Hypophosphatemia in the setting of metabolic bone disease: case reports and diagnostic algorithm

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Abstract: Osteoporosis is the most commonly encountered metabolic bone disease, and metabolic bone-disease clinics have been established to assist in the diagnosis and treatment of uncommon causes of low bone-mineral density. Hypophosphatemia leading to metabolic bone disease may be encountered, and an understanding of phosphate homeostasis can aid in the diagnosis. Two cases of hypophosphatemia leading to low bone-mineral densities were seen at the University of Alabama at Birmingham Osteoporosis Clinic. We developed a diagnostic algorithm, and the laboratory values of each patient were tested with the algorithm. The algorithm, incorporating the use of a spot urine phosphate and spot urine creatinine level at the time of initial serum metabolic profile evaluation, accurately determined the cause of hypophosphatemia in each case.

Keywords: diagnostic algorithm, hypophosphatemia, metabolic bone disease, osteomalacia

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Introduction

Metabolic bone diseases, such as osteoporosis and even osteomalacia, are more common than generally appreciated in the general practice setting, and specialty clinics can help with more complex cases. In the workup of low bone-mineral density (BMD), hypophosphatemia leading to metabolic bone disease should be considered. A standard algorithm for the initial workup of hypophosphatemia in this setting may help to improve the timeliness of diagnosis. We present two cases of hypophosphatemia from uncommon causes leading to reduced BMD. We developed a hypophosphatemia algorithm after prior diagnosis and applied the patients' results to the algorithm to test its accuracy.

Case 1 initial presentation

A 43-year-old White man was referred to the multidisciplinary University of Alabama at Birmingham (UAB) Osteoporosis Clinic after experiencing skeletal fractures and pain. Until the onset of symptoms, he reported no prior fractures. One year earlier, he was bodyboarding with his family at the beach and noted rib pain. He was evaluated by a primary-care physician (PCP) who ordered radiographs that were consistent with rib fractures. Later, he bumped his foot at his home and had persistent pain. He was seen by an orthopedic surgeon who ordered radiographs of the foot that showed fracture and osteopenia. A bone scan was performed that was suggestive of healing lumbar compression fractures. Upon evaluation, he reported one prior episode of nephrolithiasis, no prolonged glucocorticoid usage, and a family history of osteogenesis imperfecta. Physical examination was positive for pain to palpation of the right foot. Dual-energy X-ray absorptiometry (DXA) was performed and revealed Z-scores of −2.6, −1.6, and −1.3 in the lumbar spine, femoral neck, and total hip, respectively. Initial laboratory evaluation was pertinent for creatinine 70.72 μmol/L (reference range: 61.88–114.92 μmol/L), calcium 2.30 mmol/L (2.10–2.54 mmol/L), phosphate 0.41 mmol/L (0.77–1.61 mmol/L), alkaline phosphatase 244 U/L (39–117 U/L), 25-(OH) vitamin D 18 ng/ml (30–100 ng/ml), and intact parathyroid hormone (iPTH) 67.2 pg/ml (12–90 pg/ml). Vitamin D was repleted with ergocalciferol over a 2-month period.

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Case 2

A 49-year-old, postmenopausal White woman was referred to the multidisciplinary UAB Osteoporosis Clinic by her PCP after a DXA was obtained with T-scores of −2.8, −3.8, and −3.5 in the lumber spine, femoral neck, and total hip, respectively. She reported entering menopause at age 40 years but never took hormone-replacement therapy. She denied a history of glucocorticoid use. She had a Billroth 1 gastroduodenotomy at age 33 years due to gastric outlet obstruction secondary to gastric ulcers. Since the procedure, she had suffered with stricture formation at the anastomosis site with recent upper endoscopy reporting a 10 mm opening after dilatation. She experienced weight loss and difficulty in gaining weight since the procedure but denied diarrhea or eating disorder. She was a smoker. Physical examination was pertinent for a weight of 39 kg with a body mass index (BMI) of 14.8 kg/m^2, temporal wasting, and visible ribs. Initial laboratory evaluation was pertinent for creatinine 35.36 µmol/L (35.36–106.08 µmol/L), calcium 2.32 mmol/L (2.10–2.55 mmol/L), phosphate 0.45 mmol/L (0.77–1.61 mmol/L), alkaline phosphatase 108 U/L (39–117 U/L), 25-(OH) vitamin D 45 ng/ml (30–100 ng/ml), and iPTH 29.2 pg/ml (12–90 pg/ml).

