Review Article

Hypophosphatemic rickets

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ABSTRACT

Hypophosphatemic rickets is a disorder of bone mineralization caused due to defects (inherited/acquired) in the renal handling of phosphorus. This group includes varied conditions, X-linked hypophosphatemic rickets being the most common inheritable form of rickets. The other common forms are autosomal dominant hypophosphatemic rickets and tumor-induced osteomalacia. Although these conditions exhibit different etiologies, increased phosphatonins form a common link among them. Fibroblast growth factor 23 (FGF23) is the most widely studied phosphatonin. Genetic studies tend to show that the phosphorus homeostasis depends on a complex osteo-renal axis, whose mechanisms have been poorly understood so far. Newer disorders are being added as the mechanisms in this axis get discovered. This review focuses on the clinical, biochemical, genetic features and management of hypophosphatemic disorders leading to defective mineralization.

Key words: $1,25(OH)_2D_3$, autosomal dominant hypophosphatemic rickets, fibroblast growth factor 23, hypophosphatemia, tumor-induced osteomalacia, X-linked hypophosphatemic rickets

Introduction

Rickets is a common condition in children that occurs due to a defect in bone mineralization which leads to abnormalities of growth plate cartilage that are predominantly observed in long bones. It may occur due to deficiency of calcium, phosphorous, or vitamin D.[1] The equivalent in adults is a generalized softening of the skeleton due to defective mineralization, known as osteomalacia. Rickets in children is often accompanied by osteomalacia. The major problems of rickets in childhood are growth retardation and bone deformity. In contrast, adult patients with osteomalacia present with muscle weakness and bone pain.

Rickets can be classified into two major groups: calcipenic and phosphopenic. The disorders responsible for each of these types are summarized in Figure 1. Hypophosphatemia is a common denominator of both groups of rickets.[2] It prevents apoptosis in the hypertrophic cells in the growth plate. In the absence of apoptosis, the hypertrophic cells accumulate in the growth plate and form the rachitic bone.[3] In calcipenic rickets, phosphaturia leading to hypophosphatemia occurs due to secondary hyperparathyroidism. In phosphopenic rickets

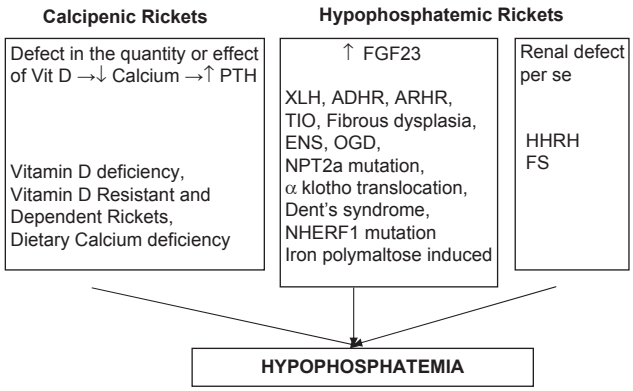

Figure 1: Classification of rickets (ADHR: autosomal dominant hypophosphatemic rickets, ARHR: autosomal recessive hypophosphatemic rickets, ENS: epidermal nevus syndrome, FGF23: fibroblast growth factor 23, FS: Fanconi syndrome, HHRH: hypophosphatemic rickets with hypercalciuria, NPT2a: sodium phosphate cotransporter 2a, NHERF1: sodium hydrogen exchange regulator factor 1, OGD: osteoglophonic dysplasia, PTH: parathyroid hormone, TIO: tumor-induced osteomalacia, Vit D: vitamin D, XLH: X-linked hypophosphatemic rickets)

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(hypophosphatemic rickets), phosphate deficiency is the primary defect that results most commonly from increased renal excretion of phosphate. It is associated with normal or slightly elevated serum parathyroid hormone (PTH). The differences between calcipenic and phosphopenic rickets are summarized in Table 1.

Hypophosphatemic rickets is the most common type of nonazotemic, refractory rickets in Indian children.[4] Most of the hypophosphatemic disorders are inherited, though they may rarely be acquired [tumor-induced osteomalacia (TIO), drug-induced Fanconi syndrome]. They may exist as isolated defects or associated with generalized proximal tubular dysfunction (Fanconi syndrome).

