Clinical Review

Clinical Disorders of Phosphorus Metabolism

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Deranged phosphorus metabolism is commonly encountered in clinical medicine. Disturbances in phosphate intake, excretion and transcellular shift account for the abnormal serum levels. As a result of the essential role played by phosphate in intracellular metabolism, the clinical manifestations of hypophosphatemia and hyperphosphatemia are extensive. An understanding of the pathophysiology of various phosphate disorders is helpful in guiding therapeutic decisions.

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In human tissues phosphorus exists in both organic and inorganic forms. Organic phosphorus comprises the phospholipids, nucleic acids and phosphoproteins that are needed for cellular integrity and metabolism. Intracellular inorganic phosphorus provides substrate for the synthesis of energy-generating compounds including adenosine triphosphate (ATP). Serum phosphorus is mostly in inorganic forms consisting of orthophosphate ions. In adults the normal serum phosphorus level ranges from 3.0 to 4.5 mg per dl. The human body contains about 600 to 700 grams of phosphorus, of which 80% to 85% is found in bone, 10% to 15% in soft tissue and only about 1% in the extracellular fluid (ECF).[1] In normal persons, the serum phosphorus level undergoes a diurnal variation of as much as 1.5 mg per dl, with the nadir between 8 AM and noon and the peak between 2 AM and 6 AM.[2] These fluctuations are likely the result of meals and a circadian rhythm of parathyroid hormone secretion.

The average dietary phosphorus intake varies from 800 to 1,200 mg per day. The percentage of dietary phosphorus absorbed by the intestine remains remarkably constant at 60% to 65% over a wide range of phosphorus intake (4 to 30 mg per kg per day).[3] Thus, the dietary intake of phosphorus is an important determinant of the amount of phosphorus absorbed. In addition, phosphate absorption is regulated by vitamin D, mainly through the action of its active metabolite, 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D_3). Phosphorus is present in most food, especially red meat, dairy products, fish, poultry and the legumes. Phosphorus is absorbed as phosphate ions from the intestinal lumen and distributed in the ECF. From the ECF, phosphates are handled by two general processes: an intracellular-extracellular shift and renal excretion. The absorbed phosphate is first "buffered" by shifting into the soft tissue cells (and probably also the skeleton). In time, any excess phosphate is ultimately excreted by the kidneys. Shifts of phosphate between extracellular and intracellular compartments cause immediate changes in the serum phosphorus level without changes in the total phosphorus balance. Renal phosphate excretion is determined by the difference between phosphate filtered at the glomerulus and phosphate absorbed by the tubule. Normally about 85% of the filtered phosphate is reabsorbed by the tubule and the remaining 15% is excreted in the urine.[4] The maximal tubular phosphate reabsorptive capacity (TmP) plays a major role in maintaining a long-term, steady-state serum phosphorus concentration—that is, the higher the TmP, the higher the serum phosphorus concentration. The total body phosphorus balance is maintained by urinary excretion of the excess phosphate absorbed by the intestine. In a person who is in phosphorus balance, the urinary phosphate concentration would equal the phosphate absorbed. Factors that may influence renal phosphate reabsorption are listed in Table 1.

Hypophosphatemia and Phosphorus Depletion

The terms hypophosphatemia, phosphorus deprivation and phosphorus depletion should be differentiated. Hypophosphatemia simply means a serum phosphorus concentration below the range found in a normal population. Phosphorus deprivation is generally used to indicate selective omission of phosphorus from the diet, sometimes accompanied by the administration of intestinal phosphate binders. Phosphate depletion denotes a state in which the body phosphorus store is actually reduced. The distinction between phosphorus deprivation and phosphorus depletion is important because many biochemical changes attributed to phosphorus depletion in fact develop within hours of removing phosphorus from the diet—that is, long before an appreciable net phosphorus loss from the body can occur.

Starvation leads to a catabolic state with loss of water, nitrogen, potassium, phosphorus and magnesium in the same proportion as in the tissues. The phosphorus content of the remaining tissue would therefore be normal for the reduced body mass. Thus hypophosphatemia is not a feature of starvation per se.

Sustained hypophosphatemia encountered in clinical practice generally represents conditions with an abnormally reduced TmP, rather than phosphorus deprivation or depletion. Hypophosphatemia associated with ample phosphate in the urine suggests an abnormally low TmP as the cause for the reduced serum phosphorus concentration. A reduced TmP can be caused by excessive parathyroid hormone secretion or by intrinsic tubular transport defects. In such conditions, a total body phosphorus balance may still be maintained and phosphorus depletion may not develop. The laboratory characteristic of phosphorus deprivation and phosphorus depletion is hypophosphatemia associated with the virtual absence

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ABBREVIATIONS USED IN TEXT

ADP = adenosine diphosphate
AMP = adenosine monophosphate
ATP = adenosine triphosphate
cyclic AMP = adenosine 3′:5′-cyclic phosphate
ECF = extracellular fluid
GFR = glomerular filtration rate
PTH = parathyroid hormone
TmP = maximal tubular phosphate reabsorptive capacity

of phosphate in the urine.[5] There are exceptions, however. Conditions associated with an accelerated intracellular phosphate shift, such as respiratory alkalosis and insulin administration (vide infra), may also show diminished urinary phosphate excretion. Hypophosphatemia associated with these conditions is clearly not the result of phosphorus deprivation or phosphorus depletion.

