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DISTURBANCES OF PHOSPHATE BALANCE: HYPOPHOSPHATEMIA

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SUMMARY – Hypophosphatemia when combined with phosphate depletion (that is, not due to phosphate shift into the cells) can cause a variety of signs and symptoms. The manifestations depend in large part upon the severity and chronicity of the phosphate depletion, with the plasma phosphate concentration usually being below 0.32 mmol/L in symptomatic patients. The major conditions associated with symptomatic hypophosphatemia are chronic alcoholism, intravenous hyperalimentation without phosphate, and chronic ingestion of antacids. Severe hypophosphatemia can also be seen during treatment for diabetic ketoacidosis and with prolonged hyperventilation.

Key words: *Hypophosphatemia – physiopathology; Hypophosphatemia – etiology; Hypophosphatemia – diagnosis; Hypophosphatemia – therapy; Phosphorus – metabolism*

Introduction

Phosphate is a ubiquitous intracellular anion that is essential for membrane structure and energy transport in all cells. In particular, phosphate is necessary to produce adenosine triphosphate (ATP), which provides energy for nearly all cell functions. Phosphate is also necessary in red cells for the production of 2,3-diphosphoglycerate (2,3-DPG), which facilitates the release of oxygen from hemoglobin.

Reducing available phosphate may compromise any organ system, alone or in combination. The critical role that phosphate plays in every cell, tissue, and organ explains the systemic nature of injury caused by phosphate deficiency.

Hypophosphatemia is defined as mild (0.65-0.81 mmol/L), moderate (0.3-0.65 mmol/L), or severe (<0.3 mmol/L).

Mild to moderate hypophosphatemia is usually asymptomatic. Major clinical sequels usually occur only in severe hypophosphatemia.

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As in case of other intracellular ions, a decrease in the serum level of phosphate should be distinguished from a decrease in total body storage of phosphate[1].

Metabolism of Phosphorus

The physiologic concentration of serum phosphorus (phosphate) in normal adults ranges from 0.8 to 1.44 mmol/L. Serum phosphorus shows diurnal variation of 0.2-0.3 mmol/L, the lowest concentration occurring between 8 a.m. and 11 a.m., as well as seasonal variation, the highest serum phosphorus concentration being recorded in summer and lowest in winter. Serum phosphorus concentration is markedly higher in growing children and adolescents than in adults, and is also increased during pregnancy.

Of the phosphorus in the body, 80% to 85% is found in the skeleton. The rest is widely distributed throughout the body in the form of organic phosphate compounds. In the extracellular fluid, including serum, phosphorus is mostly present in the inorganic form. In serum, more than 85% of phosphorus is present as the free ion and less than 15% is protein-bound.

Phosphorus plays an important role in several aspects of cellular metabolism, including adenosine triphosphate

synthesis. Phosphorus is also an important component of phospholipids in cell membranes. Changes in phosphorus content, concentration, or both modulate the activity of a number of metabolic pathways.

The kidney plays a major role in the regulation of phosphorus homeostasis. Most of the inorganic phosphorus in serum is ultrafiltrable at the level of the glomerulus. At physiologic levels of serum phosphorus and during normal dietary phosphorus intake, approximately 6 to 7 g/d of phosphorus are filtered by the kidney. Of this amount, 80% to 90% is reabsorbed by the renal tubules and the rest is excreted in the urine. Most of the filtered phosphorus is reabsorbed in the proximal tubule by way of a sodium gradient-dependent process (Na-Pi cotransport) located on the apical brush border membrane. Recently two distinct Na-Pi cotransport proteins have been cloned from the kidney (type I and type II Na-Pi cotransport proteins). Most of the hormonal and metabolic factors that regulate renal tubular phosphate reabsorption, including alterations in dietary phosphate content and parathyroid hormone, have been shown to modulate the proximal tubular apical membrane expression of the type ll Na-Pi cotransport protein[2].

Causes of Hypophosphatemia

There are three major mechanisms by which hypophosphatemia can occur (Table 1):

- redistribution of phosphate from the extracellular fluid into cells,
- decreased intestinal absorption of phosphate, and
- increased urinary phosphate excretion.

