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Acid-Base and Electrolyte Teaching Case

A Physiologic–Based Approach to the Evaluation of a Patient With Hyperphosphatemia

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Phosphate is required for skeletal mineralization, cellular energy regulation, synthesis of cell membranes and nucleic acids, and a variety of cell signaling pathways. Extracellular serum phosphate concentration is determined by the balance of gastrointestinal phosphate absorption, skeletal turnover, distribution in intracellular compartments, and renal phosphate excretion. An integrated system of hormones, receptors, and phosphate transporters regulates phosphate homeostasis, and a variety of hereditary and acquired perturbations in these regulators can result in hyperphosphatemia. Although kidney failure is the most common cause of hyperphosphatemia encountered by nephrologists, hyperphosphatemia that presents in patients with early stages of chronic kidney disease or normal kidney function should prompt a detailed evaluation that can be diagnostically challenging. In this teaching case, we describe a case of hyperphosphatemia out of proportion to the degree of decrease in glomerular filtration rate. We present a practical parathyroid hormone–based diagnostic approach that illustrates the current understanding of phosphate regulation in clinically meaningful terms for the practicing nephrologist. Finally, we illustrate how measurement of fibroblast growth factor 23 could be integrated in the future when the test becomes more widely available.
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INDEX WORDS: Hyperphosphatemia; calcium-sensing receptor; hypoparathyroidism; parathyroid hormone; fibroblast growth factor 23.

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.

INTRODUCTION

Phosphate homeostasis is orchestrated by a complex integrated system of hormones, including fibroblast growth factor 23 (FGF-23), parathyroid hormone (PTH), and 1,25-dihydroxyvitamin D; receptors, including the calcium-sensing receptor (CaSR) and receptors for FGF, PTH, and vitamin D; and sodium-dependent phosphate transporters in the gut and kidney. Perturbations in these factors can cause abnormal serum phosphate levels.

Hyperphosphatemia is one of the most common laboratory abnormalities encountered by practicing nephrologists, but it is seen most commonly in patients with advanced stages of chronic kidney disease (CKD) and end-stage kidney disease in whom the cause is almost always clear. In contrast, hyperphosphatemia in patients with intact or mild to moderately decreased kidney function can present a diagnostic challenge. We present a systematic approach to the evaluation of a patient with hyperphosphatemia that illustrates the complex mechanisms that regulate serum phosphate and the pathophysiology of hyperphosphatemic disorders.

CASE REPORT

Clinical History and Initial Laboratory Data

A 40-year-old woman is referred for evaluation of hyperphosphatemia and decreased kidney function. During a pre-employment health screening, laboratory testing showed a serum phosphate level of 6.3 mg/dL (2.0 mmol/L). The patient was a recent immigrant to the United States and had not seen a physician in several years. She had a history of nephrolithiasis and a poorly defined "calcium problem" for which she had been prescribed calcium and calcitriol several years earlier. She did not recall the doses, but had stopped taking the medications 3 months earlier when her supply was depleted. The patient reported that her mother also had taken calcium and vitamin D supplements before she died of a malignancy. She had no siblings and no other significant family history.

Physical examination findings were unremarkable. Laboratory testing showed an elevated serum creatinine level, hyperphosphatemia, hypocalcemia, hypercalciuria, hypomagnesemia, and a low-normal PTH level (Table 1). Blood cell counts, liver function test results, and lipid panels were all within reference ranges. Kidney ultrasound revealed symmetric 10.2-cm kidneys with evidence of nephrocalcinosis.

Additional Investigations

Given the clinical constellation and possible autosomal dominant inheritance, genetic testing was undertaken and revealed that

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Table 1. Laboratory Data

Serum tests	Reference Range	Initial Data	Follow-up
Sodium (mEq/L)	135-145	140	139
Potassium (mEq/L)	3.4-4.8	4.1	3.6
Bicarbonate (mEq/L)	23-32	25	27
Creatinine (mg/dL)	0.8-1.3	1.5	1.5
eGFR (mL/min/1.73 m^2)	>60	41	41
Total calcium (mg/dL)	8.4-10.2	7.6	8.1
Ionized calcium (mEq/L)	2.24-2.64	1.94	2.06
Magnesium (mEq/L)	1.5-2.3	1.1	1.8
Phosphate (mg/dL)	2.5-4.5	6.3	5.1
PTH, intact (pg/mL)	11-80	11	15
25(OH)D (ng/mL)	30-60	27	25
$1,25(OH)_2D$ (pg/mL)	25-66	16	20
Urinary tests			
Urinary calcium excretion (mg/d)	<200	315	180
Urinary phosphate excretion (mg/d)	600-1,200	825	710
Urinary sodium excretion (mmol/d)	50-150	255	165