Discussion

The evaluation of patients with metabolic bone disease often requires consideration of various causes. While osteoporosis is by far the most commonly encountered metabolic bone disease, patients may have abnormal BMD values within the osteoporosis range that necessitate further workup for other metabolic bone disorders.[1] Osteomalacia is often a result of conditions involving vitamin D or phosphate metabolism and must be considered in these cases of low bone mass with other biochemical abnormalities.[2] While many of the causes of vitamin D deficiency are determined with relative ease, the causes of hypophosphatemia are more broad (Table 1).[3] In the absence of an easily accessible algorithm, the time to diagnosis can be extended.

The physiological maintenance of phosphate homeostasis involves an interplay between intestinal absorption, renal reabsorption, and excretion, and redistribution between the extracellular phosphate, intracellular spaces, and the bone phosphate storage pool.[4,5] It has been estimated that 85% of total body phosphate is stored in bones and teeth, and only 1% is stored in the extracellular fluid.[6] To determine the cause of hypophosphatemia, the mechanisms of phosphate homeostasis must be evaluated for alterations that have led to a phosphate-insufficient state.

The initial analysis for hypophosphatemia involves the evaluation of urinary excretion of phosphate to determine if the process involves a normal or abnormal renal response to hypophosphatemia. Under normal conditions, low serum phosphate should lead to increased reabsorption of phosphate and low urine excretion.[4] Decreased intestinal absorption and intracellular shifting of phosphate are the two pathways that involve a normal renal response. Measurement of urinary phosphate is required to determine renal response and can be obtained with a 24 h urine phosphate collection or calculated with the formula for fractional excretion of phosphate (FEPO4) using random urine and serum phosphate and random urine and serum creatinine values [FEPO4 = (UPO4 × PCr × 100)/(PPO4 × UCr)]. An appropriate renal response is determined by a 24 h urinary phosphate of less than 100 mg/day or a FEPO4 that is less than 5%.[3]

Dietary phosphate is found in many foods, with dairy, meats, and cereals being the richest sources. Intestinal phosphate absorption occurs primarily in the duodenum and the jejunum *via* active cellular and passive paracellular pathways, and up to 75% of dietary phosphate is absorbed in the small intestine.[7] The active cellular absorptive pathway is dependent on the luminal sodium/phosphate (Na/Pi) co-transporter type 2b.[4] In addition, 1,25-$(OH)_2$ vitamin D is involved in a feedback loop with serum phosphate levels in that decreased serum phosphate levels lead to an increase in 1,25-$(OH)_2$ vitamin D levels. Increased 1,25-$(OH)_2$ vitamin D consequently leads to increased intestinal absorption of phosphate.

Mechanisms of hypophosphatemia that lead to a reduction in intestinal absorption affect this pathway. Vitamin D is the major hormone that acts upon this pathway, and deficiency of serum vitamin D can lead to decreased intestinal absorption of phosphate.[7] Malabsorptive states such as chronic diarrhea, celiac disease, chronic pancreatitis, and altered small bowel anatomy can lead to reduction in available phosphate for intestinal absorption. Similarly, an absolute phosphate deficiency in the diet seen in starvation, anorexia, and alcoholism can reduce available phosphate.[3]

Table 1. Common causes of hypophosphatemia. The two major groups are divided by either decreased or increased urinary phosphate.

