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Acid-Base and Electrolyte Teaching Case

Evaluation of Hypophosphatemia: Lessons From Patients With Genetic Disorders

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Phosphate is a key component of several physiologic pathways, such as skeletal development, bone mineralization, membrane composition, nucleotide structure, maintenance of plasma pH, and cellular signaling. The kidneys have a key role in phosphate homeostasis, with 3 hormones having important roles in renal phosphate handling: parathyroid hormone, fibroblast growth factor 23 (FGF-23), and 1,25-dihydroxyvitamin D. Independent of the genetic diseases affecting the FGF-23 pathway (such as hypophosphatemic rickets), hypophosphatemia is a frequent condition encountered in daily practice, and untreated critical hypophosphatemia can induce hemolysis, rhabdomyolysis, respiratory failure, cardiac dysfunction, and neurologic impairment. Rapid correction thus is necessary to avoid severe complications. The aims of this teaching case are to summarize the causes and biological evaluation of hypophosphatemia and provide an overview of our current understanding of phosphate metabolism.

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INDEX WORDS: Fibroblast growth factor 23 (FGF-23); hypophosphatemia; hypophosphatemic rickets; tumor-induced osteomalacia.

Note from Feature Editor Jeffrey A. Kraut, MD: This article is part of a series of invited case discussions highlighting either the diagnosis or treatment of acid-base and electrolyte disorders. Advisory Board member Glenn Nagami, MD, served as the Consulting Editor for this case.

INTRODUCTION

Phosphate is a key element for several physiologic pathways, such as skeletal development, bone mineralization, membrane composition, nucleotide structure, maintenance of plasma pH, and cellular signaling.[1] The vast majority of phosphate is in bone, but the kidneys have a key role in phosphate homeostasis, with 2 hormones playing important roles in renal phosphate handling: parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23). Both hormones have hypophosphatemic effects by decreasing tubular phosphate reabsorption, but opposite effects on the regulation of 1,25-dihydroxyvitamin D. The third main regulator of phosphate metabolism is 1,25-dihydroxyvitamin D, which increases phosphate intestinal absorption and inhibits PTH synthesis. An overview of phosphate physiology, with intestinal absorption, renal excretion, and bone metabolism, is shown in Fig 1.

Hypophosphatemia is defined in adults as a serum phosphate level <2.5 mg/dL (<0.8 mmol/L), and severe hypophosphatemia, as a serum phosphate level <1 mg/dL (<0.3 mmol/L).[2] In children, hypophosphatemia is defined according to age-related normal range.[3] Severe hypophosphatemia can induce proximal muscular weakness, respiratory failure, rhabdomyolysis, neurologic impairment (eg, irritability, paresthesias, seizures, and coma), cardiovascular dysfunction (eg, arrhythmia, congestive heart failure, and cardiomyopathy), platelet dysfunction (eg, thrombocytopenia and hemorrhage), hemolysis, metabolic acidosis, and osteomalacia.[4] Children with hypophosphatemia from defects of tubular reabsorption of phosphorus (eg, hypophosphatemic rickets and proximal tubulopathy, such as de De Toni-Debré-Fanconi syndrome or Dent disease) also can experience growth retardation, bone deformities, and rickets. In the early 2000s, the key role of FGF-23 and its regulators in phosphate physiology was discovered. Overexpression of FGF-23 initially was described in pediatric patients with autosomal dominant hypophosphatemic rickets,[5] but it also was associated rapidly with tumor-induced osteomalacia in adults and other types of hypophosphatemic rickets in children.[6]

The aims of this teaching case are to summarize the causes and biological evaluation of hypophosphatemia in adults and provide an overview of our current understanding of phosphate metabolism.