The tubular maximum reabsorption of phosphate per glomerular filtration rate (TMP/GFR) (calculated by nomogram[5]) provides the best estimate of renal phosphate loss. In the absence of secondary hyperparathyroidism, decreased TMP/GFR indicates renal phosphate loss as the primary defect. Although most patients have normal 25-OH vitamin D levels, low levels do not rule out hypophosphatemic rickets, especially in those from Indian ancestry.[6] After renal phosphate wasting is documented by TMP/GFR measurement, the next important step is to determine whether the phosphate loss is isolated or accompanied by other tubular losses.

Interaction of Major Players Involved in Phosphate Homeostasis

Knowledge regarding the pathophysiology of phosphate homeostasis is essential for better understanding of hypophosphatemic rickets. Fibroblast growth factor 23 (FGF23), PTH, and calcitriol play a major role in the phosphate homeostasis and their interaction is summarized in Figure 2. FGF23, a phosphatonin, is the most important player that is implicated in the pathogenesis of most of the disorders with hypophosphatemic rickets/osteomalacia. It binds to FGF receptor 1c (FGFR1c) on cell membranes. Klotho is another important protein in the phosphate homeostasis. Interaction of Klotho with the FGFR1c converts it into a receptor specific for FGF23 function.[7] Decrease in the serum phosphorus level decreases FGF23 and PTH levels, while $1,25(OH)_2D$ level is increased. Increase in serum phosphorus leads to opposite changes. Calcitriol $[1,25(OH)_2D]$ increases serum phosphorus and FGF23, while it decreases PTH.[8] Increase in FGF23 leads to decrease in PTH and calcitriol levels. PTH increases calcitriol and FGF23 levels.[8-10]

Table 1: Differences between calcipenic and phosphopenic rickets

Features	Calcipenic rickets	Phosphopenic rickets
Muscle weakness	Present	Absent*
Bony pain	Common	Uncommon
Extremities involved	All limbs equal	Predominantly lower limbs
Tetany	May be present	Absent
Enamel hypoplasia	May be present	Absent
Dental abscess	Absent	May be present
Serum calcium	Low/normal	Normal
Serum phosphorus	Low	Low
Alkaline phosphatase	Markedly elevated	Mild to moderately elevated
Parathyroid hormone	Elevated	Normal/minimally elevated
Osteopenia and osteitis fibrosa	Present	Absent

*Present in tumor-induced osteomalacia

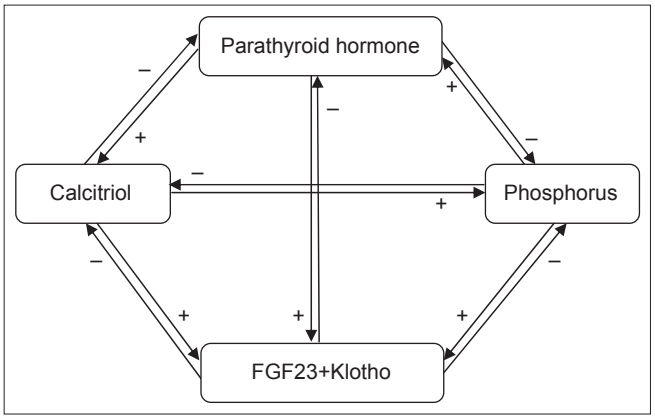

Figure 2: Interaction of major players involved in phosphate homeostasis

X-linked Hypophosphatemic Rickets

X-linked hypophosphatemic (XLH) rickets is an X-linked dominant disorder first described by Albright in 1939. It is the most common cause of heritable rickets, with an incidence of 1:20,000 live births.[11] It accounts for more than 80% of familial hypophosphatemic rickets. Phosphate regulating gene with Homologies to Endopeptidase on X chromosome (*PHEX*) mutations are also described in familial hypophosphatemic rickets patients of Indian origin.[6]

XLH rickets occurs due to inactivating mutations in *PHEX* which encodes a metalloprotease that cleaves small peptide hormones. It is expressed in bone, teeth, and parathyroid glands, but not in kidney. It does not seem to cleave FGF23 directly, but is involved in the downregulation of FGF23 by an unknown mechanism.[12,13] This is illustrated in Figure 3. Mutations can be detected in 50–70% of the affected patients.[14,15] The severity of the disease and specific clinical manifestations are variable even among members of the

