Ann. Rev. Nutr. 1988. 8:121–48

CONSEQUENCES OF PHOSPHATE IMBALANCE

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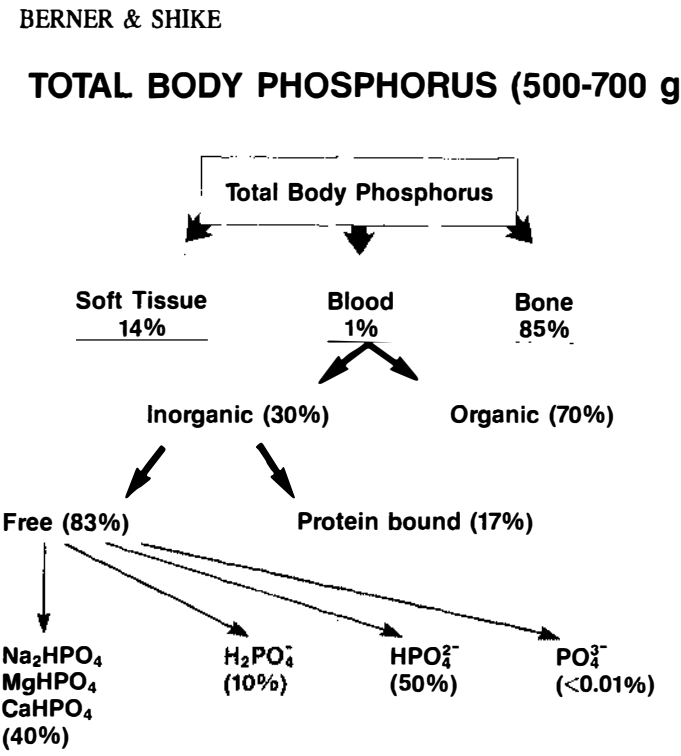

Figure 1 Distribution of phosphorus in humans

PHOSPHORUS DISTRIBUTION AND FUNCTION IN HUMANS

Phosphorus[1] (P) is the sixth most abundant element in the human body (after oxygen, hydrogen, carbon, nitrogen, and calcium). It constitutes approximately 1% of the total body weight. About 85% of the body P is found in bones, 14% in cells in soft tissues, and 1% in extracellular fluids (85, 116, 185) (Figure 1).

In bone, phosphate is a constituent of the crystal hydroxyapetite $Ca_{10}(PO_4)_6(OH)_2$, which is deposited in the organic matrix during the mineralization process and gives the bone its strength. The ratio of P to Ca in the bone is normally 1:2 (71). Phosphorus is essential for bone mineralization; deficiency interrupts this process and results in osteomalacia.

In soft tissues, phosphate plays different roles as (*a*) a structural component, (*b*) a factor in intermediate metabolism, and (*c*) a component of

[1]The term "phosphorus" refers to the element P. Phosphate denotes the anion PO_4^{3-}, Routine laboratory serum measurements determine the concentration of phosphorus, but this is often reported as "phosphate." Physiologically, phosphorus exists principally as phosphate; therefore, the term "phosphate" is used throughout the chapter.

genetic material. Phospholipids are major constitutents of cell membranes and intracellular organelles. In DNA and RNA, phosphate is an essential part of the nucleic acids. Phosphate is a constituent of highly active intracellular compounds. Release of high energy phosphate by hydrolysis of adenosine triphosphate (ATP) provides the main energy source for various metabolic processes and for muscle contraction. In the mitochondrion, phosphate-containing proteins play essential roles in the electron transport system. Another phosphate-containing compound, the cyclic adenosine monophosphate cAMP, is an important secondary messenger that mediates the intracellular effects of different hormones such as the parathyroid hormone, antidiuretic hormone, and epinephrine. The level of intracellular phosphate is an essential regulator of enzymes in the glycolytic pathway (98, 180). Inside the erythrocyte the concentration of 2,3-diphosphoglycerate (2,3-DPG) plays a crucial role in oxygen availability to the tissues. In phosphate deficiency, synthesis of 2,3-DPG is decreased, which increases the affinity of oxygen to hemoglobin and thus decreases the release of oxygen to the tissues (76, 108, 179). Consequently, ATP production is decreased. In addition, irreversible degradation of AMP to inosine monophosphate occurs (58) and creates a shortage of this ATP precursor.

About 70% of blood phosphate is in the organic form, as a constituent of phospholipids (Figure 1). The remaining 30% is inorganic phosphate (orthophosphate). Clinical laboratory measurements of plasma phosphate refer to the P in inorganic fractions. Inorganic phosphate circulates either bound to proteins (15%) or "free" (85%) (116, 153). At physiological pH, about 50% of free phosphate circulates in the form of HPO_4^{2-}, 10% as $H_2PO_4^-$, 40% as a component of sodium, calcium, and magnesium salts, and less than one hundredth percent actually as phosphate, PO_4^{-3} (116, 153, 177) (Figure 1). The normal plasma levels of phosphate in the adult range between 2.2 and 4.4 mg/dl, with values about 50% higher in babies and 30% higher in children (70, 142). These higher levels of plasma phosphate in the pediatric group are thought to be secondary to the effects of growth hormone (153). The plasma phosphate serves as an exchange pool between the various phosphate-containing and regulating organs (intestines, bones, kidneys, cellular phosphates). In addition, it serves as a buffer. Phosphate excretion through the kidneys is one of the important mechanisms that maintains acid-base balance.

The widespread structural and metabolic functions of phosphate make it essential in the utilization of other nutrients, particularly nitrogen. Tissues contain constant ratios of nitrogen and minerals (in adult nonskeletal tissue, the N:P:Na:K:Cl is 1:0.06:1.2:3.0:0.72 (156), while in the muscle the ratio is 1:2.03:0.93:3.2:0.69 (47). The provision of adequate amounts of nitrogen without adequate phosphate results in suboptimal utilization of nitrogen (156).

PHOSPHATE HOMEOSTASIS

The plasma levels of phosphate are not as tightly controlled as those of calcium, although both share the same homeostatic hormones (PTH, 1,25-$(OH)_2D$, and calcitonin), and are mostly stored in the same crystal in the bone (172).

