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Review

Fibroblast Growth Factor 23 and Hypophosphatemia: A Case of Hypophosphatemia along the Rickets-Osteomalacia Spectrum

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Fibroblast growth factor 23 · Phosphorus · Osteomalacia

Abstract
Phosphorus is a key component of bone, and a deficiency results in poor mineralization along with other systemic symptoms of hypophosphatemia. Various causes of hypophosphatemia with renal wasting of phosphorus have been identified. These include the Fanconi syndrome, various genetic mutations of fibroblast growth factor 23 (FGF23) handling and the sodium/phosphate cotransporter, and those due to FGF23 secretion by mesenchymal tumors. Depending on the cause, vitamin D metabolism may also be impaired, which may amplify the deficiency in phosphorus and render treatment more challenging. Here, we report a case of hypophosphatemia and multiple stress fractures in a 20-year-old male college student living with chronic bone pain and anxiety about suffering further fractures. We further review the literature regarding this spectrum.

Introduction

Normal phosphate balance is an important determinant of normal development and mineralization of bone. Calcium and phosphate comprise two critical elements of the hydroxyapatite crystals which contribute to bone mineralization and tensile strength.

During the formation of new bone, osteoblasts lay down bone matrix in orderly lamellae at the bone surface. In the process of mineralization, osteoblasts deposit hydroxyapatite

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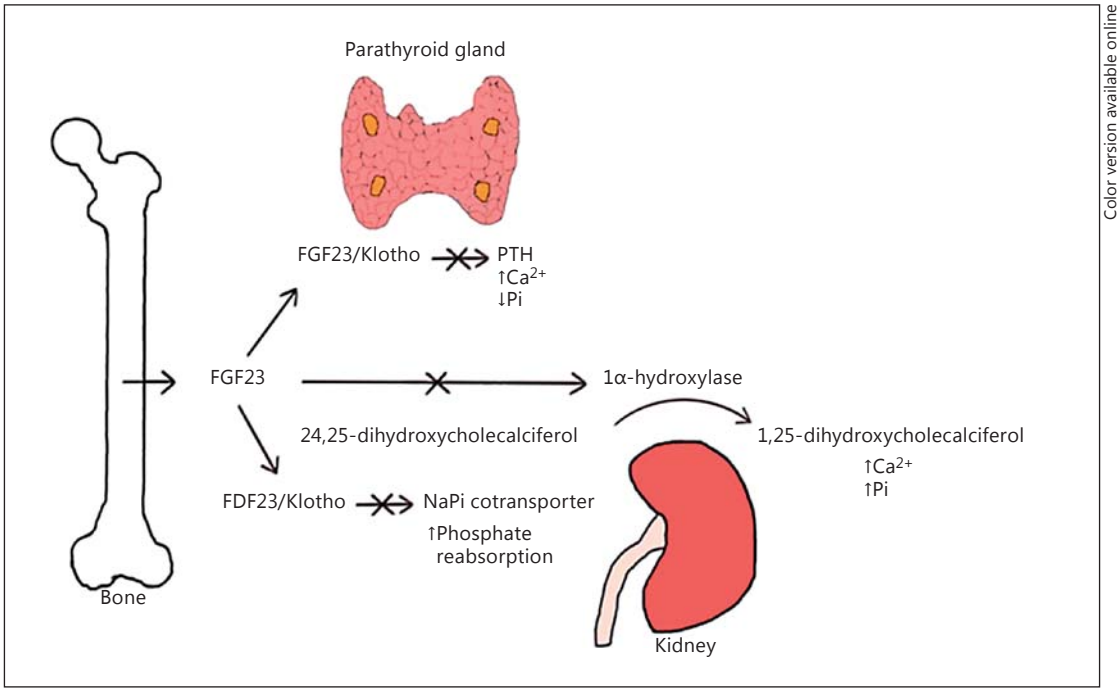

Fig. 1. FGF23-mediated pathways. FGF23 is secreted into circulation from osteoblasts and osteocytes where it targets the FGF23/Klotho receptor complex in the kidney and parathyroid gland. FGF23 reduces the expression of the NaPi cotransporter and 1α-hydroxylase in the kidney and inhibits PTH secretion in the parathyroid gland. Reduction in the expression of the NaPi cotransporter and 1α-hydroxylase results in decreased serum phosphate levels and impaired bone mineralization.

crystals on collagen layers to produce lamellar bone [1, 2]. These osteoblasts then transform into osteocytes whose function is to nurture this new architectural environment of the bone by signaling to neighboring cells and producing factors that regulate mineral balance, including fibroblast growth factor (FGF) 23 [3, 4]. Because pathological conditions prevail in the presence of too much or too little phosphorus, understanding the role of FGF23 in maintaining appropriate levels of serum phosphate is of paramount importance.

