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X-LINKED HYPOPHOSPHATEMIA: UNDERSTANDING AND MANAGEMENT

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SUMMARY

X-Linked hypophosphatemia (XLH) is a disease of phosphorus metabolism resulting from mutations in PHEX on the X chromosome that encodes for phosphate-regulating neutral endopeptidase, X-linked (PEX), a membrane-bound metalloendopeptidase that is predominantly expressed in bone and teeth. The disease manifests in children as rickets, which progresses to osteomalacia in adults. Hypophosphatemia is the primary biochemical disturbance underlying the rickets and osteomalacia. Decreased tubular reabsorption of phosphate, the direct cause of hypophosphatemia, is due to increased plasma fibroblast growth factor 23 (FGF-23) acting on renal tubular sodium/phosphate cotransporters. Three mouse models of XLH have been developed and have greatly helped unravel the pathophysiology in humans and the exploration of new approaches to medical management. Current treatments are unsatisfactory. They do not cure the disease, but only partially relieve some of the skeletal and biochemical abnormalities, and result in several undesirable side effects. New treatments aimed at decreasing plasma FGF-23 activity show significant potential for reversing both the biochemical and rachitic/osteomalacic abnormalities.

INTRODUCTION

X-Linked hypophosphatemia (XLH) is a disease of phosphorus metabolism resulting from mutations in *PHEX* on the X chromosome that encodes for phosphate-regulating neutral endopeptidase, X-linked (PEX), a membrane-bound metalloendopeptidase that is predominantly expressed in bone and teeth. Inactivating mutations result in an increase in plasma fibroblast growth factor 23 (FGF-23) secreted by bone, which, in turn, leads to disturbances in phosphate homeostasis and skeletal and dental abnormalities. The disease manifests in children as rickets, which progresses to osteomalacia in adults. Hypophosphatemia is the primary biochemical disturbance underlying the rickets and osteomalacia. Decreased tubular reabsorption of phosphate, the direct cause of hypophosphatemia, is due to increased plasma FGF-23 acting on renal tubular sodium/phosphate cotransporters (NaPi). The precise mechanism whereby PEX increases FGF-23 has not been established, but PEX is probably involved directly or indirectly in FGF-23 expression in bone. High plasma FGF-23 also decreases renal 1,25-dihydroxyvitamin D secretion, which further disturbs phosphorus metabolism by reducing intestinal phosphorus absorption.

Three mouse models of XLH have been developed and have greatly helped unravel the pathophysiology in humans and the exploration of new approaches to medical management. Current treatments remain unsatisfactory. They do not cure the disease, but only partially relieve some of the skeletal and biochemical abnormalities, and result in several undesirable side effects. However, new treatments aimed at decreasing plasma FGF-23 activity show great potential for reversing both the biochemical and rachitic/osteomalacic abnormalities. This review will briefly describe human phosphorus metabolism and plasma phosphate homeostasis, outline renal hypophosphatemic diseases, focus on the clinical features of XLH and its pathophysiology, outline mouse models of the disease, and finally, discuss current and potential treatments for the medical management of patients with XLH.

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PHOSPHORUS METABOLISM AND PLASMA PHOSPHATE HOMEOSTASIS IN HUMANS

Phosphorus metabolism

Phosphorus is an essential element for cell function. It occurs in the body in organic and inorganic (Pi) states, both of which are involved in a wide range of cellular and tissue processes, including energy transfer, molecular signaling, cell membrane and nucleotide structure, acid base balance and bone strength.

In bone, phosphorus is present largely as the calcium salt hydroxyapatite ($Ca_5[PO_4]_3OH$) (1). The mineral crystal confers strength and rigidity to the osteoid bone matrix, while simultaneously serving as the major body reservoirs for both phosphorus and calcium. About 85% of body phosphorus and over 99% of body calcium reside in bone. This close relationship between phosphorus and calcium in bone resonates in several aspects of their plasma homeostasis and endocrine regulation.

Phosphorus absorption occurs throughout the small bowel by both diffusion and active transport, which is regulated by 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) (2). Since about 80% of dietary phosphorus is absorbed and closely parallels dietary protein, phosphorus deficiency and hypophosphatemia due to diet rarely occur except in premature infants.