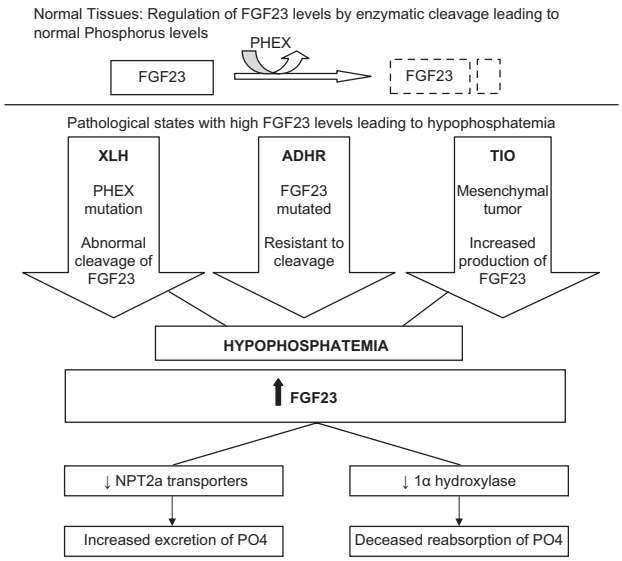

Figure 3: Pathophysiology of FGF23-mediated hypophosphatemic rickets (XLH: X-linked hypophosphatemic rickets, ADHR: autosomal dominant hypophosphatemic rickets, TIO: tumor-induced osteomalacia, FGF23: fibroblast growth factor 23)

same family. In a recent study, patients with clearly deleterious (that resulted in premature stop codons, which included nonsense mutations, insertion or deletion and splice site mutations) *PHEX* mutations had lower tubular reabsorption of phosphate and 1,25$(OH)_2$D levels than those with plausible causative mutations (which included missense mutations and an in-frame three-nucleotide deletion). This finding suggested that the type of *PHEX* mutation might predict the XLH phenotype.[16] In addition to the mineralization defect induced by hypophosphatemia, an intrinsic osteoblast defect also contributes to the bone disease and does not appear to respond to conventional treatment.

Unlike vitamin D deficiency, craniotabes and rachitic rosary are not seen, and the first usual finding is frontal bossing which may appear as early as 6 months of age. As the child starts walking, progressive limb deformities become evident leading to disproportionate short stature with short limbs. Lower limbs are more affected leading to coxa vara, genu valgum, and genu varum. Dental abnormalities are common and may often be the presenting complaints.[17] These abnormalities include abscessed noncarious teeth, enamel defects, enlarged pulp chambers, and taurodontium.[18] Adults may present with short stature, bone pains, pseudofractures, and enthesopathy.

Biochemical evaluation would reveal low serum phosphorus, normal calcium, normal or slightly elevated PTH, and decreased TMP/GFR (calculated by nomogram).[5] There is increased FGF23 and low or inappropriately normal 1,25 $(OH)_2D_3$.

Current standard of care is phosphate replacement in the form of phosphate mixture and with 1,25$(OH)_2D_3$ or 1-OHD_3. Some patients can have marked improvement in bony deformity with treatment, hence corrective osteotomy should be considered only after adequate duration of medical therapy. As the child progresses to adulthood, the phosphate requirements decrease due to closure of epiphyses and decreased bone turnover.[2] Some patients may not require treatment in adulthood. Hence, only those adults who are symptomatic in the form of bone pains, muscle weakness, or pseudofractures require therapy.

Phosphate is generally administered at 20–40 mg/kg/day in three to five divided doses (up to a maximum of 2–3 g/day). Calcitriol is used in doses of 1–3 μg/day.[2] The phosphate dose is titrated gradually to avoid intolerance in the form of diarrhea. Therapy should be targeted to maintain serum phosphorus in the low normal range, normalize alkaline phosphatase, and prevent secondary hyperparathyroidism, hypercalcemia, or hypercalciuria. Serum calcium, phosphorus, creatinine, and spot urinary calcium/creatinine should be monitored every 3–4 months. PTH levels should be checked annually. Nephrocalcinosis and tertiary hyperparathyroidism are the potentially serious complications of therapy.[19] Renal ultrasound should be done at the baseline and yearly thereafter. Phosphate and calcitriol treatment leads to concurrent increases in circulating FGF23 concentrations, which may diminish therapeutic effect or contribute to complications of therapy.[20]

In 2005, a systematic analysis concluded that there is no sufficient evidence to support the use of growth hormone (GH) in children with XLH.[21] A recent study has demonstrated the efficacy of GH in children with XLH where there was significant improvement in height SDS without worsening of skeletal disproportion.[22] Administration of single dose of calcitonin in XLH patients causes a significant and sustained drop in the circulating levels of FGF23 and an increase in the serum levels of phosphorus. [23] Short-term treatment with cinacalcet suppresses PTH, leading to increase in TMP/GFR and serum phosphate. [24] However, long-term studies are required to verify the persistent benefits of these drugs. Isolated C-terminal tail of FGF23 alleviates hypophosphatemia, while anti-FGF23 antibodies ameliorate hypophosphatemia and improve the muscle strength and movements with no effect on growth in hyp mice.[25,26] However, their use in human subjects with hypophosphatemic rickets is still under evaluation.

