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Hypophosphatemia in a patient with an eating disorder

A 32-year-old woman presented to the emergency department for hypophosphatemia. She had a history of an eating disorder and had recently started treatment at an inpatient eating disorder treatment center. There, her electrolyte levels were screened routinely. She had visited the emergency department twice within the previous 3 weeks because of hypophosphatemia as low as 1.0 mg/dL (reference range 2.5–4.5). On both occasions, this laboratory finding had been detected with screening at her care facility, and she had been discharged from the emergency room following phosphorus repletion.

On this presentation, her only symptoms were mild fatigue, poor short-term memory, and 1 week of intermittent diarrhea that began only after she started taking oral potassium phosphate 500 mg 3 times daily. She described memory difficulty over 1 to 2 weeks, noting trouble with concentration and feeling "hazy." She had a history of bulimia nervosa, but no recent vomiting or laxative or diuretic use.

MEDICAL HISTORY

Her medical history included iron deficiency anemia thought to be secondary to heavy menses. Two months earlier, blood testing had shown the following results:

- Hemoglobin 10.8 g/dL (reference range 11.5–15.7)
- Mean corpuscular volume 79 fL (80–100)
- Red blood cell distribution width of 14.5% (11.5–14.5%)
- Normal white blood cell and platelet counts
- Ferritin 12.3 ng/mL (13.0–150.0).

The patient had not tolerated oral iron due to gastrointestinal side effects and had received intravenous ferric carboxymaltose 3 weeks and 1 week prior to presentation. Her only medication was oral potassium phosphate 500 mg 3 times daily, which had been started after her second emergency department visit. She had no notable family history of kidney problems or gastrointestinal disease.

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ELECTROLYTE ABNORMALITIES

1 Which of the following is not a common electrolyte abnormality associated with vomiting and bulimia nervosa?

- ☐ Hypokalemia
- ☐ Hypophosphatemia
- ☐ Hyponatremia
- ☐ Hypernatremia

Recurrent vomiting associated with bulimia nervosa leads to loss of stomach acid, composed primarily of hydrochloric acid. Its loss leads to increased serum pH and hypochloremia. Hypochloremia in turn blocks renal bicarbonate excretion by inhibiting the activity of the bicarbonate-chloride exchange channel present in the collecting duct epithelium, causing increased serum bicarbonate and metabolic alkalosis.[1] In response to the elevated serum bicarbonate, hydrogen shifts to the vascular space to buffer the bicarbonate, and there is a subsequent intracellular shift of potassium to balance the electrochemical gradient.[2,3] Hypokalemia can result.

Hypernatremia would be an unexpected electrolyte abnormality associated with vomiting and bulimia nervosa. Gastrointestinal losses such as vomiting and diarrhea commonly lead to a hypovolemic hypotonic hyponatremia due to extrarenal losses of sodium and subsequent water reabsorption.[4] Therefore, hyponatremia would be a more typical finding than hypernatremia.

REFEEDING SYNDROME

Refeeding syndrome can result in hypophosphatemia and hypokalemia, and patients with bulimia are at increased risk of this condition. Refeeding syndrome is marked by varying electrolyte and metabolic abnormalities after the reintroduction of food, either orally or via artificial nutrition, after an extended period of low intake.[5] There is no universal definition of refeeding syndrome, making it difficult to diagnose or study.[6]

A person with malnutrition needs energy to maintain essential cellular functions, so the body uses stores of phosphate found mainly in bone and soft tissue to generate adenosine triphosphate.[7] With the reintroduction of food in an energy-depleted state, the accompanying increase in insulin leads to intracellular shifting of both potassium and phosphorus in the setting of total body electrolyte depletion.[5] This precipitated drop in phosphorus can result in clinical manifestations of refeeding syndrome, such as respiratory distress from muscular dysfunction, and hypotension and arrhythmias from cardiac dysfunction.[5] The drop in phosphorus can also cause decreased production of 2,3-diphosphoglycerate, leading to tighter oxygen affinity by hemoglobin and ultimately to tissue hypoxia.[5] Thus, the clinical manifestations of severe hypophosphatemia can include sequelae from depletion of adenosine triphosphate and tissue hypoxia, with metabolic encephalopathy, cardiac arrhythmias, respiratory muscle weakness, proximal myopathy, rare cases of rhabdomyolysis, and hemolytic anemia.[5,6]

LOSING PHOSPHORUS

On arrival at the emergency department, the patient's blood pressure was 119/74 mm Hg, her heart rate was 74 beats per minute, and her body mass index was 24 kg/m^2. She had no muscle weakness or tenderness, her cardiac examination was normal with no extra heart sounds or signs of heart failure, and she had normal respiratory effort. Neurologically, she was alert and oriented, with no paralysis or paresthesia, but she reported impaired ability to recall recent events without overt confusion.

