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Teaching Point
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An unusual case of hyperphosphatemia in a vitamin D-deficient patient with tuberculosis

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Introduction

Vitamin D deficiency is associated with several alterations in mineral metabolism [1]. Initially, the development of secondary hyperparathyroidism maintains normal circulating 1,25-dihydroxyvitamin D (1,25-vitamin D) and serum calcium values, but both these values decrease in advanced vitamin D deficiency. Serum phosphorus values usually decrease because of secondary hyperparathyroidism, but rarely are serum phosphorus values high [1]. The rare variant of hyperphosphatemia with vitamin D deficiency has been attributed to an acquired pseudohypoparathyroidism type II resulting from hypocalcemia and/or receptor desensitization from chronically elevated parathyroid hormone (PTH) values [1, 2].

The paradigm for phosphate regulation changed dramatically with the discovery of bone-derived hormone fibroblast growth factor 23 (FGF23), which allows bone to interact with other organ systems involved in the regulation of mineral homeostasis. FGF23 inhibits production of 1, 25-vitamin D, renal phosphate reabsorption and secretion of PTH [3]. In turn, 1,25-vitamin D and phosphate stimulate FGF23 production. We present a case of intermittent hyperphosphatemia associated with severe vitamin D deficiency in which 25-hydroxyvitamin D (25-vitamin D) and 1,25-vitamin D were markedly decreased in the absence of impaired renal function. In contrast to previous reports of pseudohypoparathyroidism with severe vitamin D deficiency, hypocalcemia was absent and the PTH value was normal. We hypothesize that an abnormal FGF23 response may have played a role in the hyperphosphatemia observed in this patient.

Case description

A 46-year-old African-American male was brought to the Veterans Administraton West Los Angeles Medical Center by the Los Angeles County Health Department for treatment of tuberculosis. His past history was significant for cocaine use and hypertension. He had presented 9 months earlier with a lingular infiltrate that was resistant to conventional therapy for pneumonia. One month later, the patient was hospitalized for 5 weeks during which he had a positive sputum for acid fast bacillus (AFB) and a sputum culture grew *Mycobacterium tuberculosis*. He was treated with rifampin, isoniazid, pyrazinamide and ethambutol. Isoniazid was replaced with a fluoroquinolone when sensitivities showed that the organism was isoniazid resistant. The patient was discharged on a regimen of levaquin, rifampin, ethambutol and pyrazinamide but only took these medications for 30 days. His current admission was mandated by Los Angeles County Health because of nonadherence to treatment. The patient was restarted on his antituberculous medications but sputums for AFB and cultures remained positive even after 4 months of treatment despite attempts to maximize treatment such as crushing tablets to increase absorption, addition of other fluoroquinolones and, based on follow-up cultures, restarting isoniazid. Moreover, a chest computerized tomography scan performed 3 months after admission showed an extension of the infiltrate. Four months into his current admission, it was noted that despite normal renal function the patient had had intermittent episodes of hyperphosphatemia during the previous 8 months (Figure 1). Additional tests were ordered to determine the etiology of the hyperphosphatemia.

Evaluation of hyperphosphatemia

Serum creatinine, total calcium and PTH values were normal and the phosphate threshold clearance [maximal tubular reabsorption of phosphate/glomerular filtration rate (TmP/GFR)] was high, 5.8 mg/dL (1.87 mmol/L), when his serum phosphorus was in the high normal range (Table 1). Values of 25-vitamin D and 1,25-vitamin D were severely deficient (Table 1). Twenty-four-hour urine calcium excretion was normal. Further evaluation was limited because the patient refused most additional blood and urine studies.

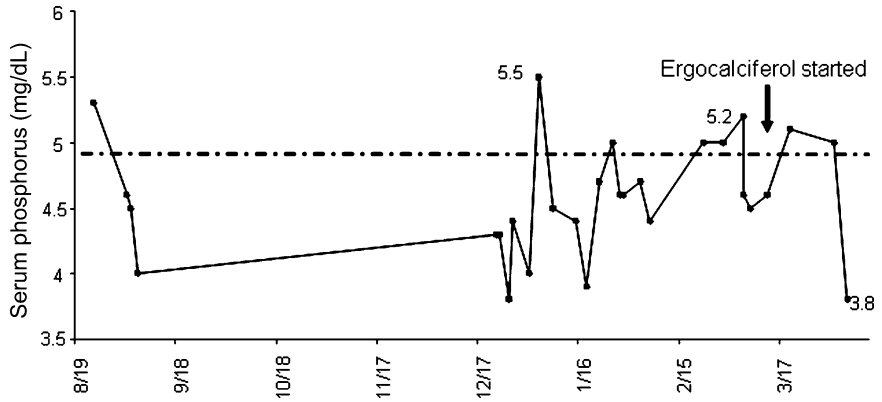

Fig. 1. Serial serum phosphorus values. The normal range of serum phosphorus is 2.5–4.9 mg/dL (0.78–1.52 mmol/L). The dashed line indicates the upper limit of normal. To convert to SI units divide by 3.1. Patient was started on ergocalciferol 50 000 U daily on 3/15.

