39-Year-Old Woman With Severe Weakness

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A 39-year-old woman presented to the emergency department (ED) with progressive weakness. Her medical history was notable for iron deficiency anemia, gastroesophageal reflux disease (GERD), and obesity after Roux-en-Y gastric bypass 10 years previously. Active home medications included omeprazole (40 mg daily) and 2 recent intravenous (IV) infusions of ferumoxytol (510 mg elemental iron per dose). Several months prior to her ED presentation, the patient experienced tingling in both hands and feet, new-onset dyspnea with climbing stairs and sexual activity, and intermittent episodes of fatigue, which gradually increased in frequency and severity. During the week leading up to her ED presentation, the patient had diffuse myalgias and found herself too weak to get herself out of bed, climb stairs, or perform other activities of daily living. She reported no nausea, vomiting, chronic diarrhea, dyspnea at rest, or chest pain.

The patient's vital signs were within normal limits on initial presentation (temperature, 37.1 °C; heart rate, 90 beats/min; respiratory rate, 18 breaths/min; and oxygen saturation, 98% while breathing room air). Body mass index (calculated as weight in kilograms divided by height in meters squared) was 38 kg/m^2. Pertinent examination findings included a strawberry-red tongue, decreased peripheral reflexes, and 4/5 strength in her left leg. The patient was alert and oriented without other focal deficits. There was no rash or edema. Abdominal and cardiopulmonary examination results were unremarkable. Dietitian evaluation deemed the patient well-nourished without evidence of sarcopenia, fluid accumulation, or weight loss. Notable laboratory findings included the following (reference ranges provided parenthetically): white blood cell count, 13.1 × 10^9/L (3.4 to 9.6 10^9/L); potassium, 3.4 mmol/L (3.6 to 5.2 mmol/L); glucose, 146 mg/dL (70 to 140 mg/dL); serum iron, 59 µg/dL (35 to 145 µg/dL); and ferritin, 269 µg/L (11 to 307 µg/L). Hemoglobin value, platelet count, and sodium, chloride, bicarbonate, creatinine, serum urea nitrogen, calcium, thyroid-stimulating hormone, and magnesium levels were within normal limits. Micronutrient assessment revealed the following: total vitamin D, 15 ng/mL (20 to 50 ng/mL), including a vitamin D2 level of 5.9 ng/mL and vitamin D3 level of 7.3 ng/mL; pyridoxal-5-phosphate, 22 µg/L (5 to 50 µg/L); ascorbic acid, 0.2 mg/dL (0.4 to 2.0 mg/dL); and vitamin K, 0.05 ng/mL (0.1 to 2.2 ng/mL). Vitamin A, vitamin E, thiamine, folate, riboflavin, and niacin levels were within normal limits. Chest radiography and computed tomography revealed no acute abnormalities.

1. **Which *one* of the following is the *most likely* cause of the patient's symptoms?**
   a. Congestive heart failure
   b. Anemia
   c. Deconditioning
   d. Autoimmune disease
   e. Hypophosphatemia

Although congestive heart failure can cause dyspnea on exertion, other signs of volume overload including orthopnea, paroxysmal nocturnal dyspnea, rales, and lower extremity edema were not present on examination. Severe anemia (including iron deficiency anemia) can be associated with tachycardia, systolic ejection murmurs, dyspnea, conjunctival pallor, high-output heart

See end of article for correct answers to questions.

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failure, and more rarely fatigue with muscular weakness.[1] However, this patient was receiving routine IV iron supplementation with serum ferritin and hemoglobin levels within normal limits. Deconditioning can lead to fatigue and dyspnea on exertion, but it does not explain paresthesia, aching pains, or profound fatigue at rest. Autoimmune disease, such as systemic lupus erythematosus, can cause fatigue; however, this patient did not have rheumatologic signs and symptoms such as malar rash, serositis, pancytopenia, and arthritis. Hypophosphatemia can cause paresthesias, fatigue, and shortness of breath from diaphragmatic weakness. Our patient's phosphorus level was 0.6 mg/dL (2.5 to 4.5 mg/dL). Her ionized calcium level was 4.4 mg/dL (4.6 to 5.4 mg/dL), parathyroid hormone (PTH) value was 125 pg/mL (15 to 65 pg/mL), and vitamin D level was 18 ng/mL.