Causes of Hypophosphatemia and Phosphorus Depletion

Hypophosphatemia may result from three general mechanisms. They are increased phosphate shift into cells and bone, decreased intestinal phosphate absorption or increased intestinal loss of phosphate and inappropriate urinary phosphate loss through a reduction in the renal phosphate reabsorptive capacity.[6] Chronic, stable hypophosphatemia of moderate severity—serum phosphorus level 1.5 to 2.5 mg per dl—is generally caused by a reduction in the maximal renal phosphate reabsorptive capacity and does not manifest characteristics of the phosphorus depletion syndrome. Severe hypophosphatemia—serum phosphorus level less than 1.5 mg per dl—on the other hand, is often associated with phosphorus deprivation or depletion and may be accompanied by clinical manifestations of the phosphorus depletion syndrome.[7] It is obvious, however, that hypophosphatemia does not always indicate phosphorus depletion. Figure 1 summarizes the hypophosphatemic disorders encountered in clinical practice.

TABLE 1.—*Factors Influencing Renal Handling of Phosphates*

- Decreased renal phosphate absorption
  - Hormonal
    - Parathyroid hormone
    - Glucocorticoids
    - Sex hormones
    - Calcitonin
    - Thyroid hormone
  - Metabolic
    - High dietary phosphate intake
    - Metabolic acidosis
    - Alcoholism
    - Urinary alkalinization
  - Diuresis
    - Diuretics
    - Osmotic
    - Extracellular fluid volume expansion
- Increased renal phosphate absorption
  - Hormonal
    - Insulin
    - Vitamin D metabolites
    - Growth hormone
  - Metabolic
    - Dietary phosphate restriction
    - Hypercalcemia
    - Hypermagnesemia

Hypophosphatemia Associated With Other Mineral Disorders

Increased phosphate shift into cells and bone. The most common cause of acute hypophosphatemia in inpatients is the intravenous administration of carbohydrate, usually glucose. The reduction in serum phosphorus concentration is usually modest and transient. Fructose administration, on the other hand, may lead to a more prolonged and pronounced decrease in the serum concentration of phosphorus.[8] This is due to the intracellular trapping of phosphate as fructose 1-phosphate. The lack of negative feedback by the end-product fructose 1-phosphate on the enzyme fructokinase allows for the continual cellular uptake of phosphate. Severe hypophosphatemia may develop, especially in those with congenital fructose intolerance.

The nutritional recovery syndrome was first observed during rapid refeeding of severely malnourished prisoners of war. The modern equivalent of this syndrome can be seen in the intravenous feeding of patients with severe debilitation or anorexia nervosa, especially if the hyperalimentation solutions are deficient in phosphates.[9] The anabolic state from refeeding promotes an intracellular shift of phosphate and may lead to severe hypophosphatemia, frequently associated with hypokalemia and hypomagnesemia.

Respiratory alkalosis is a common cause of moderate to severe hypophosphatemia.[10] Hyperventilation-induced hypocapnia leads to a secondary reduction of intracellular carbon dioxide and an increase of intracellular pH, which activates phosphofructokinase. This results in accelerated glycolysis, and the enhanced glucose phosphorylation promotes transcellular phosphate influx. Salicylate overdose and gram-negative sepsis are thought to cause hypophosphatemia through respiratory alkalosis. In addition, the massive release of catecholamines with sepsis also promotes cellular uptake of phosphate.[11]

Rapid tumor growth may cause hypophosphatemia by increasing the phosphate demand for cell proliferation and growth, especially in patients with lymphomas.[12] The underlying mechanism of hypophosphatemia was thought to be rapid tumor growth and the high intracellular phosphate content of a lymphoblast compared with a mature lymphocyte.

The "hungry bone syndrome" is a rare disorder in which

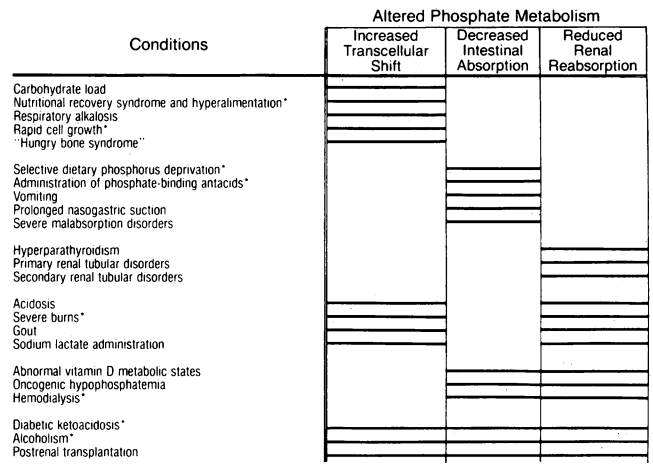

Figure 1.—Clinical conditions associated with hypophosphatemia: the role of the three major pathophysiologic mechanisms. —denotes the mechanism(s) responsible for hypophosphatemia in a given clinical condition, *denotes conditions that may cause severe hypophosphatemia and phosphorus depletion

hypophosphatemia develops as a result of therapy, leading to rapid new bone formation in a severely demineralized skeleton. This may follow a subtotal parathyroidectomy in a patient with primary or secondary hyperparathyroidism.

