

Interdisciplinary management of FGF23-related phosphate wasting syndromes: a Consensus Statement on the evaluation, diagnosis and care of patients with X-linked hypophosphataemia

Andrea Trombetti^{1,2}, Nasser Al-Daghri³, Maria Luisa Brandi⁴, Jorge B. Cannata-Andía^{5,6,7,8}, Etienne Cavalier⁹, Manju Chandran¹⁰, Catherine Chaussain^{11,12}, Lucia Cipullo¹³, Cyrus Cooper^{14,15,16}, Dieter Haffner¹⁷, Pol Harvengt¹⁸, Nicholas C. Harvey^{14,15}, Muhammad Kassim Javaid¹⁶, Famida Jiwa¹⁹, John A. Kanis^{20,21}, Andrea Laslop²², Michaël R. Laurent²³, Agnès Linglart^{24,25}, Andréa Marques^{26,27}, Gabriel T. Mindler^{28,29}, Salvatore Minisola³⁰, María Concepción Prieto Yerro³¹, Mario Miguel Rosa³², Lothar Seefried³³, Mila Vlaskovska³⁴, María Belén Zanchetta³⁵ and René Rizzoli¹✉

Abstract | X-linked hypophosphataemia (XLH) is the most frequent cause of hypophosphataemia-associated rickets of genetic origin and is associated with high levels of the phosphaturic hormone fibroblast growth factor 23 (FGF23). In addition to rickets and osteomalacia, patients with XLH have a heavy disease burden with enthesopathies, osteoarthritis, pseudofractures and dental complications, all of which contribute to reduced quality of life. This Consensus Statement presents the outcomes of a working group of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, and provides robust clinical evidence on management in XLH, with an emphasis on patients' experiences and needs. During growth, conventional treatment with phosphate supplements and active vitamin D metabolites (such as calcitriol) improves growth, ameliorates leg deformities and dental manifestations, and reduces pain. The continuation of conventional treatment in symptom-free adults is still debated. A novel therapeutic approach is the monoclonal anti-FGF23 antibody burosumab. Although promising, further studies are required to clarify its long-term efficacy, particularly in adults. Given the diversity of symptoms and complications, an interdisciplinary approach to management is of paramount importance. The focus of treatment should be not only on the physical manifestations and challenges associated with XLH and other FGF23-mediated hypophosphataemia syndromes, but also on the major psychological and social impact of the disease.

Renal phosphate wasting syndromes comprise a heterogeneous group of diseases with multiple causes that manifest biochemically as hypophosphataemia. The differential diagnoses of hypophosphataemia are many and the first step is to check whether reduced serum levels of phosphate are due to decreased renal tubular reabsorption of phosphate (TRP). After exclusion of parathyroid hormone (PTH)-driven decreased renal

tubular phosphate reabsorption, two other main causes of renal phosphate wasting should be investigated: defects in intrinsic renal phosphate transport and fibroblast growth factor 23 (FGF23)-related causes, such as X-linked hypophosphataemia (XLH)¹.

This Consensus Statement focuses on XLH as a cause of renal phosphate wasting and mentions acquired tumour-induced osteomalacia (TIO) as a differential

✉e-mail: rene.rizzoli@unige.ch
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diagnosis. XLH is a genetic disease characterized by rickets and osteomalacia and caused by pathogenic variants in *PHEX* (which encodes phosphate-regulating neutral endopeptidase *PHEX*)². Owing to the variety of symptoms that can manifest, patients with XLH require the care of a large range of medical specialities, including paediatricians, rheumatologists, endocrinologists, nephrologists, orthopaedic surgeons, neurologists,

rehabilitation specialists and dentists, across the life-course. All specialities are complementary, fulfilling an interdisciplinary patient-centred approach. In 2021, an international expert working group was convened by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) to discuss the features of this interdisciplinary management strategy to address patients' demands as well as unmet needs. The result of the working group discussions is this Consensus Statement, which provides the most current and robust clinical evidence on management of XLH.

After a brief review of the normal mineralization process and the key components involved, this Consensus Statement covers the clinical manifestations of phosphate depletion, the evaluation of a patient with hypophosphataemia and the diagnostic work-up that leads to the diagnosis of hypophosphataemia related to FGF23 excess. The Consensus Statement is centred on XLH and its main differential diagnoses in terms of clinical manifestations, as well as management via a multidisciplinary approach.

Since the last clinical practice recommendations for XLH that were released in 2019 (REF.³), several original studies have been published that cover the clinical manifestations of the disease and describe the clinical efficacy of the anti-FGF23 monoclonal antibody burosumab in treating this condition, including patient-reported outcomes. This more robust evidence base now permits, in this Consensus Statement, revised and updated clinical recommendations on the use of this novel agent in the treatment of XLH.

Methodology

This Consensus Statement provides the consensus of an expert working group of ESCEO in Geneva (Switzerland), under the auspices of the WHO Collaborating Centre for Public Health Aspects of Musculoskeletal Health and Aging (Liège, Belgium). The group comprised a diverse panel of 25 expert clinicians from 14 countries chosen for their expertise and publication record in XLH and related disorders, including orthopaedic surgeons, physical and rehabilitation medicine specialists, rheumatologists, endocrinologists, nephrologists, paediatricians, geriatricians, clinical biochemists and clinical pharmacologists. The group also included two patients with XLH and one relative.

In advance of the first hybrid in-person–virtual meeting on 5 February 2021, experts were assigned specific topics on which they conducted extensive narrative literature reviews. Topics considered by the group included: pathophysiology of phosphate wasting syndromes; laboratory assessment; burden of XLH disease; management of phosphate wasting syndromes in children and adolescents; management of phosphate wasting syndromes in adults; management of TIO; and the role of dentists and orthopaedic surgeons in the management of patients with phosphate wasting syndromes. At the meeting, the experts presented the results of these reviews, together with draft recommendations, to the wider group, which included patient representatives. During the discussion, the 2019 Evidence-Based Guideline³ was updated with

Author addresses

- ¹Division of Bone Diseases, Department of Medicine, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland.
- ²Division of Geriatrics, Department of Rehabilitation and Geriatrics, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland.
- ³Chair for Biomarkers of Chronic Diseases, Biochemistry Department, College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia.
- ⁴F.I.R.M.O. Foundation, University of Florence, Florence, Italy.
- ⁵Hospital Universitario Central de Asturias (HUCA), Oviedo, Spain.
- ⁶Universidad de Oviedo, Oviedo, Spain.
- ⁷Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain.
- ⁸Retic REDinREN-RICORS, 2040-ISCIII, Madrid, Spain.
- ⁹Department of Clinical Chemistry, University of Liege, CHU de Liège, Liège, Belgium.
- ¹⁰Complicated Metabolic Bone Disorders Clinic, Osteoporosis and Bone Metabolism Unit, Department of Endocrinology, Singapore General Hospital, Singapore, Singapore.
- ¹¹Université de Paris, Institut des maladies musculo-squelettiques, URP2496, UFR Odontologie, Montrouge, France.
- ¹²AP-HP, FHU DDS-Net, Centre de Référence des Maladies Rares du Métabolisme du Calcium et du Phosphore, Service médecine bucco-dentaire, Hôpital Bretonneau, GH Paris Nord Université de Paris, Paris, France.
- ¹³Patient representative with XLH, Geneva, Switzerland.
- ¹⁴MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK.
- ¹⁵NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK.
- ¹⁶NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK.
- ¹⁷Department of Paediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany.
- ¹⁸XLH Belgium, Belgian association of patients with XLH (a member of the International XLH Alliance), Waterloo, Belgium.
- ¹⁹Chair of the Committee of Patients Societies at the International Osteoporosis Foundation, Osteoporosis Canada, Toronto, Canada.
- ²⁰Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia.
- ²¹Centre for Metabolic Bone Diseases, University of Sheffield Medical School, Sheffield, UK.
- ²²Scientific Office, Federal Office for Safety in Health Care, Vienna, Austria.
- ²³Centre for Metabolic Bone Diseases, University Hospitals Leuven, Leuven, Belgium.
- ²⁴Paris-Saclay University, INSERM U1185, Le Kremlin-Bicêtre, France.
- ²⁵AP-HP, endocrinology and diabetes for children, Reference centre for rare diseases of calcium and phosphate metabolism, OSCAR network, Platform of expertise for rare diseases of Paris Saclay Hospital, Bicêtre Paris Saclay Hospital, Le Kremlin-Bicêtre, France.
- ²⁶Rheumatology Department, Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal.
- ²⁷Health Sciences Research Unit: Nursing (UICiSA:E), Nursing School of Coimbra, Coimbra, Portugal.
- ²⁸Department of Paediatric Orthopaedics, Orthopaedic Hospital Speising, Vienna, Austria.
- ²⁹Vienna Bone and Growth Center, Vienna, Austria.
- ³⁰Department of Clinical, Internal, Anaesthesiologic and Cardiovascular Sciences, 'Sapienza', Rome University, Rome, Italy.
- ³¹Agencia Española de Medicamentos Y Productos Sanitarios, Madrid, Spain.
- ³²Departamento de Neurociências, Laboratório de Farmacologia Clínica E Terapêutica Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal.
- ³³Orthopedic Department, University of Würzburg, Würzburg, Germany.
- ³⁴Medical Faculty, Department of Pharmacology, Medical University Sofia, Sofia, Bulgaria.
- ³⁵Instituto de Investigaciones Metabólicas (IDIM), Universidad del Salvador, Buenos Aires, Argentina.

the literature released since its publication. Discussions were held and experts deliberated on the quality, scope and context of the collected evidence, and the recommendations made. Further evidence was incorporated as suggested by members at the meeting. Agreement on statements and recommendations between all co-authors, including the patients, was obtained after extensive discussions, and during critical iterative revisions of the manuscript drafts, leading to consensus on all items. We did not grade the strength of the recommendations.

An executive writing group (A.T., R.R.) was appointed to undertake preparation of the first draft of the manuscript based on draft recommendations as agreed by all participants at the meeting. This draft manuscript was then circulated to all the members of the expert group, and patient representatives, for critical revision. Any additionally identified high-quality evidence published following the expert group meeting was subsequently incorporated by the executive writing group. The first author coordinated the preparation of the final version of the manuscript, which was circulated to the entire expert group for final approval of the content and of the contained recommendations, which had been provisionally approved unanimously at the group meeting. Following the unanimous final endorsement of the recommendations and content by all members of the expert group, the Consensus Statement was submitted for publication. The patient representatives were invited to provide their comments at all steps of the discussions.

