Approach to the Hypophosphatemic Patient

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Hypophosphatemia is commonly missed due to nonspecific signs and symptoms, but it causes considerable morbidity and in some cases contributes to mortality. Three primary mechanisms of hypophosphatemia exist: increased renal excretion, decreased intestinal absorption, and shifts from the extracellular to intracellular compartments. Renal hypophosphatemia can be further divided into fibroblast growth factor 23-mediated or non-fibroblast growth factor 23-mediated causes. Proper diagnosis requires a thorough medication history, family history, physical examination, and assessment of renal tubular phosphate handling to identify the cause. During the past decade, our understanding of phosphate metabolism has grown greatly through the study of rare disorders of phosphate homeostasis. Treatment of hypophosphatemia depends on the underlying disorder and requires close biochemical monitoring. This article illustrates an approach to the hypophosphatemic patient and discusses normal phosphate metabolism. (***J Clin Endocrinol Metab*** **97: 696–706, 2012)**

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- Recognize the causes and symptoms of hypophosphatemia and select appropriate diagnostic testing.
- Apply strategies to diagnose and manageacute and chronic hypohosphatemia.

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Case

A 65-yr-old man developed right medial knee pain while golfing. A tibial stress fracture was identified. He then developed a contralateral stress fracture and generalized pain and weakness in his legs and back. He had no previous history of fracture or childhood rickets. He has type 2 diabetes, hypercholesterolemia, and hypertension, treated with glipizide, quinapril, rosiglitazone, and atorvastatin. He was taking hydrocodone/acetaminophen, rofecoxib, and tramadol for pain, plus 1000 mg of calcium and 600 units of vitamin D daily. Family history was unremarkable.

On examination, he was hypertensive (147/81 mm Hg), weight was 99.2 kg, and height was 182 cm. He had normal dentition, without intraoral masses. He had a cataract in his left eye. He had no palpable masses in his neck or extremities. Examination of lungs, heart, and abdomen was normal, except for a systolic murmur. He required a walker to ambulate, used his arms to rise from a chair, but could do a sit-up. Laboratory testing revealed calcium of

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Abbreviations: ADHR, Autosomal dominant hypophosphatemic rickets; FD, fibrous dysplasia; FGF23, fibroblast growth factor 23; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; 1,25OHD, 1,25-dihydroxyvitamin D; 25OHD, 25-hydroxyvitamin D; TIO, tumor-induced osteomalacia; TmP/GFR, tubular maximum reabsorption of phosphate per unit of glomerular filtrate; XLH, X-linked hypophosphatemia.

8.9 mg/dl, creatinine of 0.8 mg/dl, 25-hydroxyvitamin D (25OHD) of 26 ng/ml, 1,25-dihydroxyvitamin D (1,25OHD) of 25 pg/ml, alkaline phosphatase that had risen from 66 to 171 U/liter, and serum phosphate ranging from 1.1 to 1.7 mg/dl.

Background

Phosphate is involved in a variety of processes including acid-base buffering, postreceptor signaling, energy transfer, and information storage and translation in DNA and RNA. The primary repository (85%) of phosphate is in the bone, where calcium and phosphate (in hydroxyapatite) provide skeletal strength and rigidity (1). Outside of bone, most phosphate is intracellular.

Phosphate is abundantly present in many foods. Isolated dietary phosphate deficiency is uncommon, and deficiency usually occurs with generalized malnutrition. Intestinal phosphate absorption is up-regulated by 1,25OHD. In equilibrium, about 300 mg of phosphate moves into and out of bone daily in adults. Phosphate is freely filtered at the glomerulus and then reabsorbed, but proximal tubular reabsorption is inhibited by both PTH and fibroblast growth factor 23 (FGF23).

For adults, hypophosphatemia is generally defined by serum phosphate concentration below 2.5 mg/dl (0.8 millimolar). However, infants have higher normal phosphate ranges than adults, and these values gradually decline throughout childhood and adolescence to adult levels (2, 3). Young children also have higher renal phosphate thresholds than adults (tubular maximum reabsorption of phosphate per unit of glomerular filtrate, TmP/GFR) (2). This is likely an accommodation to an increased need for phosphate to adequately mineralize the growing skeleton because phosphate concentrations within the adult normal range cause rickets in infancy. Many clinical laboratories do not report age-appropriate normal ranges for phosphate, resulting in missed or delayed diagnoses of hypophosphatemia in children.