Three main organs are involved in maintenance of phosphate balance: (*a*) the intestinal tract, which is the absorption organ; (*b*) the kidneys, which are the most important excretion organ; and (*c*) the bones, which are the reservoir of phosphate.

The dietary intake of phosphorus can vary substantially with the kind of foods eaten. Studies of the American diet reveal that the amount of ingested P has been stable since the beginning of the century and averages about 800–1500 mg/day (135, 149). Diets that provide sufficient protein and calories also contain phosphorus in adequate amounts, regardless of the source of protein, carbohydrates, and fat. Milk and its products are the richest source of phosphorus in the diet, but phosphorus is widely available in other foods, such as meat, fish, poultry and eggs, and peanuts (135). Therefore, phosphate depletion secondary to inadequate dietary intake is extremely rare (70). Phosphate is absorbed all along the intestinal tract, with the jejunum being the most active absorptive site (91, 184). It is excreted into the gastrointestinal tract with the digestive juices in the amount of approximately 200 mg/day (193), about two thirds of which is reabsorbed (153). Saliva and bile acids are the most important gastrointestinal secretory fluids of phosphate (194).

Animal and human studies suggest two mechanisms for phosphate intestinal absorption. The first, which takes place mainly in the proximal intestines, is a Na-dependent active transport and can be blocked by arsenate, diphosphonate, mercury (39), and calcitonin (29, 79). This active transport can be enhanced by 1,25 $(OH)_2D$ and is linearly related to the Na concentration in the gastrointestinal lumen (39). The second intestinal absorptive mechanism operates mainly in the jejunum and ileum and is linearly related to the phosphate concentration in the intestinal lumen (39). When the oral phosphate intake is low, the reduced intraluminal phosphate concentration does not allow passive diffusion, and active absorption in the proximal small bowel becomes the main absorptive mechanism.

The intestinal absorption of phosphate is influenced by the endocrine system and by interaction with other substances in the intestinal lumen. Vitamin D enhances phosphate absorption independently of its effect on calcium absorption. From all vitamin D metabolites, 1,25-$(OH)_2D$ seems to be the most active in enhancement of phosphate intestinal absorption (16, 21, 80, 144). Other forms of vitamin D such as 24,25-$(OH)_2D$ were not shown to be active in phosphate absorption in the rat jejunum (33). Parathyroid

hormone exerts an indirect enhancing effect on intestinal phosphate absorption by stimulating synthesis of 1,25-$(OH)_2D$ in the kidney. Calcium has both direct and indirect effects on phosphate intestinal absorption. The direct effect is mediated through formation of insoluble complexes with phosphate in the intestinal lumen, thus decreasing the bioavailability and absorption of both phosphate and calcium (34). The indirect effect is mediated through the effect of calcium on vitamin D metabolism. The synthesis of 1,25-$(OH)_2D$ is inversely related to the serum calcium (29, 72), independently of PTH (178), and as noted above 1,25-$(OH)_2D$ enhances phosphate intestinal absorption. Calcium overabundance in the gastrointestinal tract, with a calcium-to-phosphate ratio over 3, can result in decreased phosphate absorption and deficiency (37, 100).

The relative amounts of Ca and P in the intestinal lumen may have another important implication. It has been hypothesized (134, 187, 188) that ionic calcium in the colonic lumen forms nonsoluble complexes with free bile acids and fatty acids. By forming these complexes, calcium can protect the colonic mucosa from the damaging effects of these acids. Free bile acids and fatty acids are thought to enhance cellular profileration in the colonic mucosa (27, 109), a process that can lead to neoplastic changes and eventually to cancer. In the presence of high concentrations of phosphate in the intestinal lumen, calcium becomes bound to phosphate in nonsoluble complexes; this decreases the amount of ionized calcium available for neutralization of free bile and fatty acids and their damaging effect on the mucosa. The most potent cation that produces nonabsorbable complexes with phosphate is aluminum. This is the rationale for using aluminum salts as phosphate binders in therapy of hyperphosphatemia in renal failure. Prolonged use of aluminum salts can result in the phosphate depletion syndrome (28, 111). Low sodium in the intestinal lumen reduces phosphate absorption (124), while high K increases it (69, 174).

The kidney is the main regulatory organ for maintenance of phosphate balance. In the healthy human, the kidney excretes phosphate in an amount equal to the net phosphate absorption in the gut (which is the amount absorbed minus that excreted into the gut) thus maintaining a zero balance. The urinary phosphate excretion of individuals eating the average American diet is 600–800 mg/day (98). In states of phosphate depletion, the kidney responds by reducing the urinary phosphate excretion virtually to zero, thus conserving it in the body (48, 161).

About 90% of the plasma phosphate is filtered at the glomerulus (68). No phosphate is excreted into the renal tubuli (194). Renal phosphate reabsorption occurs mainly in the proximal tubule through an active process. The fractional urinary excretion can vary between 0.1 and 20% and thus serves as a powerful homeostatic mechanism (90, 97, 104). The precise details of the

tight regulation of phosphate reabsorption in the renal tubules have not been fully elucidated. It is known that the primary regulatory factors are the serum phosphate and, to a lesser degree, PTH (98). Increased serum phosphate enhances urinary excretion while PTH decreases it.

The conservation of phosphate by the kidney in phosphate-deprived animals does not depend on PTH (62, 132, 191) or vitamin D (22). During phosphate deprivation for a period as short as two days, its transport across the proximal tubuli increases (131, 143). With prolonged phosphate deprivation the whole nephron conserves phosphate. In states of phosphate depletion, resistance to the phosphaturic effects of exogenous PTH develops (62, 143, 170, 174). Thus, low serum level phosphate is the most potent regulator of phosphate conservation, acting both by enhancing the reabsorption in the tubuli and by desensitizing them to the hyperphosphaturic effect of PTH and control of vitamin D hydroxylation (175). Parathyroid hormone exerts its phosphaturic effect through cAMP in the tubular cells. It has been suggested (49) that cAMP, which inhibits a protein kinase, induces an increase in gluconeogenesis. In the process, NAD^+ is produced and this inhibits phosphate uptake across the brush borders of the tubular cells (49).