Table 1. Laboratory values

Pararameter	Before vitamin D	After vitamin D	Normal range	SI units
Serum creatinine (mg/dL)	0.8	0.9	0.5–1.4	umol/L = mg/dL × 88.4
Serum calcium (mg/dL)	9.0	9.8	8.4–10.2	mmol/L = mg/dL × 0.25
Ionized calcium (mmol/L)	1.22	ND	1.15–1.29	
Serum phosphorus (mg/dL)	4.4–5.2[a]	3.8	2.5–4.9	mmol/L = mg/dL × 0.31
25 hydroxyvitamin D (ng/mL)	2.0	63.9	9–38	nmol/L = ng/mL × 2.5
1,25-dihydroxyvitamin D (pg/mL)	5.9	33.3	15.9–55.6	pmol/L = pg/mL × 2.4
PTH (pg/mL)[b]	32.1	ND	14–72	ng/L = pg/mL × 1.0
TmP/GFR (mg/dL)	5.8	ND	[c]	mmol/L = mg/dL × 0.31
Albumin	3.5		3.2–4.8	g/L = g/dL × 10
Total protein (g/dL)	7.6		5.9–8.3	
ABG—pH/HCO3/pCO2 (U/mmol-L/mmHg)	7.42/27.6/43			
Twenty-four-hour urine				
Phosphorus (mg/day)	612	ND		mmol/day = mg/day × 0.031
Calcium (mg/day)	174	ND		mmol/day = mg/day × 0.025
Creatinine (mg/day)	1480	ND		mmol/day = mg/day × 0.0884

[a]The range of serum phosphorus values the month prior to vitamin D treatment.
[b]Measured with Bayer Advia Centaur assay.
[c]The appropriate value for the TmP/GFR is dependent on the level of serum phosphorus. The value should be low (<2.5 mg/dL or 0.78 mmol/L) in the presence of hyperphosphatemia if renal function is normal, as it was in this patient.

Treatment

Treatment with oral ergocalciferol was started at 50 000 IU daily for 1 week, followed by 50 000 IU weekly. Two weeks after starting vitamin D, sputum AFB smears became negative for the first time in 4 months, and 3 weeks after the start of vitamin D treatment, the 25-vitamin D and 1, 25-vitamin D values had risen to 63.9 ng/mL (159.4 nmol/L) and 33.3 pg/mL (79.9 pmol/L), respectively. Serum phosphorus decreased to 3.8 mg/dL and serum calcium increased from 9.0 to 9.8 mg/dL (2.25–2.45 mmol/L) (Table 1). The patient was discharged on antituberculous medications and ergocalciferol but did not return for follow-up appointments.

Discussion

Phosphate homeostasis is maintained by the combination of intestinal phosphate absorption, phosphate influx and efflux to and from bone and intracellular stores and renal excretion of phosphate [2]. In steady-state conditions, the primary determinant of serum phosphorus and phosphate balance is the renal reabsorption of phosphate by the proximal tubule [4]. Hyperphosphatemia develops when a perturbation of the steady state results from either (i) an increased exogenous or endogenous phosphate load which exceeds the renal capacity to excrete phosphate or (ii) decreased renal excretion of phosphate due to either a decrease in GFR or excessive reabsorption of phosphate secondary to abnormal proximal tubule function (Table 2). In the present case, there was no apparent excess phosphate load and multiple estimated GFRs (eGFRs) were normal (eGFR 103–157 mL/min/m^2), suggesting that the patient had either pseudohyperphosphatemia or an abnormality in proximal l tubular reabsorption of phosphate.