Clinical Presentation

Symptoms are nonspecific and are more common with severe and acute hypophosphatemia. Many patients with mild hypophosphatemia are asymptomatic, and hypophosphatemia may be an incidental finding. Generalized muscle weakness is the most common symptom of hypophosphatemia, and weakness and fatigue are frequent symptoms with acquired hypophosphatemia. However, weakness is infrequent in patients with congenital forms, such as X-linked hypophosphatemia (XLH). Other neurological symptoms (including paresthesias, dysarthria, altered mental status, seizures, and neuropathy) are reported with severe hypophosphatemia, but these are rare presenting symptoms for hypophosphatemia in general (4–7). Acute severe hypophosphatemia can be life-threatening and is associated with mortality and impaired cardiac and respiratory function among hospitalized patients (8).

Myalgia may accompany weakness in some patients, but severe acute muscle pain may indicate rhabdomyolysis resulting from hypophosphatemia. Hypophosphatemia may also cause intravascular hemolysis. During cell lysis, intracellular phosphate and proteins such as myoglobin are released, which can cause renal damage and hyperphosphatemia, obscuring previous hypophosphatemia.

Patients with chronic hypophosphatemia develop osteomalacia and resultant bone pain. Pain may occur with or without pseudofractures. However, osteomalacia requires time to develop and is not present during acute hypophosphatemia. Growing children with prolonged hypophosphatemia from any etiology develop rachitic features, including genu valgum or varum, frontal bossing, widening of the ends of long bones, and short stature.

A careful history of both prescription and nonprescription medications may identify the cause of hypophosphatemia (Table 1). In addition, family history may reveal a heritable disorder, although some patients with inherited hypophosphatemia may be unaware of their family diagnosis (9).

Diseases of Hypophosphatemia

Three primary mechanisms of hypophosphatemia exist: increased renal excretion, decreased intestinal absorption, and movement of phosphate from the extracellular to intracellular compartments. The initial step in diagnosis involves determining whether hypophosphatemia is renal or nonrenal. Renal hypophosphatemia can be FGF23-mediated or non-FGF23-mediated. Some renal or gastrointestinal mechanisms for hypophosphatemia may cause either acute or chronic hypophosphatemia. Movement of phosphate into cells can cause acute hypophosphatemia, usually following a period of phosphate depletion. Multiple mechanisms may coincide in some patients.

Renal

The classic, and most common, inherited renal phosphate wasting disorder is XLH. XLH usually presents with typical signs of rickets in young children, accompanied by hypophosphatemia, inappropriately low or normal 1,25OHD, and low TmP/GFR. The inheritance pattern is

TABLE 1. Differential diagnosis of hypophosphatemia

Increased renal excretion		Impaired intestinal absorption or intake	Transcellular shifts	Others
FGF23-mediated	Non-FGF23-mediated			
XLH (*PHEX*)	Hyperparathyroidism	Impaired dietary intake	Refeeding syndrome	Mannitol
ADHR (*FGF23*)	HHRH	Phosphate binders	Glucose infusion	Bisphosphonates
ARHR (*DMP1, ENPP1*)	Diuretics: acetazolamide, thiazides, loop diuretics	Sevelamer	Insulin infusion	
TIO		Antacids containing calcium, magnesium, aluminum	Salicylate poisoning	
FD	Fanconi syndrome		Hyperventilation	
Linear sebaceous nevus syndrome	Genetic causes: Dent's disease, cystinosis, NaPi2a mutations, others	Alcoholism	Respiratory alkalosis	
Postrenal transplantation hypophosphatemia	Drug induced: toluene, streptozocin, ifosfamide, cisplatin, tetracyclines, aminoglycosides, antiretrovirals (tenofovir, adefovir), and imatinib	Premature infants	Catecholamines	
Iron polymaltose infusions		Malabsorption		
		Vitamin D deficiency		
		Vitamin D metabolism defects		
		1α-hydroxylase deficiency		
		Vitamin D receptor mutation		

See Refs. 1, 7, 14, 18–21, 23, 26, 27, 30–36, 39, 40, 43–46, 53, 70, 78–81.

X-linked dominant. Consequently, both males and females are affected, and there is no male-to-male transmission of the disease. However, severity of disease varies widely, even within a kindred (10). Poor linear growth is common, often despite adequate medical treatment. Some data suggest that earlier diagnosis and treatment improve height outcomes (11). However, patients often still require orthopedic surgical procedures (such as femoral or tibial osteotomies) to modulate the progression of lower extremity deformities. Additional features of XLH include frequent dental abscesses and the development of enthesopathy (calcification of tendons and ligaments). Enthesopathy frequently causes joint stiffness and can be the most limiting feature of the disease in adulthood. Adults commonly have significant osteoarthritis with resulting joint pain (12).

