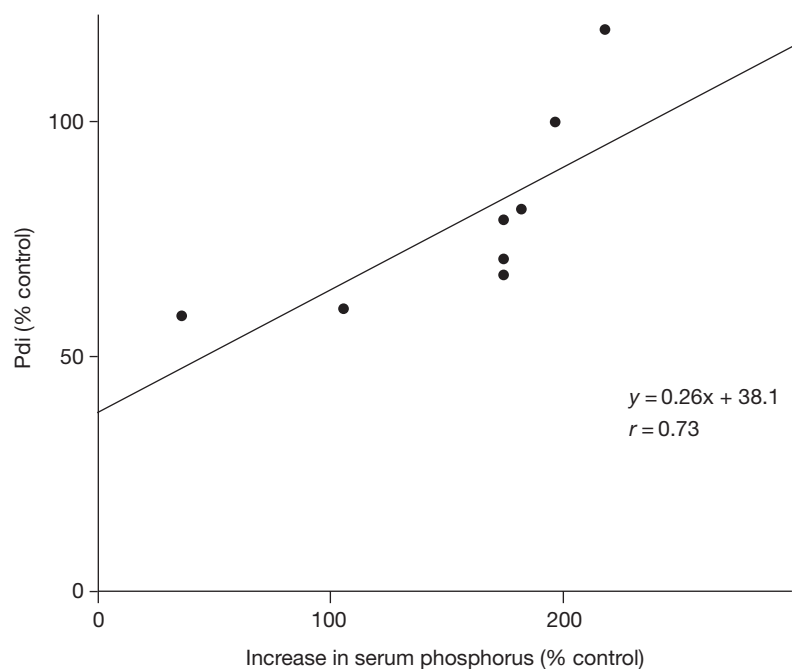
### GLOSSARY

#### $p_{50}$

The partial pressure of oxygen at which hemoglobin is 50% saturated with oxygen



**Figure 2** Correlation between the decrease in maximal inspiratory pressures and the severity of hypophosphatemia. Maximal inspiratory pressures at study entry are shown, plotted as a function of initial serum phosphate concentrations for hypophosphatemic patients (open symbols) and normophosphatemic control patients (filled symbols);  $r=0.50$ ,  $P<0.02$ . Reproduced with permission from reference 70 © (1988) Excerpta Medica, Inc. MIP, maximal inspiratory pressure.



**Figure 3** Hypophosphatemia impairs the contractile properties of the diaphragm during acute respiratory failure. Individual increases in transdiaphragmatic pressure are generated during phrenic stimulation after correction of hypophosphatemia, as a function of the concomitant increase in serum phosphorus concentration. The solid line represents the computed regression for the experimental data. The coefficient of correlation ( $r=0.73$ ) was significant ( $P<0.0005$ ). Reproduced with permission from reference 71 © (1985) Massachusetts Medical Society. Pdi, increases in transdiaphragmatic pressure.

Hypophosphatemia also impairs the contractile properties of the diaphragm during acute respiratory failure.<sup>71</sup> In a group of eight patients with moderate hypophosphatemia and respiratory failure or mechanical ventilation, diaphragmatic function was evaluated prior to and following infusion of phosphorus. Transdiaphragmatic pressure generated at functional residual capacity during bilateral supramaximal electrical stimulation of the phrenic nerves was measured. Transdiaphragmatic pressure increased in all eight patients and the increase correlated with the change in serum phosphorus concentration (Figure 3).<sup>71</sup> In another study, hypophosphatemia ( $\leq 2.5$  mg/dl [0.8 mmol/l]) was found in 34 (21.5%) of 158 patients with respiratory illness; hypophosphatemia was not associated with the severity of the respiratory illness. Indices of renal phosphorus handling indicated inappropriately high rates of phosphate excretion given the degree of hypophosphatemia (low percentage tubular reabsorption of phosphorus, and low renal phosphate threshold/glomerular filtration rate values). The prevalence of hypophosphatemia was significantly greater among COPD patients taking one or more drugs that stimulate renal phosphate excretion (xanthine derivatives, corticosteroids, loop diuretics,  $\beta$ 2-adrenergic bronchodilators). Despite the phosphorus content of both peripheral and respiratory muscles of COPD patients being reduced in another series, in this study a relationship between muscle and serum phosphorus concentrations was demonstrable in the case of peripheral muscles only.<sup>72,73</sup>