Pseudohyperphosphatemia should be suspected when an elevation in serum phosphorus or an inability to measure serum phosphorus is reported in patients with normal renal function, especially, as in this patient, in the presence of a normal serum calcium concentration [5]. Spurious hyperphosphatemia has been observed in several conditions, the most common of which is dysproteinemia (Table 2). Hyperglobulinemia may produce a spurious elevation in serum phosphorus because dilution or deproteinization of

Table 2. Causes of hyperphosphatemia

Pseudohyperphosphatemia
Dysproteinemia
Multiple myeloma
Waldenstrom's macroglobulinemia
Reactive hyperglobulinemia due to chronic infection or inflammation
Hyperlipidemia
Hyperbilirubinemia
In vitro hemolysis
Heparin
Alteplase
Excessive phosphate load
Exogenous
Increased GI absorption—vitamin D intoxication, oral phosphate loads such bowel purgatories and phosphate enemas
Intravenous phosphate administration
Excessive skin absorption—white phosphorus burns
Endogenous
Cell breakdown—rhabdomyolysis, hemolysis, tumor lysis
Cellular phosphate shifts—diabetic and lactic acidosis
Decreased renal excretion
Decreased GFR
Renal failure, acute or chronic
Excessive tubular reabsorption
Hypoparathyroidism
Pseudohypoparathyroidism
Genetic
Severe hypomagnesemia
Severe vitamin D deficiency
Growth hormone excess
Estrogen deficiency
Thyrotoxicosis
Familial tumoral calcinosis
FGF23 mutation
Klotho mutation
GALNT3 mutation[a]
Bisphosphonate therapy

[a]GALNT 3, UDP-*N*-acetyl-alpha-D-galactosamine:polypeptide *N*-acetylgalactosaminyltransferase 3.

the serum sample is inadequate for the degree of hyperglobulinemia. Protein produces turbidity in the analyzed sample that interferes with the colorimetric assay for serum phosphorus that depends on the color change induced by the reduction of phosphomolybdic acid. Excessive lipids in the serum sample may also increase turbidity and interfere with the assay. This patient had a normal total plasma protein and did not have hyperglobulinemia or a monoclonal spike on a serum protein electrophoresis. In addition, his lipid profile and liver function tests were normal. Pseudohyperphosphatemia can also result from *in vitro* hemolysis of the serum sample. In such a case, measurement of the phosphorus concentration in the serum sample is accurate but is elevated by the release of intracellular phosphate. However, hyperphosphatemia is absent *in vivo*. Pseudohyperphosphatemia from *in vitro* hemolysis is generally accompanied by pseudohyperkalemia from the simultaneous release of intracellular potassium. Serum potassium values were never elevated in this patient with values of 3.77, 3.87 and 4.30 mmol/L when three serum phosphorus values exceeded 5.0 mg/dL (1.61 mmol/L). Other factors that can interfere with the assay include hyperbilirubinemia, heparin and alteplase, but none were an issue in this case.

The high TmP/GFR in this patient indicates that an abnormality in the renal tubular reabsorption of phosphate was inducing hyperphosphatemia [4]. PTH and dietary phosphate have been considered the main factors regulating proximal tubular reabsorption of phosphate but recently additional phosphaturic factors, termed phosphatonins, have been identified (Table 3) [2]. The role of these phosphatonins in phosphate homeostasis is undergoing intensive investigation. FGF23, the most widely studied phosphatonin, suppresses expression of the sodium–phosphate cotransporters in the brush border of the renal proximal tubule [4]. FGF23, produced by osteocytes and late-stage osteoblasts, exerts its effects through a receptor system that uses the antisenescence protein, klotho, as a cofactor for binding [2, 4]. Klotho markedly enhances the affinity of FGF23 for fibroblast growth factor receptors (FGFRs) and provides tissue specificity for the action of FGF23. While the principal effects of FGF23 occur in the proximal tubule, the hormone appears to initially interact with the distal convoluted tubule, the site of renal klotho expression. Precisely, how the FGF23-induced signal generated in the distal convoluted tubule is transmitted to the proximal tubule is unknown [2, 4]. It is also unclear which FGFRs are responsible for the renal actions of FGF23, although it appears that FGFR1 plays a predominant role [4].