XLH is caused by inactivating mutations in *PHEX* (13), which lead to increased bone expression of the phosphate-regulating hormone FGF23 (14). FGF23 enters the circulation and acts primarily at renal tubular FGF receptors, in conjunction with the coreceptor klotho (15), decreasing proximal renal tubular phosphate reabsorption and 1,25OHD production, and also increasing vitamin D degradation (16). Although these effects on phosphate transport and 1,25OHD metabolism occur in the proximal tubule, FGF23 signaling appears to start in the distal tubule (17). Mechanisms translating the initial distal tubule signal to proximal tubule effect have not been determined. Nevertheless, FGF23 excess causes the biochemical phenotype of XLH. Less common autosomal recessive forms of hypophosphatemic rickets are caused by inactivating mutations in both dentin matrix protein 1 (*DMP1*) and in ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*), both with hypophosphatemia due to excess FGF23 (18–20).

Mutations in *FGF23* resulting in impaired cleavage cause FGF23 excess in autosomal dominant hypophosphatemic rickets (ADHR) (21–23). These patients have an interesting clinical phenotype characterized by variability in age of clinically evident disease and incomplete penetrance (24). Hypophosphatemic rickets may develop during childhood, like XLH patients. However, a significant number of subjects from the same kindreds had a delayed onset of phenotype, with normophosphatemia and normal growth without rickets during childhood, to be followed by onset of hypophosphatemic osteomalacia in adolescence or adulthood. Most ADHR patients with delayed onset have been women (23–25). Furthermore, some subjects have later normalized their serum phosphate and stopped therapy. These changes over time are due to alterations in FGF23 (23) concentrations, suggesting that ADHR patients are intermittently regulating FGF23 and phosphate normally.

FGF23-mediated hypophosphatemia also occurs associated with focal sites of abnormal FGF23 production, including fibrous dysplasia (FD) of bone, linear sebaceous nevus syndrome, and tumor-induced osteomalacia (TIO). FD can be associated with café au lait macules and precocious puberty or other endocrine hyperfunction in McCune-Albright syndrome. Consequently, patients with FD should be tested for additional endocrine abnormalities. Phosphate wasting and FGF23 concentration correlates with the total amount of FD lesions (26). Linear sebaceous nevus syndrome is a neuroectodermal disorder associated with seizures, developmental defects, and cutaneous lesions producing FGF23 (27).

Acquired chronic renal phosphate wasting should prompt consideration of TIO, although ADHR, FD, and some types of Fanconi syndrome may also present after childhood. The biochemical phenotype of TIO is identical to that of XLH, but may be more severe. Many tumor types have been reported, including some malignant tumors, but in general these tumors are small, benign, and can be located anywhere in the body. The majority of tumors are classified as phosphaturic mesenchymal tumors of a mixed connective tissue type (28). Multiple

phosphatonins have been implicated in TIO, but FGF23 is the most consistent and well-characterized (29–32). If measurement can be made, elevated circulating FGF23 concentration is a sensitive indicator of TIO (30). However, it is not specific because many other disorders involve high FGF23 concentrations.

Hypophosphatemia occurring after renal transplant is caused by prolonged excess FGF23 production acquired during chronic kidney disease (33). Excess FGF23 production gradually resolves over time but may require treatment with phosphate and calcitriol with gradual tapering of doses until the elevated FGF23 resolves.

Some renal disorders associated with phosphate wasting are not FGF23-mediated, but are due to direct tubular abnormalities. Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is due to mutations in NaPi2c, a sodium-dependent phosphate cotransporter in the renal proximal tubule (34). Contrary to XLH patients, those with HHRH develop an appropriate increase in 1,25OHD and resultant hyperabsorption of calcium, hypercalciuria, and a propensity to nephrolithiasis. Fanconi syndrome is due to a variety of drugs, toxins, or genetic causes, resulting in variable renal losses of phosphate, calcium, and other ions; glucosuria; and aminoaciduria. Some genetic causes of hypophosphatemia due to Fanconi syndrome include mutations in chloride channel 5 (Dent's disease), sodium phosphate cotransporter 2a (NaPi2a), and cystinosin (*CTNS*, causing nephropathic cystinosis) (35–37).

Posthepatic resection hypophosphatemia is common and can last several days, but the cause is unclear. Although renal phosphate losses occur, this transient hypophosphatemia does not appear to be mediated by either FGF23 or PTH (38).

Nonrenal

Impaired phosphate intake or gastrointestinal absorption causes acute or chronic hypophosphatemia, but shifts from the extracellular compartment to the intracellular compartment cause acute hypophosphatemia. Frequently acute hypophosphatemia is nonrenal in origin, but it often involves a combination of factors.

