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EDUCATIONAL REVIEW

Mineralized tissues in hypophosphatemic rickets

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Abstract

Hypophosphatemic rickets is caused by renal phosphate wasting that is most commonly due to X-linked dominant mutations in *PHEX*. *PHEX* mutations cause hypophosphatemia indirectly, through the increased expression of fibroblast growth factor 23 (FGF23) by osteocytes. FGF23 decreases renal phosphate reabsorption and thereby increases phosphate excretion. The lack of phosphate leads to a mineralization defect at the level of growth plates (rickets), bone tissue (osteomalacia), and teeth, where the defect facilitates the formation of abscesses. The bone tissue immediately adjacent to osteocytes often remains unmineralized ("periosteocytic lesions"), highlighting the osteocyte defect in this disorder. Common clinical features of XLH include deformities of the lower extremities, short stature, enthesopathies, dental abscesses, as well as skull abnormalities such as craniosynostosis and Chiari I malformation. For the past four decades, XLH has been treated by oral phosphate supplementation and calcitriol, which improves rickets and osteomalacia and the dental manifestations, but often does not resolve all aspects of the mineralization defects. A newer treatment approach using inactivating FGF23 antibodies leads to more stable control of serum inorganic phosphorus levels and seems to heal rickets more reliably. However, the long-term benefits of FGF23 antibody treatment remain to be elucidated.

Keywords Bone · Hypophosphatemia · Mineralization · Phosphate · Rickets · Vitamin D

Introduction

Hypophosphatemic rickets is, as the name says, a skeletal disorder that is characterized by hypophosphatemia. As phosphate is essential for mineralization, hypophosphatemia leads to a mineralization deficit. This primarily affects the tissues where mineralization physiologically occurs—bones, teeth, and growth plate cartilage. In growing children, the mineralization defect affects all three tissues. The growth plate abnormalities are responsible for the main skeletal manifestations of rickets—deformities of the lower extremities and slow growth [1–3]. In adults, where the growth plates have fused, the mineralization defect still affects bone tissue and teeth.

Hypophosphatemic rickets is caused by renal phosphate wasting that is most commonly due to dominant mutations in the phosphate-regulating endopeptidase gene (*PHEX*). As *PHEX* is located on the X chromosome, mutations in this gene lead to the X-linked form of hypophosphatemic rickets (XLH), which has a prevalence of about 1 in 20,000 [4–6]. Mutations in other genes are much rarer causes of hypophosphatemic rickets (Table 1) [7–9, 3]. Very rarely, the clinical picture of hypophosphatemic rickets can be caused by a fibroblast growth factor 23 (FGF23)-producing tumor, an entity that is called tumor-induced osteomalacia [3]. Finally, hypophosphatemia and rickets can be part of a renotubular Fanconi syndrome and other complex syndromes, and can be caused by acquired disorders leading to renal tubular dysfunction [10, 3].

Determining the exact cause of hypophosphatemic rickets is important, not only for genetic counseling but also for treatment decisions. Several detailed reviews on this topic have recently been published [10, 3, 2, 11, 12], and therefore this information is not replicated here. The focus of the present review is to discuss the consequences of hypophosphatemic rickets on mineralized tissues. As XLH is by far the most prevalent form of hypophosphatemic rickets, the bone disease associated with XLH has been investigated in some detail, whereas the information is quite limited for the other conditions. This review will therefore mainly focus on the skeletal manifestations of XLH.

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Table 1 Genetic causes of hypophosphatemic rickets

Gene	Transmission	Disease (OMIM#)
FGF23 increased		
PHEX	XLD	X-linked HR (307800)
FGF23	AD	Autosomal dominant HR (193100)
DMP1	AR	Autosomal recessive HR Type 1 (241520)
ENPP1	AR	Autosomal recessive HR Type 2 (613312)
FAM20C	AR	Raine syndrome (259775)
FGF23 not increased		
SLC34A3 (codes for NaPi2c)	AR	HR with hypercalciuria (609826)
CLCN5	XLR	X-linked recessive HR (300554)

AD autosomal dominant, *AR* autosomal recessive, *HR* hypophosphatemic rickets, *OMIM* Online Mendelian Inheritance in Man (https://omim.org/), *XLD* X-linked dominant, *XLR* X-linked recessive

Pathophysiology

Bone is a composite material that consists of minerals, collagenous and non-collagenous proteins, lipids, and water. There are three main types of bone cells: osteoblasts, responsible for forming bone by secreting type I collagen-rich extracellular matrix (ECM); osteoclasts, the cells that resorb bone; and osteocytes, the terminally differentiated osteoblasts that are trapped within the bone and play a key role in inorganic phosphate homeostasis.

Phosphate and calcium are the main minerals in bone. In the presence of collagen-containing extracellular matrix, phosphate and calcium precipitate in the space within and around collagen fibers [13]. This process can be regulated by mineralization inhibitors, such as mineral binding proteins (e.g., osteopontin), or small mineral ions (e.g., pyrophosphate) that are present in the bone microenvironment. An osteoblast-derived enzyme, alkaline phosphatase, cleaves pyrophosphate and thus removes an inhibitor of mineralization. Alkaline phosphatase therefore plays an essential role on bone mineralization.