Autosomal Dominant Hypophosphatemic Rickets

Autosomal dominant hypophosphatemic rickets (ADHR)

displays incomplete penetrance and variable age of onset. FGF23 is mutated at the cleavage site, leading to impaired cleavage of intact molecule, thereby prolonging its activity and phosphaturia[27] [Figure 3].

Based on the age of presentation, two subgroups of ADHR are described. One subgroup presents during childhood and mimics XLH. The other subgroup presents during adolescence or adulthood with bone pain, weakness, and pseudofractures, but no deformity. Some patients with childhood-onset ADHR may have postpubertal spontaneous remission of biochemical abnormalities. Biochemical findings and management of patients with ARHR are similar to those with XLH.

Autosomal Recessive Hypophosphatemic Rickets

Autosomal recessive hypophosphatemic rickets (ARHR) type 1 occurs due to loss of function mutations in dentin matrix protein 1, a noncollagenous bone matrix protein expressed in osteoblasts and osteocytes.[28] This protein has a role in osteocyte proliferation and in the downregulation of FGF23. Another form of ARHR (ARHR 2) has been recently described. It occurs due to loss of function mutations in ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1).[29] ENPP1 generates inorganic pyrophosphate (PPi), an essential physiologic inhibitor of calcification, and may be associated with aberrant ectopic calcification disorders (generalized arterial calcification of infancy) in some cases.[30] Clinical manifestations, biochemical findings, and management of patients with ARHR are similar to those with XLH.

Hereditary Hypophosphatemic Rickets with Hypercalciuria

The genetic defect in hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is loss of function mutation in the gene that encodes NaPi2c (*SLC34A3*).[31-33] A novel mutation in this gene has also been reported in an Indian patient who had rickets since childhood and developed nephrolithiasis during adulthood.[34] Bone pain, muscle weakness, and pseudofractures are the common presenting complaints, while no dental abnormalities are reported. They are more prone to develop nephrolithiasis.[35] FGF23 level is normal and 1,25$(OH)_2D$ levels are appropriately elevated for low phosphorus levels. These patients also exhibit hypercalciuria which predispose them to nephrolithiasis. The management of patients with HHRH differs from those with XLH since the former does not require calcitriol, which may worsen hypercalciuria and increases the predisposition for nephrocalcinosis. Supplementation with phosphate forms the mainstay of its treatment.

Fanconi Syndrome

Although hypophosphatemic rickets is often an isolated renal abnormality, sometimes it may be associated with generalized proximal tubular dysfunction. This may manifest in the form of glycosuria, hypokalemia, proximal renal tubular acidosis, hyperuricosuria, and generalized aminoaciduria. This syndrome may result from various underlying conditions including cystinosis, Lowe's syndrome, drugs, Fanconi Bickel syndrome, etc.[36]

Tumor-Induced Osteomalacia or Oncogenous Osteomalacia

This is an acquired and paraneoplastic disorder caused due to humoral products known as phosphatonins produced by the tumors.[37] The implicated tumors are generally mesenchymal tumors of long bones, distal extremity, sinuses, nasopharynx, groin, etc. They are benign, slow growing, and predominantly of phosphaturic mesenchymal tumor of mixed connective tissue (PMTMCT) origin.[38] They can present at any age with longstanding history of bone pains and muscular weakness. They may present as early as infancy.[39] They usually go undiagnosed for many years.[40] Biochemical evaluation reveals results similar to that of XLH. Complete surgical removal of the underlying tumor provides definitive cure. Hence, it is important to localize the underlying tumor. Localization can be done with octreotide scintigraphy, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) [Figure 4], whole-body magnetic resonance imaging (MRI), or whole-body venous sampling of FGF23. When the tumor remains obscure, phosphate and 1,25$(OH)_2D_3$ are given in a manner similar to that of XLH. Other therapies that