Dietary phosphate deficiency is not usually an isolated deficiency, but is usually combined with vitamin D and other nutritional deficiencies. Premature infants require higher mineral intake than older infants for skeletal mineralization and thus require additional mineral supplementation, especially if fed with human milk (39). Acutely or chronically ill patients often have impaired nutritional intake or gastrointestinal absorption predisposing to hypophosphatemia. Antacids or other phosphate-binding agents impair absorption, causing acute or chronic hypophosphatemia (1). Parenteral nutrition may contribute to hypophosphatemia if insufficient phosphate is provided.

Any conditions resulting in poor overall nutrition, such as alcoholism, anorexia, severe malabsorption, and starvation, can cause phosphate depletion. Sometimes serum phosphate is normal, despite overall depletion before nutritional intervention. During refeeding, phosphate is shifted into cells for glucose utilization, resulting in hypophosphatemia. Patients with refeeding syndrome are also at risk for hypokalemia and hypomagnesemia. Likewise, phosphate depletion results from hyperglycemia-induced osmotic diuresis in the diabetic ketoacidosis patient. Once insulin administration begins, glucose utilization and cellular phosphate uptake increase and hypophosphatemia develops (1).

Similarly, during salicylate poisoning or rapid mechanical ventilation, phosphate moves into cells due to respiratory alkalosis (5, 40). Anxiety-induced hyperventilation may likewise cause transient hypophosphatemia (41). These acute forms of hypophosphatemia quickly improve with resolution of respiratory alkalosis.

Multiple drugs and toxins induce acute or chronic hypophosphatemia through a variety of mechanisms: isolated phosphaturia, Fanconi syndrome, intestinal phosphate binding, or intracellular uptake of phosphate (Table 1). In one study, 82% of inpatient acute hypophosphatemia were attributed to medications (42). Some forms of iv iron cause hypophosphatemia and osteomalacia due to increased FGF23 concentrations (43–45). Increased urinary excretion of phosphate may complicate diuretic and corticosteroid use. Mannitol can cause a pseudohypophosphatemia due to an assay artifact, but it may also have a mild phosphaturic effect (1). Although phosphate concentrations increase during advanced chronic kidney disease, daily or continuous hemodialysis and phosphate binders can sometimes induce hypophosphatemia (46).

Evaluation

Physical examination

A comprehensive physical examination should identify consequences of hypophosphatemia and clues to an underlying cause. Special focus should be on the musculoskeletal exam, looking for signs of weakness, pathological fractures or pseudofractures, and skeletal deformities. Bone pain may be present, but severe muscle pain may indicate rhabdomyolysis. In children, rachitic features should be noted, and in adults rachitic features suggest chronic hypophosphatemia since childhood. Short stature with increased upper to lower segment ratio also suggests

previous childhood rickets, even without leg deformities. Decreased range of motion at the spine, hips, and other large joints can indicate calcified entheses, a common feature in adults with XLH. Facial asymmetry or deformation of long bones may be signs of underlying FD. Maxillary bones are common sites of FD, whereas the sinuses are a common location for tumors causing TIO. If TIO is suspected, a thorough examination for palpable soft tissue masses should be performed. Hepatomegaly may suggest either an underlying tumor or chronic alcoholism. Skin findings such as café au lait macules (FD and McCune Albright syndrome) and linear sebaceous nevi should be noted.

Laboratory assessment

Laboratory assessment should establish the underlying cause of hypophosphatemia (Table 2). During treatment of diabetic ketoacidosis, or refeeding, or after known medications, the cause of hypophosphatemia is usually clear. Otherwise, the first step is to determine whether hypophosphatemia is renal or nonrenal in origin. This requires assessment of the TmP/GFR (Fig. 1) (47). Simultaneous collection of fasting second morning void urine and blood is usually sufficient; if the results are unclear, however, a specific fasting 2-h morning urine collection should be performed, with blood sampling halfway through the collection. The tubular reabsorption of phosphate is calculated and is used with serum phosphate to determine the TmP/GFR from a nomogram (Fig. 1). The TmP/GFR normal range approximates the same numerical range as the age-appropriate serum phosphate concentration in milligrams per deciliter. If both serum phosphate and TmP/GFR are low, this indicates inappropriate renal phosphate wasting. A normal (or high) TmP/GFR indicates renal conservation of phosphate, and hence a nonrenal cause of hypophosphatemia.