Her phosphorus level was still low at 1.6 mg/dL, but her potassium, bicarbonate, calcium, magnesium, and creatinine levels were normal. A complete blood cell count showed normal white blood cell and platelet counts. The hemoglobin was 11.1 g/dL with a mean corpuscular volume of 81.2 fL and a red blood cell distribution width of 17.2%.

The patient was given 45 mmol of intravenous sodium phosphate and admitted to the internal medicine floor. Glucose was not administered.

2 Where is most phosphorus reabsorbed by the kidney?

- ☐ Proximal convoluted tubule
- ☐ Loop of Henle
- ☐ Collecting duct
- ☐ Distal collecting duct

Phosphorus is unique among clinically relevant electrolytes in that nearly all reabsorption occurs in the proximal convoluted tubule alone.[8] This aspect of renal phosphate handling has two significant clinical applications:

- Commonly used medications that act in other parts of the nephron, such as loop or thiazide diuretics, do not cause phosphorus dysregulation
- Proximal tubular dysfunction leading to hypophosphatemia usually manifests as Fanconi syndrome, which results in a recognizable set of other electrolyte and urinary changes such as a nonanion gap metabolic acidosis, hypouricemia, mild proteinuria, glucosuria, and hypokalemia.

LOW PHOSPHORUS DESPITE REPLETION

The patient's history of an eating disorder initially suggested a diagnosis of refeeding syndrome leading to hypophosphatemia. She was put on a phosphorus-rich diet with aggressive repletion of phosphorus. On the date of admission, she received 150 mL of oral phosphorus solution and 45 mmol of intravenous sodium phosphate. The following day, she received 60 mL of oral phosphorus solution and 18 mmol of intravenous potassium phosphate. On the third day, she received 30 mmol of intravenous sodium phosphate and 18 mmol of intravenous potassium phosphate.

Phosphorus repletion must be done with caution, particularly when given intravenously. Intravenous phosphorus can precipitate with calcium, leading to hypocalcemia, arrhythmias, and calcium-phosphate crystal formation in the kidneys. Therefore, repletion in this patient involved a combination of oral and intravenous routes with twice-daily monitoring to avoid overrepletion. General guidelines for oral repletion of hypophosphatemia above 1 mg/dL are to give 1,000 to 2,000 mg per day divided into 3 doses.[9] The maximum recommended regimen for intravenous phosphate repletion for patients with normal calcium levels and renal function is 0.64 mmol/kg of elemental phosphorus given over 6 to 8 hours.[9]

Repeat phosphorus levels remained low, between 1.6 and 2 mg/dL, despite ongoing repletion. Urinalysis did not show proteinuria or glucosuria. There was less concern about fasting or postprandial phosphorus level changes because patients with normal renal function have a maximal postprandial increase of 5% at 3 hours after eating.[10] While insulin drives intracellular shifting of phosphorus in the postprandial state, patients without renal impairment can balance phosphorus to prevent large swings in serum phosphorus levels. In patients with chronic kidney disease, serum phosphorus level changes are more pronounced, with phosphorus levels decreasing about 7% postprandially.[10]

MEDICATION AND HYPOPHOSPHATEMIA

3 Which of the following medications is not associated with renal phosphorus wasting?

- ☐ Cisplatin
- ☐ Spironolactone
- ☐ Acetazolamide
- ☐ Intravenous iron

Spironolactone acts in the collecting duct where phosphorus is not significantly reabsorbed, so it is not associated with renal phosphorus wasting. Since most phosphorus is absorbed in the proximal tubule, acetazolamide has a large phosphaturic effect.[7] Its phosphaturic effect is thought to be linked to either a direct effect on the reabsorption of phosphorus in the distal tubule, or more likely via the inhibition of carbonic anhydrase, causing lowered cotransport of sodium and phosphate in the proximal tubule.[7] Cisplatin can cause a proximal tubular injury, leading to phosphorus wasting.[11] Intravenous iron can cause phosphorus wasting. Hypophosphatemia is more associated with the ferric carboxymaltose formulation.[12]