FGF23 is a phosphaturic hormone produced by bone which plays an important role in the regulation of normal serum phosphate levels. In the kidney, FGF23 exerts its phosphate-lowering effects by binding to a FGF23-Klotho complex in the brush border membrane of proximal renal tubules where it reduces the expression of sodium/phosphate (NaPi) cotransporters, leading to decreased phosphate reabsorption [3–12]. Furthermore, FGF23 downregulates the expression of the 1α-hydroxylase enzyme and enhances the expression of the 24-hydroxylase enzyme which ultimately reduces 1,25-dihydroxycholecalciferol, resulting in reduced gut absorption of phosphorus [7]. The renal actions of the FGF23-Klotho complex are mediated through activation of the mitogen-activated protein kinase, phosphoinositide 3-kinase, and phospholipase C-Y signaling pathways common to the entire FGF receptor family [8]. Parathyroid hormone (PTH) is also important in regulating both calcium and phosphorus and thus optimal bone mineralization (fig. 1).

Genetic defects involving the proper production and degradation of FGF23, along with defects in the expression and activity of the NaPi cotransporters, present with decreased serum phosphate levels, thus predisposing to metabolic bone disease. A number of mutations

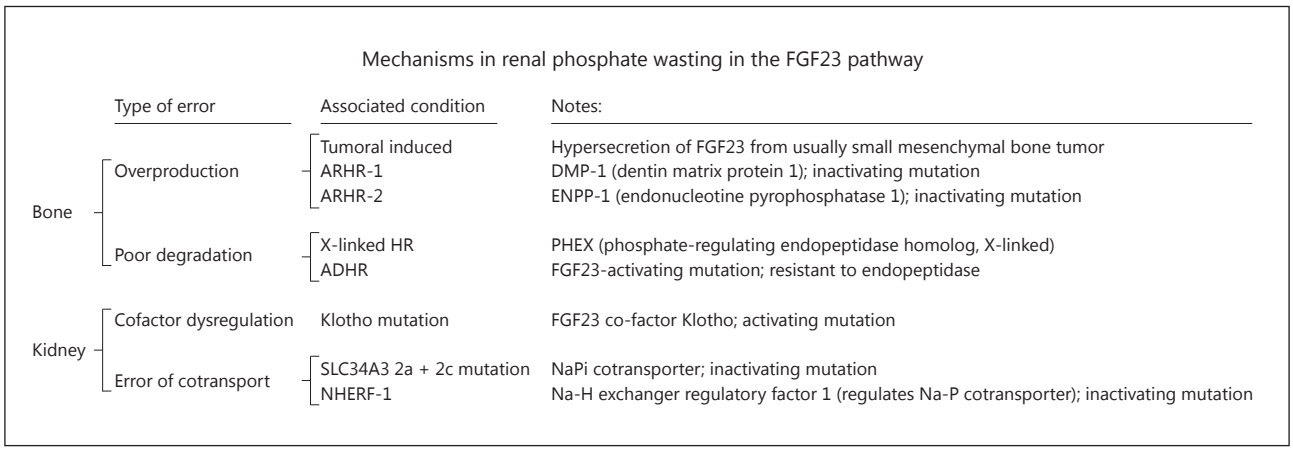

Fig. 2. FGF23-mediated hypophosphatemia can be categorized by the type of genetic or acquired abnormality impacting the involved pathway. Among these are errors in the overproduction and degradation of FGF23 as seen in bone and in tumor-induced osteomalacia, autosomal recessive hypophosphatemic rickets types 1 and 2 (ARHR-1 and ARHR-2). Errors in degradation of FGF23 in bone occur in X-linked hypophosphatemic rickets and autosomal dominant hypophosphatemic rickets (ADHR). Errors of cofactor dysregulation in the kidney occur with mutations in Klotho. Errors of cotransport in the kidney occur with inactivating mutations in SLC34A3 and sodium-hydrogen exchange regulatory factor 1 (NHERF-1).

have been identified which result in the overproduction and reduced degradation of FGF23, in addition to the overexpression of NaPi cotransporter in the proximal tubule cell brush border [9–11] (fig. 2)