Decreased renal phosphate reabsorption also occurs as a result of increased plasma levels of phosphate, steroid hormones (26, 50), thyrocalcitonin (97), and acute respiratory and metabolic acidosis (11, 145, 181, 199). Factors that increase phosphate reabsorption in the renal tubuli include reduced dietary intake, insulin (41, 101), thyroid hormone (19, 54, 126, 152), growth hormone (36), glucagon (51), and metabolic (130, 199) and respiratory alkalosis (11).

Extracellular volume expansion is associated with inhibition of phosphate reabsorption in the proximal tubule (90, 97), while volume contraction enhances it (44, 90, 94, 97). Diuretics have a phosphaturic effect, which is mediated by different mechanisms. Furosemide, increases phosphate urinary excretion indirectly. Its calciuric effect enhances PTH secretion and this in turn inhibits tubular phosphate reabsorption (24, 98, 99). The carbonic anhydrase inhibitor Diamox® diminishes phosphate reabsorption in the proximal tubuli independently of the effect of PTH (13, 89). Hypokalemia decreases the sensitivity of PTH receptors to the hormone (7, 14, 183) and this decreases phosphate urinary excretion.

Vitamin D, and particularly its metabolite 1,25-$(OH)_2$D, is an important hormonal regulator of calcium and phosphate levels in the blood. The activity of 1,25$(OH)_2$D is mediated by intracellular proteins. Vitamin D affects phosphate homeostasis and balance through the following mechanisms:

1. Direct stimulation of intestinal absorption of phosphate (33, 80, 91).
2. Enhancement of bone resorption with mobilization of calcium and phos-

phate (31, 43) into the plasma. This effect is independent of PTH. The metabolite 24, 25-$(OH)_2D$ is thought to enhance bone mineralization (21, 22, 31, 43, 71,139) and thus removal of phosphate from the plasma into the bone.

3. The effect of vitamin D on the renal handling of PO_4 is thought to be indirect: the increase in serum calcium mediated by $1,25(OH)_2D$ suppresses PTH secretion, and thus enhances phosphate reabsorption in the tubuli (6, 48).

SIGNIFICANCE OF HYPOPHOSPHATEMIA

The significance of hypophosphatemia is related to the clinical setting in which it occurs. It can be a manifestation of total body phosphate deficiency resulting in the potentially lethal phosphate deficiency syndrome. Hypophosphatemia can also be a result of acute phosphate shifts from the serum into the cells. As long as such acute shifts occur without prior intracellular phosphate depletion, the condition is usually benign and is not associated with significant intracellular metabolic alterations. As has been noted earlier, less than 1% of total body phosphate is in the extracellular space. Consequently, small shifts of no more than 200 mg of phosphate from the extracellular fluids into the cells can induce significant changes in the serum phosphate levels.

Hypophosphatemia Without Cellular Phosphate Depletion

Administration of glucose or fructose and feeding after starvation are the main causes of shifts of large amounts of phosphate from the extracellular fluid into the cells (78, 98, 116). The phosphate is needed inside the cells for phosphorylation of glucose and fructose and for ATP synthesis. It is well established that glucose load (as given in the glucose tolerance test) induces a transient reduction in the serum phosphate levels (42, 78). In feeding after starvation, hypophosphatemia can occur when insufficient phosphate is given. Again, the carbohydrate load given during feeding causes phosphate shifts into the cells, resulting in hypophosphatemia. The degree of prior starvation and phosphate losses determines whether the hypophosphatemia associated with the feeding would be benign or would be associated with the phosphate depletion syndrome. Respiratory alkalosis of any cause can induce hypophosphatemia by increasing phosphate shifts into the cells (130). The mechanism is thought to be secondary to an increase in the glycolytic pathway induced by the alkalotic milieu of the cells. Glycolysis enhances utilization of phosphate and thus induces shifts from the extracellular fluid into the cell. Hypophosphatemia seen in a variety of clinical settings such as sepsis, salycilate poisoning, acute gout, hepatic coma, and hyperventilation can be explained by the associated respiratory alkalosis (130).

The diagnosis of this condition is based on the clinical setting in which it occurs, and by ruling out the phosphate deficiency syndrome. It is usually benign and does not require specific treatment.

The Phosphate Deficiency Syndrome

The phosphate deficiency syndrome (PDS) usually occurs when hypophosphatemia is present in association with a decrease in the cellular phosphate content. This syndrome has a wide range of clinical and metabolic manifestations, which are consequences of the intracellular depletions.

The PDS is usually a chronic syndrome with a gradual onset of symptoms seen in a situation of long-standing negative phosphate balance due to decreased gastrointestinal phosphate influx or increased urinary losses. A more acute form of the syndrome can be seen when a patient with preexisting phosphate depletion is given intensive alimentation (enterally or parenterally) without adequate amounts of phosphate. In such cases, the a priori depleted cell quickly utilizes its remaining phosphate, and there is a rapid shift of plasma phosphate into the cells. However, this process does not provide all the phosphate required for cellular metabolism. A life-threatening syndrome with severe hypophosphatemia and intracellular phosphate deficiency develops.

CAUSES OF THE PHOSPHATE DEFICIENCY SYNDROME

Phosphate is widely available in various foodstuffs, such as milk, red meat, poultry, fruits, and vegetables (135). It is also very effectively conserved by the kidney (44). Thus, hypophosphatemia and phosphate depletion secondary to inadequate dietary intake are extremely rare. Table 1 lists various clinical conditions in which hypophosphatemia and phosphate depletion may develop. The primary feature of these conditions is the excessive loss of phosphate through the urine and/or stool.