The skeleton deposits Pi during osteoblastic formation of new bone and releases it by osteoclastic resorption of old bone on a continuous basis, which simultaneously maintains optimal skeletal strength and calcium and phosphate homeostasis. In children, the bone phosphate balance is positive and formation exceeds resorption; in young adults the phosphate balance is zero (Fig. 1), and with aging, there is a net loss of bone and phosphate balance becomes negative. The mineralization of osteoid as it is deposited and its subsequent maturation into healthy calcified matrix is a complex vital process that is still not well understood (3, 4). However, the extracellular fluid concentration of Pi plays a fundamental role in this process and severe chronic hypophosphatemia invariably causes failure of osteoid mineralization, resulting in rickets in children and osteomalacia in adults.

The kidney is the main organ regulating plasma Pi concentrations in the steady state. It regulates the amount of Pi reabsorbed from the renal filtrate by saturable Pi transporters in the renal tubule, the primary transporter being the type 2A sodium/phosphate cotransporter (NaPi-2a) (5). The kidney has a tubular maximum capacity for Pi reabsorption (TmP). Diseases that lower TmP produce steady-state hypophosphatemia, whereas those that increase TmP produce hyperphosphatemia. However, it should be noted that TmP is not a sharp transition point, but there is a non-unity relationship ("splay") over about 2 mg/dL of the plasma Pi range (6). TmP can be estimated clinically by measuring plasma Pi and creatinine and urine Pi and creatinine in urine collected for about 2 h after an overnight fast, with blood sampled at the midpoint of the urine collection. TmP can be derived by nomogram (7) or calculated by the equation:

$$TmP = P\text{-}P_E/1\text{-}0.1Log_e\ (P/\ P_E)$$

where P = plasma Pi and P_E = urine Pi x plasma creatinine/urine creatinine (8).

The highest recommended dietary intake of phosphorus established by the Food and Nutrition Board of the Institute of Medicine in 1997-2001 is 1250 mg/day. However, the dietary phosphorus requirement is difficult to define. Because of the close concordance between phosphorus and protein intake and because phosphorus intake and output remain equal over a wide range of dietary intake, without a change in plasma Pi, there does not appear to be an intake at which negative phosphorus balance develops in healthy adults. On the other hand, high intakes of medications that bind phosphorus, such as calcium carbonate, aluminum hydroxide and sevelamer hydrochloride (9), reduce absorption and result in phosphorus depletion and reduced plasma Pi. Conversely, dietary phosphate supplements increase plasma Pi.

Plasma phosphate homeostasis

Plasma contains about 12 mg/dL of phosphorus. However, only about one-third of this is inorganic (Pi). This is the fraction, often misnamed as "plasma phosphorus", that is involved in plasma homeostasis. About 80% of the Pi is "free", with the remainder bound to protein. The free Pi occurs as several ion species and also as complexes with calcium, magnesium and sodium. In the fasting state plasma Pi has a relatively wide concentration range of 2.5-4.9 mg/dL in adults. During childhood the plasma level is higher than in adults but gradually falls from a mean of about 6 mg/dL in the newborn to plateau at the adult range by age 20 (10). Plasma and urine Pi have measurable increases after meal ingestion, indicating that absorption efficiency is high, a wide plasma concentration range is