Table 1. Major causes of hypophosphatemia

1.	*Internal redistribution*
	Increased insulin, particularly on refeeding
	Acute respiratory alkalosis
	Hungry bone syndrome
2.	*Decreased intestinal absorption*
	Inadequate intake
	Antacids containing aluminum or magnesium
	Steatorrhea and chronic diarrhea
3.	*Increased urinary excretion*
	Primary and secondary hyperparathyroidism
	Vitamin D deficiency or resistance
	Fanconi's syndrome
	Miscellaneous: osmotic diuresis, proximally acting diuretics
	Acute volume expansion

Internal redistribution

Stimulation of glycolysis increases the formation of phosphorylated carbohydrate compounds in the liver and skeletal muscle. The source of this phosphate is the inorganic phosphate in the extracellular fluid, and as a result, serum phosphate concentration (and urinary phosphate excretion) fall rapidly. This occurs in several situations, the most important being increased insulin secretion, acute respiratory alkalosis and hungry bone syndrome.

Increased insulin secretion, particularly on refeeding

The administration of insulin or glucose, in normal subjects, results in only a small decrease in serum phosphate concentrations. Mild hypophosphatemia can also be induced by the administration of glucagon and epinephrine.

Severe hypophosphatemia may develop in patients with uncontrolled diabetes. Although these patients may initially present with normal or elevated serum phosphorus levels, total body stores are invariably low[3]. Severe acidosis causes decomposition of labile organic intracellular phosphate compounds, and phosphate ions shift into the extracellular fluid where, because of osmotic diuresis, they are filtered at an increased rate resulting in high urinary losses[4]. As insulin is administered, glucose enters the cells, followed by serum phosphorus. Although urinary excretion is then markedly reduced, the end result is the possibility of severe hypophosphatemia due to a combination of total body deficit and sudden shifts into the intracellular space. The development of hypophosphatemia may result in further insulin resistance and glucose intolerance[5]. Hypophosphatemia induced coma occurred in a patient treated for diabetic ketoacidosis[5].

Acute respiratory alkalosis

The fall in partial pressure of carbon dioxide during acute respiratory alkalosis results in a similar change in the cells, because carbon dioxide readily diffuses across cell membranes. The resulting rise in intracellular pH stimulates phosphofructokinase activity which in turn stimulates glycolysis[6]. Extreme hyperventilation in normal subjects can lower serum phosphate concentrations to below 0.32 mmol/L[7], and it is probably the most common cause of marked hypophosphatemia in hospitalized patients[8]. Less pronounced hypophosphatemia may occur during the increase in ventilation after successful treatment of severe asthma[9].

Hungry bone syndrome

Parathyroidectomy (for hyperparathyroidism) or rarely thyroidectomy (for hyperthyroidism) in patients with pre-existing osteopenia can rarely result in marked deposition of calcium and phosphate in bone in the immediate postoperative period. This phenomenon called 'hungry bone' syndrome, may be associated with marked hypocalcemia (which may be symptomatic) and hypophosphatemia.

Decreased intestinal absorption

Normal adults are in phosphate balance. Their dietary intake of phosphate, which usually ranges from 800 to 1500 mg/day, is usually well in excess of gastrointestinal losses, and therefore variation in the intake usually has little effect on phosphate homeostasis. There is little regulation of gut apsorption. Approximately 80% of dietary phosphate is absorbed in the small intestine. In addition, 150 to 200 mg *per* day are secreted in the colon.

Inadequate intake

Poor intake alone is rarely responsible for severe phosphate depletion because of rapid renal adaptation, whereby renal tubular phosphate reapsorption approaches 100%, and therefore urinary phosphate excretion approaches zero[10,11]. If phosphate deprivation is prolonged and severe (intake of less than 100 mg *per* day), then continued colonic phosphate secretion can lead to hypophosphatemia. More often, poor intake is combined with chronic diarrhea to cause markedly negative phosphate balance.

Steatorrhea and chronic diarrhea

Steatorrhea or chronic diarrhea can cause mild to moderate hypophosphatemia due to decreased phosphate absorption from the gut and renal phosphate wasting, the latter caused by secondary hyperparathyroidism induced by concomitant vitamin D deficiency.

Antacids containing aluminum or magnesium

The consequence of severe hypophosphatemia in patients taking antacids may be serious. These drugs cause net loss of phosphate from the body by binding to both ingested and secreted phosphate, with the resulting formation of insoluble aluminum or magnesium phosphate salts. Prolonged high-dose treatment with these drugs can cause hypophosphatemia, osteomalacia, and myopathy[11].