Decreased absorption or increased loss of phosphate in the intestine. Because of the universal presence of phosphate in food, a selective dietary phosphorus deficiency is generally achieved only under experimental conditions. Certain aluminum- and magnesium-containing antacids avidly bind to intestinal phosphate and render it nonabsorbable. When this condition is superimposed on poor oral intake, vomiting or prolonged nasogastric suction, severe hypophosphatemia may result. Malabsorptive disorders per se rarely cause significant phosphorus depletion.

Reduced maximal renal phosphate reabsorptive capacity. Hyperparathyroidism is a common cause of moderate hypophosphatemia. The parathyroid hormone (PTH) reduces the renal phosphate reabsorptive capacity and leads to a low serum phosphorus level. Primary renal tubular disorders associated with hypophosphatemia include renal tubular acidosis and the renal Fanconi syndrome.[13] The conditions that lead to secondary renal tubular dysfunction and renal phosphate wasting are depicted in Figure 1.

Both increased intracellular phosphate shift and decreased renal phosphate reabsorptive capacity. Acidosis induces decomposition of intracellular organic compounds with release of inorganic phosphate, which is subsequently excreted in the urine.[1] Hypophosphatemia generally develops during the treatment of acidosis from resynthesis of organic compounds and intracellular shift of inorganic phosphate.

A severe burn injury may also induce hypophosphatemia.[14] The lowest serum phosphorus level is commonly seen on the fifth day. The hypophosphatemia may last from two to ten days. Possible mechanisms include respiratory alkalosis from gram-negative sepsis and pain as well as rapid tissue rebuilding. These patients also have an inappropriate phosphaturia in the presence of severe hypophosphatemia, suggesting a defect in renal tubular phosphate reabsorption.

The hypophosphatemia of untreated gout has been attributed to respiratory alkalosis produced by pain-induced hyperventilation and a reduction in renal phosphate reabsorption due to tubular damage.[7,15]

Sodium lactate infusion promotes phosphaturia through volume expansion. In addition, volume expansion leads to a decrease in serum calcium levels, causing release of the parathyroid hormone, which in turn reduces renal phosphate reabsorption. Lactate infusion also increases hepatic glucose production and the consequent intracellular phosphate shift.[1]

Reduced renal phosphate reabsorptive capacity and decreased intestinal absorption of phosphate. Hypophosphatemia, renal phosphaturia and impaired intestinal absorption of calcium and phosphate are common features of vitamin D-deficient, -dependent and -resistant rickets or osteomalacia.[1]

Oncogenic hypophosphatemia is an interesting entity associated with mesenchymal tumors.[16] The underlying mechanism is unclear but may be related to an increased sensitivity to the phosphaturic effect of PTH, a reduced level of 1,25-dihydroxyvitamin D_3 or the production of an unknown phosphaturic agent.

Severe hypophosphatemia has been described in patients receiving dialysis and attributed to a combination of phosphate loss through dialysis and the intensive use of phosphate-binding antacids.[17]

Increased intracellular phosphate shift and reduction in both renal phosphate reabsorptive capacity and intestinal absorption of phosphate. In clinical practice, severe hypophosphatemia is often seen in patients recovering from diabetic ketoacidosis and from alcoholic withdrawal. Patients with diabetic ketoacidosis often have decreased phosphate intake from anorexia, nausea and vomiting before being admitted to hospital. Concomitant metabolic acidosis enhances the breakdown of intracellular organic phosphates, and the catabolic effects of insulin deficiency promote a phosphate shift into the ECF, leading to increased phosphaturia. Glycosuria and ketonuria induce a further renal phosphate loss. Before treatment, despite normal or even increased serum phosphorus levels, these patients have a total body phosphorus deficit. During treatment, administering insulin promotes glycolysis and oxidative phosphorylation with a rapid shift of phosphates into the cells. In addition, vigorous fluid replacement may enhance renal phosphate excretion. Usually 6 to 12 hours following the initiation of therapy for diabetic ketoacidosis, the serum phosphorus level may fall precipitously.

Another clinical setting in which severe hypophosphatemia often arises is in a patient admitted to hospital with chronic alcoholism.[18] The patient may have decreased phosphate intake from a poor diet or vomiting. Steatorrhea and malabsorption due to chronic pancreatitis and alcoholic cirrhosis may lead to vitamin D deficiency and a resultant hyperparathyroidism. Both conditions lead to increased renal and intestinal loss of phosphates. In addition, concomitant alcoholic ketosis, hypokalemia and hypomagnesemia may promote further renal phosphate clearance.[19,20] During hospital stay, nutritional repletion with intravenous administration of a glucose solution will lead to increased cellular phosphate uptake. This transcellular phosphate shift is further enhanced by respiratory alkalosis from alcohol withdrawal, hepatic encephalopathy or concomitant sepsis. The use of phosphate-binding antacids to treat gastrointestinal bleeding or of lactulose further aggravates hypophosphatemia. Severe hypophosphatemia can typically develop 24 to 72 hours after hospital admission.