In chronic hypophosphatemia, osteomalacia develops and the total (or bone-specific) alkaline phosphatase is usually in the high or high-normal range. Concomitant hypercalcemia during hypophosphatemia suggests hyperparathyroidism, whereas hypocalcemia suggests vitamin D deficiency or other abnormality in vitamin D metabolism. 25OHD should be measured because vitamin D deficiency may accompany poor nutrition and phosphate deficiency. In FGF23-mediated disorders, 1,25OHD will be inappropriately low or normal during hypophosphatemia, but in other disorders, the physiological response to hypophosphatemia results in elevated 1,25OHD concentrations. Measuring PTH allows for determination of hyperparathyroidism, although patients with FGF23-mediated disorders may also develop hyperparathyroidism (48, 49). FGF23 measurement is not yet routinely available in clinical practice but is potentially useful in evaluating chronic hypophosphatemia (29).

Assessing urine calcium and creatinine in either a fasting or 24-h specimen allows for detection of hypercalciuria that can be seen in Fanconi syndrome, hypercalcemic hyperparathyroidism, and some inherited forms of hypophosphatemia. Aminoaciduria, proteinuria, micro-

TABLE 2. Expected laboratory values in the untreated state for selected causes of hypophosphatemia

	Serum phosphate	Serum calcium	Serum ALP	Serum PTH	Serum 25OHD	Serum 1,25OHD	Serum FGF23	TmP/GFR	Urine calcium
Renal hypophosphatemia (TmP/GFR low)									
FGF23-mediated									
XLH, ADHR, ARHR, TIO, FD, postrenal transplant	↓	⇆	↑	⇆, ↑	⇆	⇆, ↓	↑	↓	⇆, ↓
Non-FGF23-mediated									
Hyperparathyroidism	↓	↑	⇆, ↑	↑	⇆	↑	⇆, ↑	↓	↓, ⇆, ↑[a]
HHRH (NPT2c)	↓	⇆[b]	↑	↓, ⇆	⇆	↑	↓	↓	↑
Posthepatic resection hypophosphatemia	↓	⇆	⇆, ↑	⇆	⇆	⇆	↓	↓	⇆
Diuretics (acetazolamide, thiazides, loop diuretics)	↓	⇆, ↑	⇆	⇆	⇆	⇆	↓	↓	⇆
Fanconi syndrome[c]	↓	⇆, ↓	⇆, ↑	⇆, ↑	⇆	⇆, ↓	↓	↓	↑
Nonrenal hypophosphatemia(TmP/GFR normal or high)									
Impaired intestinal absorption or intake									
Impaired dietary intake or malabsorption[d]	↓	⇆, ↓	⇆, ↑	⇆, ↑	⇆, ↓	↓, ⇆, ↑	↓	↑	↓
Phosphate binders[d,e]	↓	⇆, ↑	⇄, ↑	⇆	⇆	↑	↓	↑	↓
Intracellular uptake									
Refeeding syndrome	↓	⇆	⇆	⇆	⇆, ↓	↓, ⇆, ↑	↓	↑	↓

ALP, Alkaline phosphatase; ↓, below normal range; ⇆, within normal range; ↑, above normal range.

[a] Urine calcium depends on severity of hyperparathyroidism.

[b] In HHRH, serum calcium may be high normal, and PTH may be low.

[c] Urinary wasting of other electrolytes, glucose, and amino acids.

[d] Serum and urine calcium, and serum PTH may be variable. In isolated dietary phosphate deficiency or isolated phosphate malabsorption (most commonly with phosphate binders) 1,25OHD may be up-regulated, leading to increased calcium absorption and potentially hypercalciuria and hypercalcemia.

[e] In chronic kidney disease (often treated with phosphate binders), calcium and alkaline phosphatase may be low, and phosphorus, FGF23, and PTH are usually high.