Nutritional Repletion: Oral, Enteral, and Parenteral Nutrition

Nutritional repletion of the malnourished patient implies the provision of sufficient calories, protein, and other nutrients to allow accelerated tissue accretion. In the course of this process, cellular uptake and utilization of phosphate increase, and when insufficient amounts of phosphate are provided, an acute state of severe hypophosphatemia and intracellular phosphate depletion with serious clinical and metabolic consequences can occur. This chain of events has been well described in experimental animal studies (169) and has been proposed as one of the mechanisms of the refeeding syndrome observed in starved prisoners of war fed overzealously, particularly with

Table 1 Causes of hypophosphatemia

Nutritional repletion (oral, enteral, TPN)
Gastrointestinal malabsorption
Use of phosphate binders
Starvation
Diabetes mellitus
Alcoholism
Increased urinary losses due to tubular dysfunction or other causes

carbohydrates (57, 159). The morbidity of feeding malnourished prisoners seemed to decrease significantly with the consumption of skim milk, which provides large amounts of potassium and phosphorus (57, 135).

The introduction of total parenteral nutrition (TPN) facilitated studies on the metabolism of various nutrients and on the clinical and metabolic consequences of their deficiency. In TPN, the exact composition of the administered solutions is known and can be controlled effectively. When TPN therapy was introduced, solutions were either lacking or provided insufficient amounts of various nutrients (P, Zn, Cu, essential fatty acids, etc). The administration of TPN accelerated metabolic processes that required the lacking nutrients, and thus induced deficiency states of specific nutrients.

Initially, the source of amino acids in TPN solutions was the hydrolysis products of proteins such as casein. The protein hydrolysates contained small amounts of various minerals. Therefore, patients received small doses of phosphorus even when it was not intentionally added to the TPN solutions, so manifestations of phosphate depletion were uncommon. With the introduction of synthetic amino acid solutions as the protein source, reports of TPN-induced hypophosphatemia with a wide spectrum of manifestations appeared in the literature (5, 38, 76, 167, 179, 189). Interestingly, it has been noted (201) that these reports about TPN-induced hypophosphatemia were described more in the North American than in the European literature. This has been attributed to the fact that European TPN regimens included mostly casein hydrolysates as a protein source and varying degrees of fat emulsions as caloric sources. Fat emulsions contain phosphate in the phospholipids that are added to the solutions to ensure emulsification of the triglycerides. Thus, the European TPN regimens provided phosphate inadvertantly from both protein and lipid solutions while the American regimen, using synthetic amino acids as protein source and glucose as the sole caloric source, were devoid of phosphate.

Many patients for whom TPN is indicated have a certain degree of total body phosphate depletion due to malabsorption, starvation, and increased catabolism. When TPN without adequate phosphate is administered to such patients an acute state of intracellular phosphate deficiency can develop.

The observations on hypophosphatemia following glucose infusions (15, 67) suggest that TPN-induced hypophosphatemia and PDS are induced by the large glucose load administered in TPN. Other mechanisms include increased urinary losses of phosphate with excretion of amino acids (127) and impaired calcium and phosphate accretion in the bone (162–164).

Patients receiving TPN with inadequate amounts of phosphate have been reported to develop widespread manifestations of the phosphate depletion syndrome (161). These include myopathy with respiratory failure (9, 133), decrease in cardiac muscle contractility (136), central nervous system disturbances ranging from confusion to coma (146, 155), peripheral neuropathies manifested as parasthesias (167, 190), and death (189). Hematological abnormalities included decreased red blood cell levels of P, ATP, and 2,3-DPG, which lead to hemolysis (76, 179), and decreased chemotaxis and bacteriocidity of phagocytes (38).

In detailed balance studies Rudman et al (156) determined phosphorus requirements in TPN and the effect of phosphorus balance on the accretion of other nutrients. They showed that in malnourished patients maintained on parenteral nutrition, the daily phosphorus requirements amount to 0.018 g/kg ideal body weight (1.25 g is average of a 70-kg patient). They have also shown that phosphorus-deficient TPN solutions impaired retention of N, K, and Cl. Even in the presence of zero or negligible phosphate accretion, patients continued to gain weight, but the increments in weight consisted mainly of adipose tissue with little or no increase in protoplasm or extracellular fluids. Thus, the inclusion of sufficient amounts of phosphate in TPN solutions is essential to prevent the PDS, to achieve optimal utilization of other nutrients, and to ensure appropriate composition of the weight gained.

Daily amounts of ~1000 mg provide the maintenance TPN phosphorus requirements of most adult patients. During the first days of TPN treatment in severely malnourished or diabetic patients, the formula of the intravenous feeding may need to be fortified with additional amounts of elemental phosphorus ranging between 250 and 1000 mg.

Enteral feeding regimens usually use commericial nutrient solutions. These solutions contain sufficient amounts of phosphorus and provide between 500 and 900 mg for each 1000 calories. Patients who receive all their nutrients from such solutions for prolonged periods (up to 2 years) maintain normal serum phosphate and do not have manifestations of phosphate deficiency (M. Shike, unpublished data). However, when such solutions are administered to patients with severe phosphate depletion, additional amounts of phosphate may be required to achieve and maintain normal serum phosphate (98, 161). Such additional amounts are best given separately from the enteral feeding to prevent precipitation of insoluble phosphate salts in the intestine.

Gastrointestinal Malabsorption

Diseases leading to gastrointestinal malabsorption can cause hypophosphatemia and phosphate depletion through different mechanisms, which include (33, 168)

1. Phosphate malabsorption secondary to decreased absorptive capacity of the intestines. This situation occurs in diseases that affect large areas of the small bowel such as Crohn's disease, celiac disease, short bowel syndrome, and radiation enteritis;
2. Malabsorption of vitamin D, which as noted above plays a role in phosphate intestinal absorption;
3. Increased urinary losses due to secondary hyperparathyroidism induced by calcium malabsorption.

Phosphate Binders

Antacids, widely used for treatment of peptic ulcer disease, contain Mg and Al, both of which bind phosphate and form nonsoluble complexes in the intestines and thus prevent phosphate absorption. There are ten well-documented cases in the literature of antacid-induced phosphate depletion syndrome (2, 10, 17, 32, 37, 45, 63, 75, 110, 112) and recently an eleventh case (107) has been reported with widespread metabolic and clinical manifestations. Interestingly, one of the reported cases (2) had hypophosphatemia despite renal failure. The duration of antacid therapy in patients with this syndrome ranged between 2 and 12 years prior to diagnosis, by which time widespread clinical and metabolic manifestations of the phosphate depletion had emerged. Although the clinical PDS syndrome takes a long time to develop, hypophosphatemia can occur within two weeks of initiation of antacid therapy, particularly when the diet is deficient in phosphorus (112). Antacid-induced hypophosphatemia can occur in healthy individuals, in patients with peptic ulcers, and even in patients with renal failure treated overzealously for hyperphosphatemia (1). In recent years, the availability of histamine H_2 blockers for treatment of peptic ulcer disease decreased the need for using phosphate-binding antacids for prolonged periods.