Hypophosphatemia may be seen in a third of patients following a renal transplant.[21] A reduced renal phosphate reabsorptive capacity is an important contributing factor. The possible mechanisms for renal phosphate wasting include persistent hyperparathyroidism, subnormal graft function, corticosteroid and diuretic therapy and chronic volume expansion. The use of phosphate-binding antacids for peptic ulcer prophylaxis leads to a decreased intestinal absorption of phosphate. In addition, the resolution of hyperparathyroidism coupled with an increase in circulating 1,25-dihydroxyvitamin D_3 associated with the recovery of renal function may promote healing of renal osteodystrophy with a rapid and sometimes profound skeletal influx of calcium and phosphorus. In some chronically malnourished uremic patients, a posttransplant anabolic state may promote a further intracellular shift of phosphate for soft tissue synthesis.

Clinical Consequences of Severe Hypophosphatemia and Phosphorus Depletion

Multiple organ dysfunction may occur as a result of severe hypophosphatemia and phosphorus depletion. These disturbances from hypophosphatemia commonly occur in patients with chronic debilitation, often in a setting of preexisting cellular injury.

The clinical sequelae of severe hypophosphatemia and phosphorus depletion are the result of three critical biochemical disturbances.[22] First, the level of 2,3-diphosphoglycerate in erythrocytes is decreased, leading to increased oxygen affinity of the hemoglobin and a resultant tissue hypoxia. Second, there is a decrease in the intracellular concentration of ATP, the energy source needed for cell functions. Third, inorganic phosphate is a crucial cofactor in the glyceraldehyde-phosphate-dehydrogenase step of the Embden-Meyerhof pathway, and a deficiency of intracellular inorganic phosphate may impair glycolysis.

The critical determinants of cellular injury appear to be the level of inorganic phosphate and adenine nucleotide in the cytosol.[23] When cytosolic ATP decreases below a critical level, cellular dysfunction or necrosis may ensue. The cytosolic inorganic phosphate is essential for the formation of ATP from adenosine diphosphate (ADP). In addition, intracellular inorganic phosphate has an important role in determining the cellular pool of adenine nucleotides. Normally, ATP, ADP and adenosine monophosphate (AMP) are related by the following reaction:

$$2\,ADP \rightleftharpoons AMP + ATP$$

A major degradation pathway for AMP is the irreversible deamination to inosine monophosphate through the action of AMP-deaminase. This enzyme is inhibited by a normal intracellular phosphate concentration. Therefore, a significant reduction in intracellular inorganic phosphate may result in AMP degradation and a decrease of the total adenine nucleotide pool. In addition, a drop in ATP concentration enhances the action of 5′-nucleotidase, which further reduces the amount of nucleotides. Any demand in energy production may place the cell in jeopardy of disintegrating from a further decrease in intracellular ATP concentration.

The various systemic dysfunctions in severe hypophosphatemia and phosphate depletion are summarized in Figure 2.

Experimental evidence points to a significant impairment of the cardiovascular system in patients with severe hypophosphatemia. An increased cardiac index was found in critically ill hypophosphatemic patients given phosphorus replacement.[24] A decreased myocardial stroke work was also found in dogs with chronic phosphorus deficiency.[25] Decreased vascular reactivity to angiotensin II and norepinephrine has been shown in phosphorus-depleted animals.[26]

Acute respiratory failure from respiratory muscle weakness is a serious complication of severe hypophosphatemia. Reversible hypophosphatemia-induced diaphragmatic weakness and pulmonary insufficiency have been shown.[27] Hypophosphatemia may induce hyperventilation, possibly the result of poor tissue oxygenation from decreased erythrocyte 2,3-diphosphoglycerate levels. Hyperventilation leads to respiratory alkalosis and a further lowering of the serum phosphorus level. The vicious cycle may finally induce hypoventilation due to respiratory muscle fatigue.

Various neurologic manifestations may follow phosphorus depletion. Severe hypophosphatemia can result in a metabolic encephalopathy with paresthesia, tremor, ataxia, weakness, irritability, confusion, seizure and eventually coma.[28] This has been shown in patients receiving phosphate-deficient hyperalimentation and could be prevented with adequate phosphate supplementation.

Muscle biopsies from hypophosphatemic persons with alcoholism have shown a decrease in cellular phosphorus and an increase in intracellular sodium, chloride and water. This may account for the generalized weakness or proximal myopathy seen in some hypophosphatemic patients. Severe hypophosphatemia may induce rhabdomyolysis with elevated serum creatine kinase levels.[29] This is usually asymptomatic or clinically mild. Occasionally profound weakness, muscle pain and acute myoglobinuric renal failure may develop.