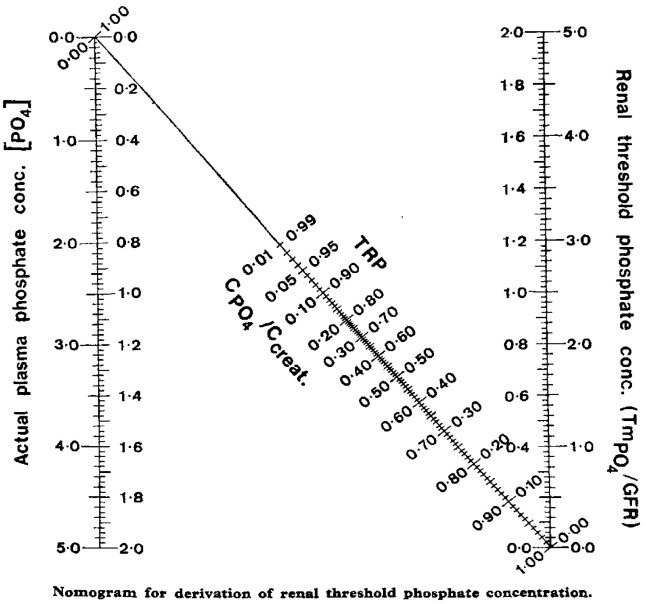

FIG. 1. Nomogram for determining TmP/GFR. The tubular reabsorption of phosphate (TRP) is calculated using the formula: 1 − [(urine phosphate ∗ serum creatinine)/(serum phosphate ∗ urine creatinine)]. *Left axis,* PO_4 indicates phosphate in mg/dl to the outside of the axis and mmol/l to the inside of the axis. *Right axis,* $TmPO_4$/GFR is the renal threshold phosphate concentration in mg/dl to the outside of the axis and in mmol/l to the inside of the axis. CPO_4 is the clearance of phosphate. Ccreat is the clearance of creatinine. [Reprinted from R. J. Walton and O. L. Bijvoet: Nomogram for derivation of renal threshold phosphate concentration. *Lancet* 306:309–310, 1975 (47), with permission. © Elsevier.]

globulinuria, and glucosuria are also indicators of Fanconi syndrome.

Imaging

For most acute hypophosphatemia, imaging is not necessary unless required to evaluate neurological, cardiac, or respiratory complications. For chronic hypophosphatemia, imaging is performed to evaluate both causes and consequences of hypophosphatemia.

Plain radiographs of areas of deformity noted on physical examination or of specific sites of pain should be performed to detect signs of rickets, FD, or pseudofractures. With severe osteomalacia, ^{99}technetium bone scintigraphy may demonstrate increased uptake at multiple areas, including ribs and pseudofractures. FD lesions may also be detected by bone scintigraphy (26). Computed tomography or magnetic resonance imaging is used to more fully characterize craniofacial or spinal FD lesions and evaluate possible neurovascular impingement.

When TIO is suspected, imaging should be directed by thorough physical examination because tumors may be palpable. Tumors causing TIO are often difficult to find. A wide variety of imaging techniques have been used to detect causative tumors, including plain radiographs, computed tomography, magnetic resonance imaging, octreotide scanning, and combined positron emission tomography/computed tomography (50–56). Whole body imaging techniques may offer an advantage. However, there appears to be a reporting bias for positive detection of tumors with various modalities. In our experience, sensitivity of each method is limited. A tumor is probably located only about half the time, despite multiple imaging techniques (30, 31). Furthermore, sometimes an identified lesion represents false positivity and is not causative of hypophosphatemia. Sometimes after multiple negative imaging studies, tumors are subsequently identified when tests are repeated after a few years.

Selective venous sampling for FGF23 concentrations has identified 18 tumors in five different reports (57–61). An estimated sensitivity of 87% and specificity of 71% were reported for a minimum intact FGF23 ratio of 1.6 between the maximum FGF23 concentration and the mean of the other sites sampled (61). However, false-positive results were noted, and venous sampling was nondiagnostic for six patients without otherwise identifiable lesions on comprehensive imaging (1, 61). Although this technique has potential, we recommend that it be considered experimental.

Hypophosphatemic osteomalacia is sometimes discovered as low bone density on dual-energy x-ray absorptiometry scanning. This is more common with acquired hypophosphatemia, and treatment rapidly improves bone density. However, although the mechanism is uncertain, patients with XLH often have mildly increased bone density, despite active osteomalacia (62).

Bone biopsy for osteomalacia is not typically needed but shows increased unmineralized osteoid and delayed mineralization rate. Biopsy of patients with XLH shows periosteocytic halos that are not present in TIO patients (55).

Management

Treatment will alter some diagnostic tests, so it is useful to obtain the proper biochemical testing to identify renal or nonrenal hypophosphatemia before initiating treatment. Treatment should address the underlying cause when possible, removing causative drugs or addressing dietary deficiencies. Acute severe hypophosphatemia in hospitalized patients may contribute to respiratory or hemodynamic instability, and a 2- to 4-fold increase in mortality is reported in prospective and retrospective studies (63, 64), while repletion can improve hemodynamic or respiratory instability.

When treating acute hypophosphatemia, the underlying cause must be addressed when possible. Intravenous phosphate is appropriate in the acute setting: when criti-

cally ill, when enteral intake is impaired, or when oral phosphate is not tolerated, especially when serum phosphate is less than 1.5 mg/dl. When hypophosphatemia is an expected complication of medical treatment, such as in refeeding syndrome, chronic alcoholic patients, or diabetic ketoacidosis, phosphate is added to maintenance iv fluids to prevent or treat hypophosphatemia, usually in the form of potassium phosphate.