Circulating phosphate levels are regulated primarily by three main hormones: parathyroid hormone, calcitriol (1,25-dihydroxy-vitamin D), and FGF23 [14]. The predominant effect of parathyroid hormone is to reduce serum phosphate levels by preventing its reabsorption in the kidney and thereby increasing urinary excretion. Calcitriol is produced through the hydroxylation of 25-hydroxy-vitamin D in the proximal renal tubule cells and increases phosphate absorption in the intestine. FGF23 is secreted mainly by osteocytes and regulates the expression of NaPi2a and NaPi2c, the sodium-phosphate cotransporters in proximal kidney tubule cells. FGF23 also suppresses the production of calcitriol in the kidney.

PHEX codes for a membrane-bound zinc metallo-endopeptidase that is predominantly expressed in bone (predominantly osteocytes) and teeth (odontoblasts) [15]. The physiological function of this enzyme and its substrates are not entirely clear, even though some studies suggest that PHEX cleaves extracellular matrix proteins that are involved in bone mineralization, such as osteopontin [16]. The fact that loss of function mutations in *PHEX* lead to a dominant phenotype is somewhat surprising, as diseases caused by inactivating mutations in enzymes are usually recessive. Females with a loss of function mutation in one *PHEX* allele also have an unaffected allele that should code for normal PHEX protein, but they nevertheless develop XLH. The mechanisms explaining this dominant phenotype caused by inactivating *PHEX* mutations remain to be determined.

Even though there are many gaps in our present understanding of PHEX, it is well established that absent or decreased PHEX activity causes an increase in the production of FGF23 by osteocytes and leads to elevated circulating levels of FGF23 [10, 15] (Fig. 1). However, the exact pathomechanistic link between *PHEX* mutations and increased FGF23 expression remains to be elucidated. Elevated levels of circulating FGF23 downregulate the expression of NaPi2a and NaPi2c, and thus cause renal phosphate wasting [3, 10]. Increased circulating FGF23 also decreases the expression of 1-alpha hydroxylase, the enzyme that converts 25-hydroxy-vitamin D to calcitriol. FGF23 also upregulates 24-hydroxylase, which metabolizes calcitriol. Both actions contribute to lower circulating calcitriol levels, which will further decrease serum phosphate levels.

The mineralization defect in bone and cartilage

Low systemic phosphate levels interfere with mineralization of both growth plate cartilage and bone tissue. Normal growth plate cartilage consists of successive layers of resting chondrocytes, proliferating chondrocytes, and hypertrophic chondrocytes. The zone of hypertrophic chondrocytes adjacent to the metaphysis normally mineralizes and the chondrocytes undergo apoptosis. Mineralization of growth

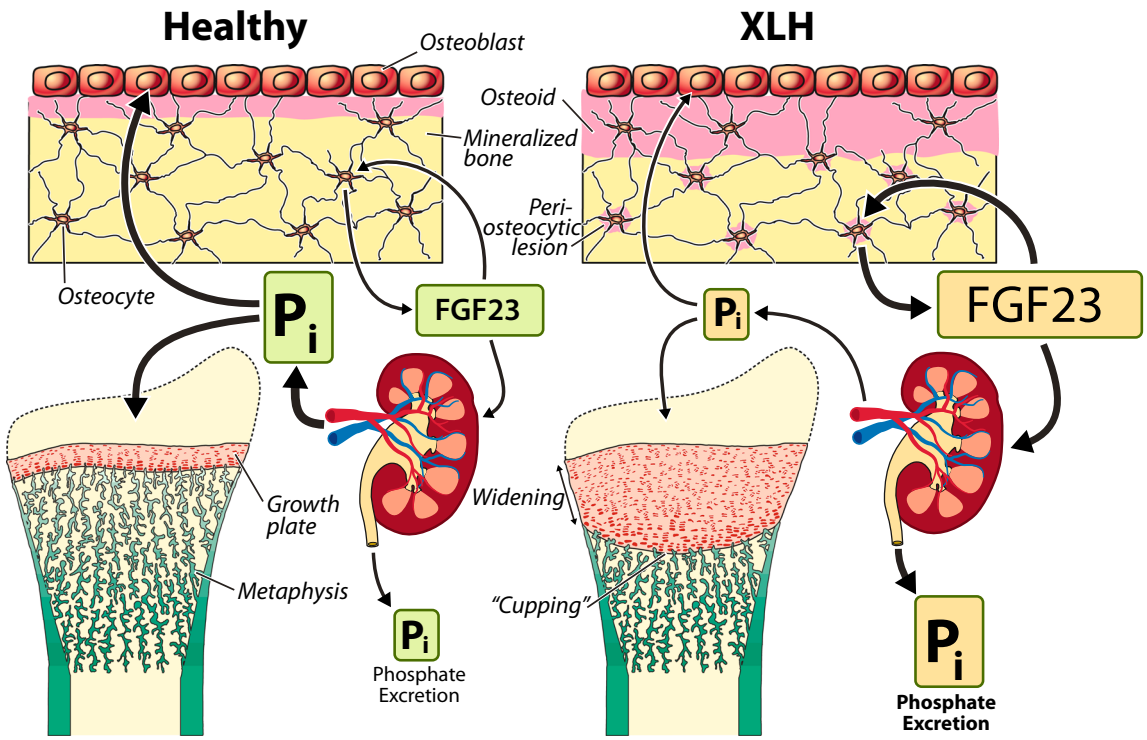

Fig. 1 Schematic representation of XLH bone pathophysiology. In XLH bone, osteocytes secrete increased amounts of FGF23. In a paracrine manner, increased FGF23 production by osteocytes contributes to the development of periosteocytic lesions, which are localized mineralization defects surrounding osteocyte lacuna. A systemic endocrine effect of increased FGF23 levels is to suppress renal phosphate reabsorption, causing low serum inorganic phosphorus levels. This in turn leads to a mineralization defect at the growth plate level, which becomes visible on radiographs as widening of growth plates and cupping of metaphyses. Histologically, growth plate chondrocytes lose their columnar arrangement