Physiology of bone mineralization

Phosphate is involved in a wide variety of essential cellular functions⁴. For example, phosphate is a constituent of molecules such as ATP, as well as nucleotides in DNA and RNA. Furthermore, phosphate contributes to intracellular signalling molecules, such as cAMP and membranous glycerophospholipids, and signal transduction pathways. Phosphate has an important role as an extracellular fluid (ECF) buffer in blood and urine. Importantly, phosphate is a major constituent of bone and teeth in the form of calcium phosphate crystals (hydroxyapatite)⁵.

Intestinal absorption of phosphate occurs by passive paracellular and active transcellular vitamin D-dependent mechanisms, with 1,25-dihydroxyvitamin D (1,25(OH)₂D or calcitriol) enhancing the expression of sodium-dependent phosphate transport protein 2B⁶. Renal tubular phosphate reabsorption adapts blood concentrations of phosphate to the needs of the organism in relation to growth, and cartilage and bone mineralization. Indeed, the kidney is able to regulate the maximal reabsorptive capacity, which is expressed as the ratio of maximal TRP to glomerular filtration rate (TmPi/GFR) in the proximal tubule in response to variations in dietary phosphate intake. Concentrations of phosphate in ECF and phosphate homeostasis are regulated by serum PTH along with other mechanisms, with a central role played by FGF23 (REFS^{7,8}). Secreted by osteocytes and osteoblasts, FGF23 increases renal phosphate excretion by downregulating the expression of sodium-dependent phosphate transport protein 2A

and sodium-dependent phosphate transport protein 2C, and triggering their internalization and degradation in the apical brush border membrane of the proximal tubule^{7,9,10}. FGF23 also directly decreases renal proximal tubule production of 1,25(OH)₂D, by suppressing the expression of 25-OHD-1 α -hydroxylase (encoded by *CYP27B1*). By increasing expression of vitamin D₃ 24-hydroxylase, FGF23 also catabolizes 25-hydroxyvitamin D (25(OH)D or calcifediol) and 1,25(OH)₂D into inactive forms¹¹, which leads to reduced intestinal phosphate and calcium absorption¹².

The maintenance of a normal concentration of phosphate in ECF is important for hydroxyapatite crystal formation and the mineralization process. With chronic hypophosphataemia, phosphate availability at the mineralization front is reduced. This deficit is responsible for the development of rickets in children and adolescents, and osteomalacia in adults. Whether 1,25(OH)₂D has a role in mineralization that is independent of its effect on intestinal mineral absorption is a matter of debate. Indeed, in experimental models of severely vitamin D-deficient rats, infusion of calcium and phosphate without vitamin D permitted bone growth, cartilage and osteoid mineralization similar to that observed with vitamin D administration alone. This finding supports the view that vitamin D exerts an indirect effect on bone mineralization through maintenance of normal serum levels of calcium and phosphate^{13,14}. Other experimental studies in vitamin D receptor-null mice and in mice with mutations in *Cyp27b1* (REF.¹⁵) showed that provision of sufficient amounts of calcium and phosphate rescues the rickets phenotype¹⁶. Hypophosphataemia leads to rickets by impairing caspase-mediated apoptosis of hypertrophic chondrocytes¹⁷. On the other hand, 1,25(OH)₂D might directly promote osteoblast differentiation and production of matrix vesicles in vitro, thereby enabling mineralization^{18,19}. Moreover, numerous proteins that promote mineralization are regulated by 1,25(OH)₂D (REF.¹⁹). A 2020 clinical case report described an infant girl with concomitant hypophosphataemia and vitamin D-deficiency rickets despite normal serum values of calcium and phosphate, which was treated by cholecalciferol (vitamin D₃) administration²⁰, consistent with a direct effect of vitamin D on the mineralization process.

Manifestations of phosphate depletion

Disorders with hypophosphataemia have a variety of manifestations that depend upon the underlying pathophysiological mechanism as well as the severity and the duration of phosphate depletion, and whether hypophosphataemia presents during the growth period or in adulthood¹. Intracellular phosphate depletion leads to a decrease in red blood cell 2,3-diphosphoglycerate and ATP concentrations; the latter has multiple cellular functions in the central nervous system and in skeletal and smooth muscle cells, and decreased ATP levels in skeletal muscle possibly contribute to proximal myopathy that has been described in hypophosphataemia²¹. Severe hypophosphataemia can be associated with neuromuscular symptoms and altered cardiac or respiratory function, even though only weak evidence demonstrates

a causal relationship¹. In hypophosphataemia, the changes that occur at the growth plate and mineralization defects contribute to the skeletal deformities and growth alterations that are the dominant clinical manifestations in childhood. The clinical features of genetic forms of hypophosphataemia manifesting in early life are listed in BOX 1. Of note, osteomalacia, which manifests in adults with hypophosphataemia, is a risk factor for pseudofractures².

Evaluating patients with hypophosphataemia

Age-adjusted references of phosphate values need to be considered when evaluating patients with suspected hypophosphataemia. In addition, serum levels of phosphate exhibit a circadian rhythm, with a peak at around 3.00 a.m. and a nadir at around 11.00 a.m.²². In some rare cases, phosphate assay interference can occur due to the presence of monoclonal immunoglobulin²³, medications (such as high-dose liposomal amphotericin B, niacin or excessive use of phosphate binders)²⁴ or hyperbilirubinaemia²⁵, which can result in pseudohypophosphataemia. This interference should be ruled out before any further evaluation.

In children, the maximal TRP can be calculated from fasting blood and urine samples using the formula: $TmPi/GFR = \text{plasma phosphate concentration} - ((\text{urinary phosphate concentration} \times \text{plasma creatinine concentration}) / \text{urinary creatinine concentration})$ ^{26,27}. Although non-fasting specimens can be sampled, a fasting state usually implies a morning sample collection, ensuring some consistency in the measurements during the phosphate circadian rhythm. An appropriate reference range according to the formula used should be applied.

To evaluate renal tubular phosphate reabsorption in adults, $TmPi/GFR$ is calculated from fasting paired plasma and second morning void urine samples (obtained 2 h after the first void urine) for phosphate and creatinine measurement²⁸. This parameter can be obtained using the nomogram of Walton and Bijvoet²⁸ or using the algorithm of Kenny and Glen²⁹. According to Kenny and Glen, if fractional TRP is less than or equal to 0.86, then $TmPi/GFR = TRP \times \text{serum phosphate concentration}$. By contrast, if TRP is greater than 0.86, then $TmPi/GFR = \alpha \times \text{serum phosphate concentration}$, where $\alpha = 0.3 \times TRP / (1 - (0.8 \times TRP))$. The ratio of maximal TRP to GFR varies with age, and higher values are seen during the accelerated growth period in children than are seen in adults³⁰. Normal values of $TmPi/GFR$ range from 0.8 to 1.35 mmol/l GFR in adults.

Once renal phosphate wasting is demonstrated in children or adults, four important regulating hormones of phosphate metabolism should be evaluated; these are: FGF23, PTH (both phosphaturic factors), 25(OH)D and 1,25(OH)₂D, which is the active form of vitamin D. After skin synthesis of vitamin D or ingestion of vitamin D-containing foods or supplements, vitamin D is hydroxylated in the liver to produce 25(OH)D, which is the most abundant vitamin D metabolite. 25(OH)D has a half-life of several weeks and its blood concentration reflects vitamin D status of the individual. A second hydroxylation event occurs on 25(OH)D

in the kidneys by 25-OHD-1 α -hydroxylase to produce 1,25(OH)₂D. This second hydroxylation is tightly regulated by variations in the circulating levels of PTH and ECF concentrations of calcium or phosphate. Serum concentrations of 1,25(OH)₂D can be normal even in individuals with severe vitamin D deficiency. The half-life of 1,25(OH)₂D is between 5 and 8 h, depending on the method used to assess it and the study³¹⁻³³. In the past, 1,25(OH)₂D was measured by poorly specific radioimmunoassays. Over the past 10 years, automated immunoassays and liquid chromatography tandem mass spectrometry methods have become available, and these offer improved specificity³⁴; however, precision errors remain high according to the Vitamin D External Quality Assessment Scheme external control. Furthermore, no standard reference calibrator nor reference method exists for 1,25(OH)₂D measurement³⁵. As is the case for serum levels of phosphate, 1,25(OH)₂D levels also vary with age. Values are highest during the first three years of life and then decrease, remaining stable thereafter^{36,37}. Age-specific reference intervals should thus be used. A low or inappropriately normal plasma level of calcitriol in the presence of hypophosphataemia might be suggestive of FGF23 excess.

FGF23 is an endocrine member of the family of fibroblast growth factors and is primarily produced by osteocytes and osteoblasts³⁸. FGF23 is a protein with 251 amino acids; however, a 24-amino acid signal peptide is removed before secretion and the mature secreted FGF23 protein is approximately 32 kDa³⁹. The production of FGF23 is mainly stimulated by 1,25(OH)₂D and a high phosphate diet^{40,41}. Many other factors are known to affect FGF23 production, such as PTH, calcium and inflammation. However, the balance between production and degradation by cleavage of the mature FGF23 protein is maintained during inflammation^{42,43}. Mature FGF23 is cleaved by proprotein convertases at

Box 1 | Clinical features of genetic hypophosphataemia that manifest in early life

- Rickets or osteomalacia
 - Varus or valgus deformity of the lower limbs
 - Wrist widening
 - Sternocostal rachitic rosary
 - Frontal bossing
 - Dolichocephaly
 - Maltorsion of the tibia and femur
 - Coxa vara
 - Craniosynostosis
 - Disproportionate short stature (short legs, with fairly preserved trunk length)
- Disease-specific gait alterations
 - Increased lateral trunk movement (observed as 'waddling motion')
 - Intoeing gait
 - Decreased joint range of motion
- Muscle weakness
- Dental complications
 - Dental necrosis with severe abscesses
 - Maxillofacial cellulitis
 - Early tooth loss

the carboxy terminus between amino acids 179 and 180 (REF.⁴⁴). Of note, mutations that cause loss of function of *PHEX* result in increased circulating levels of FGF23 and this increase explains many but not all XLH-associated complications⁴⁵.