Increased urinary excretion

The kidney exerts a major influence on phosphate balance. Renal phosphate transport occurs in the proximal tubule and in the distal tubule[10]. Phosphate reabsorption is linked to sodium reabsorption *via* a sodium-phosphate cotransporter in the luminal membrane. This transporter uses the favorable inward concentration gradient for sodium (the cell sodium concentration is less than 25 mmol/L, well below 145 mmol/L concentration in the tubular lumen) to drive the active reabsorption of phosphate.

There are two major physiologic regulators of renal tubular phosphate reabsorption: the serum phosphate concentration itself, because even mild phosphate depletion stimulates phosphate reabsorption *via* the sodium-phosphate cotransporter. Phosphate depletion also leads to increased synthesis of new transporters, further increasing tubular phosphate reabsorption. The other is parathyroid hormone (PTH), which increases phosphate excretion by diminishing the activity of the sodium-phosphate cotransporter[10]. Phosphate reabsorption is also inhibited by glucose *via* an unknown mechanism.

Primary and secondary hyperparathyroidism

Any cause of hypersecretion of PTH can lead to hypophosphatemia. This occurs in primary hyperparathyroidism and in secondary hyperparathyroidism induced by any of the causes of vitamin D deficiency. Most patients with primary hyperparathyroidism have mild hypophosphatemia. It may be more severe in those with vitamin D deficiency and secondary hyperparathyroidism, because they have not only increased urinary phosphate excretion but also decreased gastrointestinal phosphate absorption.

Vitamin D deficiency and resistance

Vitamin D deficiency can cause hypophosphatemia both by decreasing gastrointestinal phosphate absorption and by causing hypocalcemia and secondary hyperparathyroidism, resulting in increased urinary phosphate excretion. Vitamin D deficiency can occur as the result of a decreased intake or absorption, reduced sun exposure, increased hepatic catabolism, decreased endogenous synthesis, or end-organ resistance.

Primary renal phosphate wasting

There are several rare syndromes characterized by isolated urinary phosphate wasting. The resulting hypophosphatemia is the primary cause of rickets and, in contrast to vitamin D deficiency or resistance, hypocalcemia is not present. A similar syndrome occurs as an acquired disorder in patients with oncogenic osteomalacia. These patients usually have tumors of mesenchymal origin, often a sclerosing type of hemangioma, that probably produce the postulated phosphatic hormone.

Fanconi syndrome

The Fanconi syndrome refers to a generalized impairment in proximal tubular function leading to urinary wasting of compounds normally reabsorbed in the proximal tubule. The consequences are hypophosphatemia, osteomalacia, renal glucosuria, hypouricemia, aminoaciduria, and type 2 renal tubular acidosis due to bicarbonate loss in urine. Serum calcitriol concentrations are either low or inappropriate normal. The Fanconi syndrome is rare in adults. It is most often due to multiple myeloma.

Miscellaneous

Other factors that can increase urinary phosphate excretion are osmotic diuresis (most often due to glucosuria), proximally acting diuretics (acetazolamide and some thiazide diuretics that also have carbonic anhydrase inhibitory activity such as metalazone), and acute volume expansion (which diminishes proximal sodium reabsorption).

Symptoms and Signs of Hypophosphatemia

Hypophosphatemia, when combined with phosphate depletion, can cause a variety of signs and symptoms[1,3] (Table 2). The manifestations depend in large part upon the severity and chronicity of the phosphate depletion, with the plasma phosphate concentration usually being below 0.32 mmol/L in symptomatic patients. The major conditions associated with symptomatic hypophosphatemia are chronic alcoholism, intravenous hyperalimentation without phosphate, and chronic ingestion of antacids. Severe hypophosphatemia can also be seen during treatment for diabetic ketoacidosis and with prolonged hyperventilation.

Hypophosphatemia can impair myocardial performance. The reduction in cardiac output may become clinically significant, leading to congestive heart failure, when the plasma phosphate concentration falls to 0.32 mmol/L.

Severe hypophosphatemia can lead to metabolic encephalopathy that is basically due to tissue ischemia. Typical presenting symptoms include irritability and paresthesias, which can progress to confusion, seizures, delirium, and coma[3,14,15].