plate cartilage is a prerequisite for its invasion by blood vessels that originate in metaphyseal bone and start the replacement of growth plate cartilage by bone tissue [17].

In mouse models of XLH, such as the Hyp mouse, chondrocyte proliferation is decreased, the zone of hypertrophic chondrocytes in the growth plate is widened as chondrocytes fail to undergo apoptosis, and the junction between cartilage and bone is irregular [18–20]. In human XLH, this is reflected radiologically by widening of the growth plates and loss of a clear border between growth plate and metaphysis (Fig. 2a).

The histological appearance of rachitic growth plate in the Hyp mouse resembles that of other mouse models of rickets with hypophosphatemia, whether FGF23 is increased or not [18, 19, 21]. It is therefore not obvious that increased FGF23 has a major direct effect on the rickets phenotype beyond causing hypophosphatemia. This is also suggested by the observation that treatment of the Hyp mouse with calcitriol or the vitamin D analog ED71, which increase serum phosphate, normalizes growth despite leading to a further increase in circulating FGF23 [22–24].

Regarding the mineralization of bone tissue, osteoblasts normally secrete organic bone matrix and then mineralize it by incorporating calcium, phosphate, and other minerals. In the bone tissue of healthy children, this mineralization process starts about 2 weeks after the bone matrix has been secreted [25]. The time difference between the secretion of organic bone matrix by osteoblasts and the start of mineralization is called the mineralization lag time [26]. When phosphate is not available in sufficient quantity to support mineralization, the mineralization lag time increases and unmineralized organic bone matrix, called osteoid, accumulates (Figs. 1 and 3). Increased mineralization lag time and increased amount of osteoid in bone tissue are the defining features for diagnosing osteomalacia in bone histomorphometry, the quantitative assessment of bone tissue [26]. Osteomalacia thus is a disorder of bone tissue mineralization. Even though bone histology has traditionally focussed on trabecular bone, osteomalacia affects the mineralization of both trabecular and cortical bone (Fig. 4).

In XLH, disordered mineralization is not limited to the surfaces of trabecular and cortical bone. There is also a distinctive mineralization defect around osteocytes that are buried within mineralized bone ("periosteocytic lesions," Figs. 1 and 4). These periosteocytic lesions highlight the role of osteocytes in the remodeling and mineralization of the bone matrix that immediately surrounds them [27]. It has been suggested that periosteocytic lesions are caused by mineralization inhibitors such as osteopontin and pyrophosphate that accumulate around osteocyte lacunae as an indirect consequence of *PHEX* mutations [28, 29]. Studies in Hyp mice found that the increased FGF23 secretion by osteocytes suppresses alkaline phosphatase