FGF23 assays can either detect the intact (full-length) and biologically active form of mature 227-amino acid FGF23, or both the intact protein and C-terminal fragments that result from cleavage. The antibodies used in the assays recognize epitopes within the amino-terminal and C-terminal domains, which flank the cleavage point, or they recognize only the epitopes within the C-terminal portion. These FGF23 assays are generally considered as reliable⁴⁶. Nine assays recognizing only the 'intact' form are commercially available: seven manual enzyme-linked immunosorbent assays (ELISA) and two automated chemiluminescent assays^{47,48}. In addition, three ELISAs that recognize both the intact form and the C-terminal fragments (generally called 'C-terminal' assays) are available. Most of these FGF23 assays are for research use only. The various FGF23 assays are described in Supplementary Table 1 (REF.⁴⁹). The units used for the results of all FGF23 assays differ between the C-terminal (relative units, RU, per millilitre) and the intact methods (picograms per millilitre or picomoles per millilitre). No synthetic or purified natural FGF23 is available for use as a standard method nor a reference method. Of note, FGF23 is more stable in EDTA plasma (plasma with an excess of a powerful chelating agent) than in serum at room temperature. Furthermore, FGF23 values obtained in EDTA plasma are also higher than those obtained in serum^{47,50}. Nevertheless, whether plasma or serum should be used for FGF23 assessment is very assay-specific. Although some assays can be accurate with either plasma or serum, best practice is to use the sample type recommended by the manufacturer.

For initial diagnostic purposes, fasting phosphate and FGF23 plasma samples should be collected 1 to 2 weeks after phosphate and calcitriol discontinuation, if the patient under evaluation is already receiving some treatment. Interestingly, the 2018 approved treatment for XLH (the monoclonal antibody against FGF23, burosumab) can interfere with the FGF23 assay⁵¹. A reference range of 22.7 to 93.1 ng/l was established in 908 healthy individuals aged 18 to 89 years for the Diasorin Liaison FGF23 assay¹⁷. Of note, individuals older than 60 years and men have slightly higher blood concentrations of FGF23 than younger individuals and women⁴⁷. For paediatric use, age-dependent and sex-dependent reference range data have been published with the C-terminal FGF23 assay of Immutopics⁵². However, intact FGF23 measurements are probably more reliable for the diagnosis of FGF23-mediated hypophosphataemia, as they can reveal inappropriately normal levels of intact FGF23, such as those seen in XLH or TIO^{48,53}.

Once elevated or inappropriately normal blood levels of FGF23 are demonstrated in a patient with hypophosphataemia, different possible causes can be considered. TABLE 1 shows the main differential diagnoses of FGF23-mediated hypophosphataemia.

Evaluation of the patient with hypophosphataemia: recommendations.

- When measuring circulating phosphate levels in a patient with suspected hypophosphataemia, consider assay interference by monoclonal immunoglobulin, medications or hyperbilirubinaemia.
- Discriminate between renal and non-renal causes of hypophosphataemia by measuring TmPi/GFR.
- Evaluate the four important hormones that regulate phosphate metabolism; these are FGF23, PTH, 25OHD and 1,25(OH)₂D.
- A low or inappropriately normal plasma level of calcitriol in the presence of hypophosphataemia might be suggestive of FGF23 excess.
- Detecting inappropriately normal or elevated blood levels of intact FGF23 in a patient with hypophosphataemia using an intact FGF23 assay is compatible with the diagnosis of FGF23-mediated hypophosphataemia.

Genetic causes of FGF23-mediated hypophosphataemia

XLH is due to a loss-of-function pathogenic variant in *PHEX*, which is located on Xp22.11. *PHEX* is a membrane protein expressed in bone and teeth tissues⁵⁴. The precise mechanism by which *PHEX* mutations lead to FGF23 gene overexpression and/or its decreased catabolism is unknown. With an incidence estimated at 3.9 affected individuals per 100,000 live births^{55,56}, XLH is the most frequent cause of hypophosphataemic rickets of genetic origin (80% of individuals with genetic phosphate wasting syndromes have XLH). The UK prevalence is estimated to be 1.5 patients per 100,000 children and 1.6 patients per 100,000 adults, with an excess mortality⁵⁷. By contrast, in Norway, XLH prevalence is 1.7 patients per 100,000 children⁵⁸ and in southern Denmark prevalence is 4.8 patients per 100,000 children⁵⁵. Such variation in the prevalence (which ranges from 1 in 20,000 to 1 in 60,000) of the disease could be related to selection bias or different genetic backgrounds across populations.

A second inherited form of hypophosphataemia related to FGF23 excess is autosomal dominant hypophosphataemic rickets (ADHR). This condition is caused by pathogenic variants at the cleavage site of *FGF23*, which precisely target Arg179 and Ser180, thus inducing a resistance to proteolytic degradation in FGF23 (REF.⁵⁹). The clinical and biochemical phenotype of ADHR seem particularly sensitive to iron deficiency. In normal individuals, iron deficiency stimulates FGF23 transcription but also increases FGF23 cleavage, which results in normal circulating levels of intact FGF23 (REF.⁶⁰). In ADHR, iron deficiency stimulates production of FGF23 as usual, but it is not efficiently cleaved and thus becomes elevated^{61,62}.

Autosomal recessive hypophosphataemic rickets (ARHR) exists in three forms. First, ARHR type 1 is caused by biallelic variants in *DMP1*, which encodes an extracellular matrix protein that is important for proper mineralization of bone and dentin⁶³. Second, ARHR type 2 is caused by biallelic variants in *ENPP1* (REF.⁶⁴), which encodes an enzyme involved in the

Table 1 | Main differential diagnoses of FGF23-mediated hypophosphataemia

Disease (gene)	Clinical signs and symptoms	Biochemical parameters							Radiographic characteristics
		FGF23 ^a	1,25(OH) ₂ D	Ca ²⁺	PTH	ALP	Calciuria ^b	Comment	
Genetic forms									
XLH (<i>PHEX</i>)	Rickets, dental abscesses, enthesopathy, articular pain	↑ or normal	Normal ^c	Normal	Normal or ↑	↑	↓	NA	Dense bones, ↑BMD, pseudofractures, enthesopathy, early osteoarthritis
ADHR (<i>FGF23</i>)	Variable expression	↑ or normal ^d	Normal ^c	Normal	Normal or ↑	↑	↓	NA	NA
ARHR type 1 (<i>DMP1</i>)	Can be present as sclerosing bone disease	↑ or normal	Normal ^c	Normal	Normal or ↑	↑	↓	NA	Dense vertebral bodies
ARHR type 2 (<i>ENPP1</i>)	Generalized arterial calcifications, with or without multisystem manifestations	↑ or normal	Normal ^c	Normal	Normal or ↑	↑	↓	NA	Generalized arterial calcifications
ARHR type 3 (<i>FAM20C</i>)	Cerebral calcifications, perilacunar osteomalacia on bone biopsy, peculiar facial features	↑ or normal	Normal ^c	Normal	Normal or ↑	↑	Unknown	NA	Dense bones, ↑BMD, pseudofractures, enthesopathy
α-Klotho translocation (<i>KL</i> translocation)	Macrocephaly, prominent forehead, dysplasia of the nasal bones with exaggerated midfacial protrusion	↑	Normal ^c	Normal	↑	↑	↓	α-Klotho translocation is associated with more severe hypophosphataemia than XLH	Rickets
Fibrous dysplasia – McCune–Albright syndrome (somatic <i>GNAS</i>)	Café-au-lait spots or naevi, focal bone lesions	Normal or ↑	Normal ^c	Normal or ↓	Normal or ↑	↑	↓	Hyperfunctioning endocrinopathies	Focal bone lesions
Cutaneous skeletal hypophosphataemia syndrome (somatic <i>RAS</i> genes)	Mosaic skeletal dysplasia, epidermal naevi and moles	Normal or ↑	Normal ^c	Normal or ↓	Normal or ↑	↑	↓	Possible development of tumours	NA
Osteoglophonic dysplasia (<i>FGFR1</i>) or opsismodysplasia (<i>INPPL1</i>)	Very short stature, severe skeletal dysplasia	Normal	Normal ^c	Normal	Normal or ↑	↑ or normal	Normal	NA	Severe bone dysplasias, non-ossifying bone lesions, hypodontia
<i>SGK3</i> mutation	Rickets	NA	NA	NA	NA	NA	NA	Unclear pattern	Rickets
Acquired forms									
Intravenous iron preparation use	In the context of iron deficiency with parenteral administration of iron	NA	NA	NA	NA	NA	NA	↑Intact FGF23; ↓C-terminal FGF23	Rickets and/or osteomalacia are uncommon
TIO	No family history of rickets or osteomalacia, no dental manifestations	Normal or ↑	Normal ^c	Normal or ↓	Normal or ↑	↑	↓	NA	Rickets and/or osteomalacia

↑, elevated; ↓, decreased; 1,25(OH)₂D, 1,25-dihydroxyvitamin D; ADHR, autosomal dominant hypophosphataemic rickets; ALP, alkaline phosphatase; ARHR, autosomal recessive hypophosphataemic rickets; BMD, bone mineral density; FGF23, fibroblast growth factor 23; NA, not available; PTH, parathyroid hormone; TIO, tumour-induced osteomalacia; XLH, X-linked hypophosphataemia. ^aIntact FGF23. ^b24-h urinary calcium excretion. ^cDecreased relative to the serum concentration of phosphate. ^dFGF23 varies with iron deficiency.

generation of pyrophosphate. Biallelic pathogenic variants in *ENPP1* lead to generalized arterial calcification of infancy (GACI). Children who survive GACI can go on to develop ARHR type 2 (REF.⁶⁵). In one series of 247 adults and children with GACI, 11 initially presented with ARHR type 2. All had *ENPP1* pathogenic variants and seven had evidence of ectopic calcifications⁶⁶. Third, ARHR type 3 is associated with biallelic pathogenic variants that inactivate *FAM20C* (which encodes a secreted protein kinase that induces posttranslational modification of FGF23 and enhances the processing of FGF23 protein), preventing FGF23 degradation⁶⁷. Of note, a *de novo* translocation adjacent to *KL* (which encodes α -klotho) between chromosomes 9 and 13 has been described, which results in elevated circulating levels of α -klotho and FGF23 (REF.⁶⁸). The disorder featured hypophosphataemic rickets and severe hyperparathyroidism, with a phenotype characterized by specific facial features and skull anomalies.