Starvation

Tissue breakdown in starvation releases various minerals (P, K, Zn) into the plasma, with subsequent losses in the urine. Thus, gradual total body depletion of these minerals may occur. The plasma levels of phosphate in starvation may be maintained in the normal range through the continuous release of phosphate from tissue catabolism. This is an important point to consider when nutritional repletion is undertaken since the normal plasma phosphate may not reflect the body phosphate depletion. Adequate amounts of phosphate in the

diet or formula given after starvation must be provided to prevent acute intracellular phosphate depletion.

Diabetes Mellitus

Patients with well-controlled diabetes mellitus do not have excessive losses of phosphate. In the presence of hyperglycemia, especially when accompanied with polyuria and acidosis, phosphate is lost through the urine in excessive amounts, up to 7.5 mg/kg body weight daily (8, 82, 118, 132). In ketoacidosis, intracellular organic components tend to be broken down, releasing large amounts of phosphate into the plasma, which is subsequently lost in the urine (60, 82). This process, combined with the enhanced osmotic phosphate diuresis that is secondary to glycosuria, ketonuria, and polyuria, causes large urinary losses of phosphate and subsequent depletion. The plasma phosphate is usually normal or slightly elevated in the ketotic patient, in spite of the excessive urinary losses, because of the continuous large shift of phosphate from the cells into the plasma. In the corrective treatment of ketoacidosis, administration of fluids and insulin induces large shifts of phosphate back into the cells with ensuing hypophosphatemia. Thus, within a few hours of treatment of ketoacidosis a state of severe hypophosphatemia may develop unless large amounts of phosphate are administered (8, 118). It has been shown experimentally that following a brief episode of acidosis the reinstitution of normal levels of intracellular organic phosphate may take up to 10 days (66).

Alcoholism

There are multiple causes for phosphate depletion in the chronic alcoholic, including decreased dietary intake, malabsorption, increased urinary losses (85, 121), hypomagnesemia, and hypokalemia (7, 191), and secondary hyperparathyroidism. It is unclear whether alcohol directly increases urinary losses of phoshate. In one study (115) significant amounts of phosphate were excreted in the urine following alcohol infusion. In other studies of normals and chronic alcoholics, no such effect of alcohol was noted (81, 88). It must be emphasized that chronic alcoholism results in widespread metabolic abnormalities, which may indirectly mediate the effect of alcohol on phosphate metabolism. Thus, alcohol-induced hypomagnesemia and hypokalemia can result in urinary phosphate wasting, while dehydration and impaired urinary function may cause the opposite.

Acidosis in the alcoholic is another mechanism that can induce excessive phosphate losses in the urine with subsequent phosphate depletion (147, 173, 176). Ketoacidosis occurs in alcoholics whose diets are inadequate and lactic acidosis develops in severe alcoholics whose redox state is impaired. In both causes of acidosis, breakdown of intracellular phosphate-containing com-

pounds can occur with release of phosphate into the plasma and subsequent loss through the urine.

When phosphate-depleted alcoholics are admitted to a hospital, acute hypophosphatemia may be precipitated by the administration of glucose and antacids, sepsis, and metabolic acidosis. This sequence of events can easily be prevented by paying appropriate attention to phosphate status and requirements.

Increased Urinary Losses

As noted earlier, the kidney plays an essential role in phosphate conservation. Disruption of this function can cause large urinary losses with subsequent phosphate depletion and hypophosphatemia. Abnormalities in tubular handling of phosphate have been implicated in the genesis of hypophosphatemia induced by hypokalemia (7, 183), hypomagnesemia (165, 191), renal tubular acidosis, systemic acidosis (62, 145), acute gout (46), paraneoplastic syndrome (129, 138, 158), and hypothyroidism (126, 152). During the recovery phase from severe burns hypophosphatemia may occur secondary to massive diuresis with phosphaturia, and an increase in phosphate utilization during tissue reconstruction (85). A similar phenomenon was seen in the course of treatment of hypothermia (106).

In the rare genetic disorder X-linked hypophosphatemic rickets, there is a renal tubular defect that impairs phosphate reabsorption and results in excessive urinary phosphate losses and subsequent phosphate depletion (122, 166, 195). It is unclear whether the renal tubular defect in this disease is primary or secondary to a hormonal disorder (150, 160).

Fanconi's syndrome is the name of a group of disorders characterized by dysfunction of the proximal renal tubule that results in wasting of glucose, amino acids, and phosphate (142), and inability to excrete an acid load (renal tubular acidosis). Fanconi's syndrome may be idiopathic (sporadic or familial), a manifestation of a genetic metabolic disease, (cystinosis, Wilson's disease, galactosemia), acquired (amylosidosis, multiple myeloma, nephrotic syndrome, heavy metal poisoning), or associated with an intrinsic kidney disease such as medullary cystic disease. The extensive losses of phosphate, glucose, and amino acids and the renal tubular acidosis may be found individually or in various combinations. Hemodialysis against a low phosphate level can also result in hypophosphatemia (1, 18), particularly in patients using phosphate-binding antacids concomitantly.

CLINICAL MANIFESTATIONS OF HYPOPHOSPHATEMIA

As noted above, hypophosphatemia can result in tissue hypoxia (secondary to the decrease in red blood cell 2,3-DPG) and in impairment in the generation

of ATP. The central role of oxygen and ATP in cellular metabolism explains the widespread clinical and metabolic manifestations of phosphate depletion and hypophosphatemia (Table 2).

Constitutional symptoms such as anorexia, malaise, debility, lethargy, and joint stiffness have been described in association with hypophosphatemia (110). These symptoms can be present in addition to the specific manifestations described below.