Decreased urinary phosphate
-Intracellular shift
Increased insulin levels: diabetic ketoacidosis, insulin-dependent diabetes, refeeding syndrome
Hungry bone syndrome
Acute respiratory alkalosis
Tumor consumption: lymphoma, leukemia blast crisis
Sepsis
-Decreased intestinal absorption
Vitamin D deficiency
Malabsorption: bowel surgery, pancreatitis, Crohn's, celiac disease, chronic diarrhea
Chronic kidney/liver disease
Phosphate absorption inhibitors: niacin, phosphate binders, antacids
Nutritional deficiency: anorexia, alcoholism, marasmus
Increased urinary phosphate
-Increased urinary losses
Primary/secondary hyperparathyroidism
Medications: tenofovir, acetazolamide, bicarbonate, IV iron
Tumor-induced osteomalacia/mutations
Fanconi syndrome

Finally, certain medications can bind to phosphate to reduce intestinal absorption, including phosphate binders, antacids, and niacin.[3]

Intracellular shifts, or redistribution, of phosphate is a second cause of hypophosphatemia in the setting of a normal renal response. Unlike the mechanisms involved with decreased intestinal absorption of phosphate, those involved with intracellular shifts of phosphate are more varied and more often seen in acutely ill individuals. Most commonly, intracellular shifts of phosphate are caused by insulin-dependent pathways or acute respiratory alkalosis.[6] Common insulin-dependent pathways include insulin use in diabetic patients, diabetic ketoacidosis, and the refeeding syndrome seen in malnourished patients. The role of insulin in these conditions is to shift phosphate, along with glucose, from the extracellular to the intracellular compartment.[8]

Hyperventilation is the root cause of hypophosphatemia in acute respiratory alkalosis, as well as sepsis.[6] As the respiratory rate increases, the intracellular carbon dioxide level drops leading to increased intracellular pH. Increased pH induces glycolytic pathways involving phosphofructokinase, which increase sugar phosphate production and increase intracellular movement of phosphate. Similarly, shifts from the extracellular space into the intracellular space can occur in lymphoma or leukemia blast crisis due to the metabolic demands of actively dividing cells.[9]

As mentioned previously, a majority of phosphate in the body is stored in the bones. During hyperparathyroidism, bone turnover is elevated. After parathyroidectomy, the balance of calcium and phosphate homeostasis is abruptly shifted. This results in a net shift of phosphate, calcium, and magnesium from the extracellular space to the

bones and is referred to as the hungry bone syndrome. Like most of the mechanisms of phosphate redistribution, hungry bone syndrome results in an acuity that is more likely to be seen in a hospitalized patient.[10]

The final pathway of hypophosphatemia involves an abnormal renal response to hypophosphatemia that leads to renal wasting of phosphate. This inappropriate renal response is determined by measurement of a 24 h urinary phosphate greater than or equal to 100 mg/day or a FEPO4 that is greater than or equal to 5%.[3] The most common cause of hypophosphatemia in this pathway is by either primary or secondary hyperparathyroidism. Parathyroid hormone causes a decrease in serum phosphate levels by inhibiting the Na/Pi co-transporter in the proximal tubule. Most phosphate reabsorption occurs *via* this co-transporter in the proximal tubule and inhibition or internalization leads to increased phosphate excretion.[7] Other causes to consider include the Fanconi syndrome that can lead to phosphate wasting in the renal tubules. In addition, several medications such as calcitonin, glucocorticoids, diuretics, and tenofovir, among others, can lead to downregulation or inhibition of renal tubule transporters.[3,11–13]

Fibroblast growth factor-23 (FGF23) is another hormone that has been shown to alter phosphate reabsorption in the renal tubule. Several entities have been associated with increased FGF23 levels, including genetic conditions of phosphate wasting such as X-linked hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets, and fibrous dysplasia, as well as tumor-induced osteomalacia (TIO).[3] The genetic conditions are caused by variable mutations, but the result is increased FGF23 levels either from alterations to the gene itself or from increased bone production. TIO is caused by ectopic production of FGF23 from soft-tissue tumors.[14]