Given anatomic absorption deficits following gastric bypass operation, patients should routinely supplement micronutrients clinically guided by the procedure performed. This patient was not taking routine vitamin supplementation.

2. **Which *one* of the following is the *best* test to perform next in determining the etiology of this patient's hypo phosphatemia?**
   a. Fecal phosphate quantification
   b. Skeletal survey
   c. Renal ultrasonography
   d. Serum creatine kinase and hemolysis panel
   e. Fractional excretion of urinary phosphate

Gastrointestinal (GI) tract losses of phosphate are one of the major causes of hypophosphatemia,[2] which is why phosphate binders such as sevelamer are widely used for hyperphosphatemia of renal disease; however, fecal phosphate levels are not routinely measured in vivo. Calcium and phosphate contribute to bone matrix formation. Nevertheless, skeletal survey is unlikely to reveal a definitive diagnosis, especially given the lack of skeletal findings on history and examination. Although renal ultrasonography is occasionally performed to assess for asymptomatic nephrolithiasis or nephrocalcinosis during surgical evaluation of patients with primary hyperparathyroidism, it is not typically utilized to characterize the etiology of hypophosphatemia. Hemolysis and rhabdomyolysis can cause hypophosphatemia, although this patient has no signs to suggest muscle breakdown or hemolytic anemia such as abnormal results on complete blood cell count, jaundice, or splenomegaly. In settings of hypophosphatemia, the kidneys will reabsorb urinary phosphate if they are functioning appropriately. A fractional excretion of more than 5% suggests a renal etiology, and a value of less than 5% suggests a GI etiology.[1] An alternative approach is to measure the 24-hour urine phosphate level, with a value greater than 100 mg suggesting a renal etiology.[3] Our patient's 24-hour urine phosphate level was 768 mg.

3. **Which *one* of the following is the underlying predisposition toward hypophosphatemia in this patient?**
   a. Primary hyperparathyroidism
   b. Transcellular shift of serum phosphate
   c. Hungry bone syndrome
   d. Inadequate phosphate intake
   e. Malabsorption

Primary hyperparathyroidism causes renal phosphate wasting and decreased GI absorption of phosphate, typically resulting in hypophosphatemia and hypercalcemia. Our patient had hypocalcemia, refuting this diagnosis. Indeed, our patient's elevated PTH level suggests secondary hyperparathyroidism in response to hypocalcemia. This patient's hypocalcemia and hypovitaminosis D likely resulted from poor absorption of vitamin D and calcium following changes secondary to gastric bypass, as well as impaired vitamin D metabolism from chronic kidney disease. The discrepancy between our patient's total and ionized calcium is likely secondary to a PTH-mediated decrease in albumin-calcium binding.[4] Although secondary hyperparathyroidism can explain hypophosphatemia, the mild changes in the vitamin D and ionized calcium levels in this patient do not correlate

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with the severe degree of hypophosphatemia, nor do these changes from a chronic process fit the timeline of a sudden exacerbation. Intracellular shift of phosphate can be induced by insulin, refeeding syndrome, β_2-agonism, and increased serum pH, none of which were occurring in our patient.[1] Following parathyroidectomy, patients may experience hungry bone syndrome, in which bone mineralization occurs in the sudden absence of PTH, drawing phosphate into the bone from the serum.[1] Inadequate phosphate intake is rare outside of severe malnutrition (eg, anorexia nervosa). Conversely, phosphate absorption can be severely impacted by various physiologic factors, such as low vitamin D and PTH levels and intestinal changes following gastric bypass operation.[1] Chronic nutritional malabsorption following gastric bypass 10 years previously contributed to this patient's low total body phosphorous stores, but the patient remained asymptomatic, likely due to renal compensation.