Note: eGFR estimated using the 4-variable Modification of Diet in Renal Disease Study equation. Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667; serum calcium in mg/dL to mmol/L, ×0.2495; ionized calcium and serum magnesium in mEq/L to mmol/L, ×0.5; serum phosphate in mg/dL to mmol/L, ×0.3229; 25(OH)D in ng/mL to nmol/L, ×2.496; $1,25(OH)_2D$ in pg/mL to pmol/L, ×2.6. No conversion necessary for sodium, potassium, and bicarbonate in mEq/L and mmol/L and PTH in pg/mL and ng/L.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone.

the patient was heterozygous for an activating mutation in the gene encoding the CaSR, indicating autosomal dominant hypoparathyroidism.[1]

Diagnosis

(1) Autosomal dominant hypoparathyroidism due to an activating mutation of the CaSR gene. (2) CKD stage 3 due to nephrocalcinosis.

Clinical Follow-up

The patient was prescribed calcium acetate, 667 mg, 3 times daily with meals; magnesium oxide, 400 mg, 3 times daily; hydrochlorothiazide, 25 mg, twice daily; a sodium-restricted diet; and liberalized water intake to maintain urine flow >2 L daily. Calcitriol therapy was not resumed. Follow-up laboratory data are listed in Table 1.

DISCUSSION

Hyperphosphatemia and hypocalcemia with an inappropriately low PTH level are hallmarks of hypoparathyroidism. Although the patient had moderately decreased kidney function, hyperphosphatemia and hypocalcemia were disproportionate to the decrease in glomerular filtration rate, and hypercalciuria is distinctly abnormal for any CKD population. These features were the clues that steered the consultant from dismissing hyperphosphatemia as simply due to CKD. Confirmation of inappropriately low PTH levels in conjunction with a suggestive family history led to genetic testing that established a molecular diagnosis of autosomal dominant hypoparathyroidism due to an activating mutation of the CaSR. The history of nephrolithiasis and the finding of nephrocalcinosis in the setting of hypoparathyroidism could be indicative of excessive use of calcium and calcitriol supplementation and highlight both the physiologic contribution of the kidney to the pathogenesis of hypoparathyroidism and one of the major obstacles to its effective management.

Normal Phosphate Homeostasis

Gut. Phosphate is absorbed throughout the small intestine through paracellular transport and 1,25-dihydroxyvitamin D–dependent active transport through the sodium-dependent phosphate transporter 2b (NPT2b; encoded by the *SLC34A2* gene).[2,3] It is estimated that vitamin D–dependent absorption is of secondary importance,[4] accounting for only up to 20% of total phosphate absorption under conditions of normal phosphate intake.[5] This concept is supported by studies that demonstrate that inactivating mutations of NPT2b do not have an abnormal phosphate homeostasis phenotype.[6] In contrast, passive absorption appears to be nonsaturable, such that greater phosphate intake leads to greater net absorption. Although absorption or "bioavailability" of dietary phosphate varies by source (animal vs plant sources vs inorganic food additives), it is estimated that approximately 66%-75% of net intake is absorbed.[7] Given the wide variability in dietary phosphate intake and relative lack of regulation of its absorption in the gut, the kidney is ultimately responsible for regulating phosphate balance.

Bone. In steady states of bone turnover, flux of phosphate into and out of bone is balanced. Phosphate efflux from bone is stimulated by PTH-mediated bone resorption, which mobilizes both phosphate and calcium into the extracellular fluid. Although FGF-23 is secreted by osteocytes, its direct effects on bone are unclear.

Kidney. Phosphate is freely filtered by the glomerulus and ~90% is reabsorbed by the proximal tubule (ie, fractional excretion is ~10%). Proximal tubular phosphate reabsorption is mediated by transport through apical NPT2a and NPT2c (encoded by *SLC34A1* and *SLC34A3*, respectively), inactivating mutations of which cause phosphate wasting and hypophosphatemic rickets in both animal models and humans.[8,9] These transporters are regulated by PTH, FGF-23, and perhaps unknown hormones secreted by the gut.[10] The tremendous renal reserve for phosphate excretion explains why most pa-