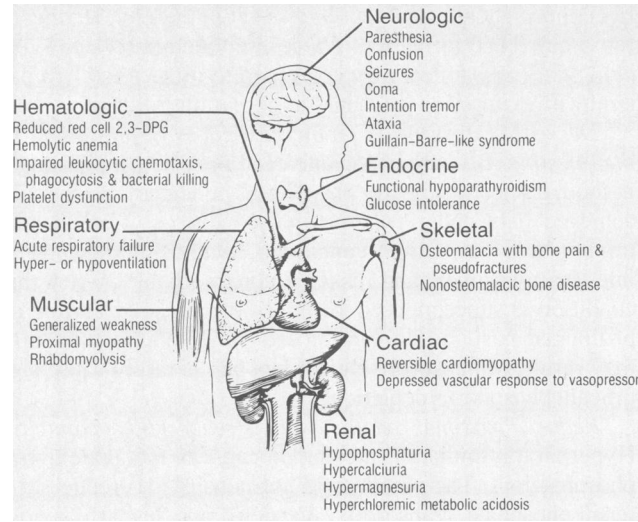

Figure 2.—The clinical manifestations of severe hypophosphatemia and phosphorus depletion are shown. 2,3-DPG = 2,3-diphosphoglycerate

Hemolytic anemia is a rare complication of phosphorus depletion but may occur when serum phosphorus values fall below 0.5 mg per dl.[30] Such a drop in the serum phosphorus level leads to a decrease in intracellular inorganic phosphate in erythrocytes. This in turn leads to impaired glycolysis with a fall in intracellular ATP. The elasticity of the red cell membrane is maintained by a microfilament system dependent on ATP for energy sources. Therefore, insufficient ATP may cause erythrocyte rigidity and may lead to fragmentation in the microcirculation. Another important biochemical consequence of hypophosphatemia in erythrocytes is the drop in 2,3-diphosphoglycerate, which leads to a leftward shift in the hemoglobin-oxygen dissociation curve. The increased oxygen binding by erythrocytes will result in a decreased peripheral oxygen delivery and tissue hypoxia.[31]

Experimental studies have shown defects of chemotaxis, phagocytosis and bacterial killing in leukocytes of hypophosphatemic animals. This may be related to impaired microtubular actions from low cellular ATP levels and abnormal membrane synthesis.[32]

Thrombocytopenia, decreased platelet survival and impaired clot retraction have been shown in animals with induced hypophosphatemia.[33] These may be due to a reduction of platelet ATP content. Similar clinical findings have not been observed in humans, however.

Metabolic acidosis may also result from severe hypophosphatemia by three mechanisms.[34] First, a decrease in titratable acid excretion follows hypophosphaturia. Second, a fall in renal ammonia excretion due to hypophosphatemia leads to decreased acid excretion. Third, renal tubular bicarbonate reabsorption may be reduced, which can lead to a hyperchloremic metabolic acidosis. Clinically the degree of acidosis is usually mild as a result of skeletal buffering from mobilization of both phosphorus and bicarbonate. Severe metabolic aci-

dosis, however, has been observed in hypophosphatemic malnourished children receiving hyperalimentation.[34] This may be related to defective mobilization of skeletal buffers.

A state of functional hypoparathyroidism exists in patients with severe hypophosphatemia and phosphorus depletion.[35]

Diagnostic Approach

Generally the cause of hypophosphatemia is apparent from the history or clinical setting under which it occurs. Measuring the urinary phosphorus concentration is helpful in difficult cases.[36] A fractional phosphate excretion of less than 10% or a 24-hour phosphorus output of less than 100 mg should lead to a search for causes other than renal phosphate wasting. Such patients may have a transcellular phosphate shift, an increased nonrenal loss or a decreased phosphate intake or absorption. A transcellular phosphate shift is the most common cause of hypophosphatemia in an inpatient.

Renal phosphate wasting is suggested by a urinary fractional phosphate excretion of greater than 20% or a 24-hour phosphorus output of more than 100 mg in the presence of hypophosphatemia. An associated increase in urinary glucose, amino acid, bicarbonate and uric acid levels points to the renal Fanconi syndrome as the underlying disease. Measuring serum calcium and PTH levels will distinguish hyperparathyroidism from the other causes of renal phosphate leak.

Treatment

At normal body pH (7.40), serum phosphorus exists in two forms, $H_2PO_4^-$ and $HPO_4^=$. Their relationship can be expressed by the following chemical reaction:

$$H_2PO_4^- \rightleftharpoons H^+ + HPO_4^=$$

The relative proportion of these ions in the serum can be calculated from the Henderson-Hasselbalch equation:

$$pH = pK + \log [HPO_4^=]/[H_2PO_4^-]$$

Because normal serum pH is 7.40 and the physiologic pK is 6.80, we have:

$$7.40 = 6.80 + \log [HPO_4^=]/[H_2PO_4^-]$$

or

$$0.60 = \log [HPO_4^=]/[H_2PO_4^-]$$

And antilog 0.60 = 4, therefore:

$$[HPO_4^=]/[H_2PO_4^-] = 4$$

or

$$[HPO_4^=] = 4\,[H_2PO_4^-]$$

Because the orthophosphate ions are expressed in a molar concentration in the Henderson-Hasselbalch equation, the molar ratio of $HPO_4^=$ to $H_2PO_4^-$ is 4:1 under normal serum pH. A solution containing the two orthophosphate ions in the above ratio will have a pH of 7.40 and is commonly called a "neutral phosphate" solution.

It follows that in normal serum, every 5 mmol per liter of serum phosphate contains 4 mmol per liter of divalent phosphate and 1 mmol per liter of monovalent phosphate, giving a total of 9 negative charges per 5 phosphate ions, or a valence of 9/5 = 1.8. Therefore, the interconversion of serum phosphate from millimoles to milliequivalents at normal serum pH is 1 mmol = 1.8 mEq.