4. **Which *one* of the following additional factors led to this patient's acute, symptomatic hypophosphatemia?**
   a. IV iron supplementation
   b. Serum pH changes related to obesity
   c. Gastric pH changes related to GERD
   d. Decreased gastric motility from immobilization
   e. Fanconi syndrome

Our patient's 24-hour urine phosphate level was 768 mg, strongly suggestive of renal phosphate losses as mentioned previously.

Intravenous iron therapy is a well-described cause of renal phosphate wasting.[2] This phenomenon occurs due to fibroblast growth factor 23 (FGF-23) secretion triggered by IV iron formulations leading to excess renal wasting and decreased intestinal absorption of phosphate. Alkalosis can cause hypophosphatemia via transcellular shifts. Obese patients with chronic obesity hypoventilation syndrome may have development of chronic respiratory acidosis. GERD and decreased gastric motility do not cause acute phosphate losses. Fanconi syndrome is a rare disorder of the proximal convoluted tubules leading to excess renal losses of glucose, bicarbonate, phosphorus, uric acid, and potassium[5] with associated non–anion gap metabolic acidosis.[5] No acid-base disorders were present in this patient.

5. **What is the *best* next step in the management of this patient?**
   a. IV potassium phosphate and oral calcitriol
   b. Oral phosphate and oral ergocalciferol
   c. IV sodium phosphate and oral calcitriol
   d. IV calcium gluconate and IV sodium phosphate
   e. IV sodium phosphate alone

Current guidelines for phosphate repletion include oral replacement for mild deficiency (>2.0 mg/dL), whereas IV repletion is appropriate for values of less than 1.0 mg/dL or acute symptomatic presentation.[3] This patient's severe, symptomatic hypophosphatemia warranted IV repletion. With concomitant hypokalemia, potassium phosphate was the preferred formulation. Furthermore, the vitamin D deficiency also required intervention with simultaneous oral calcitriol along with oral ergocalciferol. Oral phosphate repletion would not be sufficient given the severity of illness. Intravenous sodium phosphate could have addressed the hypophosphatemia but not hypokalemia. Care should be taken with simultaneous calcium and phosphate repletion because the elements can bind together, leading to calcium-phosphate precipitation.[3] Given that the patient was not experiencing signs of acute hypocalcemia, such as heart block or seizure, it would be more appropriate to target phosphate deficiency first.

The patient received several rounds of IV electrolyte repletion, resulting in improvement in generalized weakness. She was discharged with an oral repletion regimen, and her serum phosphorus level normalized after several weeks.

DISCUSSION

Phosphate is one of the major electrolytes in human physiology and plays a vital role in innumerable intracellular biochemical