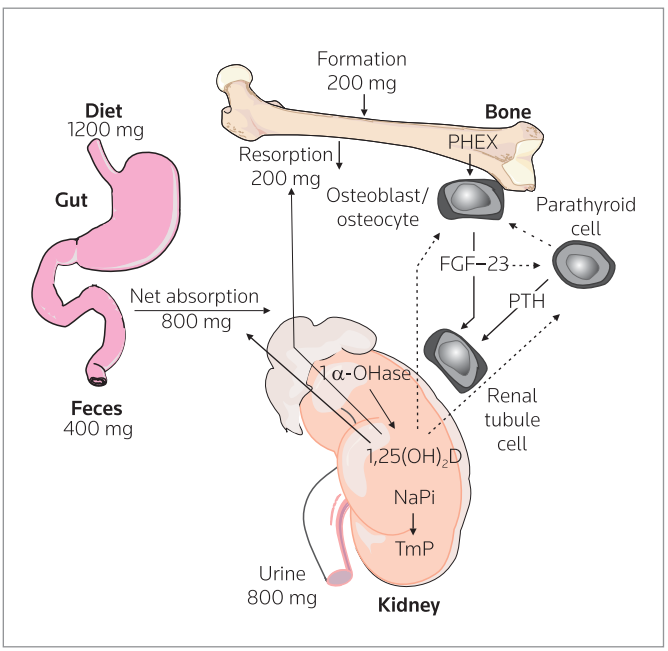

Figure 1. The FGF-23/PTH/$1,25(OH)_2D$ endocrine axis regulating Pi transport and metabolism in the gut/bone/kidney organ axis in an adult in phosphorus balance. From a normal dietary phosphorus intake of 1200 mg/day, 800 mg is absorbed (→) from gut into blood, 400 mg is excreted in feces, 800 mg is excreted in urine, 200 mg is deposited (→) in bone, and 200 mg resorbed (→) from bone. Fibroblast growth factor 23 (FGF-23) secreted (→) from bone and parathyroid hormone (PTH) secreted (→) from the parathyroid gland act on the renal sodium/phosphate (NaPi) cotransporters to decrease tubular maximum capacity for inorganic phosphorus (TmP). FGF-23 acts on 25-hydroxyvitamin D-1α hydroxylase (1α-OHase) to decrease 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) secretion, which decreases Pi gut absorption and Pi bone resorption. In contrast, PTH acts on 1α-OHase to increase $1,25(OH)_2D$ secretion, which increases Pi gut absorption and Pi bone resorption. There are also regulatory pathways between the secretion of FGF-23 (-->) and PTH, between PTH (-->) and FGF-23, and between $1,25(OH)_2D$ (-->) PTH and FGF-23, which promote the fine modulation of Pi homeostasis and metabolism.

tolerated without adverse effects, and the plasma concentration is not under tight homeostatic control.

There are three main hormones regulating plasma Pi homeostasis. FGF-23 (11) and parathyroid hormone (PTH) (12) lower plasma Pi by acting on the kidney tubular NaPi cotransporters to reduce TmP. $1,25(OH)_2D$ raises plasma Pi by increasing Pi absorption from the gut (13) and Pi resorption from bone (14). None of the hormones regulates plasma Pi by a classical rapid negative feedback mechanism, and thus far, a unique Pi receptor has not been identified. Importantly, the three hormones interact to modulate one another's secretion. FGF-23 downregulates renal $1,25(OH)_2D$ (15, 16) and PTH (17, 18), $1,25(OH)_2D$ downregulates PTH (19) and upregulates FGF-23 (20), and PTH upregulates $1,25(OH)_2D$ (21) and FGF-23 (22). Thus, plasma Pi homeostasis and metabolism are controlled by the FGF-23/PTH/$1,25(OH)_2D$ endocrine axis regulating the Pi transport organ axis comprising kidney/bone/gut (Fig. 1).

FGF-23 is a member of the fibroblast growth factor family. The protein, comprising 251 amino acids, is encoded by the *FGF23* gene located at 12p13.3. The *N*-terminal 24 amino acids are cut at secretion to yield the intact biological molecule 25-251. The hormone is also readily split at Arg179 and Ser180 to yield two non-biologically active molecules that appear in the circulation as *N*- and *C*-terminal fragments along with the intact hormone. The intact hormone has a concentration of 10-50 pg/mL in healthy subjects. Mutations in the gene can lead to a protein that is resistant to proteolytic cleavage, resulting in increased activity (23). FGF-23 acts through a composite receptor comprising basic fibroblast growth factor receptor 1 (FGFR-1) and Klotho (24, 25), mutations which lead to inactivation and FGF-23 resistance (26). The *N*-terminal region binds to FGFR-1 and the *C*-terminal region to Klotho. The hormone is produced in bone by osteoblasts and osteocytes (27). The regulators of FGF-23 secretion remain to be clearly identified. A change in plasma Pi does not rapidly result in changes in plasma FGF-23. However, over a period of days, direct relationships among Pi intake and plasma Pi and FGF concentrations develop (28).