Case/Evaluation

Here, we present the case of a 20-year-old male college student with hypophosphatemia and multiple stress fractures, currently living with chronic bone pain and anxiety about suffering further fractures. He had been experiencing recurrent stress fractures since September 2012, at which time he developed bilateral shin fractures diagnosed by MRI. In the spring of 2013, he developed a right third metatarsal stress fracture while playing tennis with physical exam findings of direct pain to palpation of the third metatarsal on the right foot. The only reported medication he was taking at the time was ibuprofen 400 mg by mouth as needed for pain. The following summer, he developed left sided chest pain while he was swimming and was subsequently found to have a fracture of left sixth rib with physical exam findings of tenderness to palpation over the bilateral, anterior chest wall, specifically over the nipple lines and intercostal spaces of the 6th to 8th ribs. In May 2013, he developed pain in his lumbar and sacral spine and was found to have disc protrusion at the L5–S1 level. The patient denied any family history of bone disorders or fractures.

In 2015, he experienced diffuse pain while walking and was evaluated at a student health center with findings of an elevated serum alkaline phosphatase level of 294 units/l which subsequently trended upward. Initial evaluation included a metabolic panel, serum magnesium, phosphorus, intact PTH, 25-hydroxy vitamin D (25-OH Vit D), 1,25-dihydroxyvitamin D (1,25-OH Vit D), thyroid hormone levels, and FGF23. Urine studies included a spot creatinine, glucose, amino acids, phosphorus, and fractional excretion of phosphorus (FEPi), in addition to 24-hour urine phosphorus, calcium, and creatinine. Imaging with a bone scan was obtained along with evaluation using bone densitometry. Genetic testing was pursued to screen for mutations involved in abnormal renal handling of phosphorus including chloride voltage-gated channel 5 (CLCN5), phosphate-regulating endopeptidase homolog, X-linked (PHEX), ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), dentin matrix acidic phosphoprotein 1 (DMP1), solute carrier family 34 member 3 (SLC34A3), and FGF23 sequentially as appropriate.

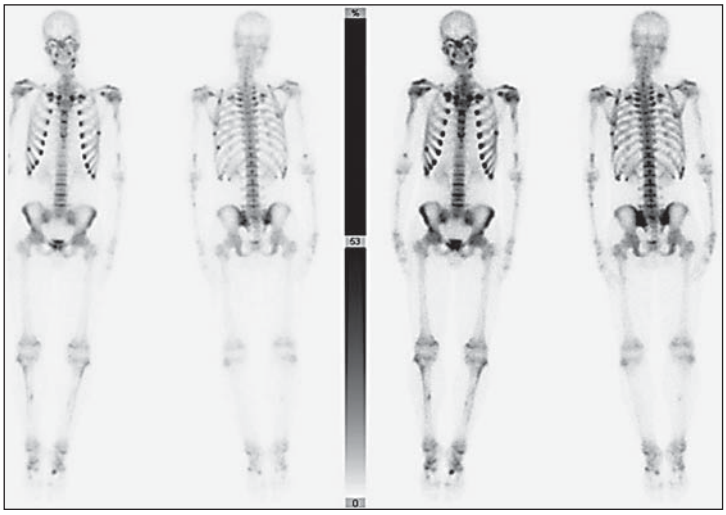

Fig. 3. Bone scan revealing multiple areas of increased uptake of technetium-99 (Tc-99m-hydroxymethane diphosphonate) in the bilateral proximal humeri, distal humeri, left proximal forearm, bilateral ribs, bilateral tibias, and bilateral metatarsals.

Table 1. Results of laboratory investigation

Lab test	Patient lab result	Reference value
Alkaline phosphatase, units/l	384	40–129
Serum phosphorus, mg/dl	1.3	2.7–4.5
Intact PTH, pg/ml	27.1	15–65
Serum calcium, mg/dl	9.2	8.6–10.2
Serum magnesium, mg/dl	2.4	1.7–2.6
25-OH Vit D, ng/ml	36	30–80
1,25-OH Vit D, pg/ml	21	18–64
24-hour urine calcium, mg/24 h	149	100–250
24-hour urine phosphorus, mg/24 h	>2,000	400–1,300
24-hour urine creatinine	1,997 mg/24 h	980–2,220 mg/24 h
FEPi, %	26.3	<5
FGF23, RU/ml	108	≤180

Laboratory and Imaging Results

Relevant laboratory data included an alkaline phosphatase of 384 units/l and a serum phosphorus as low as 1.3 mg/dl, both of which were persistently abnormal on repeat analysis. His intact PTH was 27.1 pg/ml, 25-OH Vit D was 36 ng/ml, 1,25-OH Vit D was 21 pg/ml, serum magnesium was 2.4 mg/dl, and serum calcium was 9.2 mg/dl. A 24-hour urine collection contained 149 mg of calcium, 950 mg of phosphorus, >2,000 mg of phosphorus on repeat check, and his FEPi was 26.3% (normal <5%) suggesting significant renal phosphorus wasting. An FGF23 level was 108 relative units (RU)/ml (<180 RU/ml) (table 1).