Excessive proximal tubular reabsorption of phosphate may result from a variety of disorders (Table 2) but the underlying cause is usually from hypoparathyroidism or a resistance to PTH action. The PTH value in this case was normal indicating there may have been resistance to

Table 3. Phosphatonins and associated genetic disorders

Phosphatonins	Clinical syndrome with deficiency or excess
FGF23	Excess
	Tumor-induced osteomalacia
	X-linked hypophosphatemic rickets
	Autosomal dominant hypophosphatemic rickets
	Autosomal recessive hypophosphatemia
	Deficiency
	Tumoral calcinosis
Secreted frizzled-related protein 4 (sFRP-4)	Excess
	Tumor-induced osteomalacia
	X-linked hypophosphatemic rickets
Fibroblast growth factor 7 (FGF-7)	Excess
	Tumor-induced osteomalacia
Matrix extracellular phosphoglycoprotein (MEPE)	Excess
	Tumor-induced osteomalacia
	X-linked hypophosphatemic rickets

PTH. Several conditions are associated with PTH resistance or pseudohypoparathyroidism (Table 2). The most striking abnormality in the present case was severe vitamin D deficiency. With vitamin D deficiency, serum phosphorus values usually decrease because of the associated hyperparathyroidism, but hyperphosphatemia has been reported to occur when vitamin D deficiency is severe [1, 6]. The hyperphosphatemia is postulated to result from a resistance to the phosphaturic effects of PTH from (i) autologous desensitization of the PTH receptor by persistently elevated levels of PTH [7] and/or (ii) hypocalcemia leading to a post-receptor defect in which there is an insensitivity to PTH-induced cyclic adenosine monophosphate generation [1].

The present case is unique because hyperphosphatemia occurred despite the absence of hypocalcemia and secondary hyperparathyroidism indicating that other factors likely contributed to the elevation in serum phosphorus. An attractive possibility is an abnormality in the FGF23 hormonal system given its role in the regulation of phosphate homeostasis and vitamin D metabolism. A substantial body of evidence indicates that FGF23, similar to PTH, is normally involved in the regulation of phosphate balance via its phosphaturic effect, but in contrast to PTH, FGF23 lowers 1, 25-vitamin D levels which further decreases the phosphate burden by decreasing intestinal phosphate absorption [4].

The production and action of FGF23 can be modified by several factors, which may be altered in vitamin D deficiency (Figure 2). The most potent regulatory factor appears to be 1,25-vitamin D which stimulates FGF23 production when administered to animals or humans [8]. Therefore, low 1,25-vitamin D levels could result in an impairment in FGF23 production and a decrease in serum FGF23 levels. In addition, 1,25-vitamin D may also modify the phosphaturic action of FGF23. In vitamin D receptor knockout mice 1,25-vitamin D levels and FGF23 levels were found to be substantially higher than in wild-type mice despite comparable levels of serum phosphorus that were achieved after feeding both groups a 'rescue diet' [9]. The mechanism for the resistance to FGF23 is unclear but could be related to the regulation of klotho by 1,25-vitamin D [8]. An impact of a low 1,25-vitamin D level on the FGF23 response to hyperphosphatemia is further suggested by data from other conditions associated with hyperphosphatemia and low 1,25-vitamin D, including hypoparathyroidism and states of acute estrogen and testosterone withdrawal [2, 10]. A lack of 1,25-vitamin D would not be an issue in the majority of vitamin D-deficient patients in whom 1,25-vitamin D levels are not as severely depressed as they were in this case [6].

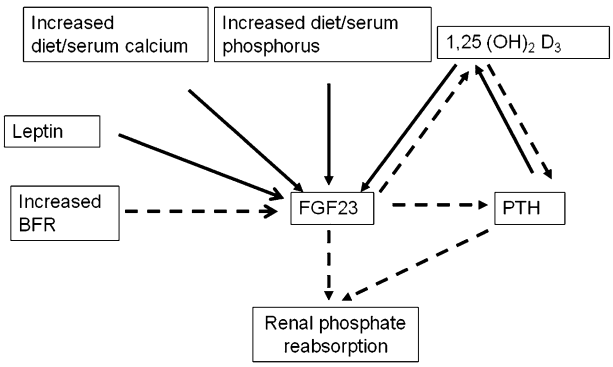

Fig. 2. The complex interplay between factors that regulate FGF23 values. Solid lines indicate stimulatory actions, while dashed lines indicate inhibitory actions. Increased dietary/serum phosphorus, dietary/serum calcium, 1,25-vitamin D and leptin stimulate, while increased BFR inhibits FGF23 production. FGF23 inhibits phosphate reabsorption by the renal proximal tubule, inhibits 1,25-vitamin D production by the kidney and directly inhibits PTH secretion by the parathyroid gland. PTH also inhibits renal proximal tubule reabsorption of phosphate but stimulates 1,25-vitamin D production.