Diagnosis of genetic causes of FGF23-mediated hypophosphataemia: recommendations.

- In addition to the main biochemical features, the diagnosis of XLH is based on the clinical evidence of rickets, radiographic signs and when possible, a positive family history (which is seen in 50–70% of patients) with a dominant transmission^{69,70}.
- Given the difficulties in the differentiation of the multiple possible diagnoses, and given also that the anti-FGF23 antibody, burosumab, is only approved for use in XLH (and in TIO in certain countries), the diagnosis of XLH should be confirmed by genetic analysis of *PHEX* in children and adults.
- In case of a negative family history, a panel of other forms of genetic hypophosphataemia should be tested^{3,69,71}. 20–30% of patients with XLH are estimated to have spontaneous disease with no family history^{69,72}.
- In the absence of a genetic finding or family history, a diagnosis of TIO should be considered (see later text).

Acquired causes of FGF23-mediated hypophosphataemia

Intravenous iron therapy. Administration of ferric carboxymaltose to individuals with iron deficiency is responsible for acquired hypophosphataemia. Other intravenous iron preparations can also induce hypophosphataemia, although less frequently than ferric carboxymaltose. In the setting of iron deficiency, which stimulates FGF23 expression, intravenous iron therapy interferes with the cleavage of FGF23, producing high circulating levels of intact FGF23, and an increased ratio of intact FGF23 to C-terminal FGF23 (REFS^{60,73,74}).

Tumour-induced osteomalacia. TIO is a rare acquired disorder mediated by FGF23 that is produced by often benign mesenchymal tumours. This condition has also been observed in several cancers (for example, prostate and breast)^{75,76}. The biochemical features of TIO are similar to those of XLH, with hypophosphataemia, low TmPi/GFR, low or inappropriately normal circulating

levels of 1,25(OH)₂D, and high or inappropriately normal circulating levels of FGF23 (REF.⁷⁷). However, clinical features such as dental complications, enthesopathy or osteoarthritis are less commonly found in TIO than in XLH. This difference might be due to the development of the disorder during adulthood and/or a short disease duration⁷⁸. Although XLH can be associated with increased BMD in certain patients, BMD is typically low in TIO⁷⁹, with an important deterioration in bone microarchitecture⁸⁰. The tumours in TIO are usually small, with slow growth and can be located anywhere in the body. Once the diagnosis is established, identifying the location of the tumour might be difficult despite a multitude of sophisticated imaging modalities currently available (for example, PET-CT with ⁶⁸Ga-DOTATATE or fluorodeoxyglucose). These examinations can be followed up with targeted venous sampling to determine if suspect lesions found on imaging are secreting FGF23 (REF.⁸¹). Effort should be made to find the tumour, with repeated scans at annual or 2-year intervals, as complete surgical tumour resection is curative and leads to a spectacular clinical improvement and increases in BMD⁷⁹. When tumour resection is not possible, due to an inability to locate or access the tumour, medical treatment and management are similar to those in XLH. Among new therapeutic procedures, image-guided tumour ablation⁸² and the anti-FGF23 monoclonal antibody burosumab have shown promising results⁸³.

Diversity of XLH clinical manifestations

XLH has clinical manifestations that affect many different organs and tissues. BOX 2 summarizes pathophysiological changes and clinical implications by organ in XLH. In a 2019 survey that involved 232 adults and 90 children with XLH⁸⁴, bowing of the femur was reported in 63% and bowing of the tibia was reported in 72% of children. A similar prevalence was found in adults. Of note, 47% of children and 94% of adults reported surgical interventions, most commonly osteotomy, followed by epiphysiodesis. History of fracture or pseudofractures was reported in 44% of adults. In a meta-analysis, 18% to 52% of adult patients with XLH experienced fractures or pseudofractures⁸⁵. Despite conventional treatment with phosphate supplements and vitamin D metabolites during childhood, 57% reported a history of orthopaedic surgery. Another study showed an unexpected reduction in survival in adult patients with XLH⁵⁷.

In some children with XLH, craniosynostosis results from premature fusion of the cranial sutures during growth^{86,87}. The pathophysiology of this complication has not been fully elucidated but might involve an upregulation of FGF receptor 2 (FGFR2) or FGFR3 signalling and cross-binding of FGF23 with FGFR2 and FGFR3, which affects intramembranous and endochondral ossification of the skull⁸⁸. Patients with XLH can also have a disproportionately short stature³, which does not correct even with treatment from birth onwards and despite correction of leg deformities.

Besides the clinical and radiological evidence of rickets that is present in a large proportion of patients with XLH, muscle weakness has been reported in 30% of children and 60% of adults⁸⁴. Compared to an age-matched

Box 2 | Pathophysiological changes and clinical implications by organ in X-linked hypophosphataemia

Bone

Pathophysiological changes

- Impaired mineralization: increased unmineralized osteoid due to hypophosphataemia
- Decreased calcitriol production (including locally)
- Local suppression of tissue non-specific alkaline phosphatase (TNAP)
- Accumulation of osteopontin and aspartic acid-rich motif peptide (pASARM)
- Decreased chondrocyte differentiation, which impairs caspase-mediated apoptosis of hypertrophic chondrocytes
- Increased perilacunar pyrophosphate

Clinical implications

- Rickets or osteomalacia

Cartilage

Pathophysiological changes

- Lower extremity deformity with altered biomechanics
- Intrinsic defects in articular cartilage might occur

Clinical implications

- Early osteoarthritis

Kidney

Pathophysiological changes

- Related to conventional treatment
- Fibroblast growth factor 23 (FGF23) effect on tubular reabsorption of calcium and sodium

Clinical implications

- Nephrocalcinosis
- Nephrolithiasis
- Chronic kidney disease
- Hypertension

Cardiovascular system

Pathophysiological changes

- Conventional treatment-related decrease in glomerular filtration rate
- Secondary hyperparathyroidism
- FGF23-driven increased renal sodium reabsorption
- Direct FGF23 effect

Clinical implications

- Hypertension
- Possible left ventricular hypertrophy

Ligament and tendons

Pathophysiological changes

- Direct FGF23 effect
- Increase strain on entheses due to bowing of the bones

Clinical implications

- Enthesopathy

Muscle

Pathophysiological changes

- Hypophosphataemia
- Possible direct FGF23 effect

Clinical implications

- Muscle weakness, pain and stiffness

Skull

Pathophysiological changes

- Up-regulation of fibroblast growth factor receptor 2 (FGFR2) and FGFR3 signalling and cross-binding of FGF23 with FGFR2 and FGFR3
- Affecting intramembranous and endochondral ossification of the skull

Clinical implications

- Craniosynostosis
- Arnold–Chiari type 1 malformations

Spine

Pathophysiological changes

- Ligamentum flavum mineralization
- Facet joint hypertrophy
- Ossification of the anterior and posterior longitudinal ligament

Clinical implications

- Spinal stenosis

Teeth

Pathophysiological changes

- Direct FGF23 effect during early dental development
- Accumulation of small integrin-binding ligand N-linked glycoproteins and pASARM
- Local repression of TNAP

Clinical implications

- Dental necrosis with severe abscesses
- Periodontitis
- Tooth loss

Ear

Pathophysiological changes

- Disrupted ion balance
- Temporal bone malformation
- Inflammation
- Local repression of TNAP

Clinical implications

- Hearing loss

and sex-matched population, affected individuals display normal muscle volume, but a lower muscle density and lower muscle strength and power⁸⁹. The reasons for muscle weakness are unknown and might be linked with hypophosphataemia and deficient energy delivery to the muscle by decreased muscle ATP synthesis, as well as with limb deformities and deconditioning. This manifestation will require further efforts to be completely understood⁹⁰.

Early osteoarthritis and enthesopathy (calcification of the tendons and ligaments in close proximity to

bone) can limit the mobility of patients with XLH and cause pain. In one study in adult patients with XLH (aged >30 years), 80% of patients had early osteoarthritis and 100% of patients had enthesopathy⁹¹, which explains the high proportion of individuals with XLH who live with pain. Enthesopathy and spinal stenosis are common (affecting 27% and 19% of adults with XLH, respectively), as are dental abscesses, which affect 51% of children and 82% of adults with XLH. Nearly all adults with XLH experienced pain in another study⁸⁴.

The mechanism of enthesophyte development is poorly understood and might result from a direct effect of FGF23 (REFS^{92,93}). Conventional therapy does not notably influence enthesopathy^{94,95}. The bowing of the long bones might potentially increase strain on the entheses. The mechanisms underlying early osteoarthritis development are not completely understood and cannot be fully explained by abnormal mechanical loading due to skeletal deformities. However, the mechanisms through which increased FGF23 might interfere with cartilage development require further investigation⁹⁶.

Among extra-skeletal manifestations, neurological manifestations also occur due to spinal stenosis or type I Chiari malformation (defined as brain tissue that extends into the cervical spinal canal)⁹⁷. Clinically important spinal canal stenosis and spinal cord or nerve compression are the consequence of ossification of the posterior longitudinal ligament in conjunction with hypertrophy of the facet joints, thickening of the laminae and calcification of the ligamenta flava^{98,99}. Of note, hearing loss has been reported in 16% to 76% of individuals with XLH^{2,100–102}. However, the mechanism is unclear¹⁰³.

Nephrocalcinosis has not been reported in untreated patients with XLH but is considered an adverse effect of conventional treatment (particularly phosphate supplements) and occurs through treatment-related development of hypercalciuria, hyperphosphaturia and/or

secondary hyperparathyroidism¹⁰⁴. FGF23 has also been suggested to enhance renal calcium reabsorption via the transient receptor potential cation channel subfamily V member 5 (TRPV5) channel in the distal tubule, which could potentially promote cellular calcium accumulation and calcification, as does PTH^{105–107}. The frequency of nephrocalcinosis is highly variable and ranges from 30% to 70% in patients with XLH³. Nephrocalcinosis might be associated with hypertension and left ventricular hypertrophy¹⁰⁵. In patients with XLH, FGF23 might also have a direct effect on cardiomyocytes and vessels, as is seen in chronic renal failure; however, circulating levels of FGF23 in XLH are well below those encountered in renal failure, making a myocardial direct toxic effect less likely¹⁰⁸.