PTH, comprising an 84-amino-acid protein, is secreted by the parathyroid cell in a classic negative feedback loop in response to fluctuations in plasma calcium acting through the calcium-sensing receptor (CaS) (29), a transmembrane receptor on the parathyroid cell. In the kidney, PTH acts through the PTH receptor to increase calcium reabsorption, decrease TmP and increase $1,25(OH)_2D$ secretion (30). Plasma Pi does not affect PTH secretion directly, but does so indirectly both acutely and chronically through an inverse relationship with plasma calcium.

$1,25(OH)_2D$ is the renal hormone produced by metabolism of vitamin D. It is a classic steroid hormone with a broad spectrum of biological activity, acting via the vitamin D receptor (VDR), which regulates a wide range of genes (31). The relationship between NaPi-2a and 1α-hydroxylase regulation has not been clearly elucidated, but both molecules are closely related anatomically in the real tubule and in the hormones that regulate their activity.

RENAL HYPOPHOSPHATEMIA: BIOCHEMISTRY AND CLASSIFICATION

XLH is a monogenetic disease in which, as the name implies, hypophosphatemia is the major biochemical abnormality. Hypophosphatemia is usually revealed during the investigation of rickets/osteomalacia, although in subjects without overt bone disease it may be the only obvious abnormality. The first step is to establish that the hypophosphatemia is renal by determining TmP. Because there are a number of renal hypophosphatemic diseases, differential diagnosis requires further extensive biochemical evaluation, along with medical and family history, clinical examination and imaging. The renal hypophosphatemias fall into three main diagnostic categories (Table I): the first includes diseases due to increased plasma FGF-23, the second due to increased plasma PTH and the third due to defects in the renal tubular NaPi cotransporters.

Increased plasma levels of FGF-23 acting on the NaPi-2a renal tubule transporters cause the decreased TmP and plasma phosphate in XLH (32), autosomal dominant hypophosphatemic rickets (ADHR) (33, 34), autosomal recessive hypophosphatemic rickets (ARHR) (35, 36), tumor-induced (oncogenic) hypophosphatemic osteomalacia (37, 38), fibrous dysplasia of bone (39) and iron-induced hypophosphatemia (40, 41).

Increased plasma levels of PTH acting on the same NaPi-2a renal tubular transporters (12) cause the hypophosphatemia of primary hyperparathyroidism, vitamin D-deficient osteomalacia, hereditary vitamin D-dependent rickets type 1A (VDDR1A, MIM 264700) due to a defect in renal vitamin D-1α hydroxylase (42, 43), and hereditary

Table I. *Renal hypophosphatemic diseases. Disease, basic defect and plasma biochemistry are shown.*

Disease	Defect	FGF-23	$1,25(OH)_2D$	PTH	25D	AP	Ca
XLH	PHEX	H	L	H	N	H	N
ADHR	FGF-23	H	L	H	N	H	N
ARHR	DMP-1	H	L	N	N	H	N
ARHR	E-NPP 1	H	L	N	N	H	N
TIO	FGF-23	H	L	N	N	H	N
FD	FGF-23	H	L	N	N	H	N
FeIO	FGF-23	H	L	N	N	H	N
PHPT	PTH	N	H	H	N	H	H
VDO	Vitamin D	L	N	H	L	H	L
VDRR1A	1α-Hydroxylase	N	L	H	N	H	L
VDRR2A	VDR	N	H	H	N	H	L
HHRH	NaPi-2c	N	H	N	N	H	N
HRSD	NaPi-2a/NHERF-1	N	H	N	N	N	N
Fanconi	NaPi-2a	L	L	N	N	H	N