Nervous System Manifestations

Abnormalities occur both in the central nervous system and in peripheral nerves. Central nervous system damage may be manifested as a range of clinical pictures, including altered sensorium (86, 167), convulsions (167), confusions, delirium, stupor, and coma (5, 146, 155, 196). There are several reports of EEG abnormalities (18, 179) that characterize metabolic damage to the CNS. Peripheral nerve dysfunctions due to phosphate depletion manifest as parasthesias and a decrease in the nerve conduction velocity (190). Recently, sensory neural hearing loss was found in three adult patients with hypophosphatemic bone disease (125).

Hematologic Manifestations

The red blood cell (RBC) derives its high energy compounds through the glycolytic pathway. Low intracorpuscular phosphate levels impair the activity and regulation of the glycolytic enzymes glyceraldehyde-3-phosphate dehydrogenese, hexokinase, and phosphofructokinase, resulting in low levels of ATP and 2,3-DPG (58, 108, 188, 197). When the ATP levels fall, the erythrocyte becomes rigid and is entrapped in the spleen. Further reduction in the ATP levels to below 50% of the normal values, usually when serum phosphate is lower than 0.2 mg/dl (76, 108), is associated with hemolysis (76, 84). The erythrocyte ATP concentrations are highly correlated with serum phosphate (108).

Table 2 Clinical manifestations of hypophosphatemia

Type	Manifestation
Constitutional	Anorexia, malaise, debility, lethargy
Neuropsychiatric	Altered sensorium, confusion, seizures, coma, decreased motor and sensory nerve conduction
Hematologic	RBC deformity, hemolysis, impaired phagocytosis, thrombocytopathia, and hemorrhage
Metabolic	Insulin resistance and glucose intolerance
Gastrointestinal	Dysphagia, ileus, impaired liver function tests
Musculoskeletal	Rickets (osteomalacia), arthralgia, muscle weakness, rhabdomyolysis
Renal	Glycosuria, magnesuria, renal tubular acidosis

The blood smear of the phosphate-depleted patient shows fragmented erythrocytes and microspherocytes. Functionally, the red blood cells have increased osmotic fragility (76), a manifestation of membrane dysfunction. In addition to the damage to the red blood cell itself, phosphate depletion decreases its ability to deliver oxygen to the tissues. The production of 2,3-DPG is reduced, which thereby increases oxygen affinity to hemoglobin and, subsequently, causes tissue hypoxia. The consequences of hypophosphatemia on the red blood cell can be reversed with adequate phosphate supplementation (76, 84).

Reduction in leukocyte ATP content is associated with reduced phagocytic, chemotactic, and bactericidal activity (38). These abnormalities can result in an increased susceptibility to infection. The defects in the leukocyte function can be corrected by correcting the hypophosphatemia or by incubating the leukocyte with adenosine and phosphate (38).

Hypophosphatemia is also associated with reduced ATP in platelets. When the level falls below 50% of normal, clot retraction becomes impaired (197), and with further reductions there is a decrease in platelet survival, thrombocytopathia, and hemorrhages (38, 197). The bone marrow reacts by increasing the number of megakaryocytes and the production of platelets.

Gastrointestinal and Hepatic Manifestations

Hypophosphatemia affects the gastrointestinal tract mainly by disrupting the contractility of the smooth muscles of the intestines. This can lead to dysphagia, gastric atony, and ileus.

Patients with chronic hepatic failure due to cirrhosis have greater impairment of their hepatic function when they are hypophosphatemic (59, 85). Hepatic oxygen extraction was found to be worse in malnourished hypophosphatemic cirrhotic patients compared to normophosphatemic patients (148). It is suggested that the lower levels of 2,3-DPG and ATP within the erythrocytes are responsible for the greater hepatic hypoxemia in the hypophosphatemic patients (73).

Musculoskeletal Manifestations

Muscles require large amounts of high energy bonds (ATP, creatine-phosphate) and oxygen for contraction, for maintenance of membrane potential, and for other functions. Phosphate deprivation (alone or in conjunction with starvation) induces muscle cell injury characterized by a decrease in intracellular phosphate and an increase in water, sodium, and chloride (86–88). The muscular clinical manifestations of the phosphate deficiency syndrome include myalgia (18, 111, 129), objective weakness (10, 18, 111), and myopathy with histopathologic and electromyographic changes (87, 107). The most severe form of phosphate-depletion-induced myopathy is rhabdomyolysis, which can lead to renal failure. Rhabdomyolysis usually devel-

ops in patients with preexisting phosphate deficiency who develop acute hypophosphatemia. It has been described in alcoholics with preexisting subclinical myopathy (85, 86, 169) following infusion of large amounts of carbohydrates, (86, 87) and in the course of treatment of diabetic ketoacidosis (86). Hypophosphatemia can decrease muscle contractility in the diaphragm, which leads to respiratory failure (133), and in the heart, which leads to decreased cardiac output and cardiac failure (40, 136).

Hypophosphatemia may lead to osteomalacia and rickets. Skeletal defects have been reported in association with phosphate depletion of different causes: dietary deprivation in experimental animals (12, 61), use of antacids (10, 17, 37, 110), hemodialysis (1, 18), and vitamin-D-resistant rickets (56, 122, 150, 154, 171, 195). Both mineralization defects and bone resorption have been demonstrated in conjunction with phosphate depletion. The mechanism of the mineralization defect has not been elucidated (25). It has been proposed that hypophosphatemia results in a decreased calcium and phosphate multiplication product at the mineralization front (35), with a decrease in the precipitation of hydroxyapetite crystals in the bone matrix. This mechanism has been disputed because of the low equilibrium constant (K_p) of the reaction that produces apetite (A. Boskey, personal communication, 1986). The enhanced bone resorption of the phosphate depletion syndrome does not seem to be PTH mediated (150) since plasma PTH is decreased in the presence of hypophosphatemia. Increased serum levels of 1,25-$(OH)_2$D, which may accompany hypophosphatemia, could enhance bone resorption. However, elevated levels of 1,25-$(OH)_2$D have not been consistently observed in patients with phosphate depletion and bone abnormalities (107).