FGF23 is produced by osteocytes and acts on renal tubule cells to internalize the Na/Pi co-transporter and reduce reabsorption of urinary phosphate.[3] In addition, 25 hydroxyl-1-α-hydroxylase enzyme is downregulated, which reduces 25-OH vitamin D conversion to its active form, 1,25-$(OH)_2$ vitamin D.[14] This leads to an inappropriate reduction or normalization of 1,25-$(OH)_2$ vitamin D, which is typically increased in low phosphate settings as a means to increase intestinal absorption. Although these conditions are biochemically indistinguishable, a childhood history of rickets is more suggestive of mutation, whereas adult onset is more consistent with TIO. Localization of the offending tumor with resection is the treatment for TIO, and octreotide scanning, magnetic resonance imaging, and fluorodeoxyglucose-positron emission tomography/computed tomography have all been successfully used to localize tumors.[3] Commercially available genetic testing is available for determination of mutations to the *PHEX, FGF23, DMP1*, and *ENPP1* genes, however, there is some variation in available testing for *FGF23* and results should be interpreted in the context of low or inappropriately normal 1,25-$(OH)_2$ vitamin D.[3,14,15] If a 1,25-$(OH)_2$ vitamin D level is drawn and appropriately elevated, this is suggestive of an *FGF23*-independent process, and a 24 h urinary calcium should be ordered to determine if hereditary hypophosphatemic rickets with hypercalciuria may be the cause.[14–16]

We developed a diagnostic algorithm for hypophosphatemia using the physiology of phosphate homeostasis and common causes of hypophosphatemia (Figure 1).

Case 1 diagnosis

A 24 h urine collection revealed a urine phosphate level of 1296 mg/day (> 100 mg/day), suggesting increased urinary losses of phosphate. The iPTH level was normal, ruling out hyperparathyroidism as a cause. Medication history did not indicate the use of phosphate-wasting medications. Laboratory values including comprehensive metabolic profile and urinalysis did not support the diagnosis of Fanconi syndrome. At this point, there was concern for TIO as he had no childhood history of rickets. A 1,25-$(OH)_2$ vitamin D level was undetectable at < 8 pg/ml (18–72 pg/ml), even after repletion of vitamin D. FGF23 levels were drawn and elevated at 320 RU/ml (⩽ 180). An octreotide scan was ordered and revealed uptake at the right coracobrachialis origin. Surgical pathology revealed a nerve sheath tumor. A repeat phosphate and FGF23 level was normal after resection of the tumor.

Case 2 diagnosis

A 24 h urine was ordered that revealed a urine phosphate level of 99 mg/day (< 100 mg/day), suggesting either intracellular shift of phosphate