It is also apparent that changes in pH will affect the ratio of the phosphate ions and thus alter the concentration of the solution expressed in mEq per liter. To avoid confusion, all therapeutic phosphate preparations should be expressed in mmol per liter and elemental phosphorus in mg per dl because these concentrations are independent of pH. Each mmol per liter of phosphate contains 3.1 mg per dl of elemental phosphorus.

Modes of Therapy

Asymptomatic moderate hypophosphatemia usually only requires attention to the underlying cause. For hyperalimentation solutions, the addition of 15 mmol per liter of phosphate will normally prevent hypophosphatemia. The judicious use of phosphate-binding antacids in patients with peptic ulcer disease or chronic renal failure will avoid hypophosphatemia. For patients with respiratory alkalosis, treatment of the underlying disorder—sepsis, acute gout or metabolic encephalopathy—will reverse the hypophosphatemia.

Treatment of hypophosphatemia in diabetic ketoacidosis remains controversial.[37] Despite normal or elevated levels of serum phosphorus before treatment, these patients become hypophosphatemic and hypophosphaturic when given fluids and insulin. Clinical manifestations of severe hypophosphatemia usually do not develop, however, and serum phosphorus levels normalize when oral intake is resumed. In addition, several studies have failed to show a decreased insulin requirement or degree of acidosis, improved glucose metabolism or decreased erythrocyte abnormalities with phosphate supplementation. Nonetheless, the small proportion of patients who present with hypophosphatemia before treatment require close monitoring. They have significant phosphorus depletion, and severe hypophosphatemia is likely to develop during therapy for diabetic ketoacidosis. These patients may benefit from phosphate administration.

Patients with chronic alcoholism, on the other hand, frequently have phosphorus depletion at the time of admission to hospital. Frequent monitoring of their serum phosphorus levels is indicated. Phosphate supplementation may be given when an evolving trend toward hypophosphatemia becomes clear, so that a full-blown phosphorus-depletion syndrome may be aborted.

For patients with severe hypophosphatemia associated with clinical manifestations of phosphorus depletion, therapy should be instituted without delay. As a general rule, oral therapy is preferred unless the patient cannot tolerate oral feeding or has severe hypophosphatemia with life-threatening complications.

Skim milk has about 1 gram per liter of both phosphorus and calcium. It is a safe and desirable form of phosphorus supplementation. If a patient cannot tolerate lactose or a substantial fluid intake, a commercial phosphate preparation may be used. A total daily amount of 2 to 3 grams of elemental phosphorus may be given in two to four divided doses. Mild diarrhea is a frequent side effect. Various commonly available phosphate preparations are listed in Table 2.

For patients requiring parenteral administration of phosphate, caution must be exercised to prevent hyperphosphatemia. The volume of distribution of the administered phosphate has wide individual variation and is affected by the serum pH, glucose and insulin availability. In addition, phosphorus-depleted patients have pronounced hypophosphaturia and may continue to have it for some time despite correction of their hypophosphatemia. Consequently, they are vulnerable to the development of hyperphosphatemia when a large quantity of phosphate is given parenterally over a short period of time. We recommend that no more than 1 gram of ele-

mental phosphorus be given by steady infusion over 24 hours. In patients with renal failure or oliguria, potassium phosphate preparations should be avoided. An initial phosphate dose of 0.08 mmol per kg body weight (2.5 mg per kg body weight) may be given over six hours.[38] The dose may be increased to 0.16 mmol per kg (5.0 mg per kg) if a patient has serious life-threatening clinical manifestations. Thereafter, serum levels of phosphorus, calcium, potassium and magnesium should be determined and the rate of phosphate infusion adjusted accordingly. Parenteral phosphate infusion should be discontinued when the serum phosphorus level is greater than 2 mg per dl or a serum calcium level is less than 8 mg per dl.

The hazards of parenteral phosphate therapy include hyperphosphatemia, hypocalcemia, hypomagnesemia, metastatic calcification, hypotension and renal failure.[39] Diuresis may accompany phosphate administration and lead to dehydration, hypokalemia and hypernatremia. Patients with renal failure receiving parenteral phosphate therapy are especially susceptible to serious complications.

Hyperphosphatemia

Hyperphosphatemia is a frequent laboratory finding in inpatients. There are several mechanisms accounting for the increase in serum phosphorus (Table 3). By far the most common cause is from decreased renal phosphate excretion. This is generally a result of decreased glomerular filtration from renal insufficiency but may also result from an increased renal tubular phosphate reabsorption in patients without renal failure. A substantial increase in phosphate intake may lead to severe hyperphosphatemia, especially with uremic patients. Further, a large extracellular phosphate load may be a result of a transcellular phosphate shift or cell lysis. Finally, several causes for spurious elevations of serum phosphorus levels have been reported. These include specimens that have undergone prolonged refrigeration or delay before a phosphorus measurement, hemolysis, contamination with heparin sodium or detergents and the presence of hyperbilirubinemia, dysproteinemia or hyperlipidemia.[40]

In patients with chronic renal failure, the fractional excretion of phosphate by the remaining nephrons is increased, sometimes as much as 90% of a filtered load.[41] This degree of phosphaturia by individual nephrons is important in maintaining a normal serum phosphorus level in the presence of a decreasing glomerular filtration rate (GFR). But when the GFR is less than 25 ml per minute and if dietary phosphate intake is not reduced proportionately, the serum phosphorus level will rise. In turn, the filtered phosphate load will increase with a corresponding rise in phosphate excretion. A new phosphorus balance will then be established at a higher serum phosphorus level.