XLH, X-linked hypophosphatemia; ADHR, autosomal dominant hypophosphatemic rickets; ARHR, autosomal recessive hypophosphatemic rickets; TIO, tumor-induced hypophosphatemic osteomalacia; FD, fibrous dysplasia of bone; FeIO, intravenous iron-induced hypophosphatemic osteomalacia; PHPT, primary hyperparathyroidism; VDO, vitamin D-deficient osteomalacia; VDRR1A, hereditary vitamin D-dependent rickets type 1A; VDRR2A, hereditary vitamin D-dependent rickets type 2A; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; HRSD, hypophosphatemic renal calcium stone disease; Fanconi, Fanconi syndrome; PHEX, phosphate-regulating endopeptidase, X-linked; FGF-23, fibroblast growth factor 23; DMP-1, dentin matrix acidic phosphoprotein 1; E-NPP 1, ectonucleotide pyrophosphatase/phosphodiesterase 1; PTH, parathyroid hormone; 1α-hydroxylase, 25-hydroxyvitamin D-1α hydroxylase; VDR, vitamin D receptor; NaPi, sodium/phosphate cotransporter; NHERF-1, sodium-hydrogen exchange regulatory factor; H, high; N, normal; L, low; 25D, 25-hydroxyvitamin D; AP, alkaline phosphatase; Ca, calcium.

vitamin D-dependent rickets type 2A (VDDR2A, MIM 277440) due to a defect in the vitamin D receptor (44). The hypophosphatemia of primary hyperparathyroidism does not cause osteomalacia because it is relatively mild and the increased plasma $1,25(OH)_2D$ maintains Pi absorption and prevents Pi depletion. However, in the vitamin D group of osteomalacias, secondary hyperparathyroidism and phosphate malabsorption are both key factors in the pathogenesis of osteomalacia.

Mutations in the NaPi renal cotransporter system result in hypophosphatemia (5). Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is due to mutations in the *SLC34A3* gene expressing the NaPi-2c transporter system (45). Hypophosphatemia due to mutations in the *SLC34A1* gene occurs in patients with renal calcium stone disease and mild hypophosphatemia (46). Mutations in the sodium-hydrogen exchanger regulatory factor (*NHERF1, SLC9A3R1*) gene, which interacts with NaPi-2a, also cause renal hypophosphatemia and renal stone disease (47). In both acquired and hereditary forms of Fanconi syndrome, hypophosphatemia is thought to be due to damage to the NaPi renal transporters.

GENETICS OF XLH

XLH is the most common genetic form of hypophosphatemic osteomalacia (www.ncbi.nlm.nih.gov/omim, MIM 307800). XLH is unusual in that it is an X-linked *dominant* disorder, meaning that both males and females with a single mutation are affected. An affected mother passes on the gene to half her daughters and half her sons. An affected father passes on the mutation to all his daughters and none of his sons. Additionally, many sporadic cases occur.

Inactivating mutations in *PHEX*, a phosphate-regulating gene with homologies to endopeptidases on the X chromosome (48), result in abnormalities in both osteoblasts and odontoblast lineage cells. *PHEX* mutations cause a hormonally mediated renal phosphate wasting, and hypophosphatemia is responsible for osteomalacia in this disorder. *PHEX* has 22 exons and numerous mutations have been reported causing XLH. A database at McGill (http://www.phexdb.mcgill.ca/) lists known *PHEX* mutations, including missense, deletions, insertions, nonsense mutations and mutations causing abnormal splicing. As of 2008, 260 mutations were reported. Mutations have been reported affecting every exon in *PHEX*. The precise function of the PEX protein is not clear. It does not cleave FGF-23. Rather, through as yet undetermined mechanisms, PEX deficiency leads to increased FGF-23 mRNA expression and protein concentrations (49). On the other hand, transgenic overexpression of *PHEX* does not cause hyperphosphatemia or a disturbance in Pi homeostasis (50).

However, there is wide clinical variation in this disorder, with no clear genotype–phenotype correlation. In fact, members of the same family with XLH vary greatly in their skeletal and dental manifestations of XLH, from very mild to very severe (51).

CLINICAL MANIFESTATIONS OF XLH

The clinical manifestations of XLH are well described (52, 53). They can be grouped under five main clinical types: rickets and osteomalacia; short stature; enthesopathy and osteoarthritis; dentogenesis and tooth abscess; and nephrocalcinosis and hyperparathyroidism.

Rickets and osteomalacia

Patients with XLH typically present with lower extremity bowing after they start walking. Sometimes, due to screening of children of XLH patients, this may be discovered earlier due to hypophosphatemia. Infants often present with classical findings similar to those with vitamin D-deficient rickets: frontal bossing, widening of the wrists and ankles, rachitic rosary (widening and thickening of the ends of the ribs), along with femoral or tibial bowing or torsion. Once they start walking, an in-toeing gait may be observed due to torsion, and a wide-based gait is common in children and adults with XLH. Depending on the degree of femoral versus tibial involvement, either valgus or varus knee deformities may be observed. Some patients develop bone pain as part of their osteomalacia.

