AJKD
Acid-Base and Electrolyte Teaching Case

Approach to Treatment of Hypophosphatemia

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Hypophosphatemia can be acute or chronic. Acute hypophosphatemia with phosphate depletion is common in the hospital setting and results in significant morbidity and mortality. Chronic hypophosphatemia, often associated with genetic or acquired renal phosphate-wasting disorders, usually produces abnormal growth and rickets in children and osteomalacia in adults. Acute hypophosphatemia may be mild (phosphorus level, 2-2.5 mg/dL), moderate (1-1.9 mg/dL), or severe (<1 mg/dL) and commonly occurs in clinical settings such as refeeding, alcoholism, diabetic ketoacidosis, malnutrition/starvation, and after surgery (particularly after partial hepatectomy) and in the intensive care unit. Phosphate replacement can be given either orally, intravenously, intradialytically, or in total parenteral nutrition solutions. The rate and amount of replacement are empirically determined, and several algorithms are available. Treatment is tailored to symptoms, severity, anticipated duration of illness, and presence of comorbid conditions, such as kidney failure, volume overload, hypo- or hypercalcemia, hypo- or hyperkalemia, and acid-base status. Mild/moderate acute hypophosphatemia usually can be corrected with increased dietary phosphate or oral supplementation, but intravenous replacement generally is needed when significant comorbid conditions or severe hypophosphatemia with phosphate depletion exist. In chronic hypophosphatemia, standard treatment includes oral phosphate supplementation and active vitamin D. Future treatment for specific disorders associated with chronic hypophosphatemia may include cinacalcet, calcitonin, or dypyrimadole.
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INDEX WORDS: Hypophosphatemia; adenosine triphosphate (ATP); 2,3-diphosphoglycerate (2,3-DPG); fibroblast growth factor 23 (FGF-23).

Note from Editors: 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 Horacio Adrogué, MD, served as the Consulting Editor for this case. The present case discussion is the second of 2 articles discussing hypophosphatemia. In this article, Drs Felsenfeld and Levine present their approach to the treatment of hypophosphatemia; in the first teaching case, Drs Bacchetta and Salusky describe a physiologic-based approach to its diagnosis and evaluation.[1]

INTRODUCTION

Hypophosphatemia (phosphorus level <2.5 mg/dL [<0.81 mmol/L]) is uncommon in the general population, but occurs in up to 5% of hospitalized patients.[2] The incidence of acute hypophosphatemia may be as high as 30%-50% in clinical settings such as alcoholism, sepsis, or patients in intensive care units (ICUs). Sometimes acute hypophosphatemia results from redistribution of phosphate into the intracellular compartment without total-body phosphate depletion. In contrast, chronic hypophosphatemia usually is associated with total-body phosphate depletion.

Acute hypophosphatemia with phosphate depletion is associated with many clinical manifestations (Fig 1) and causes increased morbidity and mortality.[2] Treatment of hypophosphatemia depends on the cause and factors such as chronicity, severity, symptomatology, and the presence of hyper- or hypocalcemia or kidney failure. The following case highlights important issues pertaining to the development and treatment of hypophosphatemia.

CASE REPORT

Clinical History and Initial Laboratory Data

A 50-year-old man presented with abdominal pain, nausea, and vomiting. He had consumed large amounts of alcohol for 9 days. Pertinent history included alcohol dependence, alcohol withdrawal seizures, and alcohol-induced pancreatitis 1 month earlier. Physical examination was remarkable for tachycardia and abdominal tenderness. Initial laboratory data showed metabolic acidosis and elevated serum ethanol (71.8 mg/dL [15.8 mmol/L]), calcium, and phosphorus values (Table 1).

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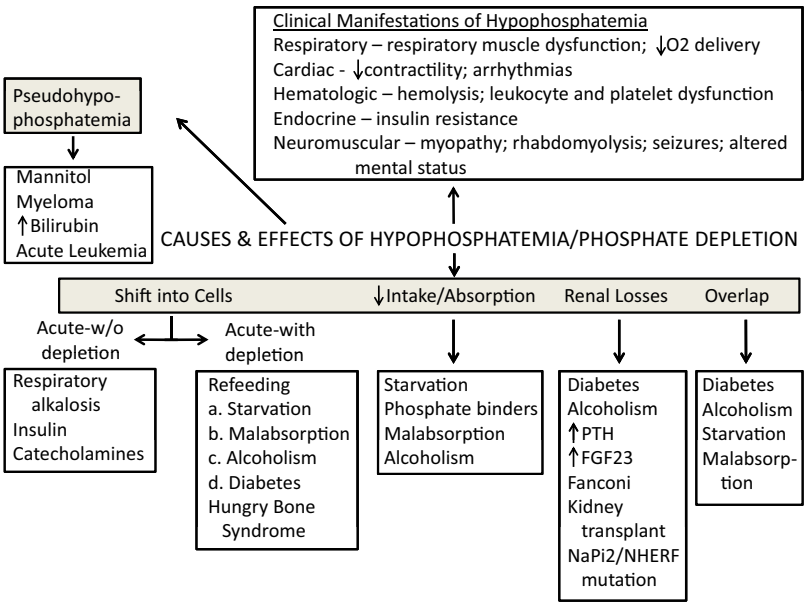