Hypophosphatemia as a cause of respiratory failure and refractory weaning from the ventilator has been reported, albeit infrequently. Most patients have had severe hypophosphatemia ( $\leq 1.0$  mg/dl [0.3 mmol/l]). Weaning from the ventilator was achieved following correction of hypophosphatemia.<sup>74–77</sup> Diaphragmatic contractility can be improved by correcting severe and moderate hypophosphatemia. We recommend evaluating the serum phosphorus concentration carefully in intubated patients and correcting it to within the normal range if possible.

**Impaired myocardial performance**

Reversible depression of myocardial performance in dogs with moderate diet-induced phosphorus depletion (serum phosphorus concentration decreased from  $5.1 \pm 0.1$  mg/dl [ $1.63 \pm 0.03$  mmol/l])

on day 0 to  $0.9 \pm 0.1$  mg/dl [ $0.28 \pm 0.03$  mmol/l] on day 35) has been demonstrated.<sup>78</sup> Human studies of the effect of hypophosphatemia on myocardial function, however, show conflicting results. Cardiac output, as thermodilution and calculated stroke work, was measured in seven patients with severe hypophosphatemia before, during and after repletion with an intravenous potassium phosphate solution. Return of serum phosphorus concentration to normal improved myocardial stroke work independently of the Starling effect.<sup>79</sup> In a later study, however, hypophosphatemia alone did not cause left ventricular dysfunction.<sup>80</sup> One explanation for this discrepancy might be the different mean serum phosphorus concentrations of patients in the two studies ( $0.97$  mg/dl [ $0.31$  mmol/l] in the first and  $1.88$  mg/dl [ $0.61$  mmol/l] in the second). The validity of this explanation was confirmed by Davis *et al.*, who showed that improvement in left ventricular performance after correction of hypophosphatemia occurred only in patients with severe hypophosphatemia ( $0.90 \pm 0.15$  mg/dl [ $0.29 \pm 0.05$  mmol/l]) and not in those with moderate hypophosphatemia ( $1.40 \pm 0.11$  mg/dl [ $0.45 \pm 0.03$  mmol/l]).<sup>81</sup>

To determine whether chronic moderate hypophosphatemia causes myocardial dysfunction, 10 patients aged 5–18 years with X-linked hypophosphatemic rickets and a mean serum phosphorus concentration of  $2.6 \pm 0.5$  mg/dl ( $0.83 \pm 0.16$  mmol/l) were examined. There was no evidence of left ventricular dysfunction (measured by echocardiography) in this human model of clinically significant long-standing hypophosphatemia. The lowest serum phosphorus concentration in this group of patients was  $1.5$  mg/dl ( $0.5$  mmol/l).<sup>82</sup> In another study, low serum phosphorus concentration ( $<2.6$  mg/dl [ $0.8$  mmol/l]) was a significant predictor of ventricular tachycardia in patients with a recent myocardial infarction.<sup>83</sup>

Correction of severe hypophosphatemia increases myocardial contractility by approximately 20%. The effect is variable between patients; some have minimal or no response, whereas large effects are observed in others. Moderate hypophosphatemia probably has very little effect on myocardial contractility.

### Diabetic ketoacidosis

Hypophosphatemia is associated with impaired glucose metabolism in both hyperglycemic

and euglycemic states. This effect is primarily a reflection of decreased tissue sensitivity to insulin.<sup>84</sup> Serum phosphorus concentration can be normal or slightly elevated in patients with untreated diabetic ketoacidosis, despite the fact that renal phosphate excretion is increased. Seldin *et al.* assessed the metabolism of glucose and cellular balance of electrolytes in diabetic acidosis. Translocation of phosphorus from the intracellular to the extracellular fluid was most rapid during the early stages, falling during treatment of ketoacidosis with insulin and fluids. Initial phosphaturia also decreased after correction of ketoacidosis.<sup>85</sup>

In another study, ketoacidosis inhibited the glycolytic enzyme phosphofructokinase in erythrocytes. As a consequence, the concentrations of glycolytic intermediates proximal to this step were increased; levels of distal intermediates, including 2,3-bisphosphoglycerate, were decreased. Although administration of insulin produced hypophosphatemia within 8–12 h, which persisted for 24 h or more, *in vitro* studies showed that acidemia was primarily responsible for the inhibition of phosphofructokinase.<sup>86</sup> Once again, while acute hemolytic anemia secondary to severe hypophosphatemia in diabetic ketoacidosis has been reported,<sup>87</sup> this is not a common clinical finding.