The bone scan showed multiple areas of increased uptake in the bilateral proximal humeri, and distal humerus, left proximal forearm, bilateral tibias, left 8th rib, and right 10th rib (fig. 3). X-ray bone survey showed thickened mature periosteal reaction along the right foot third metatarsal bone, consistent with healed stress fracture. The DEXA scan revealed a femoral-neck bone mineral density (BMD) T-score of –1.8 and a total hip BMD T-score of –1.3; both T-scores consistent with osteopenia.

Discussion

Recently, information acquired through the research of bone and renal physiology has added evidence for the complexity of mineral metabolism and the role of phosphorus in bone mineralization [13, 14]. The cross talk of the bone, kidney and parathyroid is increasingly

recognized as being critical for maintaining normal calcium and phosphorus homeostasis in bone mineralization and structural integrity. For example, the role of communication between osteocytes and the kidneys to maintain normal serum phosphorous and optimal bone mineralization is an important area of translational investigation. The case presented is highly suspicious for genetic abnormalities that result in a gain of function in FGF23 renal phosphaturic actions which can produce a characteristic osteomalacia phenotype and a predisposition to stress fractures. However, genetic analysis did not reveal a specific genotype, and FGF23 was inappropriately high for the low level of phosphate. This case and accompanying discussion addresses the role of FGF23 control of phosphate, and the intersection between the osteocyte and the brush border of the proximal tubule in maintaining normal bone mineralization.

The results of the technetium bone scan of this young man indicate that his skeleton has developed appropriately with full length of his extremities without bowing or other abnormalities associated with 'juvenal rickets' as seen in prepubertal individuals. His scan does however demonstrate uptake along the costochondral junctions which may be the postpubertal osteomalacia counterpart of the 'rachitic rosary', or costochondral beading, seen in rickets. He had normal PTH levels and calcium balance, but had an isolated renal loss of phosphate, without evidence of other compromised proximal tubule function. FGF23 normally acts on the parathyroid gland to decrease PTH secretion which, in turn, modulates renal phosphate excretion and the 1-hydroxylation of 25-hydroxyvitamin D [14]. Additionally, his inappropriately low levels of 1,25 vitamin D suggests decreased 1-hydroxylation of 25-OH Vit D to the active 1,25 dihydroxycholecalciferol which would not be expected with such overt hypophosphatemia [13, 14]. This points to a likely alteration in the FGF23 mediated pathway, and more specifically a likely abnormality in one of the various genes that control FGF23 production, as opposed to mutations in the NaPi cotransporter which would not be expected to interfere with normal 1-hydroxylation [14]. Although this young man had an FGF level in the normal range, it is suggestively inappropriate for the degree of hypophosphatemia, and this concept of 'inappropriately normal' is familiar to feedback loops important in regulating such mediators within a physiologic range.

Genetic testing of this individual was begun with evaluation of a CLCN5 mutation of a chloride ion channel, which in retrospect would not alone explain his abnormalities. Further testing will aim to identify the exact mutation likely resulting in this young man's condition. Although case reports of mesenchymal tumors have demonstrated higher levels of FGF23, as compared with 'inappropriately normal' levels, it would be important to rule out this possibility with appropriate imaging which alone can be challenging [13]. Bone biopsy is not routinely performed given that it is an invasive procedure and usually only performed in cases that cannot be diagnosed by history, physical exam, and laboratory findings [15, 16].

This young man was treated with phosphorus replacement which has been titrated up to nearly 4 g daily along with 1 μg of calcitriol. With increasing doses of phosphorus, it is important to be aware of the contents of potassium and sodium in the preparations. His phosphorus levels have maintained in the low normal range. There have been new potential therapies introduced in recent years, which include FGF23 antibodies in addition to the use of C-terminal residues of FGF23 which compete with full-size endogenous FGF23 for the FGF23 receptor-klotho complex and inhibit downstream signaling [13]. These therapies, however, are not currently available for clinical use. In addition, strategies to increase phosphate levels include use of calcitriol to increase gut phosphate absorption and have also been recommended recently [13, 17, 18]. Further understanding of the pathways involved will allow for a more precise treatment and allow patients such as this one not only to reduce recurrent stress fractures but also to enjoy a better quality of life. His family is also being screened for abnormalities in phosphate metabolism and associated bone disease.