The role that vitamin D metabolites play in the mineralization defects of the phosphate depletion syndrome is controversial. It is highly unlikely that deficiency of 1,25-$(OH)_2$D is responsible since synthesis of this metabolite is enhanced in the presence of hypophosphatemia. It has not been established whether generation of other vitamin D metabolites such as 24,25-$(OH)_2$D is impaired secondary to hypophosphatemia. Vitamin D supplementation does not protect against osteomalacia of dietary phosphate deficiency (114, 160).

Renal Manifestations

Impaired tubular function and abnormalities in handling of acid in the kidney are the main renal manifestations of hypophosphatemia. Phosphate acts as a proton trap in the kidney by converting from HPO_4^{2-} to $H_2PO^-_4$, which is excreted in the urine. Decrease in filtrable phosphoric acid may lead to renal tubular acidosis (53, 95). Subsequent systemic acidosis rarely occurs, because of the bicarbonatemia (53, 64). However, in children with the refeeding syndrome (142) systemic acidosis has been described.

Glycosuria (65) and magnesuria (119, 157, 192) have been described secondary to hypophosphatemia-induced disturbance in tubular function.

Metabolic Manifestations

As noted earlier, phosphate depletion is associated with decreased levels of intracellular ATP. This is mediated primarily by two mechanisms: (*a*) lack of phosphate available for conversion of AMP and ADP to ATP, and (*b*) decrease in RBC 2,3-DPG, which leads to decreased release of O_2 from the hemoglobin to the tissues and, consequently, to a reduction of oxidative phosphorylation, which generates the ATP. Intracellular ATP depletion causes widespread metabolic abnormalities and derangements in specific cellular functions, such as relative insulin resistance (42, 117) and decreased intestinal calcium absorption (103). Intracellular phosphate regulates the activity of various enzymes affecting (*a*) glucose metabolism: hexokinase, phosphofructokinase (98, 180); (*b*) amino acids: glutaminase (137); (*c*) nucleic acids: AMP deaminanse, 5'-nucleotidase, adenine denucleotidase (58, 93, 193); and (*d*) hormones: 25-OH-D hydroxylase (195). Increased resistance to insulin is thought to mediate the suggested impairments in glucose metabolism in patients with hypophosphatemia and vitamin-D-resistant rickets (42).

TREATMENT OF HYPOPHOSPHATEMIA AND PHOSPHATE DEPLETION

The appropriate management of hypophosphatemia and phosphate depletion requires identification of the underlying causes, treatment with supplemental phosphate when necessary, and prevention of recurrence of the problem by correcting the underlying causes. Phosphate can be administered orally, intravenously, rectally, and through dialysis fluids. Phosphate supplementation is essential in patients with profound hypophosphatemia and in those who become symptomatic. The symptoms and signs of phosphate depletion can vary, are nonspecific, and are usually seen in patients with multiple problems. This makes it difficult to identify phosphate depletion as the cause of the clinical manifestations.

Mild hypophosphatemia secondary to redistribution, with plasma phosphate levels higher than 2 mg/dl, is transient and requires no treatment. In cases of mild hypophosphatemia levels associated with phosphate depletion [serum phosphate higher than 1.0 mg/dl in adults or 2.0 mg/dl in children (83)], phosphate supplementation has to be administered in addition to treating the cause of the hypophosphatemia. Oral phosphate can be given in the form of skim milk (which contains 0.9–1.0 mg of elemental phosphorus P per ml) or in the form of Neutraphos® tablets (which contain 250 mg of P per tablet as a Na or K salt). Oral phosphate can be given in a dose up to 3 g/day. The serum phosphate levels rise by as much as 1.5 mg/dl 60 to 120 minutes after ingestion of 1000 mg of P (102).

Severe hypophosphatemia with serum levels lower than 0.5 mg/dl occurs only when there is cumulative net loss of more than 3.3 g of P (142). In these

cases, oral replacement with 6 to 10 g has to be given (142). Symptoms of hypophosphatemia are usually present after net loss of at least 10 g of P (111). When symptoms are present, 20 g of P have to be given and spread over a period of one week (3 g/day). In the presence of severe hypophosphatemia with serious clinical manifestations of phosphate depletion such as mental derangements, seizures, hemolysis, and rhabdomyolysis, intravenous phosphate must be administered. Treatment can be initiated with a dose of 2 mg/kg body weight over 6 hours (182). This dose is effective in restoring serum levels to above 1.5 mg/dl within 36 hours. There have been reports of intravenous therapy with doses as high as 7.5 mg/kg over 6 hours (105). When intravenous phosphate is administered, serum levels have to be monitored every 6 hours and the amount infused has to be adjusted. The intravenous route also has to be used in patients with mild to moderate hypophosphatemia in whom the gastrointestinal tract cannot be utilized. In such cases the dose administered intravenously should be two thirds of the recommended oral dose.

Treatment with phosphate can result in the following side effects and complications:

1. Diarrhea—orally administered phosphate is a laxative and can induce diarrhea that by itself would increase fecal phosphate losses. One gram of phosphate can usually be given daily without causing diarrhea.
2. Hyperphosphatemia can occur in patients with mild renal insufficiency.
3. Hypocalcemia can be secondary to hyperphosphatemia; therefore calcium has to be given in parallel to the phosphate (but not at the same time). When giving phosphate intravenously, serum calcium concentration has to be below 10 mg/dl and phosphate below 30 mg/dl in order to prevent their precipitation (52).
4. Hyperkalemia can be precipitated in oliguric patients by using K_3PO_4 salts.
5. Administration of Na_3PO_4 may lead to volume excess.
6. Mild acidosis from the intravenous preparations with pH of 5.7 to 6.6 or from oral Na_3PO_4 can occur (105).

The most effective approach to hypophosphatemia is prevention in susceptible conditions. Patients on total parenteral nutrition should receive the daily maintenance dose of phosphate amounting to 1000 mg in 24 hr with increases as required by the clinical and metabolic states. Alcoholic patients receiving intravenous fluids, particularly those with glucose, should receive phosphate supplementation, especially if they present with hypophosphatemia. In diabetic ketoacidosis up to 75 mg/kg of P per day may be required to restore adequate balance (8, 118, 132). Dialysis patients who usually have hyperphosphatemia may develop iatrogenic hypophosphatemia secondary to di-

alysis and the use of phosphate binder. In patients requiring prolonged antacid therapy, alternative treatment with H_2 blockers should be considered. If this is not feasible, phosphate supplementation of 250 mg of phosphate for every 100 ml of antacid should be given.