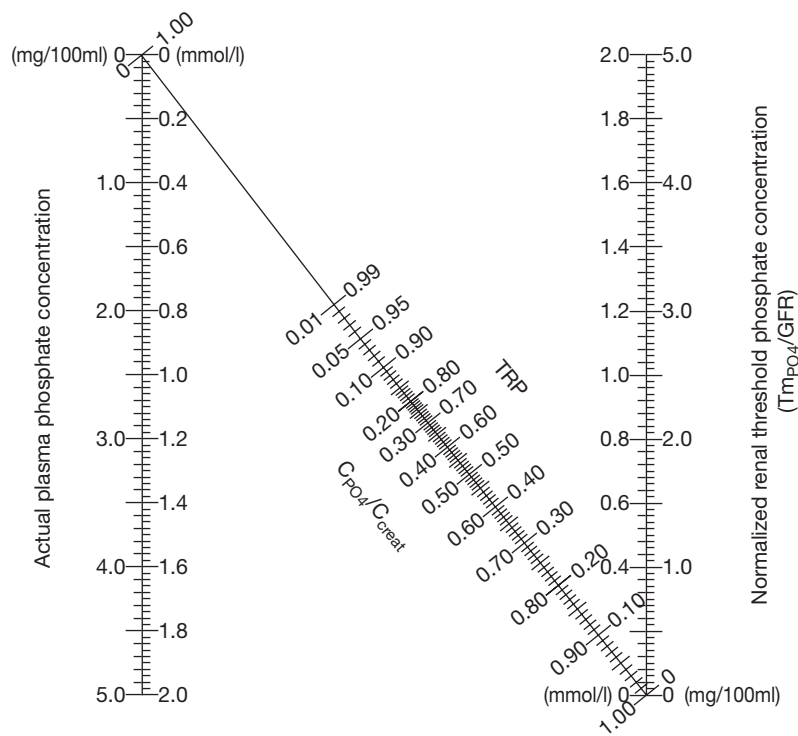
### Perturbed central nervous system

There are several case reports indicating an association between hypophosphatemia and neurological problems such as altered mental status and polyneuropathy including cranial nerves, seizure and central pontine myelinolysis.<sup>88–90</sup> Muscular weakness, paresthesia, convulsions and coma were reported in three starved patients who developed hypophosphatemia (mean serum phosphorus concentration  $0.3$  mg/dl [ $0.1$  mmol/l]) during parenteral hyperalimentation.<sup>91</sup> In most cases of neurological deficit associated with hypophosphatemia, serum phosphorus concentrations were below  $1.0$  mg/dl ( $0.3$  mmol/l). A few cases of proximal muscle weakness have been associated with serum phosphorus concentrations of  $2.2$ – $3.2$  mg/dl ( $0.7$ – $1.0$  mmol/l).<sup>92</sup>

### MANAGEMENT OF HYPOPHOSPHATEMIA

One must keep in mind that serum phosphorus concentration might not be a reliable indicator of total body phosphorus, because most phosphorus is stored intracellularly.<sup>2</sup> The first





**Figure 4** Nomogram for derivation of normalized renal threshold phosphate concentration. Reproduced with permission from reference 94 © (1975) Elsevier.  $C_{PO_4}$ , phosphate clearance;  $C_{creat}$ , creatinine clearance; GFR, glomerular filtration rate;  $Tm_{PO_4}$ , renal phosphate threshold; TRP, fractional tubular reabsorption of phosphate.