Short stature

Short stature is due to failure of the growth of the long bones from rickets and bone deformities. Patients have an elevated upper to lower segment body ratio, with short legs. Clinical severity may range from very mild with normal adult height and straight legs, to very severe with short stature and extreme leg deformities. Affected family members also show this wide variability although they all have the same mutation (51, 54).

Enthesopathy and osteoarthritis

Joint pain is the most common adult complaint in XLH, typically of the lower extremities (55). Calcification of ligaments and tendons (enthesopathy) is common and gradually develops over time (56). Most patients have symptomatic enthesopathy by the third decade, although radiographic evidence may be detected earlier. The initial consequence is joint stiffness with decreased range of motion, and some patients eventually develop painful joints. Enthesopathy is most evident at the spine and hip, although other joints are affected. Spinal cord compression also occurs and may relate to enthesophytes and osteophytes. The underlying mechanism is not clear, but in mice there is expression of receptors (FGFRs) and cofactors (Klotho) necessary for FGF-23 signaling at sites that develop enthesopathy (57). Thus, it is possible that enthesopathy may be a direct result of FGF-23 action. Osteoarthritis is increased in these patients (55), likely due to a combination of enthesopathy and abnormal mechanical forces from bone deformities due to rickets. Objective evidence for muscle weakness in XLH is not documented.

Dentogenesis and tooth abscess

Because PHEX is expressed in the teeth, it is not surprising that patients with XLH have dental abnormalities. Patients are prone to dental abscesses even without caries or trauma. The pulp chamber is enlarged. Studies differ regarding whether there is an enamel defect present (58, 59). The dentin layer is thinner and a smaller proportion is mineralized (60). The mineralized dentin has an abnormal globular appearance (61). Likewise, there is a thinner cementum layer (which attaches the tooth root to the periodontal ligament), with abnormal mineralization of this layer (60). Some of the dental abnormalities may be related specifically to Pi abnormalities or to direct effects of FGF-23 itself. FGF-23 is expressed in both the early odontoblasts and ameloblasts, and expression is increased in *PHEX*

deficiency (62). Studies do not consistently demonstrate a beneficial effect of current therapy on dental abnormalities, and both human and mouse studies indicate that the abnormal dentin mineralization is not improved by therapy (63, 64).

Nephrocalcinosis and hyperparathyroidism

In some studies, the majority of children with XLH treated with calcitriol and phosphate supplements developed nephrocalcinosis that correlated with the total phosphate dose (65, 66). In adults the incidence of nephrocalcinosis is less than in children, but also appears to be related to combined treatment with calcitriol and phosphate (59, 66). Notably, nephrocalcinosis is not reported in patients who have never been treated with either phosphate or a vitamin D analogue. Mice lacking NaPi-2a develop nephrocalcinosis, and humans lacking NaPi-2c are also at risk for nephrocalcinosis and nephrolithiasis (67, 68). In both these situations hypercalciuria develops due to increased plasma $1,25(OH)_2D$, suggesting that calcium hyperabsorption is the main etiological factor. Nephrocalcinosis can proceed in some patients to chronic renal failure.

Hyperparathyroidism is usually a biochemical feature of XLH (Table I) and may be an intrinsic feature of the disease (69). On the other hand, treatment with phosphate supplements will also produce secondary hyperparathyroidism, which may in some cases transform into tertiary hyperparathyroidism (70). Nephrocalcinosis is a feature of primary hyperparathyroidism, but it is not clear if increased PTH plays a role in the nephrocalcinosis of XLH.