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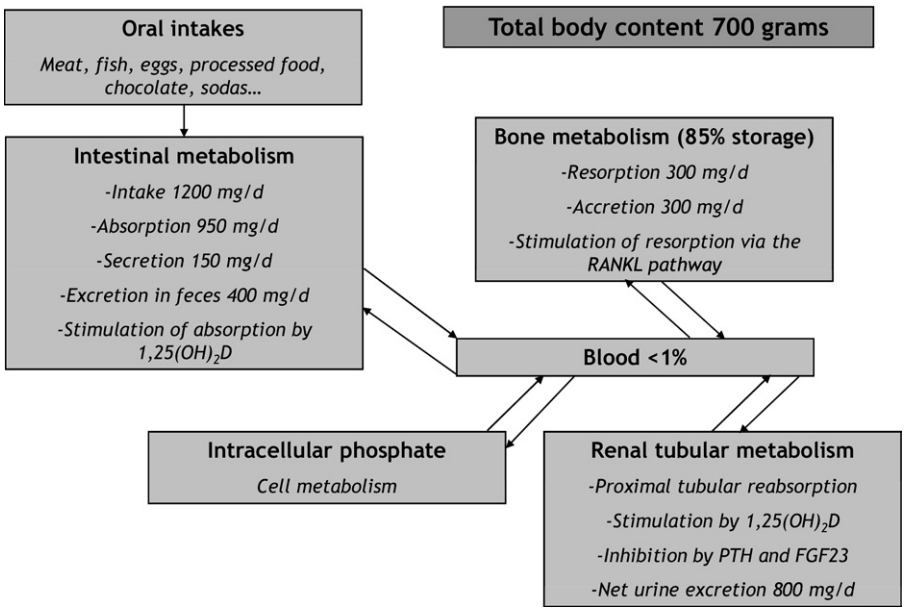

Figure 1. Overview of phosphate physiology in adults. Abbreviations: $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone; RANKL, receptor-activated nuclear factor-κB.

CASE REPORT

Clinical History and Initial Laboratory Data

A 27-year-old woman was given a diagnosis of hypophosphatemic rickets at the age of 2 years when she presented with growth retardation, bowing of the legs, and hypophosphatemia. There was no family history of phosphorus disorders. Therapy was initiated with both phosphate supplementation and alfacalcidol. Her final adult height was 154 cm, and leg deformities were very moderate, without need for surgical correction. There were no dental problems.

Additional Investigations

Mild but stable nephrocalcinosis appeared at the age of 16 years, but kidney function remained normal throughout follow-up. However, at the age of 21 years, PTH levels began to increase (ie, 80 pg/mL [80 ng/L], upper reference range of the assay of 65 pg/mL [65 ng/L]) despite continuing to receive phosphate supplements (20 mg/kg/d) and alfacalcidol (2 μg/d). PTH levels increased further (115 pg/mL [115 ng/L]), and phosphate supplements and alfacalcidol were tapered and discontinued. Nevertheless, clinical symptoms (ie, muscular and bone pain and asthenia) recurred with a serum phosphorus level of 1.5 mg/dL (0.5 mmol/L) 3 months after the initial therapeutic withdrawal, leading to the reintroduction of phosphorus (20 mg/kg/d) and alfacalcidol (1 μg/d) and the addition of native vitamin D supplementation (cholecalciferol, 100,000 U/mo).

Diagnosis

After a childhood diagnosis of hypophosphatemic rickets based on the association of bone deformities and hypophosphatemia, the patient received long-term treatment with phosphate supplements and active vitamin D sterol (alfacalcidol). As a young adult, she developed secondary hyperparathyroidism and nephrocalcinosis, 2 long-term complications secondary to therapies often observed in hypophosphatemic rickets.

Clinical Follow-up

At the age of 28 years, the patient was asymptomatic, but PTH levels increased again (from 89 to 111 pg/mL [89 to 111 ng/L]), with a normal serum calcium level, decreased serum phosphorus level (1.5 mg/dL [0.5 mmol/L], 25-hydroxyvitamin D level of 25 ng/mL (62.4 nmol/L; reference, >20 ng/mL [>50 nmol/L]), urine calcium to creatinine ratio of 0.59 (reference, <0.7), and increased bone biomarker levels (crosslaps, 10 times; osteocalcin, 1.5 times; and bone alkaline phosphatase, 9 times the upper normal value, respectively). Total alkaline phosphatase was within the upper normal level. Parathyroid ultrasounds and scintigraphy were unremarkable. Of note, glycosuria was present in the absence of diabetes mellitus, highlighting glycosuria as a rare and poorly understood feature of X-linked hypophosphatemic rickets.[7,8]

DISCUSSION

In adults, hypophosphatemia is relatively frequent in daily medical practice, affecting up to 5% of hospitalized patients and up to 30%-50% of alcoholic, septic, or critically ill patients.[1,2] Underlying hypophosphatemia will become clinically significant at times of acute stress. Refeeding after starvation is associated with phosphate depletion and urinary loss of phosphorus. At the same time, intravenous carbohydrate infusions induce transcellular phosphorus shifts that worsen the degree of hypophosphatemia.[9] In these critically ill patients, respiratory alkalosis, inadequate phosphate intake, and increased glycolysis (through the formation of phosphorylated glucose compounds) all contribute to hypophosphatemia. For example, in alcoholic patients, poor nutrition before admission, transcellular shifts secondary to intravenous fluids containing