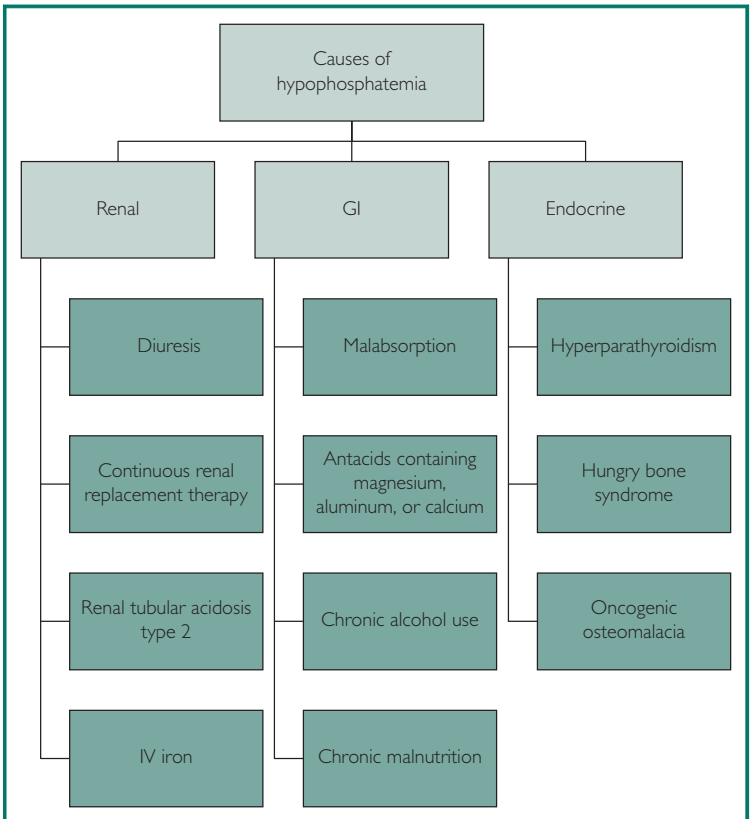

FIGURE. Common causes of hypophosphatemia. GI, gastrointestinal; IV, intravenous.

processes.[6] Most phosphate resides intracellularly. Serum phosphate is used as a surrogate for total body stores. Normal levels of serum phosphate range from 2.5 to 5 mg/dL. Mild hypophosphatemia ranges from 2 to 2.5 mg/dL, moderate from 1 to 2 mg/dL, and severe less than 1 mg/dL. Symptoms of hypophosphatemia are generally only seen with severe hypophosphatemia, although they can be seen at higher serum levels.[1]

Consistent with phosphate's role as an integral component of adenosine triphosphate, clinical manifestations of hypophosphatemia typically present in organs with high energy demands, such as the heart, nervous system, and skeletal muscles.[7] Cardiac manifestations include supraventricular and ventricular tachycardias as well as impaired contractility leading to heart failure. Neurologic symptoms can include paresthesias, tremor, seizure, confusion, and coma. Muscular symptoms can include profound generalized weakness and diaphragmatic weakness that can result in respiratory failure. Interestingly, hypophosphatemia may provoke rhabdomyolysis, and associated cellular lysis with phosphate release can mask underlying hypophosphatemia.[8]

Causes of hypophosphatemia can be divided grossly into renal losses, reduced GI uptake, and endocrinopathies (Figure).[9] In hyperparathyroidism, one of the most common endocrinopathies, elevated serum PTH, induces increased renal phosphate excretion. Following parathyroidectomy, patients may experience hungry bone syndrome in which bone mineralization occurs in the sudden absence of parathyroid hormone, drawing phosphate into the bone from the serum. Subsequently, bone mineralization occurs in the sudden absence of PTH, drawing phosphate into the bone and leading to hypophosphatemia. Vitamin D promotes phosphate uptake in the GI tract and phosphate resorption by the kidneys. Accordingly, vitamin D deficiency leads to hypophosphatemia due to decreased phosphate uptake in the gut and kidneys. Rarely, oncogenic osteomalacia, a paraneoplastic disorder in which small, benign tumors secrete phosphaturic hormones, occurs leading to excess renal phosphate losses.[8]

Reduced GI uptake of phosphate can occur with disorders of malabsorption and chronic malnutrition. Special attention must be paid to the medication list, as excessive use of antacids containing calcium, magnesium, or aluminum will bind phosphate, preventing its absorption. Intravenous iron, aminoglycosides, and certain chemotherapeutic agents can promote renal loss of phosphate. Prior studies suggest that iron supplementation increases serum levels of FGF-23 by inhibiting FGF-23 degradation. Fibroblast growth factor 23 is secreted by both osteoclasts and osteoblasts in response to raised phosphate levels in order to maintain serum homeostasis by promoting renal tubular phosphate secretion. Fibroblast growth factor 23 also inhibits calcitriol, which is needed for phosphate absorption in the intestines.[10]