ANIMAL MODELS OF XLH

There are three genetic animal models for XLH: Hyp, Gy and ska1 (71-73). Hyp has a deletion at the 3′ end of the gene that extends beyond the end of the gene, and Gy has a deletion at the 5′ end extending beyond the beginning of the gene and including additional genes. The Gy mouse has additional genes affected by a contiguous gene deletion syndrome (with inner ear genes and spermine synthase affected), and thus some features of this mouse are not part of the human XLH phenotype. The ska1 mouse model is a nitrosurea-induced point mutation that results in exon skipping at exon 8 of *Phex* mRNA. However, since multiple *PHEX* mutations are reported in human XLH, including those seen in the Hyp and ska1 mice, each of these mouse models accurately represents the human phenotype. Additional models of FGF-23 excess also mimic the Hyp phenotype. Transgenic FGF-23 overexpression using multiple promoters, or implantation of transfected CHO cells, induces hypophosphatemia and rickets in mice (15, 74, 75). Mutations in *DMP1* cause a related rare human disorder –autosomal recessive hypophosphatemic rickets– with a phenotype identical to XLH (76).

The Hyp mouse is the most thoroughly studied model and is thus known to fully match the human phenotype. This mouse is small and has shortening of long bones and histological features of rickets. The Hyp mouse has elevated FGF-23 concentrations (49), resulting in hypophosphatemia and increased alkaline phosphatase. The dental abnormalities of Hyp are similar to those in human XLH teeth. Expression of renal NaPi-2a and -2c and 1α-hydroxylase is diminished, leading to low plasma Pi and $1,25(OH)_2D$ concentrations (75). Bone FGF-23 expression and plasma FGF-23 concentrations are increased. Most of the Hyp phenotype is mediated via FGF-23, and ablation of FGF-23 (via cross with an *Fgf23*-null mouse) causes these mice to develop hyperphosphatemia (77). Studies of XLH therapies have focused on the Hyp mouse model and, as discussed below, are beginning to produce promising therapies.

TREATMENT TARGETS IN XLH

Short stature

Knee osteotomies, or alternative procedures such as hemiephysiodesis, intramedullary nailing or the Ilizarov method, are usually performed to correct bowing, but they do little for short stature or prevention of knee osteoarthritis in adulthood (78-80). The most important role for surgery is amelioration of severe deformities of long bone shape. Growth failure is considered by some to be a feature of XLH in children and height responds to combined treatment with calcitriol and phosphate supplements, as might be expected if the therapy ameliorates the rickets (65). Growth hormone therapy used to promote an increase in height has no demonstrated benefit (81), consistent with the concept that short stature is largely the consequence of lower leg deformities from rickets. The treatment of short stature remains unsatisfactory.

Enthesopathy and osteoarthritis

Surgical treatment may be required, primarily for symptoms or nerve compression. Osteoarthritis also progresses with time and is most likely secondary to the joint deformities. The pathophysiology of both conditions is unclear and treatment remains unsatisfactory.

Dentogenesis and tooth abscess

Extensive restorative dentistry may be required. Antibiotics and root canal treatment are sometimes needed and some patients may have their teeth pulled at a young age due to recurrent abscesses. Current medical treatment does not clearly improve the dental phenotype. Good oral hygiene is necessary for these patients, but specific treatment remains unsatisfactory.

Nephrocalcinosis

The pathogenesis of nephrocalcinosis is usually attributed to combined treatment with calcitriol and phosphate (65, 66). When it develops, the usual approach is to reduce the supplements of both phosphate and calcitriol in the hope of reversing the damage.

Rickets and osteomalacia

Rickets and osteomalacia are the main targets for treatment in XLH. The extracellular fluid level of Pi plays a fundamental role in osteoid mineralization and all severe chronic hypophosphatemias invariably cause failure of the osteoid mineralization rate, which is the hallmark of both rickets in children and osteomalacia in adults. In children, rickets causes disruption of the growth plates and skeletal growth failure. Three main treatment targets have been used: oral Pi supplements, pharmacological doses of vitamin D or high doses of calcitriol, and drugs to increase TmP. More recently, targeting the underlying abnormality in PHEX and FGF-23 is under investigation.