HYPERPHOSPHATEMIA

Etiology

The healthy kidney can excrete a high phosphate load and thus prevent hyperphosphatemia. The amount excreted is determined by the difference between the amount filtered in the glomerulus and that reabsorbed in the tubuli. Hyperphosphatemia usually occurs as a result of renal failure and reduced ability of the kidney to excete a phosphate load. A large influx of phosphates from the cells into the plasma can also result in hyperphosphatemia, particularly in the presence of reduced renal function. Such an influx occurs most commonly in severe hemolysis, tumor lysis syndrome, and rhabdomyolysis. In hemolysis, the disintegrating red blood cells release phosphate into the plasma. The most common tumors associated with hyperphosphatemia induced by tumor lysis syndrome are lymphomas and lymphocytic leukemia, because of the high phosphate content of the lymphocytes (151). Large amounts of phosphates are released into the plasma either because of primary cell destruction (30, 186, 200) or as a result of chemotherapy (23, 55). In rhabdomyolysis the damaged muscle releases large amounts of phosphate or phosphate-containing compounds into the plasma. The large amounts of myoglobin released during rhabdomyolysis often precipitate acute renal failure, which thus limits the ability of the kidneys to excrete the excess phosphate.

Phosphate loading through the gastrointestinal tract resulting in hyperphosphatemia can occur through enemas (74) and phosphate-containing laxatives (77, 123), particularly in the presence of some degree of renal failure.

Hypoparathyroidism, either primary or secondary, can be associated with hyperphosphatemia in the presence of normal renal function. Mild hyperphosphatemia can be seen in acromegaly (3). This is secondary to growth-hormone-induced enhancement of tubular reabsorption of phosphate. In severe hyperthyroidism up to 30% of patients may have hyperphosphatemia due to increased renal retention (19) as well as bone resorption (92). The hyperphosphatemia resolves with the return of normal thyroid function.

Ectopic Calcification

Prolonged hyperphosphatemia may be accompanied by ectopic calcification arising from the precipitation of calcium-phosphate crystals in different tissues. This happens usually when the Ca-phosphate multiplication prod-

uct is above 60 (140, 186). The anatomic distribution of calcification depends on local tissue factors, particularly necrosis (4), as well as on systemic factors such as plasma PTH levels (120). There is a predisposition for tissue calcinosis especially in the periarticular region of large joints (77, 96, 141).

The syndrome of tumoral calcinosis, first described by Duret in 1899 (cited in 98), is characterized by mild hyperphosphatemia without renal failure. It is usually of juvenile onset. PTH levels were found to be on the lower level of normal in these patients (113, 128). Diamox, which inhibits proximal tubular reabsorption of phosphate, induces phosphaturia in these patients (128). High levels of 1,25-$(OH)_2D_3$ were noted, and derangement in its regulation was suggested as a possible mechanism in this syndrome (198).

Management of Hyperphosphatemia

Hyperphosphatemia is managed primarily by managing its cause. In acute states, fluid load is helpful, as long as there is no kidney damage. In chronic conditions the use of oral phosphate binders is recommended. The most common are Al, Mg, and Ca salts. The potential side effects of these salts have to be considered, especially since most patients who require this treatment are in some degree of renal failure. Aluminum salts used for prolonged periods can induce a metabolic bone disease as well as a chronic type of encephalopathy. Magnesium is hardly excreted in renal failure and hypermagnesemia can occur. The magnesium salts can also cause diarrhea with all its complications.

SUMMARY

Phosphorus is the sixth most abundant element in the body after oxygen, hydrogen, carbon, nitrogen, and calcium. It comprises about 1% of the total body weight of humans. Eighty-five percent of it is stored in the bone in the form of hydroxyapetite crystal; 14% is in the soft tissues in the form of energy-storing bonds with nucleotides (ATP, GTP), nucleic acids in chromosomes and ribosomes, 2,3-DPG in the red blood cells, and phospholipids in the cells' membranes. Less than 1% is in the extracellular fluids.

Phosphate balance is maintained by multiple systems. The gut is responsible for the absorption of two thirds of the 4–30 mg/kg/day of phosphate intake. Absorption sites are all along the gut; in humans the most active site is the jejunum. The kidney filters 90% of the plasma phosphate and reabsorbs it in the tubuli. In states of hypophosphatemia the kidney can reabsorb the filtered phosphates very efficiently, reducing the amount excreted in the urine virtually to zero. The healthy kidney can excrete high loads of phosphate and rid the body of phosphate overload. Through the vitamin D–PTH axis the

endocrine system regulates the phosphate balance by influencing the kidney, gut, and bone. Other hormones, including thyroid, insulin, glucagon, glucocorticosteroid, and thyrocalcitonin, play a lesser role in regulation of phosphate metabolism.

Because of the complex control of phosphate homeostasis, various clinical conditions may lead to hypophosphatemia. These include nutritional repletion, gastrointestinal malabsorption, use of phosphate binders, starvation, diabetes mellitus, and increased urinary losses due to tubular dysfunction.

The clinical picture of phosphate depletion is manifested in different organs and is due mainly to the fall in intracellular levels of ATP and decreased availability of oxygen to the tissues, secondary to 2,3-DPG depletion. The various manifestations of phosphate depletion are listed in Table 2.

The treatment of hypophosphatemia consists of administering enteral or parenteral phosphate salts. An important aspect of dealing with the potentially serious effects of phosphate depletion is to prevent the depletion from happening in the first place.

Hyperphosphatemia can occur in renal failure, hemolysis, tumor lysis syndrome, and rhabdomyolysis. The treatment of hyperphosphatemia usually consists of fluid administration (in the absence of kidney failure). In chronic hyperphosphatemia, phosphate binders such as aluminum and magnesium salts can reduce the phosphate load. The use of these phosphate binders is limited by their potential side effects.

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