Prolonged hypophosphatemia produces a number of effects on both the kidney and bone. A number of patients with idiopathic hypercalcuria have mild hypophosphatemia and it has been suggested that impaired phosphate balance may be the primary abnormality, with enhanced calcium excretion representing a secondary effect.

Table 2. Signs and symptoms of hypophosphatemia

A.	*Central nervous system dysfunction*
	Metabolic encephalopathy due to tissue ischemia
	Irritability
	Paresthesias
	Confusion
	Delirium
	Coma
B.	*Cardiac dysfunction*
	Impaired myocardial contractility
	Congestive heart failure
C.	*Pulmonary dysfunction*
	Weakness of the diaphragm
	Respiratory failure
D.	*Skeletal and smooth muscle dysfunction*
	Proximal myopathy
	Dysphagia and ileus
	Rhabdomyolysis
E.	*Hematologic dysfunction*
	Erythrocyte: increased rigidity; hemolysis
	Leukocyte: impaired phagocytosis; decreased granulocyte chemotaxis
	Platelets: defective clot retraction; thrombocytopenia
F.	*Bone disease*
	Increased bone resorption
	Rickets and osteomalacia caused by decreased bone mineralization
G.	*Renal effects*
	Decreased glomerular filtration rate
	Decreased tubular transport maximum for bicarbonate
	Decreased titratable acid excretion
	Hypercalcuria
	Hypermagnesuria
H.	*Metabolic effects*
	Low parathyroid hormone levels, increased creatinine phosphokinase levels

The effects of hypophosphatemia on muscle depend on the severity and chronicity of the deficiency. Hypophosphatemia induced manifestations of muscle dysfunction include proximal myopathy (affecting skeletal muscle)[16], and dysphagia and ileus (affecting smooth muscle). In addition, acute hypophosphatemia superimposed upon the pre-existing severe phosphate depletion can lead to rhabdomyolysis[17,18].

The development of rhabdomyolysis with associated release of phosphate from the damaged muscle cells has two clinical consequences: it may mask the underlying hypophosphatemia and may therefore protect against the development of other hypophosphatemic symptoms[17,18]. The demonstration of a low plasma phosphate concentration before or after the peak muscle breakdown may be the only clue to the underlying phosphate depletion.

Because phosphorus is an integral component of bone, which contains 80% of the body's supply, it is not surprising that skeletal symptoms have been attributed to phosphorus deficiency. Hypophosphatemia stimulates bone resorption and suppresses osteoid calcification. Normal volunteers on phosphorus-deficient diets developed diffuse bone pains when serum phosphate levels fell below 0.32 mmol/L. These symptoms abated with phosphate replacement.

Hypophosphatemia can also affect each of the components of the hematopoietic system. A reduction in intracellular ATP levels increases erythrocyte rigidity, predisposing to hemolysis which can be seen when the plasma phosphate concentration falls below 0.16 mmol/L[19,20]. Diminished intracellular ATP levels reduce both phagocytosis and granulocyte chemotaxis. This complication is rare and only seen with severe hypophosphatemia.

Hypophosphatemia impairs bicarbonate resorption in the proximal tubule. The resultant increase in the distal tubule pH probably accounts for the lower urinary ammonia excretion observed in phosphorus deficiency. Because a large portion of the urinary titratable acid consists of dihydrogen phosphate, hypophosphatemia also reduces the ability of the kidneys to eliminate acid by this mechanism.

Diagnosis of Hypophosphatemia

The diagnosis of hypophosphatemia is often evident from history. In cases where the diagnosis is not apparent, the measurement of urinary phosphate excretion should be helpful. Phosphate excretion can be measured either in 24-hour urine collection or by calculation of the fractional excretion of filtered phosphate ($FEPO_4$) from a random urine specimen. The formula used to make the latter calculation is the same as that for the fractional excretion of sodium:

$$FEPO_4 = (UPO_4 \times PCr \times 100) : (PPO_4 \times UCr),$$

where U and P refer to the urine and plasma concentrations of PO_4 and creatinine (Cr).