step in management of the hypophosphatemic patient is therefore to determine whether the low serum phosphorus concentration is the result of a true total body phosphorus deficiency or a reflection of an intracellular shift of phosphorus (as in respiratory alkalosis). Measuring intracellular phosphorus and ATP might be helpful in differentiating between these conditions, but such tests are not readily available. Also, a study of intracellular orthophosphate concentration in human muscle cells and erythrocytes by  $^{31}P$  nuclear magnetic resonance spectroscopy and selective chemical assay indicated that these cells can buffer or regulate cytoplasmic phosphorus concentration when the extracellular concentration is perturbed.<sup>93</sup>

A combination of history taking, physical examination and laboratory tests—including serum calcium concentration, arterial blood gases, urinary phosphorus and creatinine concentrations to calculate the renal phosphate threshold—can identify the cause of hypophosphatemia in most cases. Indices of renal tubular reabsorption

of phosphate such as phosphate clearance ( $C_{PO_4}$ ), phosphate : creatinine clearance ratio ( $C_{PO_4}:C_{creat}$ ) and fractional tubular reabsorption of phosphate, fail to discriminate between the three major factors that determine renal phosphate excretion (i.e. net inflow from gut, bone and soft tissue, tubular reabsorption, and glomerular filtration rate). By calculating tubular reabsorption of phosphate ( $1 - C_{PO_4}:C_{creat}$ ) and using a nomogram (Figure 4), renal phosphate threshold normalized for the glomerular filtration rate ( $Tm_{Pi} = Tm_{PO_4} / GFR$ ) can be calculated. The normal range is 2.5–4.2 mg per 100 ml.<sup>94</sup>

Low  $Tm_{Pi}$  in the hypophosphatemic patient indicates an appropriate renal response to hypophosphatemia, and usually implicates gastrointestinal loss or intracellular shift. A high  $Tm_{Pi}$  in hypophosphatemia is indicative of increased renal excretion secondary to a PTH-mediated mechanism, Fanconi syndrome, XLH, autosomal dominant hypophosphatemic rickets or oncogenic osteomalacia. As there is little evidence that moderate hypophosphatemia (1.0–2.5 mg/dl [0.3–0.8 mmol/l]) has significant clinical consequences in humans, there is no need for aggressive intravenous phosphate replacement. This is particularly true in situations associated with intracellular shifts of phosphorus. As there is evidence indicating that respiratory parameters of ventilated patients improve after treatment of moderate hypophosphatemia, phosphorus should be repleted into the normal range in this clinical setting.

The role of phosphate replacement in management of diabetic ketoacidosis is controversial, particularly with respect to the effect of phosphate intermediates on tissue oxygenation. From a prospective, randomized study it was concluded that phosphate repletion might accelerate regeneration of erythrocyte 2,3-DPG in patients with diabetic ketoacidosis, but repletion had no demonstrable influence on tissue oxygenation or clinical response to low-dose insulin therapy. Phosphate replacement therapy exacerbated hypocalcemia, a finding that warrants caution when contemplating use of this treatment.<sup>95</sup>

It is generally recommended that patients with severe hypophosphatemia (<1.0 mg/dl [0.3 mmol/l]) are treated to avoid potential detrimental consequences. Administration of inorganic phosphate shows that the phosphorus storage compartments are heterogeneous. Phosphate enters several pools at varying rates

that can be altered by many factors, including simultaneous administration of glucose or insulin.<sup>96</sup> Lentz and colleagues proposed that, in a given hypophosphatemic patient, rapid shifting of phosphorus between compartments can occur during phosphorus infusion. Accordingly, neither the phosphorus compartments utilized, nor the body's deficit and response to replacement, can be predicted. These authors recommended parenteral therapy for all causes of hypophosphatemia, at an initial dose of 0.08 mmol/kg body weight (2.5 mg/kg body weight) if the onset was recent and the case uncomplicated, or 0.16 mmol/kg body weight (5.0 mg/kg body weight) if hypophosphatemia was long-standing and caused by multiple factors. They also suggest that each dose be given intravenously over 6 h.<sup>97</sup>