Some limited data exist supporting the view that patients with XLH might be prone to develop early-onset hypertension and display a higher prevalence of hypertension as compared with the general population. For example, 27% of adult patients with XLH were found to be affected by hypertension in a previous study¹⁰⁵. In patients with XLH, hypertension seems to be associated with the presence of secondary or tertiary hyperparathyroidism, nephrocalcinosis and/or reduced GFR¹⁰⁹. FGF23-induced renal sodium reabsorption could have a role in this phenomenon¹⁰⁶. Children and adults with XLH also have a high prevalence of obesity, partly due to impaired mobility in relation to chronic bone complications^{102,110}. Obesity substantially reduces gait quality in children with XLH¹¹¹. In addition, some patients with XLH also experience glycosuria, which could confuse the clinical diagnosis and might lead clinicians to suspect a Fanconi-type syndrome rather than FGF23-mediated hypophosphataemia^{112–115}.

Of note, the earlier that appropriate treatment is initiated in childhood, the lower the severity of clinical symptoms and consequences observed in adulthood^{116–118}. Moreover, adults with XLH display specific symptoms related to early development of osteoarthritis, osteomalacia with pseudofractures, impaired muscle function, chronic bone and joint pain, stiffness, impaired mobility and disability, depression¹¹⁹ and early susceptibility to dental abscesses. All these manifestations negatively affect the patient's quality of life¹²⁰ (BOX 3; FIGS 1, 2).

Management of XLH

Conventional treatment. During growth, conventional treatment with phosphate supplements and active vitamin D metabolites can be offered to all children with XLH, as soon as the diagnosis is established. The dose should be adapted to the severity of the phenotype, with starting doses ranging from 20 mg/kg to 60 mg/kg body weight per day (0.7–2.0 mmol/kg) of elemental phosphate² in four to six divided doses. Calcitriol should be given at a starting dose of 20–30 ng/kg body weight per day in one or two doses. Owing to a longer half-life than calcitriol, alfacalcidol can be given once daily at an initial dose of 30–50 ng/kg per day. A more aggressive approach has been suggested that uses high calcitriol doses of up to 40 ng/kg per day², or even short-term higher doses as a loading dose, which might help in preventing hyperparathyroidism but could also result in

Box 3 | Living with XLH — burden of XLH disease and symptoms that affect quality of life

- Pain, particularly in and along the tibia, and in joints (for example, the ankles, knees and hips).
 - Significant limitations on daily physical activities including sports and exercise, walking and standing for long periods of time. Also results in social effects, especially at school age (for example, unable to join friends or other students in sporting events and physical activities).
 - Leisure activity limitations
- Physical deformities such as bowing of the legs, short stature or misshapen head.
 - Physical deformities have major emotional and psychological consequences, from childhood through to adolescence and even into adulthood. They can lead to low self-esteem, depression, isolation and social life limitation.
- Dental complications
 - Early tooth loss
 - Alteration of quality of life
 - Aesthetic and functional disabilities
 - Abscesses
 - Pain and frequent infections
- Muscle weakness
- Stiffness
- Fatigue
- Mood alterations and depression
 - Feeling guilty for having children owing to the risk of passing on XLH to future generations
 - Questioning major life choices, such as having children
- Surgical procedures
 - Surgical procedures are associated with transient disabilities. Surgical procedures have both physical and psychological effects. Patients who require complex deformity correction will undergo a lengthy rehabilitation process. The burden of recovery (an inability to walk and being wheelchair-bound), combined with dependency on medication (opiates such as oxycodone) and loss of freedom and mobility has major emotional and mental effects, which should not be underestimated when planning and during recovery from corrective surgery.

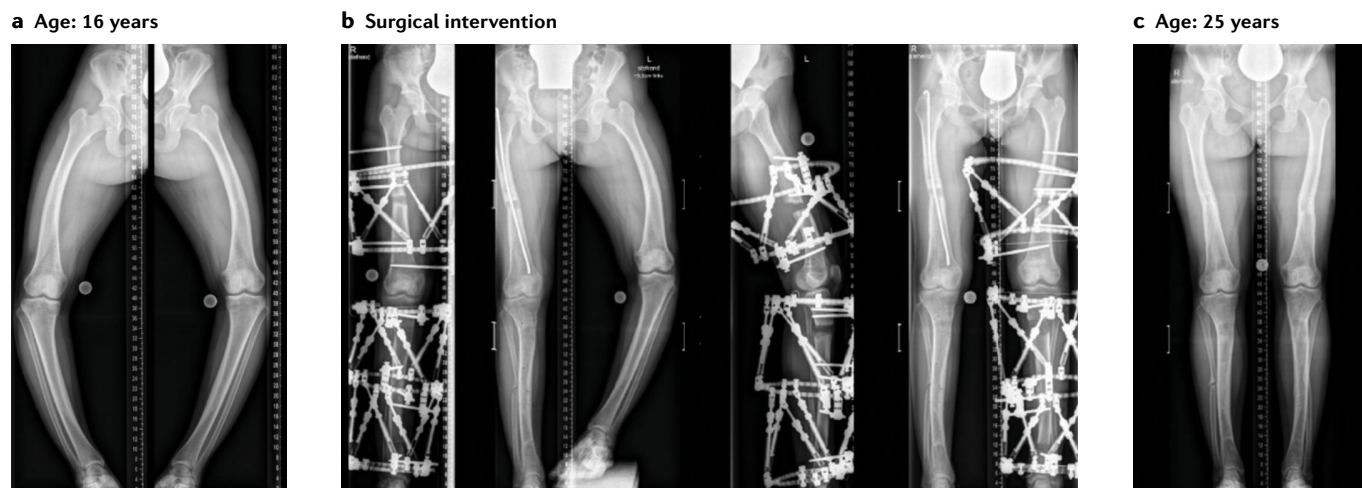


Fig. 1 | Burden of XLH disease in an adolescent patient. Radiographic images in a 16-year-old girl with X-linked hypophosphataemia (XLH)-associated rickets. The patient had sporadic disease with a confirmed *PHEX* pathogenic variant. Conventional therapy (oral phosphate supplements and calcitriol) was started in the second year of life. **a** | Severe and complex multi-apical varus deformity and maltorsion. **b** | Bilateral deformity correction and body height increase (9.5 cm) was achieved by performing multiple osteotomies and stabilization with external fixators (a Taylor Spatial Frame). **c** | Last follow-up at age 25 years (5 years after the last surgical procedure) with high patient satisfaction, high daily activity, no joint or muscle pains and excellent limb alignment. This patient illustrates the severity of bone deformities in XLH and the clinical efficacy of orthopaedic surgery in conjunction with conventional therapy. Image courtesy of C. Radler, Orthopaedic Hospital Speising, Vienna.

an increased risk of nephrocalcinosis¹²¹. Less frequent dosing with phosphate or vitamin D metabolites can be considered when serum levels of alkaline phosphatase (ALP) are in the normal range, in order to improve adherence in adolescents. Of note, reference ranges for ALP are both age-specific and sex-specific. Vitamin D deficiency should also be corrected to prevent the development of secondary hyperparathyroidism, which can worsen renal phosphate wasting.

In children, the clinical efficacy of conventional treatment is well established, in terms of improved growth and reduced severity of leg deformities, decreased occurrence of dental complications and pain control^{122–128}. As serum phosphate is measured under fasting conditions and given the short half-life of phosphate supplements (serum levels of phosphate return to baseline concentrations within 1.5 h after intake¹²⁹), fasting phosphate values might be lower than in a post-absorptive state. Thus, conventional treatment usually fails to normalize serum levels of phosphate, and to target the normalization of serum levels of phosphate is not a suitable goal. The goal of treatment is to prevent or cure rickets^{2,116}. Importantly, overtreatment with phosphate supplements should be avoided owing to the risk of nephrocalcinosis and of secondary hyperparathyroidism.

In adults, the considerable variety of phenotypes of XLH can substantially influence the appropriate treatment. Furthermore, the condition is rarely misdiagnosed as ankylosing spondylitis, early osteoarthritis or Forestier disease. In 2021, a middle-aged man was reported as being misdiagnosed with achondroplasia all through childhood and adulthood owing to his short stature and deformed extremities¹³⁰.

Long-term treatment with phosphate supplements¹³¹ and decreased production of calcitriol by FGF23 excess contribute to the development of hyperparathyroidism. Adults with XLH are particularly prone to developing

secondary and eventually tertiary hyperparathyroidism with hypercalcaemia, which affected 25% and 10% of patients with XLH respectively, in one study¹³². If available, paricalcitol could be added to conventional therapy for PTH suppression. Paricalcitol was tested in a randomized trial in patients with XLH without prevalent hypercalcaemia¹³³. Tertiary hyperparathyroidism should primarily be treated by parathyroid surgery¹³². If there are contraindications to surgery or if the patient declines this intervention, the calcimimetic cinacalcet could be considered^{134,135}.