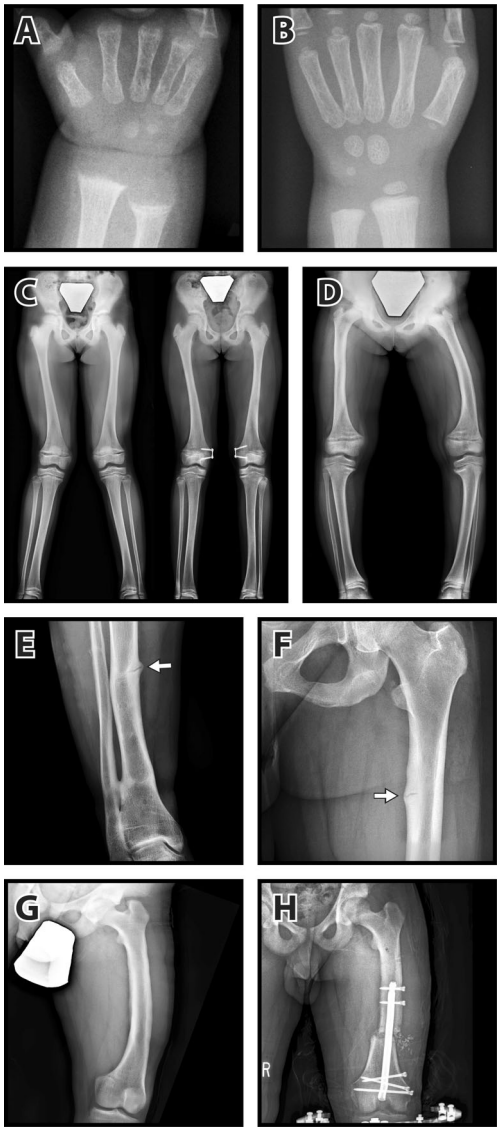

Fig. 2 Radiographs of individuals with XLH. **a** Distal forearm and wrist in an untreated 8-month old girl, showing active rickets (cupping and fraying of the radial and ulnar distal metaphyses). **b** Same patient after 26 months of treatment with phosphate and calcitriol. Complete resolution of rickets. **c** Lower extremities in a 10-year-old girl (left panel) showing genu valgum. The right panel shows complete correction of the genu valgum 11 months after bilateral distal medial hemiepiphysiodesis. **d** Lower extremities in an 8-year-old girl with genu varum. **e** Distal tibia and fibula in an 18-year-old male with treated XLH, with a medial diaphyseal pseudofracture of the tibia ("Looser zone," arrow). **f** Femur in an untreated 26-year-old female with a pseudofracture of the medial femoral diaphysis (arrow). **g** Femur in an 18-year-old male treated during growth, with marked bowing. **h** Same patient after femoral osteotomy and intramedullary nailing

expression in these cells and thereby leads to the accumulation of pyrophosphate, which in turn inhibits mineralization in the osteocytic lacuna [29]. Accordingly, periosteocytic bone remodeling is clearly abnormal in Hyp mice [27].

Thus, evidence from mouse studies suggests that the periosteocytic lesions found in XLH are a direct effect of increased FGF23 expression rather than of hypophosphatemia. In accordance with this view, periosteocytic lesions were not found in bone tissue of patients with hypophosphatemic rickets with hypercalciuria, a disorder where hypophosphatemic rickets is not associated with increased FGF23 levels [30]. Hypophosphatemic rickets with hypercalciuria however leads to similar accumulation of osteoid on trabecular bone surfaces as XLH [31], suggesting that hypophosphatemia alone is sufficient to explain the accumulation of osteoid in bone tissue.

It has been proposed that the presence of periosteocytic lesions in XLH may have functional consequences for bone homeostasis [32, 28]. Osteocytes are mechanosensing cells that are involved in the regulation of bone mass [33]. The undermineralization of osteocyte lacuna will make the bone "softer" and therefore increase the bone deformation upon mechanical loading, which will disturb mechanosensing by the osteocytes. This may contribute to the high trabecular bone mass that is often found in individuals with XLH (Fig. 5).

Bone densitometry

As discussed in the previous section, bone in XLH is characterized by a generalized mineralization defect, which means that an abnormally large amount of bone matrix remains unmineralized. A standard clinical tool for analyzing metabolic bone disorders is dual-energy X-ray absorptiometry, which measures bone mineral density (BMD). As the device only "sees" the mineral in the bone, it is intuitive to assume that a mineralization defect such as caused by XLH should result in low BMD. Nevertheless, reported BMD results in individuals with XLH are quite variable. For example, dual-energy X-ray absorptiometry studies have found that BMD results are low at the shaft of the radius [34–37] but are often elevated at the lumbar spine [36, 38, 37, 39–41].

The explanation for these apparently contradictory results probably lies in differences between trabecular bone, which is more prevalent at the spine, and cortical bone, which usually is the only type of bone tissue in the shaft of the radius. In XLH, both trabecular and cortical bone contain too much unmineralized osteoid. However, in trabecular bone, the amount of mineralized bone is also elevated. This is because, for an unknown reason, trabecula are thicker and more numerous than in healthy controls [42], as is also visible in the iliac bone sample shown in Fig. 4. Thus, the amount of mineralized trabecular bone is often elevated in XLH, at the expense of the space that is available for the bone marrow. The increased amount of mineralized trabecular bone is reflected in high trabecular BMD, as can be seen with techniques that are able to analyze trabecular and cortical bone separately (Fig. 5) [43]. In contrast, there is little scope for increasing the amount of mineralized bone tissue in the cortex, because cortical bone contains little bone marrow that could be displaced. Consequently, in the cortex, the increased amount of unmineralized osteoid will come at the