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Diuresis is associated with renal wasting of phosphate, which may be seen following administration of loop and thiazide diuretics, autodiuresis associated with volume overload, osmotic diuresis from hyperglycemia, and the diuresis phase of acute tubular necrosis. Phosphate wasting is a hallmark finding in type 2 (proximal) renal tubular acidosis.[11] In the critical care setting, continuous renal replacement therapy perpetually removes phosphate, necessitating frequent replacement. Additionally, chronic alcohol use impairs phosphate absorption and promotes its renal excretion. Many causes of increased metabolic demand, such as sepsis, systemic inflammation, and major surgical procedures, may deplete phosphate stores.[1]

Initial work-up of hypophosphatemia should evaluate for other coexisting electrolytes, such as potassium, magnesium, and calcium. Potassium and magnesium deficiencies may also result from reduced GI uptake and renal losses. Calcium and phosphate regulation are tied physiologically by PTH and vitamin D. It is reasonable to monitor PTH and vitamin D. Measuring urine phosphate allows for the calculation of fractional excretion of phosphate.

Phosphate repletion may be performed intravenously or orally. Patients with renal insufficiency will have gradual development of hyperphosphatemia, so they should only receive phosphate repletion if they have severe or symptomatic hypophosphatemia. Phosphate repletion should also be done cautiously in patients with abnormal calcium levels. Dosing should be determined by local hospital protocol. Intravenous doses generally range from 15 to 45 mmol infused over several hours to avoid transient extracellular hyperphosphatemic state. Ultimately, the underlying cause of hypophosphatemia must be identified and addressed.[12]

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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REFERENCES

1. Anand IS. Pathophysiology of anemia in heart failure. *Heart Fail Clin*. 2010;6(3):279-288.
2. Amanzadeh J, Reilly RF Jr. Hypophosphatemia: an evidence-based approach to its clinical consequences and management. *Nat Clin Pract Nephrol*. 2006;2(3):136-148.
3. Yu ASL. Disorders of magnesium and phosphorus. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 24th ed. Elsevier; 2012. 744-748.
4. Ladenson JH, Lewis JW, McDonald JM, Slatopolsky E, Boyd JC. Relationship of free and total calcium in hypercalcemic conditions. *J Clin Endocrinol Metab*. 1979;48(3):393-397.
5. Foreman JW. Fanconi syndrome. *Pediatr Clin North Am*. 2019; 66(1):159-167.
6. Leung J, Crook M. Disorders of phosphate metabolism. *J Clin Pathol*. 2019;72(11):741-747.
7. Weisinger JR, Bellorín-Font E. Magnesium and phosphorus. *Lancet*. 1998;352(9125):391-396.
8. Assadi F. Hypophosphatemia: an evidence-based problem-solving approach to clinical cases. *Iran J Kidney Dis*. 2010;4(3): 195-201.
9. Kestenbaum B, Houillier P. Disorders of calcium, phosphate, and magnesium metabolism. In: Feehally J, Floege J, Tonelli M, Johnson RJ, eds. *Comprehensive Clinical Nephrology*. 6th ed. Elsevier; 2018:124-141.
10. Ifie E, Oyibo S, Joshi H, Akintade O. Symptomatic hypophosphataemia after intravenous iron therapy: an underrated adverse reaction. *Endocrinol Diabetes Metab Case Rep*. 2019; 2019(1):19-0065.
11. Yaxley J, Pirrone C. Review of the diagnostic evaluation of renal tubular acidosis. *Ochsner J*. 2016;16(4):525-530.
12. Felsenfeld AJ, Levine BS. Approach to treatment of hypophosphatemia. *Am J Kidney Dis*. 2012;60(4):655-661.

CORRECT ANSWERS: 1. e. 2. e. 3. e. 4. a. 5. a