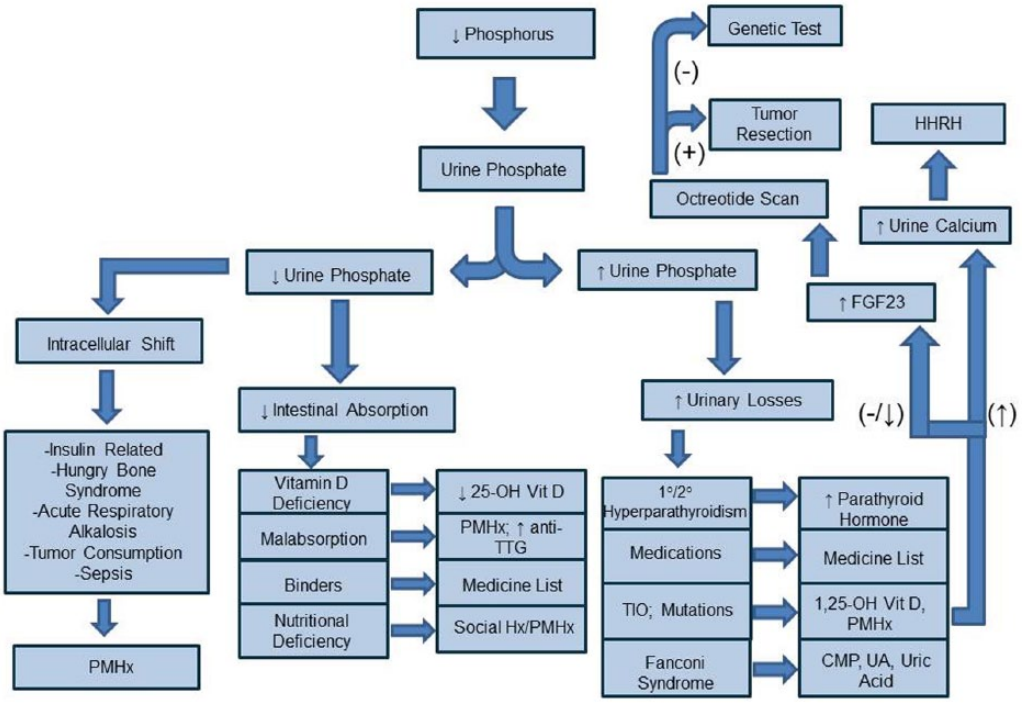

Figure 1. Diagnostic algorithm to determine the cause of hypophosphatemia. Urine phosphate is measured by 24 h urine phosphate or fractional excretion of phosphate (FEPO4) [FEPO4 = (UPO4 × PCr × 100)/(PPO4 × UCr)]. A value less than 100 mg/day or 5% indicates decreased urinary phosphate, whereas a value greater than or equal to 100 mg/day or 5% indicates increased urinary phosphate. Genetic testing refers to commercial testing for *PHEX, FGF23, DMP1*, and *ENPP1* genes. 1,25-OH Vit D, calcitriol; 25-OH Vit D, 25 hyroxy vitamin D; CMP, comprehensive metabolic panel; FGF23, fibroblast growth factor-23; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; PCr, plasma creatinine; PMHx, past medical history; PPO4, plasma phosphate; Social Hx, social history; TIO, tumor-induced osteomalacia; TTG, tissue transglutaminase; UA, urinalysis; UCr, urine creatinine; UPO4, urine phosphate.

or decreased intestinal absorption. There was no laboratory or clinical evidence of hungry bone syndrome, acute respiratory alkalosis, tumor consumption, or sepsis. Although not on insulin products, a refeeding picture was postulated. The 25-(OH) vitamin D level was normal at 45 ng/ml (30–100 ng/ml). Celiac disease was ruled out by history and negative immunoglobulin A (IgA) anti-tissue transglutaminase antibodies with normal serum IgA of 7.49mmol/L (3.6 - 24.2 mmol/L). With known anatomical changes from prior gastroduodenotomy, malabsorption remained on the differential but no history of diarrhea was noted. There was no evidence of phosphate-binding medications or medications known to be associated with phosphate wasting. She denied a history of alcoholism or anorexia, but her low BMI and physical examination was indicative of marasmus. Overall, she had a diagnosis consistent with total-body hypophosphatemia from both decreased intestinal absorption due to the gastroduodenotomy stricture leading to marasmus and possible intermittent refeeding syndrome. Her phosphate has since normalized with dilatation of stricture and aggressive phosphate supplementation.

Conclusion

We evaluated two cases with the use of the proposed algorithm and it was found to predict accurately the causes of hypophosphatemia in each case. It is important to note that phosphate is not commonly reported on the basic or comprehensive metabolic panel and needs to be ordered separately. If hypophosphatemia is suspected, it may be beneficial to order a random urine phosphate and creatinine level alongside the initial serum phosphate to help with timeliness of diagnosis. In rare cases, such as TIO, the average time from onset of symptoms until diagnosis has been estimated at 5 years.[17] The use of an algorithm to aid in the workup of hypophosphatemia may help to reduce the timeframe to diagnosis.

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Conflict of interest statement

The authors declare no conflicts of interest interest in preparing this article.

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