Intravenous phosphate should be used cautiously. Treatment of severe acute hypophosphatemia is based on small uncontrolled adult studies with only 10 to 16 patients with serum phosphate below 1.5 mg/dl per study (65–68). Varying regimens are published (Table 3), which are not validated in children. However, the response to iv phosphate is highly variable and not easily predicted by initial levels. When providing iv phosphate, serum calcium, phosphate, potassium, magnesium, and creatinine should be closely monitored (at least every 6 h), and telemetry is recommended. The most significant risks of iv phosphate are acute severe life-threatening hypocalcemia, with tetany, seizures, electrocardiogram changes and shock, and overtreatment resulting in hyperphosphatemia and hyperkalemia (because of potassium phosphate formulations). Ectopic mineralization may occur with aggressive repletion. Intravenous phosphate should not be given to hypocalcemic patients. Concomitant low calcium and phosphate suggests vitamin D deficiency, and such patients should be managed with repletion of vitamin D or calcitriol. Patients with renal failure are also at higher risk of complications from iv phosphate. In general, oral phosphate is safer and is the preferred route in the stable patient with acute or chronic hypophosphatemia. However, hypocalcemia may still occur during aggressive oral phosphate repletion.

Management of chronic hypophosphatemia depends on the underlying cause. Avoidance of phosphate binders or other causative medications and specific treatment of the underlying cause is appropriate. In Fanconi syndrome, careful replacement with phosphate and calcium may be required. HHRH is typically treated with phosphate, but not calcitriol, because 1,25OHD is appropriately elevated in these patients, resulting in hypercalciuria.

The standard medical treatment of FGF23-mediated disorders (XLH, FD, TIO, ADHR, *etc.*) is based on current

TABLE 3. Treatment of hypophosphatemia

	First author (Ref.)	Dose of elemental phosphorus	Monitoring
Acute hypophosphatemia iv phosphate regimens (serum phosphate <1.5 mg/dl)[a,b,c]	Rosen *et al.* (68)	15 mmol (464 mg) in 100 ml 0.9% saline over 2-h bolus, repeated after 6 h if needed [maximum 45 mmol (1393 mg) in 24 h]	Calcium, phosphate, potassium, magnesium, creatinine every 6 h; electrocardiogram monitoring/telemetry
	Vannatta *et al.* (67)	0.32 mmol/kg (9.9 mg/kg) infused over 12 h and repeated every 12 h until serum phosphate was >2 mg/dl	
	Clark *et al.* (66)	0.64 mmol/kg (19.8 mg/kg) over 8–12 h	
	Taylor *et al.* (adapted) (65)	If phosphate 1.0–1.7 mg/dl, give 0.4 mmol/kg (12.4 mg/kg) over 6 h, maximum dose 40 mmol (1238 mg). If phosphate <1 mg/dl, give 0.5 mmol/kg (15.5 mg/kg) over 6 h, maximum dose 50 mmol (1548 mg)	
Oral phosphate salts[b,c]	Shiber *et al.* (4), Miller *et al.* (82)	30–40 mg/kg per day in four or five divided doses	Calcium, phosphate, potassium, magnesium, creatinine every 12–24 h
Vitamin D		800 to 1000 units daily (may require more if deficient)	
Refeeding syndrome[b,c]	Stanga *et al.* (83)	0.5–0.8 mmol/kg per day (15–25 mg/kg per day) in iv fluids	Calcium, phosphate, potassium, magnesium, creatinine every 12–24 h
Chronic hypophosphatemia (especially renal phosphate wasting)[d]			
Phosphate salts[c]	Carpenter *et al.* (70)	20–40 mg/kg per day divided into four doses	Calcium, phosphate, potassium, creatinine monthly until stable, then every 3 months with alkaline phosphatase, PTH every 6 to 12 months, renal ultrasound every 1–2 yr
Calcitriol[e]	Carpenter *et al.* (70)	20–30 ng/kg per day divided into two doses	

[a] Intravenous regimens are listed from four adult studies; caution should be used if applying to children. Intravenous phosphate should be avoided in hypocalcemic or hypercalcemic patients. Intravenous doses of phosphate over 30 mmol should be given in a central venous catheter.

[b] Severe hypocalcemia may result from aggressive iv or oral phosphate repletion. Impaired kidney function may increase the risk of hypocalcemia.

[c] Potassium phosphate salts should not be used if the patient is hyperkalemic or has impaired kidney function.

[d] Primary renal phosphate wasting disorders, especially FGF23-mediated disorders such as XLH, usually require treatment with both calcitriol and phosphate. Phosphate is not used alone (without calcitriol) in XLH or when PTH is elevated because this can cause or worsen hyperparathyroidism.