Oral phosphate supplements

Oral Pi supplements are aimed at increasing plasma Pi concentration. They increase the total fractional Pi absorption from the gut and with each dose there is a corresponding rise in plasma Pi. However, since they do not affect TmP, the rise in plasma Pi is both transient and pulsatile. Probably of more importance, particularly in children, is that they prevent Pi depletion. The supplement is usually taken as a neutral mixture of sodium and potassium Pi salts ingested three to four times each day. Depending on the formulation, each tablet provides about 250 mg phosphorus. However, it also provides about 298 mg sodium and 45 mg potassium. Diarrhea and dyspepsia are common side effects which limit the amount that can be taken. Fluid retention and an increase in blood pressure from the increased sodium load and renal failure can also be of concern. Importantly, the supplement also reduces the bioavailability of dietary calcium for absorption, which chronically produces secondary hyperparathyroidism. However, studies using a mouse model and in some human patients suggest that hyperparathyroidism may also be intrinsic to increased plasma FGF-23 (15, 69, 75, 82). During phosphate treatment, urinary Pi reaches very high amounts and concentrations and thus may exacerbate nephrocalcinosis if accompanied by hyperabsorption of calcium from vitamin D treatment. Thus, although Pi supplements are considered to be part of standard of care, they only ameliorate the rickets/osteomalacia at the expense of producing several serious adverse effects.

Vitamin D in pharmacological doses, calcitriol and alfacalcidol

Pharmacological doses of vitamin D (50,000 IU/day) were originally used in the belief that XLH was a vitamin D-resistant state that could be overcome by pharmacological doses of vitamin D, and hence the earlier name of vitamin D-resistant rickets. However, like Pi supplements, they at best only partly heal the rickets/osteomalacia but put the patient at risk of chronic vitamin D intoxication.

Calcitriol and alfacalcidol were initially used in XLH because of their much higher potency than the vitamin D parent compound and the greatly reduced risk of chronic vitamin D intoxication because of their short half-life (13). It is interesting that at about the same time, the assay for plasma $1,25(OH)_2D$ established that in XLH plasma $1,25(OH)_2D$ levels were inappropriately low for the level of plasma Pi and for PTH (83), predicting an intrinsic defect in renal $1,25(OH)_2D$ production in XLH. Thus, the beneficial effect of both pharmacological doses of vitamin D and hormonal $1,25(OH)_2D$ was explained by the underlying abnormality in renal secretion of $1,25(OH)_2D$ in XLH (16, 74). More recently, it has also become established that plasma $1,25(OH)_2D$ concentrations regulate FGF-23 secretion from bone (20), and in patients with XLH combined treatment with calcitriol and phosphate increases plasma FGF-23 concentrations (84). Relatively high doses of calcitriol and alfacalcidol of > 2 μg/day are tolerated in the presence of active rickets/osteomalacia but need to be lowered as the mineralization defect is cured. A direct action of $1,25(OH)_2D$ on the mineralization process is disputed and the major effect is an increase in plasma Pi from gut absorption and bone resorption, and probably most important, the prevention of phosphate depletion.

Tubular reabsorption of phosphate

In humans with reduced TmP dipyridamole increases the tubular reabsorption (85). In Hyp mice, indomethacin has been shown to increase TmP (86). Neither agent, however, has entered clinical practice for XLH.

PHEX

Peptides mimicking PHEX action have been identified in mice which reverse bone cell mineralization in vitro. When used in vivo they increased TmP and $1,25(OH)_2D$ in both wild-type and Hyp mice. FGF-23 was decreased only in the Hyp mouse (87). Studies in humans have not been reported.

FGF-23

FGF-23 antibodies targeted at reducing plasma FGF-23 action are currently being developed to treat XLH. In the male Hyp mouse a single injection of antibody corrected the hypophosphatemia, increased plasma $1,25(OH)_2D$ and increased expression of NaPi-2a 1α-hydroxylase in the kidney. Interestingly, baseline plasma PTH was higher in the Hyp mouse and decreased with the FGF-23 antibody, suggesting that hyperparathyroidism is an intrinsic abnormality of XLH due to low plasma $1,25(OH)_2D$ and/or high FGF-23 or PTH secretion. Importantly, repeated injections in young rapidly growing Hyp mice greatly reduced the severity of rickets, reduced increased bone turnover, as measured by alkaline phosphatase, and increased long bone growth (82).

Phase I studies have now begun in adult patients with XLH (ClinicalTrials.gov Identifier NCT00830674). It will be of great interest to see if the response in adults, and eventually in children, is as promising as in the Hyp mouse.

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DISCLOSURES

The authors state no conflicts of interest.

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