Additional factors that may regulate FGF23 are frequently altered with vitamin D deficiency. An increase in either PTH or dietary/serum calcium has been proposed to stimulate FGF23 production. Also, PTH may be necessary for the full phosphaturic effect of FGF23 [8]. In the present case, neither serum calcium nor PTH were abnormal and were therefore unlikely to have contributed to any potential abnormality in FGF23. Bone formation rate (BFR) may also modify FGF23 production. FGF23 levels increase when the BFR is inhibited and decrease when the

BFR is stimulated [11]. There were no data available on the BFR in this case but the normal PTH and alkaline phosphatase values would favor the absence of an increased BFR. Leptin stimulates the production of FGF23 by bone and leptin values correlate with 25-vitamin D values [12, 13]. Therefore, a reduction in leptin values in vitamin D deficiency could potentially play a role in an inadequate FGF23 response.

There may be a physiologic benefit to a blunted FGF23 response in vitamin D deficiency. A rise in FGF23 in vitamin D deficiency would magnify the effects of substrate deficiency on the renal production of 1,25-vitamin D. FGF23 inhibits the activity of renal 1-α-hydroxylase (CYP27B1), reducing 1,25-vitamin D production and also stimulates 24 hydroxylase (CYP24) which inactivates 1,25-vitamin D as well as 25-vitamin D [14]. Therefore, there are compelling physiologic reasons for a muted FGF23 response in hypocalcemic vitamin D-deficient patients, but with hyperphosphatemia as a trade-off.

In our patient, treatment with ergocalciferol increased the concentration of serum calcium and 1, 25-vitamin D. The concurrent rise in 1,25-vitamin D and serum calcium would potentially upregulate FGF23, which in turn would normalize serum phosphorus via its phosphaturic action. The enhanced phosphaturia would also counterbalance any positive effect of vitamin D on intestinal phosphate absorption. Thus, the correction of severe vitamin D deficiency with ergocalciferol administration may have been responsible for lowering the serum phosphorus level.

It would have been instructive to have measured FGF23 levels in the present case. Unfortunately, the patient refused multiple blood tests through much of his hospital stay and failed to return for follow-up appointments after discharge, which impeded our evaluation. Thus, measurement of FGF23 levels and remeasurement of PTH and TmP/GFR after treatment could not be obtained to confirm our hypothesis.

An unanswered question is why the serum calcium and PTH values were normal in the present case despite severe vitamin D deficiency. Presumably, the PTH value was normal because the serum calcium was normal, but serum calcium is often low with severe vitamin D deficiency especially when 1,25-vitamin D values are low. There was no evidence of excessive intake of calcium to suggest that decreased calcium influx into hypoactive bone may have helped to maintain serum calcium. The only potential mitigating factor was that the patient was on hydrochlorothiazide, which can increase renal calcium reabsorption.

Beyond the scope of our discussion, but another interesting aspect of this case, was the rapid conversion to negative AFB smears after repletion with vitamin D. Vitamin D plays a critical role in the innate immune system which may explain the benefits of vitamin D repletion in the treatment of tuberculosis [15].

Conclusions

Vitamin D has many physiologic functions aside from the regulation of calcium homeostasis including the regulation of FGF23 production and modulation of the innate and adaptive immune systems. Severe vitamin D deficiency in rare instances can lead to hyperphosphatemia and a resistance to PTH action. We have hypothesized that an inadequate FGF23 response contributes to the hyperphosphatemia in vitamin D-deficient patients with either hypocalcemia and/or low 1,25-vitamin D values. The measurement of FGF23 in severely vitamin D-deficient patients could provide further insights into the role of this phosphatonin in vitamin D deficiency. Additionally, vitamin D repletion may be an important adjunctive therapy in multidrug resistant active pulmonary tuberculosis.

Teaching points

(1) In vitamin D deficiency, values for 25-vitamin D are low, while values for 1,25-vitamin D remain normal until vitamin D deficiency is severe.

(2) Even though a reduction in serum phosphorus values is generally seen with vitamin D deficiency because of elevated PTH values, hyperphosphatemia sometimes occurs from PTH resistance induced by hypocalcemia and/or autologous desensitization of the PTH receptor.

(3) FGF23, a newly discovered phosphaturic factor produced primarily in bone is a major regulator of phosphate homeostasis and inhibits 1,25-vitamin D production. In turn, FGF23 production is stimulated by 1,25-vitamin D.

(4) Mutations in the FGF23 hormonal system can result in hyperphosphatemia. We have hypothesized that a blunted FGF23 response could play a role in the development of hyperphosphatemia in some patients with severe vitamin D deficiency and normocalcemia when 1,25-vitamin D values are markedly decreased.

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