In our patient, the absence of proteinuria or glucosuria argued against proximal tubular dysfunction. The term Fanconi syndrome denotes general dysfunction of the proximal tubule, which leads to urinary loss of several key molecules, including phosphorus, amino acids, glucose, and bicarbonate.[13] While proteinuria in Fanconi syndrome is generally minimal, the detection of glucosuria is a key early diagnostic clue.[13] Causes of Fanconi syndrome in adults include exposure to certain heavy metal, some forms of monoclonal gammopathy, and Sjögren syndrome.[13] Medications that can lead to proximal tubule dysfunction include cisplatin, antiretrovirals such as tenofovir, and carbonic hydrase inhibitors such as acetazolamide and topiramate.[13] The main features of proximal tubule dysfunction that are most readily identifiable via laboratory workup are aminoaciduria and glucosuria, both of which were absent in this patient.[13]

CLOSING IN ON THE CAUSE

At this point, the hypophosphatemia had been present for almost a month, dating back to the patient's first presentation to the emergency department, and had been refractory to repletion.

In general, hypophosphatemia may be due to decreased intestinal absorption of phosphorus, diarrhea leading to phosphorus loss, internal redistribution of phosphorus (as in refeeding syndrome), and renal phosphorus loss. While the patient had a history of an eating disorder, she reported good recent oral intake without abuse of laxatives and without diarrhea to cause intestinal losses of phosphorus. Refeeding syndrome causing phosphorus redistribution had been considered initially, but her phosphorus levels remained low despite repletion.

To evaluate for renal phosphorus wasting, a 24-hour urine phosphorus excretion measurement was done. Under normal conditions, the kidney should be able to decrease phosphorus excretion significantly in response to low serum levels, so an elevated urinary phosphorus level would be unexpected with prolonged hypophosphatemia.[14] The fractional excretion of phosphorus was 45% to 70% (normal is less than 20%). Additional test results included a normal 25-hydroxyvitamin D, a normal parathyroid hormone, a low activated vitamin D of 17.9 pg/mL (reference range 18–78), and a normal fibroblast growth factor 23 (FGF-23).

4 What is the most likely cause of the patient's renal phosphorus wasting?

- ☐ Primary hyperparathyroidism
- ☐ Nutritional vitamin D deficiency
- ☐ Type 2 renal tubular acidosis
- ☐ Intravenous iron-induced renal phosphorus wasting
- ☐ FGF-23–secreting tumor

The combination of recent administration of intravenous iron and elevated urine phosphorus excretion makes intravenous iron-induced hypophosphatemia the most likely diagnosis. Intravenous iron-induced hypophosphatemia results from the interaction between iron and FGF-23,[7,12] a peptide that plays an important role in renal phosphorus handling. FGF-23 is expressed primarily by osteocytes and inhibits reabsorption of phosphorus in the proximal tubule.[15]

In the setting of hypophosphatemia, FGF-23 is downregulated to reduce phosphorus excretion and ameliorate serum phosphorus levels. As a rare side effect, intravenous iron can block the degradation of FGF-23, leading to increased serum FGF-23 levels. In that setting, FGF-23 then inhibits renal phosphorus reabsorption.[8]

In our patient, the normal level of FGF-23 is unexpected in the setting of low serum phosphorus and supports the diagnosis of intravenous iron-induced renal phosphorus wasting. FGF-23 also inhibits 1-alpha-hydroxylase expression in the kidney, leading to lower levels of activated vitamin D as seen in this patient. The low activated vitamin D levels also support intravenous iron as the culprit and can lead to a secondary elevation in parathyroid hormone that can cause phosphorus wasting.[15]

Primary hyperparathyroidism can decrease renal absorption of phosphorus while increasing reabsorption of calcium, but the patient's calcium and parathyroid hormone levels were normal, making this diagnosis unlikely.[8] Vitamin D deficiency can lead to less effective phosphorus reabsorption, as activated vitamin D assists in proximal tubule reuptake of phosphorus. But the patient's 25-hydroxyvitamin D levels were normal, so a nutritional deficiency was unlikely.[8] A type 2 or proximal renal tubular acidosis resulting from Fanconi syndrome would lead to increased excretion of phosphorus since, as noted, the proximal tubule is the main site of phosphorus reabsorption. While all causes of Fanconi syndrome present with a type 2 renal tubular acidosis, some causes of type 2 renal tubular acidosis such as familial and some sporadic forms are not associated with Fanconi syndrome.[16] The patient's urinalysis did not suggest other signs of a proximal tubulopathy such as glucosuria or proteinuria, and no acidosis was present.