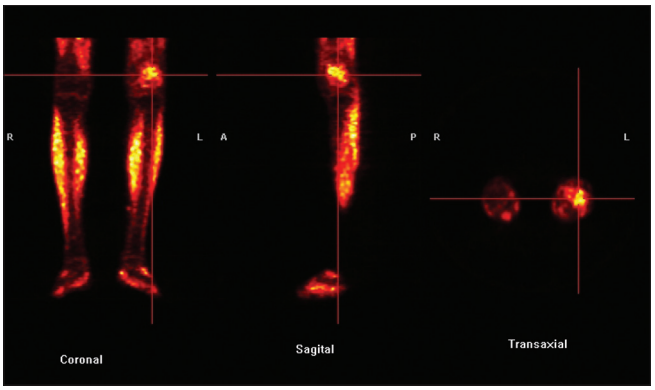

Figure 4: 18-F-FDG-PET in a patient with tumor-induced osteomalacia localizing tumor in the lower end of left femur. This tumor was removed and the histopathology showed ossifying fibroma

Table 2: Etiology and biochemistry of hypophosphatemic rickets

	Gene	Mutation	Inheritance	Pathophysiology	FGF23	1,25(OH)$_2$D	Hypercalciuria
Inherited							
XLH	*PHEX*	Loss of fn	XD	*PHEX* normally causes downregulation of FGF23	↑	N or ↓	No
ADHR	*FGF23*	Gain of fn	AD	Mutant *FGF23* is proteolysis resistant	↑	N or ↓	No
ARHR	*DMP1*	Loss of fn	AR	Loss of *DMP1* impairs osteocyte maturation and increases FGF23	↑	N or ↓	No
	ENPP1	Loss of fn	AR				
Fibrous dysplasia	*GNAS*	Gain of fn	Somatic	Increased production of FGF23 by dysplastic bone	↑	N or ↓	No
OGD	*FGFR1*	Gain of fn	AD	Increased production of FGF23 by dysplastic bone	↑	N or ↓	No
ENS	*? FGF1*	Not known	Not known	Increased production of FGF23	↑	N or ↓	No
HHRH	*SLC34A3*	Loss of fn	AR	NaPi2C loss results in phosphaturia → stimulates 1,25(OH)$_2$D	N or ↓	↑	Yes
NaPi2a Mutation	*NPT2*	Loss of fn	AD	Phosphaturia → stimulates 1,25(OH)$_2$D	Not known	↑	Yes
Acquired							
FS	_	_	_	Proximal tubular defect due to multiple myeloma/lymphoma/drugs/heavy metals	Not known	N or ↓ or ↑	Yes/no
TIO	_	_	_	Mesenchymal tumors secrete phosphatonins	↑	↓	No

AD: Autosomal dominant, ADHR: Autosomal dominant hypophosphatemic rickets, AR: Autosomal recessive, ARHR: Autosomal recessive hypophosphatemic rickets, DMP1: Dentin matrix protein 1, ENPP1: Ectonucleotide pyrophosphatase/phosphodiesterase 1, ENS: Epidermal nevus syndrome, FGF1: Fibroblast growth factor 1, FGF23: Fibroblast growth factor 23, FGFR1: Fibroblast growth factor receptor 1, fn: Function, GNAS: Guanine nucleotide binding protein (G protein), alpha stimulating, FS: Fanconi syndrome, OGD: Osteoglophonic dysplasia, HHRH: Hypophosphatemic rickets with hypercalciuria, N: Normal, NaPi: Sodium phosphate cotransporter, *NPT2*: Sodium phosphate cotransporter 2 gene, *PHEX*: Phosphate regulating gene with Homologies to Endopeptidase on X chromosome, TIO: Tumor-induced osteomalacia, XLH: X-linked hypophosphatemic rickets

have been reported to be of varied use are cinacalcet and octreotide.[41] FGF23 antibodies are also being developed. In patients with unlocalized or incompletely excised tumors, treatment with phosphate and calcitriol may provide symptom relief.[42]

Besides XLH, ADHR, ARHR, HHRH, and TIO, there are many other disorders of renal phosphate loss. These are summarized in Table 2.

Renal phosphate wasting disorders are important causes of rickets to be thought of in appropriate clinical setting. Correct identification of these disorders is important for determining therapy. In the last few years, our knowledge of a number of new inherited phosphate wasting disorders has expanded. This has contributed to the identification of previously unidentified regulators of renal phosphate reabsorption. Yet, many more mechanisms are to be unraveled and the world of phosphate homeostasis is getting fascinating day by day.

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