Ten adult normocalcemic patients with severe hypophosphatemia ( $\leq 1.0$  mg/dl [0.3 mmol/l]), two or more clinical reasons for hypophosphatemia, and normal renal function, were studied prospectively. These patients were treated with 0.32 mmol phosphorus per kg of body weight infused intravenously over 12 h. The investigators concluded that this dose was safe and efficacious.<sup>98</sup> By contrast, intravenous phosphate therapy for hypophosphatemia has been reported to cause a precipitous fall in serum calcium concentration, hypotension and acute renal failure.<sup>99</sup> In addition to the total dose, rate of administration has always been a concern in the parenteral treatment of hypophosphatemia. Potassium phosphate at a rate of 20 mmol/h (15 mmol/h elemental phosphorus) for either 1 or 2 h was administered to 85 patients. Vital signs and cardiac rhythm were continuously monitored. There were no changes in heart rhythm, serum calcium or magnesium concentrations, blood pressure or clinical status.<sup>100</sup> In a similar study in a surgical intensive care unit, 11 patients with serum phosphorus concentrations between 1.6 and 1.9 mg/dl (0.5–0.6 mmol/l) were treated with 15 mmol intravenous sodium or potassium (if serum potassium concentration was  $< 3.5$  mmol/l) phosphate over 2 h. The same dose could be repeatedly administered to a maximum of 45 mmol in a 24 h period if either the 6 h or 18–24 h follow-up postinfusion serum phosphorus concentration remained at below 2 mg/dl (0.6 mmol/l). All patients were successfully repleted using this protocol without any major adverse effects.<sup>101</sup>

**Box 1** Indications for different modes of therapy in hypophosphatemia.

- Severe hypophosphatemia ( $< 1.0$  mg/dl [0.3 mmol/l]) in critically ill, intubated patients or those with clinical sequelae of hypophosphatemia (e.g. hemolysis) should be managed with intravenous replacement therapy (0.08–0.16 mmol/kg) over 2–6 h
- Moderate hypophosphatemia (1.0–2.5 mg/dl [0.3–0.8 mmol/l]) in patients on a ventilator should be managed with intravenous replacement therapy (0.08–0.16 mmol/kg) over 2–6 h
- Moderate hypophosphatemia (1.0–2.5 mg/dl [0.3–0.8 mmol/l]) in nonventilated patients should be managed with oral replacement therapy (1,000 mg/day)
- Mild hypophosphatemia should be managed with oral replacement therapy (1,000 mg/day)

Although several studies support treatment of hypophosphatemic patients with rapid phosphorus infusion, the use of intravenous phosphorus-containing solutions is best justified in critically ill intubated patients when it has been shown that hypophosphatemia might prolong intubation. Other clinical sequelae, such as severe hemolytic anemia, might also warrant rapid repletion. Patients with moderate hypophosphatemia should be repleted orally unless they are on a ventilator (Box 1).

## CONCLUSIONS

Hypophosphatemia in hospitalized patients is often associated with refeeding, chronic alcohol use, antacid therapy, respiratory alkalosis, correction of chronic respiratory acidosis and diabetic ketoacidosis. Severe hypophosphatemia ( $\leq 1.0$  mg/dl [0.3 mmol/l]) can cause respiratory failure, delay weaning from the ventilator, and increase the duration of intensive care and hospitalization. Myocardial contractility is impaired when serum phosphorus concentration falls below 1.0 mg/dl (0.3 mmol/l), but this does not seem to cause clinical congestive heart failure. The response to phosphorus repletion is highly variable between patients. Hemolytic anemia has been reported in patients with rapidly falling serum phosphorus concentration or very severe hypophosphatemia. Moderate hypophosphatemia has no effect on myocardial contractility but does reduce diaphragmatic contractility.

**KEY POINTS**

- The kidney is a key regulator of phosphorus homeostasis
- Hypophosphatemia results from inadequate phosphorus intake/intestinal absorption, redistribution from extracellular to intracellular compartments, and/or excessive excretion
- Aggressive intravenous phosphate repletion (0.08–0.16 mmol/kg over 2–6 h) is generally only necessary when hypophosphatemia is severe
- Untreated severe hypophosphatemia (serum phosphorus <1.0 mg/dl [0.32 mmol/l]) can lead to hemolysis, rhabdomyolysis, respiratory failure and left ventricular dysfunction

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**Competing interests**

The authors declared they have no competing interests.

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