FGF-23–secreting tumors are very rare with fewer than 1,000 cases reported in the literature.[17] These tumors typically present at age 40 to 45 and are usually of mesenchymal origin.[17] FGF-23–secreting tumors can lead to renal phosphorus wasting via increased circulating levels of FGF-23 and the mechanisms listed above. More apparent symptoms of weight loss, bone pain, and fractures occur later in the disease process, but in this case an FGF-23–secreting tumor is less likely given the rarity of the condition, the younger age of the patient, and the recent usage of intravenous iron.[17] When there is concern about an FGF-23–secreting tumor, positron emission tomography with a somatostatin receptor-targeting radiotracer such as gallium-68 can help localize a tumor.[18]

DIAGNOSIS REACHED

The patient was diagnosed with intravenous iron-induced hypophosphatemia given her recent history of intravenous iron infusions, persistently low phosphorus, high fractional excretion of phosphorus, and inappropriately normal FGF-23 levels. Intravenous iron-induced hypophosphatemia is most commonly associated with ferric carboxymaltose administration but may be seen less commonly with iron polymaltose and saccharated iron oxide formulations.[19] Other risk factors for hypophosphatemia from intravenous iron include higher baseline renal function, lower body weight, and iron deficiency anemia caused by uterine bleeding.[20] Chronic kidney disease decreases the amount of filtered phosphorus, lowering the amount available to be excreted in the urine and blunting the phosphaturic side effect of high FGF-23. Therefore, patients with lower creatinine levels may be at higher risk of the side effect.[17]

Lower body weight has also been associated with a higher risk of developing hypophosphatemia from intravenous iron. Intravenous iron formulations are administered in fixed doses, so people with lower body weight experience a larger dose-response effect as they receive a relatively higher dose of iron.[17]

Intravenous iron-induced hypophosphatemia typically occurs within the first 14 days after an injection of iron, as intact FGF-23 is maximal during that time.[21] Ferric carboxymaltose has been shown to cause persistent hypophosphatemia with a median time to resolution of 84 days.[22] The mechanism by which ferric carboxymaltose and other iron formulations inhibit the cleavage of FGF-23 has not yet been discovered, making it difficult to elucidate the cause of the prolonged duration of hypophosphatemia.[23]

In FGF-23–mediated hypophosphatemia, treatment includes repletion of phosphorus and correction of the inhibited vitamin D activation through calcitriol supplementation.[24] There are currently no therapies to alter the actions of FGF-23 on the kidney.[24] Repletion of phosphorus is recommended until normalization of serum levels through serial monitoring.

OUTCOME

After several days of phosphorus replacement, calcitriol, and a high-phosphorus diet, our patient's serum phosphorus finally rose to the normal range. Given the risk of acute phosphate nephropathy and renal failure associated with intravenous phosphorus, her renal function was monitored and stayed normal throughout the duration of inpatient treatment.[24] Because of

the severity of her hypophosphatemia and continued renal loss of phosphorus, a peripherally inserted central catheter was placed. She was discharged on twice-daily infusions of 30 mmol sodium phosphorus, 1,000 mg of oral phosphorus 4 times daily, and calcitriol. Two weeks later, with ongoing normal phosphorus levels, intravenous phosphorus infusions were stopped. Her oral phosphorus dosing continued over a slow taper for 4 months before finally normalizing off treatment. She has since remained off phosphorus supplements.

TAKE-HOME POINTS

- Refeeding syndrome has no universally accepted definition, screening tools, or assessment criteria, making diagnosis, management, and risk evaluation difficult.
- Bulimia nervosa is associated with several potentially severe electrolyte abnormalities, with varying symptoms related to each one. Associated hypophosphatemia is generally short-lived and treatable with replacement therapy.
- The kidney reabsorbs most phosphorus in the proximal convoluted tubule. When investigating renal causes of hypophosphatemia, disorders of the proximal tubule should be considered as likely culprits.
- In treatment-resistant hypophosphatemia, consider intravenous iron as a potential cause, and interview the patient about any recent history of intravenous iron. The type of iron administered is relevant and should be researched. One study demonstrated the incidence of serum phosphate levels under 2.0 mg/dL for patients receiving intravenous ferric carboxymaltose at 18.5% compared with 0.8% for intravenous iron sucrose.[25]
- Information from a 24-hour renal phosphorus measurement and collection of FGF-23 levels helps characterize renal phosphate wasting and can support the diagnosis of intravenous iron-induced renal phosphate wasting.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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