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Mini-Review

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X-Linked Hypophosphatemia: A New Era in Management

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Abbreviations: AE, adverse events; ALP, alkaline phosphatase; FGF23, fibroblast growth factor 23; FGFR2, fibroblast growth factor receptor 2; LSM, least squares mean; PHEX, phosphate-regulating endopeptidase homolog X-linked; PTH, parathyroid hormone; QoL, quality of life; RGI-C, Radiographic Global Impression of Change global score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; XLH, X-linked hypophosphatemia.

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Abstract

X-linked hypophosphatemia (XLH) is a rare, hereditary, progressive musculoskeletal disease that often causes pain and short stature, as well as decreased physical function, mobility, and quality of life. Hypophosphatemia in XLH is caused by loss of function mutations in the phosphate-regulating endopeptidase homolog X-linked (*PHEX*) gene, resulting in excess levels of the phosphate-regulating hormone fibroblast growth factor 23 (FGF23), which leads to renal phosphate wasting and decreased serum 1,25-dihydroxyvitamin D production. Historically, treatment options were limited to oral phosphate and active vitamin D analogues (conventional management) dosed several times daily in an attempt to improve skeletal mineralization by increasing serum phosphorus. The recent approval of burosumab, a fully human monoclonal antibody to FGF23, has provided a new, targeted treatment option for patients with XLH. This review summarizes our current understanding of XLH, the safety and efficacy of conventional management and burosumab, existing recommendations for managing patients, and unanswered questions in the field.

Key Words: XLH, X-linked hypophosphatemia, hypophosphatemic rickets, osteomalacia, burosumab, FGF23-related hypophosphatemia

X-linked hypophosphatemia (XLH) is a rare genetic musculoskeletal disease caused by loss of function mutations in the phosphate-regulating endopeptidase homolog X-linked (*PHEX*) gene that leads to excess serum levels of the phosphate-regulating hormone fibroblast growth factor 23 (FGF23). Elevated FGF23 causes renal phosphate wasting, decreased production of serum 1,25-dihydroxyvitamin D, and increased metabolism of 1,25-dihydroxyvitamin D, leading to hypophosphatemia [1-4]. Other hypophosphatemic disorders as a result of excess FGF23 due to different genetic mutations include autosomal dominant hypophosphatemic rickets and autosomal recessive hypophosphatemic rickets [5].

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Search Strategy

This review is based on literature identified through a comprehensive search of PubMed, Google Scholar, and Scopus for the following terms through May 2019: "XLH", "X-linked hypophosphatemia", and "hypophosphatemic rickets." Additional studies were identified from references cited in the publications returned through the aforementioned search, and from UpToDate entries for "X-linked hypophosphatemia" and "Hypophosphatemia."

Pediatric patients with XLH present with rickets and osteomalacia [6] and may also have genu valgus and/or genu varum, craniosynostosis, disproportionate short stature, pain, dental abnormalities, enthesopathy, and decreases in measures of physical and global functioning [7-10]. Rickets occurs only with open metaphyses, but osteomalacia typically persists throughout life [2, 6]. Adults with XLH experience progressive accumulation of the consequences of childhood disease (eg, short stature, lower limb deformity, and craniosynostosis) and ongoing symptoms, including osteomalacia, impaired muscle function, osteoarthritis associated with long-term weight-bearing on misaligned joints, pseudofractures, fracture nonunion, pain, stiffness, and decreased mobility [3, 9-14]. In our experience, these symptoms can result in functional disability that affects the ability to work and contributes to diminished quality of life (QoL), including social isolation.

X-Linked Hypophosphatemia Overview

Genetics and Pathophysiology

XLH is the most common form of heritable hypophosphatemic rickets [8, 15], with an estimated incidence of 1 per 20 000 to 25 000 live births and a reported prevalence ranging from 1 in 20 000 to 1 in 60 000 individuals [1, 16, 17]. XLH is inherited in an X-linked dominant pattern and is thought to be 100% penetrant; however, the intensity of clinical manifestations varies. Some studies have found a nonsignificant trend toward more serious manifestations in males compared with females, potentially due to X-inactivation [9, 17-19].