An important evolving concept incorporates deranged phosphate metabolism in the pathogenesis of abnormalities characterizing the cardiorenal syndrome [12, 19, 20]. The current case report illustrates how abnormal phosphate metabolism can lead to systemic multiple organ disease including bone disease. Further, since abnormalities in phosphate metabolism may adversely affect renal and cardiac structure and function, aberrations in the FGF-Klotho signaling pathway likely play a key role in the pathogenesis of the cardiorenal syndrome.

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Disclosure Statement

The authors have nothing to disclose.

References

1 Bringhurst R, et al: Bone and mineral metabolism in health and disease; in Kasper D, et al (eds): Harrison's Principles of Internal Medicine, ed 19. New York, McGraw-Hill, 2015.
2 Shoback D, Sellmeyer D, Bikle DD: Metabolic bone disease; in Gardner DG, Shoback D (eds): Greenspan's Basic & Clinical Endocrinology, ed 9. New York, McGraw-Hill, 2011, chapter 8.
3 Liu S, Quarles LD: How fibroblast growth factor 23 works. J Am Soc Nephrol 2007;18:1637–1647.
4 David V, Dai B, Martin A, Huang J, et al: Calcium regulates FGF-23 expression in bone. Endocrinology 2013; 154:4469–4482.
5 Lederer E: Renal phosphate transporters. Curr Opin Nephrol Hypertens 2014;23:502–506.
6 Kuro-o M: Klotho as a regulator of fibroblast growth factor signaling and phosphate/calcium metabolism. Curr Opin Nephrol Hypertens 2006;15:437.
7 Liu S, Tang W, Zhou J, et al: Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. J Am Soc Nephrol 2006;17:1305–1315.
8 Yamashita T, Konishi M, Miyake A, et al: Fibroblast growth factor (FGF)-23 inhibits renal phosphate reabsorption by activation of the mitogen-activated protein kinase pathway. J Biol Chem 2002:277;28265–28270.
9 Carpenter TO: Disorders of phosphate metabolism; in De Groot LJ, Beck-Peccoz P, Chrousos G, et al (eds): Endotext. South Dartmouth, MDText.com, 2000. http://www.ncbi.nlm.nih.gov/books/NBK279172/ (updated Aug 17, 2014).
10 Rowe PS: The wrickkened pathways of FGF23, MEPE and PHEX. Crit Rev Oral Biol Med 2004;15:264–281.
11 Lorenz-Deperieux B, Benet-Pages A, Eckstein G, et al: Hereditary hypophosphatemic rickets with hypercalciuria is caused by mutations in the sodium-phosphate cotranporter gene SLC43A3. Am J Hum Genet 2006; 78:193–201.
12 Jyothsna G, Baum M: Genetic disorders of phosphate regulation. Pediatr Nephrol 2012;27:1477–1487.
13 Weber T, Liu S: Serum FGF23 levels in normal and disordered phosphorus homeostasis. J Bone Miner Res 2003;18:1227–1234.
14 Gupta D, Brietzke S, Hayden MR, Sowers JR: Phosphate metabolism in cardiorenal metabolic disease. Cardiorenal Med 2011;1:261–270.
15 Imel EA, Econs MJ: Approach to the hypophosphatemic patient. J Clin Endocrinol Metab 2012;97:696–706.
16 Recker RR: Bone biopsy and histomorphometry in clinical practice; in Rose CJ (ed): Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, ed 7. Washington, American Society of Bone and Mineral Research, 2008, p 180.
17 Linglart A, Biosse-Duplan M, Briot K, et al: Therapeutic management of hypophosphatemic rickets from infancy to adulthood. Endocr Connect 2014:1:3;13–30.
18 Ovejero D, Lim YH, Boyce AM, et al: Cutaneous skeletal hypophosphatemia syndrome: clinical spectrum, natural history, and treatment. Osteoporos Int 2016, Epub ahead of print.
19 Memon I, Norris KC, Bomback AS, et al: The association between parathyroid hormone levels and hemoglobin in diabetic and nondiabetic participants in the National Kidney Foundation's Kidney Early Evaluation Program. Cardiorenal Med 2013;3:120–127.
20 Saab G, Whaley-Connell A, Bombeck A, et al: The association between parathyroid hormone levels and the cardiorenal metabolic syndrome in non-diabetic chronic kidney disease. Cardiorenal Med 2011;1:123–130.