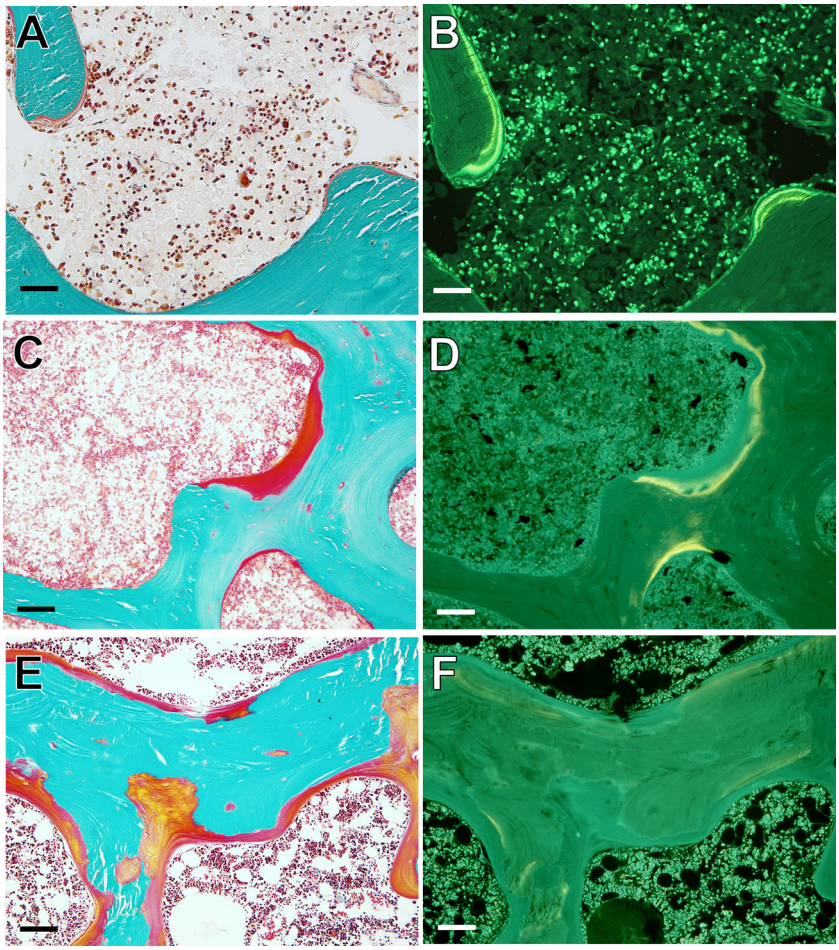

Fig. 3 Histological sections of trabecular bone tissue from the ilium in a control (**a** and **b**) and in XLH (**c** to **f**). In panels **a**, **c**, and **e**, mineralized bone is stained green, unmineralized osteoid is stained red/orange (Goldner staining). In panels **b**, **d**, and **f**, unstained sections are seen under fluorescent light, resulting in yellow color where tetracycline label has been incorporated into the bone. **a** and **b** Fourteen-year-old girl with normal bone mineralization. Osteoid thickness is 7 μm and the tetracycline double labels can be clearly distinguished. **c** and **d** Fourteen-year-old girl with XLH caused by a splice mutation in *PHEX*. Despite treatment with phosphate and calcitriol since the age of 4 years, osteomalacia is not fully controlled. Osteoid thickness is 10 μm and the tetracycline label in **d** is blurred. **e** and **f** Same patient as in **c** and **d** at age 16 years, after discontinuation of treatment with phosphate and calcitriol. Osteoid thickness is 42 μm and the tetracycline label in **f** is blurred and hardly visible

expense of mineralized bone. The BMD of cortical bone is therefore often very low in XLH (Fig. 5) [43, 44].

Clinical manifestations

The most obvious clinical consequences of XLH in children are slow growth and deformities of the lower extremities. The typical lower extremity deformities are genu valgum ("knock-knee"; Fig. 2c) and genu varum ("bow legs", Fig. 2d), which can cause pain and decreased mobility. Slow growth and short stature are mostly secondary to these abnormalities in the lower extremities, but sitting height, reflective of spine growth, is also affected [45]. Nevertheless, as the growth deficit is usually much more pronounced in the lower extremities than in the spine, XLH is commonly associated with disproportionate short stature [45].

Traumatic fractures are not a typical feature of XLH. Studies in adults with XLH even suggest that the risk of traumatic fracture is lower than in the general population [39, 46]. However, XLH is associated with discontinuities in cortical bone that usually arise without noticeable trauma and are often painful and that have been called "looser zones," "pseudofractures," "stress fractures," "insufficiency fractures," or simply "fractures" (Fig. 2e, f) [47, 1, 48]. As the variable terminology implies, the cause of these cortical discontinuities is not very clear. Bone histological analyses of similar lesions in other forms of osteomalacia have suggested they mostly consist of unmineralized osteoid [49]. In line with this view, these lesions often disappear when the mineralization defect is treated [1, 48].

Apart from deformities of the lower extremities, it has long been recognized that XLH can affect the development of the skull and craniofacial skeleton. The mechanistic basis for