The continuation of conventional treatment in adults is still debated. In a cohort of 52 adults with XLH, continuation of conventional treatment during adulthood tended to prevent dental abscess¹³⁶, and to reduce periodontitis frequency and severity¹³⁷. However, conventional treatment in adults does not seem to affect the course of enthesopathy¹³⁶. By contrast, in Hyp mice (a model of human XLH), conventional treatment did not improve enthesopathy⁹⁵ or exacerbated the mineralization of enthesis¹³⁸. Neither hearing loss nor osteoarthritis seem to be influenced by conventional treatment³. Evidence, mostly obtained from case reports, suggests the efficacy of conventional treatment on bone pain related to osteomalacia, pseudofractures and fracture healing^{2,139}. However, robust evidence that asymptomatic adults should be treated is still missing. Transient treatment regimens can be considered in those undergoing orthopaedic or dental surgery to promote bone mineralization and the healing process. If so, treatment should be started before and continued 3–6 months after the surgical intervention². When growth is completed, the dose of oral phosphate must be progressively decreased down to the lowest dose consistent with relief of symptoms. The doses of alfacalcidol or calcitriol should be adjusted to the required dose of phosphate to ensure normal mineral metabolism, as reflected by normal

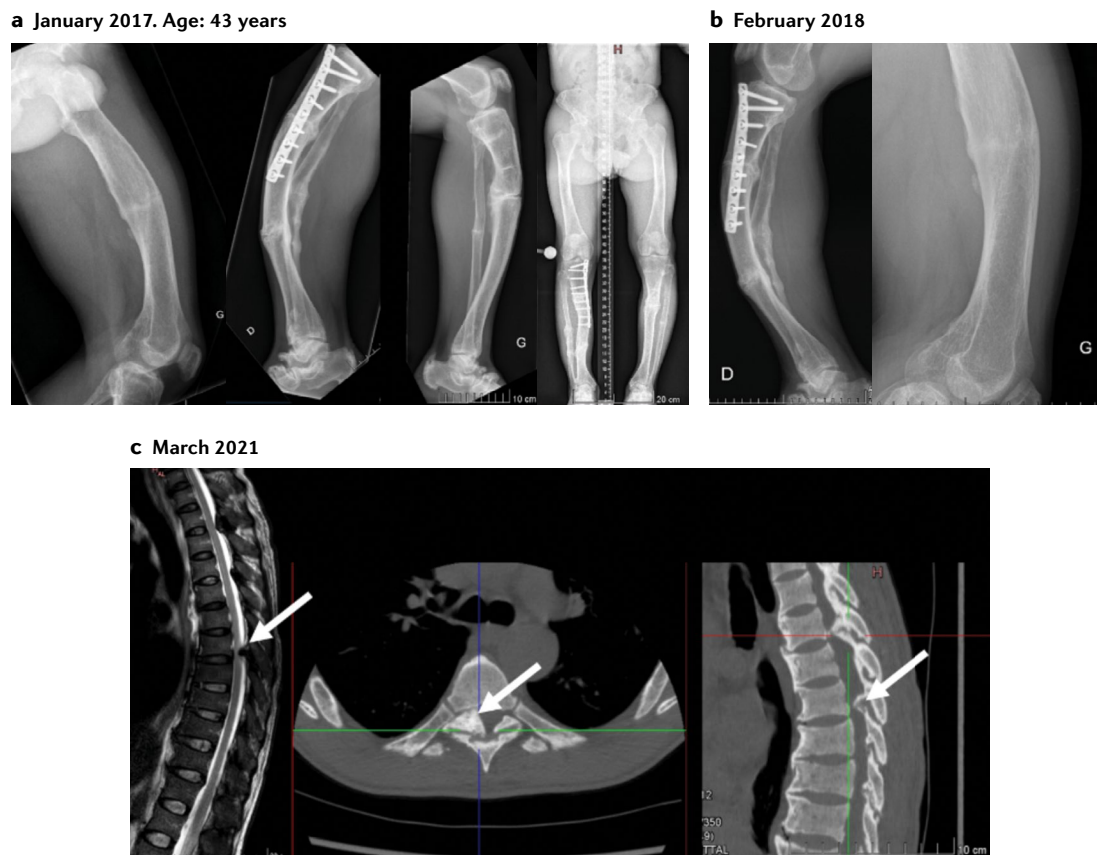


Fig. 2 | Burden of XLH disease in an adult patient. Radiographic images in a 48-year-old man with X-linked hypophosphataemia (XLH)-associated rickets that manifested with short stature, bowing of the limbs and recurrent abscesses during childhood. Phosphate supplements and active vitamin D metabolites were administered until the age of 18 years. The patient had important varus deformities of the tibias and underwent corrective surgical procedures: the first operation was a bilateral tibial osteotomy at age 20 years and a second operation was performed on the right side at age 22 years. The osteotomy site on the right fibula did not consolidate until the age of 25. **a** | At the age of 43 years, in the context of diffuse pain, X-ray evaluation showed multiple pseudofractures located on the left femur, and right and left tibias, with important deformations. **b** | Conventional treatment was started, which was associated with rapid improvement in the pain and progressive healing of the pseudofractures. **c** | At the age of 48 years, he developed symptomatic spinal cord compression at the level of thoracic vertebra 7 and thoracic vertebra 8 due to enthesopathy affecting the ligamentum flavum. He underwent a posterior decompression at the levels of compression sites (arrows indicate compression).

serum levels of ALP, PTH and calcium, without signs of nephrocalcinosis. In some instances, low-dose active vitamin D analogues might be sufficient to achieve normal mineral metabolism and symptom relief without additional phosphate supplements.

During pregnancy, the need for phosphate increases, particularly during the third trimester, with an active maternal–fetal transport by the placenta. For those patients not receiving any treatment before pregnancy, conventional treatment could be considered and continued until the end of breastfeeding. Neonates born from mothers with XLH do not display skeletal abnormalities at birth⁹¹ but preliminary findings suggest that they might have a birthweight slightly lower than normal (A. Linglart, unpublished work). In summary, we suggest that clinicians consider monitoring mineral metabolism in pregnant and lactating women and administering conventional XLH treatment if needed. Genetic testing of *PHEX* should be performed in the newborn baby. Given the time needed to get the results of such testing, we recommend screening the newborn baby at 7 days

and, if the first survey is normal, 1 month after birth with the following parameters: plasma creatinine, ALP, PTH, 25OHD and phosphate, and urinary phosphate and creatinine. These parameters can be used to calculate the TmPi/GFR, as this ratio and the serum levels of phosphate might remain in the lower normal range during the first months of life. Genetic testing is not absolutely necessary when there is a well-known family history and biochemical findings consistent with XLH. Also, in some settings, genetic testing is not available or is prohibitively expensive. Conversely, targeted genetic testing can be done fairly rapidly and inexpensively when the pathogenic variant in the relative is already known.

Adverse effects of conventional treatment. Adverse effects of conventional treatment include intestinal discomfort due to phosphate supplements, with nausea, diarrhoea, hypercalciuria and nephrocalcinosis reported in 30% to 70% of patients³. Excessive oral phosphate intake might also promote nephrocalcinosis¹⁴⁰. Secondary and tertiary hyperparathyroidism due to long-standing stimulation

of parathyroid glands by phosphate supplements and further suppression of $1,25(\text{OH})_2\text{D}$ production by FGF23 might also be seen in patients with XLH¹⁴¹.

Conventional treatment in children: recommendations.

- Vitamin D analogues and phosphate supplements can be offered to all children with XLH, as soon as the diagnosis is established.
- Starting doses of elemental phosphate range from 20 to 60 mg/kg body weight per day (0.7–2.0 mmol/kg)² in four to six divided doses, according to the severity of the disease.
- Calcitriol should be given at a starting dose of 20–30 ng/kg body weight per day, in one or two doses, or alfacalcidol once daily at an initial dose of 30–50 ng/kg per day.

Conventional treatment in adults: recommendations.

- Treatment in adults should include: vitamin D analogues (alfacalcidol 0–1.5 µg per day, once per day, or calcitriol 0–1.0 µg per day, in one or two doses) alone or with phosphate supplements (ideally smaller doses (than in children), which are evenly distributed across the day, 0–2,000 mg per day).
- Management of bone pain might be required in adults with XLH owing to osteomalacia, fractures or pseudofractures.
- In adults with XLH, clinicians should evaluate the need for orthopaedic surgery or the presence of dental complications.
- We suggest considering treatment with vitamin D analogues and phosphate supplements during pregnancy and breastfeeding. No data, to our knowledge, are available regarding the effect of therapy in postmenopausal women. Consistent evidence is still missing for treating enthesopathies.
- We do not recommend treatment of asymptomatic adult patients, unless they develop pseudofractures, even without symptoms.

Growth hormone treatment in children. Not enough evidence is available to recommend routine treatment with recombinant human growth hormone in short children with XLH¹⁴².

Rehabilitation. Specific programmes of regular physical exercises and physiotherapy should be followed by individuals with XLH to prevent or improve muscle weakness, back pain, joint pain and stiffness, and to increase mobility¹⁴³. Physiotherapy should promote muscle strength, improve balance, joint motion and general mobility, by resistance exercise training in combination with other muscle function therapy³. Leisure sport activities are recommended. Specific and tailored programme rehabilitation is often necessary after orthopaedic surgery and in those with enthesopathy or osteoarthritis³.

Burosumab treatment in children. Conventional treatment counteracts two consequences of high circulating levels of FGF23, which are hypophosphataemia and low circulating levels of $1,25(\text{OH})_2\text{D}$; however, conventional treatment does not fully correct the XLH phenotype due

to the *PHEX* pathogenic variant. Furthermore, conventional therapy increases the circulating levels of FGF23 and PTH, potentially exacerbating hypophosphataemia. Thus, a logical treatment approach is to use burosumab, a recombinant, monoclonal IgG antibody against FGF23. It is recommended that health-care providers consider burosumab treatment in children with XLH aged 1 year or older (or from 6 months, as approved in some countries, such as the USA) and in adolescents with radiographic evidence of bone disease. The indications that were recommended in the 2019 guidelines³ are overt bone disease (active rickets on plain radiography) and disease that is refractory to conventional therapy, the presence of associated complications such as pseudofractures and an inability to adhere to conventional treatment.

The superiority of burosumab over conventional treatment has been shown in terms of serum phosphate control^{144,145}, healing of rachitic bone and/or of mineralization defects, improvements in bowing of legs, improved physical ability (as measured by walking distance in the 6-min walking test) and pain control. Burosumab can also be considered as first-line therapy in children with XLH. Of note, patients included in the comparative trial were severely affected and might not have represented the full spectrum of disease severity encountered in daily practice. In addition, patients with secondary hyperparathyroidism were excluded. The effect of burosumab on longitudinal growth in children during treatment periods of up to 64 weeks was rather small (about +0.2 s.d. score), which suggests the existence of additional pathogenic factors; for example, a *PHEX* mutation-related osteoblast defect that impairs growth in children with XLH¹⁴⁵. Whether burosumab confers advantages in mildly affected individuals remains to be seen. Long-term studies are also needed to evaluate the effect of this therapy on the clinical burden of XLH, such as bone deformities, dental complications and the number of surgical interventions. Thus, in children with mild disease who are easily managed with conventional therapy, treatment with burosumab is probably not warranted because of the large annual cost of the drug (around US \$200,000). In this population, a trial of conventional therapy is indicated rather than considering burosumab as first-line therapy at present. As all the studies evaluated children aged 1–12 years^{144,145}, in some countries, the use of burosumab is limited to children in this age range. We consider this position highly questionable and recommend continuing treatment until end of growth.