[e] If hypercalciuria is present at diagnosis, this should be confirmed, and if persistent, calcitriol should be avoided because calcitriol treatment will increase calciuria. Hypercalciuria in a previously untreated patient may indicate a different type of phosphate wasting disorder, such as HHRH, which is not treated with calcitriol.

knowledge for treating XLH with calcitriol and phosphate. More thorough discussions of which patients should be treated are available elsewhere (69, 70). Almost all children with XLH require therapy, although many still require surgery to correct lower extremity deformities. Decisions about treating adults with XLH are much more complex, but patients with stress fractures and bone pain should be considered for therapy after full discussion of risks. Joint problems in XLH are not improved by current therapy (69).

Current medical therapy for FGF23-mediated disorders consists of attempting to replete the consequences of FGF23 excess. No current treatment alters the effect of FGF23 on the kidney. Because FGF23 excess inhibits both 1,25OHD production and phosphate reabsorption, patients typically receive relatively high doses of phosphate and calcitriol. This standard of care has been demonstrated to improve osteomalacia in XLH (71, 72), but it is based largely on uncontrolled retrospective studies (70). Few studies had any controls (73), and some included historical controls (74, 75).

Potassium- and sodium-phosphate salts are given in doses of elemental phosphorus ranging from 20–40 mg/kg per day in four divided doses (70). Side effects commonly include gastrointestinal distress and diarrhea, which can sometimes be limited by starting at a low dose and titrating up to the target dose. In excessive doses, oral or iv phosphate can cause an acute phosphate nephropathy and renal failure. Calcitriol dosing is usually 20–30 ng/kg per day, although transiently higher doses may be used for several months to speed healing of osteomalacia, followed by decreasing to the above maintenance dose.

This therapy requires close monitoring of serum and urine calcium, phosphate, and creatinine, with careful dose adjustment. Because treatment with phosphate and calcitriol increases the daily urine calcium and phosphate excreted, we do not target consistently normal serum phosphate concentrations. In fact, persistent normal serum phosphate concentrations may be an indication for decreasing the doses. After initial healing of osteomalacia, skeletal calcium uptake decreases and hypercalciuria or hypercalcemia indicates the calcitriol dose should be decreased. Likewise, if serum phosphate becomes elevated, the phosphate and/or the calcitriol dose should be decreased. Although not always elevated (especially in adults with XLH), the alkaline phosphatase will generally decrease during treatment.

Nephrocalcinosis, renal insufficiency, and secondary (sometimes tertiary) hyperparathyroidism can be complications of this therapy (49, 76). Consequently, we recommend monitoring of PTH at least once or twice yearly and renal ultrasounds every 1 or 2 yr in patients being treated with calcitriol and phosphate. Of note, current treatment with calcitriol and phosphate also tends to increase FGF23 concentrations (77).

In TIO, the goal of treatment should be complete resection of the tumor for surgical cure when possible. These tumors also occasionally metastasize, and recurrences may develop years after initial surgical cure. Long-term monitoring of phosphate and alkaline phosphatase is recommended to detect recurrences. If a causative tumor cannot be found and completely resected, TIO patients generally respond dramatically to medical treatment with phosphate and calcitriol as the osteomalacia heals, with resolution of weakness and bone pain, and return to full ambulation.

Back to the Patient

TmP/GFR was low (1.2 mg/dl), indicating renal phosphate wasting. There was no aminoaciduria. PTH was 45 pg/ml. Dual-energy x-ray absorptiometry revealed a T-score of −2.2 at the femoral neck. Intact FGF23 concentration was 97 pg/ml (normal, <70 pg/ml). Treatment with calcitriol and phosphate improved the patient's pain and corrected his alkaline phosphatase. His stress fractures resolved, and he returned to free ambulation. Initial imaging studies failed to reveal a likely source for TIO. Eventually, a positron emission tomography/computed tomography identified a 1.3-cm cortical lesion in the left iliac bone. Resection revealed a spindle cell neoplasm with features consistent with phosphaturic mesenchymal tumor, mixed connective tissue type. He quickly tapered off of calcitriol and phosphate salts; 3 wk after surgery, serum phosphate was 3.9 mg/dl.

Conclusion

Hypophosphatemia is commonly missed due to nonspecific signs and symptoms, but it causes considerable morbidity and can contribute to mortality. Proper diagnosis requires a thorough medication history, family history, examination, and assessment of renal tubular phosphate handling to identify the cause. Imaging studies should be directed at determining complications of hypophosphatemia and identifying potential causes such as TIO or FD. Treatment of hypophosphatemia is determined by the underlying cause. Medical treatment of renal phosphate wasting disorders can dramatically improve weakness and osteomalacia.

Acknowledgments

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