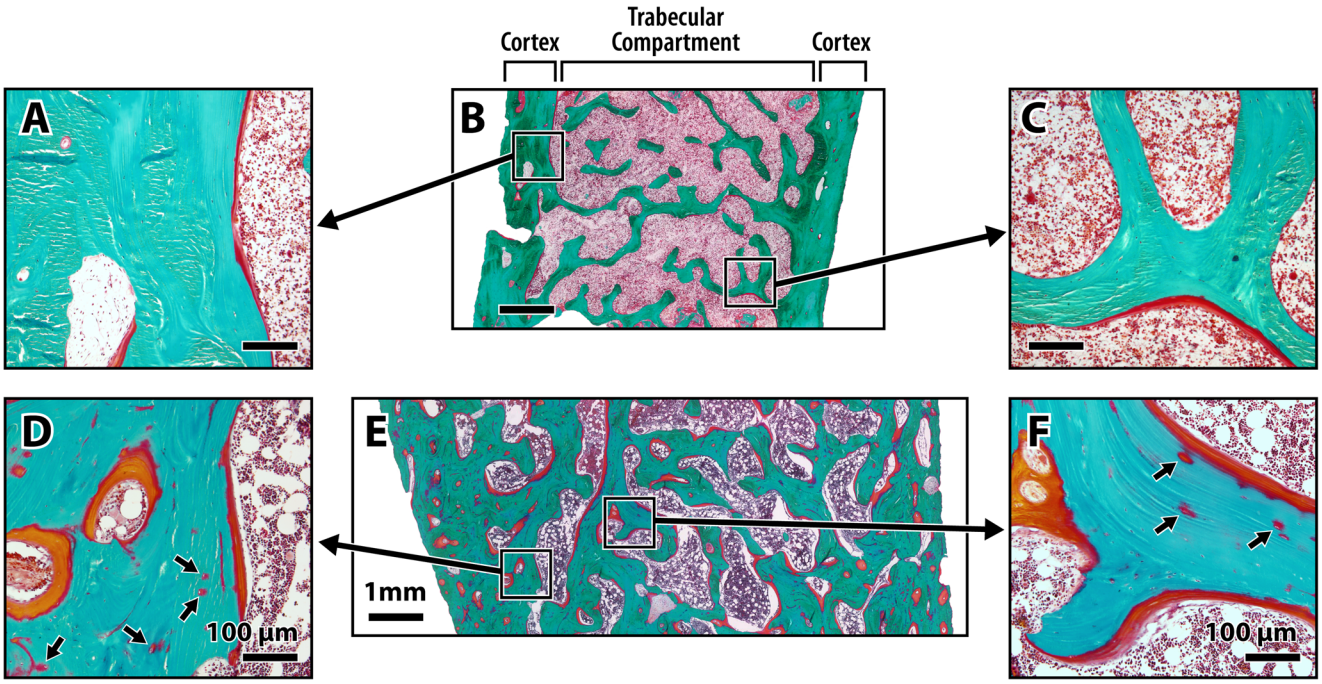

Fig. 4 Iliac bone biopsy samples from a 13-year-old female control (**a** to **c**) and a 13-year-old female with untreated XLH. Mineralized bone is stained green, unmineralized osteoid is stained red/orange (Goldner staining). Panels **b** and **e** show sections of the entire specimen. Higher-resolution images of cortical bone are shown in panels **a** and **d**. Higher-resolution images of trabecular bone are shown in panels **c** and f. Size bars represent 100 µm in panels **a**, **c**, **d**, and **f** and 1 mm in panels **b** and **e**. Accumulation of osteoid and periosteocytic unmineralized lesions (arrows) are evident in both cortical and trabecular bone. Histomorphometric analysis of trabecular bone showed that in the control sample, 0.9% of the bone consists of unmineralized osteoid, whereas in the XLH sample, 11.7% of the bone is unmineralized osteoid. However, the amount of mineralized bone is also clearly higher in the XLH sample (where mineralized bone occupies 45% of the trabecular compartment) than in the control sample (where mineralized bone occupies 22% of the trabecular compartment)

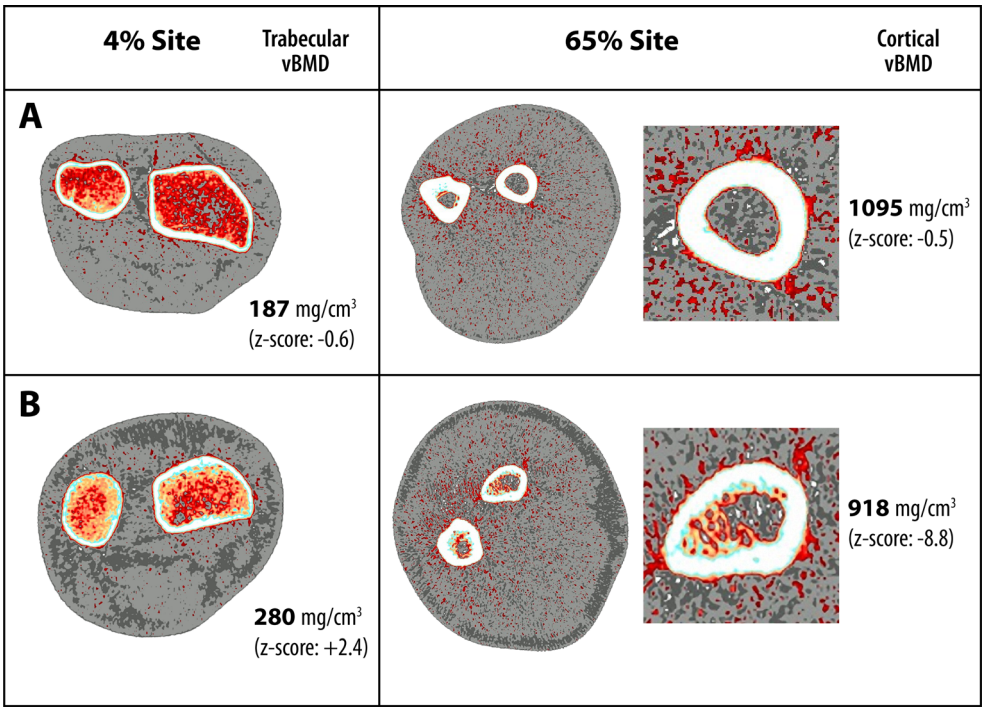

Fig. 5 Forearm peripheral quantitative computed tomography scans at the 4% site (metaphysis) and at the 65% site (diaphysis). The panels on the right show a magnification of the radius image at the 65% site. **a** Twenty-six-year-old male control. **b** Twenty-four-year-old male with XLH. Trabecular volumetric bone mineral density (vBMD) is higher in XLH. In contrast, cortical vBMD is much lower in XLH due to the mineralization defect