The starting dose of burosumab in children with XLH is 0.8 mg/kg every 2 weeks subcutaneously, and this dose is adjusted to bring fasting serum levels of phosphate within the lower end of the normal reference range for age (maximum dose 2 mg/kg per 14 days or 90 mg per 14 days). As the peak serum concentration of burosumab is reached by 7 to 11 days after injection, serum levels of phosphate should ideally be measured during that period to determine whether the treatment is causing hyperphosphataemia and between days 12 and 14 to demonstrate treatment efficacy³. The level that serum phosphate should increase to influence bone healing is currently unclear.

Burosumab treatment in children: recommendations.

- Consider burosumab treatment as first-line therapy in children with XLH aged 1 year or older (6 months in some countries, such as the USA), and in adolescents with radiographic evidence of severe bone disease.
- In children with mild disease, a trial of conventional therapy is suggested rather than considering burosumab as a first-line therapy.
- Once started, treatment with burosumab should be continued until the closure of the growth plate. A multidisciplinary evaluation should be conducted with the adult team to consider the follow-up of burosumab through adulthood.

Burosumab treatment in adults. In adults with XLH, when burosumab was administered subcutaneously every 4 weeks at a starting dose of 1 mg/kg rounded to the nearest 10 mg, the treatment was shown to normalize the serum levels of phosphate to above the lower limit of the normal range in most patients studied. Clinically, the Western Ontario and McMaster Universities Arthritis Index stiffness subscale score was improved, as was the Worst Pain Score and Physical Function sub-score of the SF-36 quality of life questionnaire^{146–150}. In a randomized double-blind placebo-controlled study, burosumab treatment in adults with XLH resulted in improved fracture healing (overt fractures and pseudofractures) at week 24 compared with placebo, and this improvement continued up to 48 weeks¹⁵¹. Treatment was also associated with improvement in histomorphometric features of mineralization defects¹⁵⁰.

Adverse effects of burosumab treatment. Burosumab treatment is well tolerated, with minor injection-site reactions, pain in the extremities, fever, rash, myalgia and headaches reported¹⁴⁴. In adults, restless legs syndrome (11.8%) was more frequently observed in the treated group than in the placebo group (7.6%)¹⁴⁹.

Burosumab treatment in adults: recommendations.

- Burosumab could be suggested as a second-line therapy in adults with XLH with overt osteomalacia, with pseudofractures that are not responding to conventional treatment or in patients intolerant to conventional treatment.

Follow-up of patients with XLH. Follow-up of both treated and untreated patients with XLH is an important aspect of management. A multidisciplinary team should be involved in the follow-up, and the examination and evaluation of the patient should be done at regular intervals (BOXES 4,5). In addition, clearly identified pathways should exist for health-care access in case of urgent clinical queries from both the patient and the patient's local health-care team. This access is best facilitated by a nominated clinician or a clinical specialist nurse.

The recommended clinical follow-up in children is shown in BOXES 4 and 5. As bone-specific ALP represents 90% of total circulating ALP in children, total ALP is a suitable biochemical parameter for the evaluation of rickets activity. In addition, the circulating levels of 25OHD and PTH should be followed, as vitamin D deficiency is frequent in these patients. Together with phosphate supplementation, vitamin D deficiency can stimulate secondary hyperparathyroidism. Of note, the use of active vitamin D metabolites is contraindicated in patients on burosumab treatment. The use of active vitamin D metabolites as part of conventional therapy is associated with the risk of hypercalcaemia and hypercalciuria; therefore, patients need to be monitored closely to identify these biochemical abnormalities.

Severity of rickets can be assessed with plain radiography examination of the wrist and/or knees. Systematic plain radiography is not recommended, but it should be done in children who are not responding to therapy, such as those with worsening of bone deformities despite medical treatment. Use of low-dose radiography (such as the EOS imaging system used in a standing position) might be an option to limit radiation exposure. Other recommendations for monitoring are listed in BOXES 4 and 5.

Multidisciplinary approach

Genetic counselling. XLH is transmitted in an X-linked dominant manner. With each pregnancy, an affected woman has a 50% chance of passing the pathogenic *PHEX* variant to her child. Mosaicism could affect the expected transmission of the gene and rare instances of mosaicism in XLH have altered the expected transmission pattern¹⁵². An affected man passes the pathogenic variant to all of his daughters and to none of his sons. Offspring who receive the pathogenic variant will be affected; however, the severity of the phenotype cannot be firmly predicted because of large intrafamilial variations³.

Box 4 | Follow-up of children with XLH

Children with XLH should be seen at regular intervals by a multidisciplinary team: at least every 3 months during the phases of rapid growth or after initiation of therapy, at least every 6 months in patients showing a positive response to treatment and/or stable condition. Recommendations for follow-up assessments (radiological, biochemical and clinical) during these regular visits, or less frequently (as indicated) are provided.

- Perform radiographs^a of the left wrist and/or knees if patients: do not respond well to therapy; show a worsening in their bone deformity under medical treatment; require orthopaedic surgery; or have unexplained bone pain.
- Perform radiographs^a of the left wrist and/or knees in adolescents with persistent lower limb deformities when they are transitioning to adult care.
- Measure height, weight, head circumference (in those aged <5 years), intercondylar distance and intermalleolar distance, and blood pressure.
- Measure BMI and annual height velocity.
- Search for hearing loss.
- Monitor spine deformity and scoliosis, manifestations related to craniosynostosis, Chiari type 1 malformation and/or cranial hypertension, and maxillary dysmorphism.
- Record head shape, history of headaches, presence of dental abscesses or maxillofacial cellulitis, bone pain, fatigue and physical function.
- Assess bone age to evaluate the growth potential in children (aged >5 years) with growth impairment in the presence of lower limb deformity, and perform orthopaedic assessment.

^aRadiographs should be standardized anterior–posterior standing full-length lower limb radiographs (utilizing the low-dose biplanar EOS system when feasible) to assess limb deformities, joint alignment and bone quality. XLH, X-linked hypophosphataemia. BOX 4 is adapted from REF.³, CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

Box 5 | Follow-up of all patients with XLH

Patients with XLH should be seen at regular intervals by a multidisciplinary team: at least every 3 months during the phases of rapid growth or after initiation of therapy, at least every 6 months in patients showing positive response to treatment and/or stable condition. Recommendations for follow-up assessments (radiological, biochemical and clinical) for patients of any age with XLH during these regular visits, or less frequently (as indicated) are provided.

- In blood samples, monitor concentrations of ALP (total serum concentration of ALP in children and BAP in adults), calcium, phosphate, creatinine, PTH and 25OHD.
- In urine, calculate the ratio of urinary calcium to creatinine in patients receiving conventional or burosumab treatment^a.
- In patients receiving burosumab treatment:
 - Monitor fasting serum levels of phosphate together with the TmPi/GFR, every 2 weeks during the first month after treatment initiation, every 4 weeks for the following 2 months (and thereafter as appropriate).
 - Measure fasting serum levels of phosphate 4 weeks after any dose adjustment.
 - Measure serum levels of 1,25(OH)₂D every 6 months, analysed together with the urinary calcium excretion^b as safety parameters.
- Skeletal assessment
 - Perform cranial MRI in case of a skull morphology in favour of craniosynostosis or clinical signs of intracranial hypertension. In patients with persistent severe headache or other central nervous system symptoms, the MRI should also include the spinal column to identify potential syrinx.
 - Routine dual X-ray absorptiometry or peripheral quantitative CT are not recommended for assessment of bone health.
- In treated patients: kidney ultrasonography should be performed at least every 2 years in patients without nephrocalcinosis, and at yearly intervals in patients with nephrocalcinosis and/or persistent hypercalciuria.
- Functional assessment: 6-min walk test and quality of life evaluation in patients aged >5 years (annual or 2-yearly intervals).
- Provide the contact details of patient association groups to patients, to inform patients of scientific discoveries, including new therapies, to support school and professional input and to provide social support.

^aThe calcium to creatinine ratio in urine spot has a low sensitivity in the detection of hypercalciuria. Periodic 24-h urine collections are preferred when the child is old enough.

^bUrinary calcium excretion should be assessed during the peak action of burosumab on 1,25(OH)₂D (7–11 days after injection). 1,25(OH)₂D, 1,25-dihydroxyvitamin D; 25OHD, 25-hydroxy vitamin D; ALP, alkaline phosphatase; BAP, bone-specific alkaline phosphatase; GFR, glomerular filtration rate; PTH, parathyroid hormone; XLH, X-linked hypophosphataemia. BOX 5 is adapted from REF.³, CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

Prenatal testing for a pregnancy at increased risk can be considered if the *PHEX* pathogenic variant has been detected in the family¹⁵³. In that case, as discussed above, targeted genetic testing can be done easily and inexpensively when the pathogenic variant in the relative is already known. Molecular genetic testing might include a single gene, such as *PHEX* sequencing, or a panel of several genes causing genetic forms of hypophosphataemia (TABLE 1). If a pathogenic variant is not detected, further assessment can include gene-targeted deletion or duplication analysis. For XLH, genetic diagnosis is established or confirmed by demonstrating a hemizygous *PHEX* pathogenic variant in an individual with XY chromosomes and a heterozygous *PHEX* pathogenic variant in an individual with XX chromosomes.

Genetic counselling: recommendations.

- Genetic counselling is recommended for patients who have been diagnosed with XLH, to understand the risk of transmission. Genetic testing during pregnancy can be performed if the patient so wishes.

- Testing for XLH in newborn babies of families affected by XLH should also be done to properly diagnose the condition, as early as possible. Delayed diagnosis or misdiagnosis can result in delayed or no treatment and consequently in poor patient outcome.

Oral health. Oral health is altered in patients with XLH. The disease impairs mineralization of the dentin and cementum¹⁵⁴ and also of the alveolar bone¹⁵⁵. The most frequently reported complications are ‘spontaneous’ dental necrosis with severe abscesses that occur in deciduous or permanent teeth, with no history of trauma or decay. These episodes can evolve to maxillo-facial cellulitis. The risk of periodontitis is also increased in adults with XLH, even in young adults, due to alterations of the periodontal tissues¹⁵⁵, which favours early tooth loss¹³⁷.