The parathyroid hormone is an important regulator in the renal excretion of phosphate.[42] Patients with hypoparathyroidism have diminished urinary adenosine 3′:5′-cyclic phosphate (cyclic AMP) production and increased renal tubular phosphate reabsorption. The serum phosphorus level in these patients ranges from 7 to 9 mg per dl.[43] Patients with idiopathic hypoparathyroidism tend to have higher serum phosphorus levels than those with surgical hypoparathyroidism. These patients also have hypocalcemia, which predisposes them to tetany and seizures.

In pseudohypoparathyroidism there is an end-organ resistance to the effect of parathyroid hormone.[44] These patients have hyperphosphatemia and hypocalcemia, and the PTH level is usually elevated. Patients with type I pseudohypoparathyroidism have low urinary cyclic AMP and phosphate

TABLE 2.—*Commonly Available Phosphate Preparations**

Preparations	*Phosphorus Content, 1 gram*	*Sodium, mEq†*	*Potassium mEq†*
Oral			
Skim milk	1,000 ml	28	39
Neutra-Phos‡	300 ml or 4 capsules	28	28
Neutra-Phos K‡	300 ml or 4 capsules	0	57
Phospho-Soda§	6.2 ml	57	0
K-Phos Neutral‖	4 tablets	50	5
K-Phos Original (Sodium Free)‖	7 tablets	0	26
Parenteral			
Hyper-Phos-K¶	15 ml	0	50
Sodium phosphate	11 ml	45	0
Potassium phosphate	11 ml	0	45

*Adapted from Lee et al.[1]
†Content in 1 gram of phosphorus.
‡Willen Drug Company, Baltimore.
§C. B. Fleet Company, Inc, Lynchburg, Va.
‖Beach Pharmaceuticals, Tampa, Fla.
¶Abbott Laboratories, North Chicago

TABLE 3.—*Common Causes of Hyperphosphatemia*

- Decreased renal phosphate excretion
  - Decreased glomerular filtration rate
    - Renal failure, chronic and acute
  - Increased tubular reabsorption
    - Hypoparathyroidism
    - Pseudohypoparathyroidism, types I and II
    - Acromegaly
    - Hyperthyroidism
    - Etidronate disodium
    - Tumoral calcinosis
- Increased phosphate intake
  - Oral or intravenous administration of phosphate
  - Phosphate-containing laxatives or enemas
  - Vitamin D intoxication
  - White phosphorus burns
- Increased extracellular phosphate load
  - Transcellular shift
    - Lactic acidosis
    - Respiratory acidosis
    - Untreated diabetic ketoacidosis
  - Cell lysis
    - Rhabdomyolysis
    - Malignant hyperpyrexia
    - Intravascular hemolysis
    - Cytotoxic therapy
    - Leukemia
    - Lymphoma
    - Acute intestinal ischemia
- Spurious hyperphosphatemia
  - Prolonged refrigeration of specimen or delay in measuring
  - Heparin sodium contamination
  - Traumatic hemolysis
  - Hyperbilirubinemia
  - Dysproteinemia
  - Hyperlipidemia
- Miscellaneous
  - Volume contraction
  - Familial intermittent hyperphosphatemia
  - Cortical hyperostosis

excretion with exogenous PTH administration. Those with type II pseudohypoparathyroidism have high urinary cyclic AMP but low phosphate excretion when given exogenous PTH. Therefore, PTH resistance can be proximal (type I) or distal (type II) to the production of cyclic AMP. In addition, certain physical anomalies may exist in patients with pseudohypoparathyroidism. These include short stature, round face, short neck, shortening of the metacarpals and subcutaneous calcifications.

Mild hyperphosphatemia may be seen in a third of patients with hyperthyroidism.[45] This is due to increased bone resorption and renal tubular phosphate reabsorption.

Acromegaly is also associated with hyperphosphatemia through an increased renal phosphate reabsorption induced by growth hormone.

The diphosphonate, etidronate disodium, is useful for treating Paget's disease. The hyperphosphatemic effect is dose-dependent and may be related to a decreased renal phosphate excretion and a transcellular phosphate shift.[46]

Tumoral calcinosis is a rare syndrome seen in young black men.[47] Patients have ectopic calcifications around large joints with associated hyperphosphatemia and normal serum calcium and PTH levels. The soft tissue calcification is due to an increased calcium-phosphate product. The pathogenesis may be enhanced renal tubular reabsorption of phosphate and calcium.

Metabolic acidosis is often associated with hyperphosphatemia. A breakdown of organic phosphate with a release of inorganic phosphate into the extracellular fluid is the likely explanation. Lactic acidosis tends to cause a greater degree of hyperphosphatemia than diabetic ketoacidosis under a similar pH.[48] This may be due to concomitant tissue hypoxia and a further transcellular phosphate shift in patients with lactic acidosis.