these abnormalities has not been elucidated in XLH, but it is known that FGF receptor signaling plays a key role in suture development; several craniosynostosis syndromes are caused by activating mutations in FGF receptors [50]. Cephalometric studies have shown that the cranial base is often flattened, and the depth of the posterior cranial fossa is reduced [51]. A recent study using computed tomography in 44 children found that 59% had some degree of fusion of the sagittal suture and a quarter of patients had Chiari I malformation (descent of the cerebellar tonsils through the foramen magnum) [52]. Although the majority of patients had no symptoms, chronic headaches were observed in some patients and complications such as increased intracranial pressure have been reported [52, 53]. Other abnormalities of the skull include thickening of the petrous bone which, in adults, can be associated with sensorineural hearing loss, tinnitus, and vertigo [54–56].

The mineralization defect of XLH also affects tooth development. Dental abscesses are a frequent problem that may be linked to enlarged pulp chambers and dental fissures that facilitate bacterial penetration into the tooth [57–59]. The mineralization defect does not only affect bone tissue but also dentin [28, 60]. Cultured dental pulp cells from individuals with *PHEX* mutations accumulate osteopontin and are less able to mineralize extracellular matrix [61].

Given that XLH leads to deficient mineralization in bone and tooth tissue, it seems paradoxical that XLH is also associated with increased mineralization of tendon and ligament insertions and of joint capsules ("enthesopathies") [62]. The majority of adults with XLH have radiological evidence of such enthesopathies at one or more skeletal sites, frequently associated with pain [63]. Low quality of life in XLH is often linked to enthesopathies [64, 65]. Individuals with enthesopathies frequently also have intracranial calcifications that seem to arise in the dura mater [66]. Calcification of the ligamentum flavum in the spinal canal can lead to spinal stenosis that is severe enough to require surgical decompression [67]. Paravertebral ligament calcification can give the appearance of very high bone density and cause neurological deficits [68, 69]. The mechanism for the increased tendency of ligaments and tendons to calcify in XLH is not clear, but mouse studies have implicated increased bone morphogenetic protein and Indian hedgehog signaling [70].

Skeletal effects of medical treatment

Medical treatment in XLH is currently in flux as new approaches based on FGF23 inactivating antibodies are being introduced. The "conventional" medical treatment of XLH with oral phosphate supplementation and calcitriol has been used for almost four decades [71], and its effects have been the subject of many studies. It is useful to review the skeletal effects of conventional treatment, as this is the benchmark against which newer treatments need to be compared.

Conventional therapy

Conventional treatment tries to replace the phosphate losses in the kidney by oral phosphate supplementation and supplements calcitriol that is suppressed by elevated FGF23. Although this general outline of the treatment approach seems to be widely accepted, the details of how to administer the treatment are not standardized. One review noted that published treatment studies had used daily body weight-based phosphate doses that varied by a factor of 6 (elemental phosphorus doses between 30 and 180 mg per kg body weight), whereas the daily dose of calcitriol varied by a factor of 8 (from 10 to 80 ng per kg body weight) [1]. There is also some variability in how many individual daily doses are administered, ranging from 3 to 5 doses per day [1]. It is widely acknowledged that the aim of the treatment is to maximize growth and to prevent bone deformities [1–3], but recommendations for treatment monitoring and determining the "correct" dose of phosphate supplementation are variable. Some authors decide about dosing according to height velocity and radiographical healing of rickets [1]. Other centers in addition use serum levels of alkaline phosphatase as key targets to adjust treatment [2]. In our practice, we follow the approach suggested by Carpenter et al. and decide about phosphate dosing according to height velocity and the appearance of growth plates on radiographs [1]. This approach will usually lead to the use of increasing doses of phosphate supplementation during childhood, with maximum doses during puberty.

As the focus of conventional treatment approaches is to optimize growth, the treatment is often discontinued when final height is achieved. However, hypophosphatemia will persist lifelong. Some authors therefore recommend also treating adults with XLH, especially those with a severe skeletal manifestations and chronic pain [1].

A potentially serious source of confusion is that some recommendations express the dose of phosphate supplementation in terms of milligrams of phosphate (PO4), whereas others express the dose in terms of milligrams of elemental phosphorus (Pi). As PO4 has a molecular weight of 95 g and Pi has a molecular weight of 31 g, the difference between these two ways to express dosages is substantial. For example, a daily dose of 1 g of Pi corresponds to a daily dose of a little over 3 g of PO4. It is therefore essential that the prescribing clinician is clear about whether the dose of phosphate supplementation is expressed as milligrams elemental phosphorus (Pi) or milligrams phosphate (PO4).

On the bone histological level, conventional treatment markedly reduces the amount of unmineralized osteoid but does not completely normalize mineralization [72, 73]. Similarly, bone densitometry studies suggest that conventional treatment increases bone mineralization of the forearm shaft but does not normalize it [34, 37, 43]. It also appears that conventional therapy does not lead to mineralization of the

periosteocytic lesions (Fig. 3c, d), which is expected, given that these lesions seem to be caused by FGF23 excess in osteocytes rather than by hypophosphatemia. Regarding teeth, conventional treatment improves the mineralization of dentin, but some residual dental defects persist and dental abscesses continue to be seen [57, 59]. Not surprisingly, the exuberant calcifications of tendons and ligaments that are often seen in adults with XLH do not seem to improve with conventional treatment, as these disease manifestations do not seem to be direct consequences of hypophosphatemia [74].