Regarding dental features, enamel looks normal but is slightly thinner in patients with XLH and wears out more rapidly than sound enamel in healthy individuals, and displays microscopic cracks. The most affected tissue in XLH is the dentin. Radiographic dental images from patients with XLH show low mineral density and enlarged pulp chambers. A characteristic sign is prominent pulp horns that extend to the dental enamel junction^{117,156}. Microscopically the dentin shows large unmineralized spaces with unmerged mineralization foci¹⁵⁷. In these unmineralized spaces, peptides derived from small integrin-binding ligand N-linked glycoproteins (known as SIBLINGs) accumulate, such as C-terminal acidic serine-rich and aspartate-rich motif (ASARM) peptides derived from matrix extracellular phosphoglycoprotein (MEPE) and osteopontin abnormal cleavage, which are strong inhibitors of biomineralization^{156,158–161}. Taken together, these dental features explain the increased susceptibility of patients with XLH to spontaneous necrosis and abscesses, whose origin is difficult to diagnose by medical practitioners and dentists not familiar with this disorder.

As stressed before, the earlier that conventional treatment is started in individuals with XLH during the growth period and in adulthood, the lower the incidence of dental abscesses¹¹⁷ and periodontitis¹³⁷. This effect occurs through an improvement in dentin and cementum mineralization as shown in observational studies^{117,137}. The effects of burosumab on dental abnormalities are rather disappointing, with a phase III comparative study in children with XLH showing more events such as spontaneous dental necrosis in the burosumab arm than with conventional treatment¹⁴⁵. A longer period of follow-up than carried out in this study might be required to observe a positive outcome on dentin and cementum mineralization. Overall, the quality of life of patients with XLH is strongly affected by dental events^{162,163}.

Oral health: recommendations.

- Patients with XLH require specific and regular dental examination (at least yearly) and appropriate care to prevent infections and early tooth loss, as well as

aesthetic and functional damage, by a dental team with expertise in XLH³.

Orthopaedic intervention. Regular paediatric orthopaedic assessment during the growth period is recommended in patients with XLH³. If surgery is needed, the orthopaedic surgeon can define the surgical plan and technique through a careful clinical examination, analysis of the deformities with full-length anteroposterior and lateral radiographs (hip to ankle) of both lower limbs in the standing position (with a calibration ball) and MRI. The type of orthopaedic management depends on the age of the patient and the type of deformity. Braces for deformity prevention with guidance of growth are no longer used in XLH because convincing evidence of efficacy is lacking¹⁶⁴. The surgical options in XLH include guided growth, osteotomies, complex deformity corrections, internal fixation and stabilization of pseudofractures, as well as joint replacement. Guided growth or temporary hemi-epiphysiodesis are used to correct coronal deformity (valgus or varus). A small plate is fixed on the medial or lateral distal femur or proximal tibia that blocks the open growth plate. After successful correction, the plate is removed. This procedure is effective in children and adolescents, minimally invasive and has a low rate of complications¹⁶⁵. The procedure has been tested in patients with XLH^{164,166–168} with success and could decrease the need of osteotomies. A limitation of this technique is that it needs growth potential. Furthermore, this technique corrects only the frontal deformity and cannot correct rotation or sagittal and diaphyseal bending of bone. A risk of recurrence is also present¹⁶⁹.

Osteotomies are another option enabling 3D correction of complex deformities. Subsequent stabilization can be performed both using internal devices as well as external fixators. Osteotomies are required when epiphyses are closed and guided surgery is no longer possible or in patients with complex deformities. Finally, arthroplasties of the hip and knee joints are possible in patients with XLH; however, these procedures require at times the simultaneous use of corrective osteotomies and special implants in patients with severe deformities^{170,171}.

Disease-specific gait deviations have been analysed in children and adults with XLH^{111,172,173}; however, they require further evaluation, as many patients with XLH report abnormal gait⁸⁴. Of note, any orthopaedic surgery should be considered only in patients with XLH who are undergoing medical treatment that corrects the underlying metabolic abnormalities, otherwise there is a notable risk of recurrence or failure of surgery. Patients who are considered for orthopaedic surgery should be referred to counselling services to prepare for and develop coping strategies for undertaking major surgery.

Symptomatic spinal cord compression due to spinal stenosis can be severe in patients with XLH and can occur at multiple levels. This complication might require neurosurgical posterior decompression and long-term follow-up⁹⁸. Chiari malformations in children with XLH can progress in adulthood and lead to severe occipitocervical headache and a variety of respiratory symptoms, and are related to sudden unexpected death.

Patient organizations and research

Patients with XLH should be informed about the potential help and additional information that can be provided by patient organizations, and should be asked to contact them if needed. This information is particularly important for the patient at the time the diagnosis is received. These organizations and patient representatives can share practical information about living with the condition, and the usefulness and adverse effects of medications, and suggest support strategies for special needs. Sharing of information and educational materials, and provision of counselling or psychosocial support, are also critical for the parents of children with XLH or the partners of affected adult patients. For parents of a child with XLH, caring for the affected child can be extremely daunting and isolating, given the rarity of the disease and the lack of support networks and information available. For spouses or partners, the disease raises fundamental questions, including uncertainties about pregnancy and the risk and impact to both the mother and the child. Establishing patient networks and ensuring access to services including genetic counselling, psychologists and counsellors, are critical in the interdisciplinary approach.

In certain parts of the world, centres of expertise can have connections with patient representatives and patient organizations. These representatives and organizations contribute to the planning, functioning and evaluation of these centres¹⁷⁴. However, such centres can be absent in other parts of the world where misdiagnoses are still common, access to treatment is not readily available and support networks are scarce, if not non-existent.

National guidelines issued from XLH centres of expertise should integrate and reflect patient preferences. In most clinical studies, treatment efficacy is evaluated through measurement of surrogate outcomes, such as serum levels of phosphate. However, how these surrogate outcomes relate to clinical benefits is unclear. Direct measures of patients' perceptions and feelings should be complementary to the evaluation of treatment effectiveness. Although disease-specific measures of patient-related outcome (PRO) are not available in XLH, concept-specific instruments measuring pain, fatigue and physical function, for example, can be used — for example, the Patient-Reported Outcomes Measurement Information System measures¹⁷⁵. Patient representatives and patient organizations are crucial in developing and establishing such measures. Such an instrument was used in a phase III clinical study of children with XLH and showed that burosumab improved PRO measures as compared with conventional treatment¹⁷⁵. Finally, given the rarity of XLH, patients should be offered information about local, regional, national and international studies they might be eligible for.

Family members

As mentioned above, parents, legal guardians and/or family members have a critical role in supporting patients with XLH, even in those affected with only a mild form of the disease. It is paramount that they are also supported when caring for patients with XLH and have adequate access to information about the disease.

Box 6 | Remaining questions and research agenda

- To better understand the pathophysiology of enthesopathy and the putative impact of burosumab on this manifestation with earlier and/or longer duration of use in the life-course than in current trials.
- To evaluate the mechanism of obesity and hypertension in children and adults with XLH and their effect on mortality.
- To further assess and document the risks and effects of XLH during pregnancy, for both the pregnant individual and the child.
- To assess the long-term effects of burosumab treatment, as well as the effects of starting the treatment before 1 year of age and its use during adolescence, on: lower-limb deformities and the need for surgical treatment; adult height; dental complications and abscess incidence; sensorineural hearing loss; pseudofracture prevention; craniosynostosis; and muscle function.
- To develop a specific and adequate physiotherapy programme for patients with XLH, aimed at reducing disabilities and disease burden.
- To develop guidelines on measures to improve motor function, to meet the needs of patients.
- To develop cohort studies to evaluate the natural history and the effect of burosumab on rare complications.
- To define the optimal serum concentration of phosphate to reduce disease burden.

XLH, X-linked hypophosphataemia.

This access is especially important given the rarity of this disease. For parents, especially those with XLH themselves, the burden starts even before the child is born. Having children can raise fundamental questions about the rate or risk of transmission, testing during pregnancy and treatment once the child is born. It also poses questions for the parents themselves; for example, to know if there are any known risks in pregnancy for women with XLH (beyond the ‘usual’ risks associated with pregnancy). Parents should be made aware of the physical, psychological, social and emotional effects of the disease, to support their child and to be able to cope

themselves. The same goes for spouses, partners and other family members.

Conclusions

Given the diversity of symptoms and complications in XLH, an interdisciplinary approach is of paramount importance, with special mention paid to dental, orthopaedic, and psychological and emotional care. Multidisciplinary follow-up of patients with XLH is mandatory and should be coordinated by a metabolic bone disease specialist. Paediatric and adult patients should be evaluated twice-yearly by a dentist, and paediatric patients should be followed up yearly by a paediatric orthopaedic surgeon specialized in XLH. Follow-up can involve dietitians, physiotherapists, occupational therapists, social workers and psychologists. Physiotherapy and occupational therapy can be helpful after surgery or to treat musculoskeletal symptoms such as stiffness, muscular weakness and disability. A dietician can help in the prevention and treatment of obesity, which is highly prevalent in patients with XLH^{102,110}. Patients should be referred to XLH patient organizations and patient representatives for information and genetic counselling. The information they provide is particularly important when patients receive the diagnosis and at critical moments later in life (for example, when considering major life choices such as pregnancy). Interaction between patients, who can share their experiences, is important and could ensure optimal adherence to follow-up and therapy and thereby a successful outcome. Some important unanswered questions remain to be explored in the area of the understanding of the pathogenesis of some complications of XLH or the effects of treatment (BOX 6).

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Author contributions

A.T. and R.R. contributed to all aspects of the article. E.C., C. Chaussain, D.H., N.C.H., A. Linglart, G.T.M., S.M. and L.S. researched data for the article, contributed substantially to the discussion of content, and reviewed and/or edited the manuscript before submission. N.A.-D., M.L.B., J.B.C.-A., M.C., L.C., C. Cooper, P.H., M.K.J., F.J., J.A.K., A. Laslop, M.R.L., A.M., M.C.P.Y., M.M.R., M.V. and M.B.Z. contributed substantially to the discussion of content, and reviewed and/or edited the manuscript before submission.

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