In rhabdomyolysis the release of intracellular phosphate stores with muscle necrosis in a setting of acute renal failure may lead to severe hyperphosphatemia.[49] Cytotoxic therapy for lymphoblastic leukemia and Burkitt's lymphoma also leads to the release of high intracellular phosphate loads into the extracellular space.[50]

Malignant hyperpyrexia is a rare complication of general anesthesia, and hyperphosphatemia may occur independent of rhabdomyolysis and acute renal failure.[51]

Clinical Manifestations

The clinical consequences of hyperphosphatemia are related to its effects on serum calcium, PTH and skeletal and soft tissues. Severe hyperphosphatemia is often associated with hypocalcemia, especially when the serum phosphorus level rises rapidly. The possible underlying mechanisms include soft tissue calcium-phosphate salt deposition, reduced bone resorption and reduced 1,25-dihydroxyvitamin D_3 formation. Symptomatic hypocalcemia may develop, leading to tetany and seizures.

Soft tissue calcification is common in hyperphosphatemic patients with chronic renal failure, hypoparathyroidism and tumoral calcinosis. The normal calcium-phosphate product is 40 mg^2 per dl^2 (10 mg per dl calcium × 4 mg per dl phosphate). The in vitro solubility product of calcium and phosphate is 58 mg^2 per dl^2. In humans, metastatic calcification is likely when this product exceeds 70 mg^2 per dl^2. Calcification may occur in the heart, blood vessels, lungs, cornea, kidneys and gastric mucosa. The alkaline intracellular milieu of the lungs, cornea, kidneys and gastric mucosa may enhance calcium-phosphate salt deposition.

Hyperphosphatemia and hypocalcemia in patients with chronic renal failure often lead to hyperparathyroidism. The elevated PTH level is an important factor in the pathogenesis of renal osteodystrophy. In addition, high PTH levels aggravate soft tissue calcification and may produce calciphylaxis with subcutaneous tissue necrosis. Experimental evidence also implicates a causal role for PTH in the pruritus and anemia of uremia.[52]

Treatment

The principles of the treatment of hyperphosphatemia are in reducing phosphate intake and promoting phosphate excretion.

In patients with normal renal function, increased phosphate intake rarely produces significant hyperphosphatemia. In hyperphosphatemia due to chemotherapy for leukemia or lymphoma, vigorous saline diuresis will lead to increased phosphaturia. Alternatively, the administration of acetazolamide, 500 mg every six hours, will enhance renal phosphate excretion through urinary alkalinization and natriuresis.[53]

In patients with chronic renal failure, restricting dietary phosphate intake to 600 to 900 mg per day can maintain normal serum phosphorus levels, provided that the GFR is greater than 30 ml per minute. When the GFR is less than 25 ml per minute, a phosphate binder will be needed. Aluminum hydroxide and aluminum carbonate liquid gels—Amphojel, Basaljel (Wyeth Laboratories, Philadelphia)—are the commonly used drugs.[54] These antacids bind to the intestinal phosphates (from both exogenous intake and endogenous secretion from the parotid glands and pancreas) and render them nonabsorbable. The usual dosage is 20 to 40 ml one hour after each meal and at bedtime. Calcium carbonate has recently been shown to normalize serum phosphorus levels in patients undergoing long-term dialysis.[55] These patients ingest an average of 8.5 grams of calcium carbonate per day (range 2.5 grams to 17 grams). The long-term side effects, such as metastatic calcification, will need to be determined.

In addition, dietary phosphate intake should be kept to less than 1 gram per day to avoid a positive phosphorus balance and to minimize the dosage of antacid needed. Nausea is a frequent side effect with the ingestion of aluminum-containing liquid gels. Desiccated gels in the form of capsules or tablets—Alu-Cap, Alu-Tab (Riker Laboratories, St Paul)—may be substituted. The dried gels have less phosphate-retaining power, however. Long-term ingestion of large quantities of aluminum-containing phosphate binders may lead to aluminum bone disease in patients on dialysis. Magnesium-containing antacids should not be used in patients with renal failure, as a decreased renal clearance of ingested magnesium will lead to magnesium intoxication.

Calcium supplementation and vitamin D metabolites are also given to dialysis patients to increase the serum calcium concentration and reduce the severity of secondary hyperparathyroidism. Hemodialysis may remove substantial extracellular phosphate and lower serum phosphorus levels transiently. Equilibration with intracellular phosphate stores, however, will restore the serum phosphorus to predialysis levels in a few hours. In patients with chronic renal failure and intractable hyperphosphatemia, a subtotal parathyroidectomy may be considered to reduce the mobilization of phosphorus from skeletal stores.

In patients with hypoparathyroidism, calcium and vitamin D supplementation are generally prescribed to correct hypocalcemia, although these patients have increased urinary calcium excretion as a result of their low PTH levels. Increasing serum calcium levels to the normal range may predispose them to nephrolithiasis. Serum calcium levels should also be monitored frequently to avoid vitamin D intoxication.

The therapy for tumoral calcinosis is dietary calcium and phosphorus restriction. The use of phosphate binders may be added. A negative calcium and phosphorus balance in these patients will lead to reductions in soft tissue calcification.

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