Low phosphate excretion

Daily phosphate excretion should be less than 100 mg and the fractional excretion of phosphate should be well below 5% (normal value is 5% to 20%) if the kidney is responding normally and renal phosphate wasting is not the cause of hypophosphatemia. The differential diagnosis of hypophosphatemia with appropriate renal phosphate retention includes increased cellular uptake and reduced net intestinal absorption. An increased cell entry is more likely if the patient has received glucose or insulin infusions, or has acute respiratory alkalosis. In the absence of these problems, the most likely cause of hypophosphatemia is chronic diarrhea (in which there is loss of phosphate in intestinal secretion), vitamin D deficiency (in which absorption of dietary phosphate is diminished), or chronic antacid intake (in which intestinal phosphate is bound to magnesium or calcium to form insoluble salts that are not absorbed).

Inappropriately high phosphate excretion

Urinary phosphate excretion above 100 mg/day or a fractional excretion of phosphate above 5% is indicative of renal phosphate wasting. This problem is due to either hypophosphatemia or renal tubular defect, both of which impair proximal phosphate reabsorption by diminishing the activity of the sodium-phosphate cotransporter.

Treatment of Hypophosphatemia

The symptoms of hypophosphatemia rarely occur unless the plasma phosphate concentration is less than 0.64 mmol/L. Serious symptoms such as rhambdomyolysis are not seen until the plasma phosphate concentration falls below 0.32 mmol/L. In many cases, it is not necessary to treat hypophosphatemia. As an example, hypophosphatemia occurring during the correction of diabetic ketoacidosis will correct spontaneously with normal dietary intake and prophylactic phosphate supplementation has been shown to be of no benefit. On the other hand, vitamin D supplementation is indicated in patients with vitamin D deficiency. Phosphate supplementation is not dependent only on plasma phosphate concentration and is indicated in patients who are symptomatic or who have a renal tubular defect leading to chronic phosphate wasting. Intravenous phosphate is potentially dangerous, since it can precipitate with calcium and produce a variety of adverse effects including hypocalcemia, renal failure, and potentially fatal arrhythmias. Thus, oral phosphate replacement is preferred with 2.5 to 3.5 grams (80 to 110 mmol) given *per* day in divided doses.

May intravenous therapy be necessary in a symptomatic patient, the dose should not exceed 2.5 mg or 0.09 mmol/kg of body weight over 6 hours[15,21]. The plasma phosphate concentration should be monitored every 6 hours and the patient switched to oral replacement when a level of 0.64 to 0.81 mmol/L is reached[1].

The observation that the acute administration of dipyridamole increases renal phosphate reabsorption in animals and humans prompted a prospective study evaluating its efficacy in 64 patients with idiopathic increased urinary phosphate losses[22]. Exclusion criteria were hypercalcemia, a history of cardiovascular disease, renal dysfunction (glomerular filtration rate of less than 70 mL/min *per* 1.73 m^2), and others (which were primarily focused on identifying patients with specific causes of phosphate wasting)[22]. The administration od dipyridamole (75 mg q.i.d.) significantly increased serum phosphorus levels in 80% of patients, with maximum effects observed after 9 months of therapy. Serum levels of parathyroid hormone and calcium were unchanged, but the concentration of $1,25(OH)_2$ vitamin D was significantly decreased. Further studies are required to determine whether dipyridamole may be effective and safe in this setting.

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Sažetak

POREMEĆAJI RAVNOTEŽE FOSFATA: HIPOFOSFATEMIJA

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Hipofosfatemija je posljedica manjka fosfora koji nije nastao uslijed pomaka fosfata u stanice. Simptomi u velikoj mjeri ovise o težini i duljini trajanja hipofosfatemije, a simptomi se u bolesnika javljaju uglavnom ako je koncentracija fosfora u plazmi ispod 0,32 mmol/L. Najvažnija stanja vezana uza simptomatsku hipofosfatemiju uključuju kronični alkoholizam, totalnu parenteralnu prehranu bez fosfata i dugotrajnu uporabu antacida. Teški oblik hipofosfatemije može se vidjeti i za vrijeme liječenja dijabetične ketoacidoze, kao i kod dugotrajne hiperventilacije.

Ključne riječi: *Hipofosfatemija – fiziopatologija; Hipofosfatemija – etiologija; Hipofosfatemija – dijagnostika; Hipofosfatemija – terapija; Fosfor – metabolizam*