Figure 1. Causes and effects of hypophosphatemia/phosphate depletion. Hypophosphatemia may be acute or chronic and results from decreased intake and/or absorption, gastrointestinal and renal/extracorporeal losses, internal redistribution, or a combination of these factors. Pseudohypophosphatemia may occur in patients with acute leukemia from increased uptake of phosphate by leukemic cells in vitro or may result from interference with the phosphate assay by mannitol, bilirubin, or dysproteinemia. Abbreviations: FGF-23, fibroblast growth factor 23; NaPi2/NHERF, sodium-phosphate 2/sodium-hydrogen exchanger regulatory factor; O_2, oxygen; PTH, parathyroid hormone.

Additional Investigations

Four liters each of normal saline solution and 5% dextrose-half normal saline solution were administered. After serum glucose level increased to 687 mg/dL (38.1 mmol/L), regular insulin was given. Hypercalcemia resolved with hydration and improved kidney function. Metoprolol and diltiazem were given for supraventricular tachycardia. Two days later, serum phosphorus level was <1.0 mg/dL (<0.32 mmol/L; Table 1).

Diagnosis

The diagnosis of severe hypophosphatemia with phosphate depletion was made. Contributing factors included poor oral intake, vomiting, intracellular redistribution of phosphate, and increased renal losses.

Clinical Follow-up

During the next 7 days, the patient was given 185 mmol of oral and intravenous potassium phosphate (K-Phos; Beach Pharmaceuticals, tampa.yalwa.com/ID_100750342/Beach-Pharmaceuticals-Div-Of-Beach-Products-Inc.html) for persistent hypophosphatemia (Table 1).

DISCUSSION

The causes of hypophosphatemia recently were reviewed[1] and our focus is on the treatment of this condition. Hypophosphatemia results from decreased intake/absorption, gastrointestinal and renal/extracorporeal losses, or internal redistribution (Fig 1). As illustrated in the present case, acute hypophosphatemia frequently results from redistribution of phosphate superimposed on phosphate depletion. Decreased intake and renal losses both contributed to phosphate depletion in the patient. An intracellular shift of phosphate then produced profound hypophosphatemia. The precipitous decrease in serum phosphorus level after initiating glucose-containing solutions indicates phosphate depletion.[3]

Chronic hypophosphatemia usually results from gastrointestinal and/or renal losses of phosphate. Renal losses can be caused by either gain-of-function mutations or acquired defects in the fibroblast growth factor 23 (FGF-23)–Klotho axis.[2,4] In addition to hypophosphatemia, low or inappropriately normal 1,25-dihydroxyvitamin D, normal serum calcium, normal or elevated parathyroid hormone (PTH), and high FGF-23 values generally are present.[2,4] Also, mutations in sodium-phosphate 2 (Na-Pi 2) transporters or associated regulatory factors, such as the sodium-hydrogen exchanger regulatory factor (NHERF), produce a similar phenotype, but with elevated 1,25-dihydroxyvitamin D levels, hypercalciuria, and stone disease.[2,4] Renal phosphate wasting is common after kidney transplant. Hypophosphatemia usually resolves within a year,[5] but can persist.[6] Contributing factors include persistent elevation of PTH and FGF-23 levels, low 1,25-dihydroxyvitamin D level, renal tubular damage, immunomodulatory agents,[6-8] and, if used, intravenous iron.[9]

Clinical consequences of hypophosphatemia are varied and differ between acute and chronic hypophosphatemia. Even when severe, acute hypophosphatemia from redistribution alone may have little consequence in the absence of phosphate depletion, and phosphate supplementation does not improve patient outcomes.[10] Conversely, severe acute hypophosphatemia with phosphate depletion results in significant clinical manifestations (Fig 1) and requires phosphate repletion. Clinical consequences of chronic hypophosphatemia primarily involve impaired growth and bone formation. Also, there is recent evidence that FGF-23–induced cardiovascular abnormalities may occur in some chronic hypophosphatemic states.[11]