At the level of the growth plates, treatment with phosphate and calcitriol is expected to heal the mineralization defect (Fig. 2a, b). The resulting improvement in growth plate activity leads to faster growth [71, 75]. However, it appears that not all variations of conventional treatment that are used in clinical practice are able to heal rickets in all patients. Recent pharmaceutical studies therefore were able to identify children with XLH who had active rickets even after long-term conventional therapy [76]. The variability in the outcome after conventional treatment is not surprising, given the variability in the severity of the underlying disease, in the treatment approaches used and, presumably, in the compliance of the patients with the demanding treatment schedule. Given the short half-life of oral phosphate supplements [77], many patients will have low phosphate levels during the night unless a night time dose is administered, further limiting treatment effects.

Conventional treatment also is not always successful in maintaining lower extremity axes within acceptable limits. Surgical interventions to straighten out legs are often required. In growing children, genu valgum and genu varum can be corrected by hemiepiphysiodesis, a relatively simple procedure that slows down growth on one side of a growth plate and leads to axis correction through growth (Fig. 2c) [78]. If bone deformities are complex or require correction after the growing years (Fig. 2g), it is usually necessary to perform osteotomies, which are far more invasive than hemiepiphysiodesis (Fig. 2h) [79, 80].

Beyond treatment with phosphate and calcitriol, several studies have used growth hormone to treat the short stature in XLH. Short-term growth rates increase, and it appears that growth hormone treatment does not worsen the body disproportion that is a usual feature of XLH [81]. However, there is little evidence that growth hormone has a beneficial effect on final height [82, 83].

FGF23 antibody treatment

Conventional treatment uses oral phosphate supplementation to compensate for the renal phosphate loss. However, serum levels of inorganic phosphorus already start to decrease 1 h after an oral phosphate dose has been taken [77]. Despite multiple daily phosphate doses, serum levels or inorganic phosphorus therefore fluctuate considerably. In contrast, an injection of FGF23 antibody will maintain serum inorganic phosphorus levels for several weeks [84]. It is intuitive to assume that the more stable correction of serum phosphorus with FGF23 antibody treatment will lead to improved control of the skeletal mineralization defect in XLH [85].

It has indeed been shown that FGF23 antibody treatment can lead to healing of rickets in children with XLH who had active rickets despite having received some form of conventional treatment [76, 86]. The rate of longitudinal growth and physical ability is improved, and bone pain decreased in these children. In adults with XLH, FGF23 antibody treatment has been associated with healing of fractures (or pseudofractures) and improved physical function [48].

Thus, FGF23 antibody treatment is easier to administer than conventional therapy (subcutaneous injections every 2 to 4 weeks vs. multiple daily doses of phosphate) and seems to have superior efficacy. Nevertheless, it is not yet clear whether FGF23 antibody treatment is able to completely heal the osteomalacia and whether it has an effect on the periosteocytic lesions.

Thus, it is unclear at present whether FGF23 antibody treatment is able to control all aspects of the mineralization defect that is associated with *PHEX* mutations. As this treatment has only recently been developed, the effects of long-term therapy on the skeleton still remain to be elucidated.

Key summary points

1. Hypophosphatemic rickets is most commonly due to X-linked dominant mutations in PHEX.
2. PHEX mutations lead to increased expression of fibroblast growth factor 23 (FGF23) by osteocytes, resulting in renal phosphate wasting.
3. The phosphate loss leads to a mineralization defect at the level of growth plates (rickets), bone tissue (osteomalacia), and teeth.
4. Short stature, deformities of the lower extremities, enthesopathies, dental abscesses, and skull abnormalities (craniosynostosis, Chiari I malformation) are common clinical features of X-linked hypophosphatemic rickets.
5. Treatment with inactivating FGF23 antibodies increases serum inorganic phosphorus levels and improves skeletal mineralization.

Multiple choice questions

1. Hypophosphatemic rickets is most commonly

   a. An acquired disorder
   b. Inherited as an autosomal dominant disorder
   c. Inherited as an X-linked dominant disorder
   d. Inherited as an autosomal recessive disorder

2. *PHEX* mutations lead to

    a. Decreased levels of circulating FGF23
    b. Decreased expression of 1-alpha hydroxylase
    c. Decreased expression of 24-hydroxylase
    d. All of the above
3. Hypophosphatemic rickets leads to a mineralization defect

    a. In trabecular bone
    b. In the growth plate
    c. In cortical bone
    d. All of the above
4. Disordered mineralization of bone tissue (osteomalacia) is characterized by

    a. A shortened mineralization lag time
    b. A lack of alkaline phosphatase
    c. Accumulation of osteoid
    d. Accumulation of osteoblasts
5. The conventional treatment of hypophosphatemic rickets includes

    a. Oral phosphate supplementation
    b. Low phosphate diet
    c. High doses of 24, 25 dihydroxy-vitamin D
    d. Low calcium diet

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Answers1. c; 2. b; 3. d; 4. c; 5. a