In healthy individuals, FGF23 is produced and secreted primarily by osteocytes in response to elevated serum phosphorus, 1,25-dihydroxyvitamin D, and parathyroid hormone (PTH) levels [20-22]. Bone-derived FGF23 binds to the Klotho-FGF receptor complex in renal tubule cells, resulting in (1) decreased production of sodium phosphate cotransporters that reabsorb filtered phosphate from the urine [23], (2) suppressed production of 1,25-dihydroxyvitamin D, and (3) increased metabolism of 1,25-dihydroxyvitamin D, thereby decreasing intestinal phosphate absorption [4, 24] (Table 1). However, *PHEX* mutations may cause dysfunction of the phosphate-sensing mechanism in osteocytes [4, 25, 26], leading to inappropriate production and secretion of serum FGF23 and thereby causing excessive renal phosphate wasting and low or inappropriately normal 1,25-dihydroxyvitamin D levels with a net effect of hypophosphatemia (Fig. 1) [2, 27]. Less commonly, hypophosphatemic rickets can result from mutations in other genes with a different inheritance pattern (reviewed elsewhere [28-30]). In addition, there is evidence

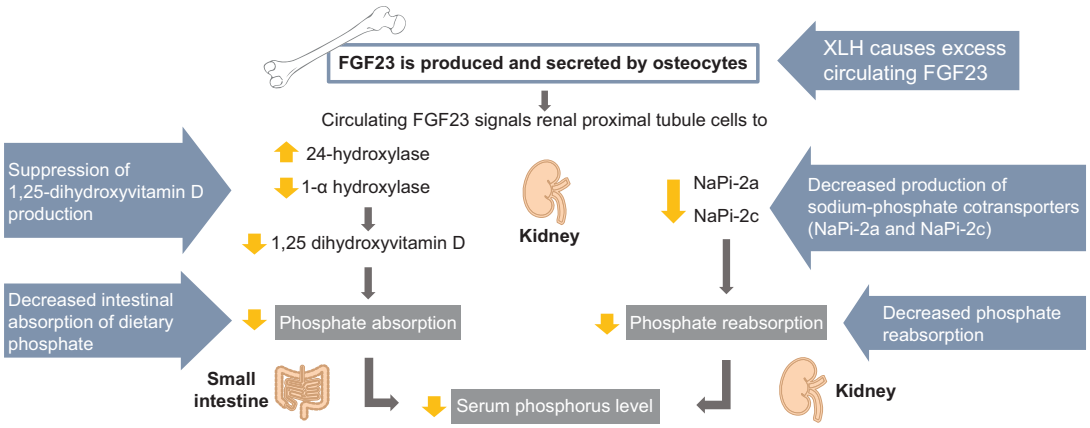

Figure 1. Fibroblast growth factor 23 (FGF23)-mediated regulation of serum phosphorus. FGF23 is a protein hormone produced primarily by osteocytes in response to elevated serum phosphate, 1,25-dihydroxyvitamin D, and parathyroid hormone levels. FGF23 binds to Klotho-FGF receptor complexes on renal tubule cells, causing (1) decreased expression of renal sodium-phosphate transporters, leading to increased excretion of phosphate in the urine, and (2) reduced 1,25-dihydroxyvitamin D (1,25$[OH]_2$D) levels, leading to decreased gastrointestinal absorption of phosphate.

in the animal model of XLH, the *Hyp* mouse, that mutations in *PHEX* impair bone mineralization independently of serum FGF23 or phosphate levels by enhancing Wnt/β-catenin signaling [31].

Diagnosis

A diagnosis of XLH is typically based on clinical, radiographic, and biochemical findings in combination with family history [9, 32]. Children with XLH usually present with lower-extremity bowing, impaired growth, and gait abnormalities during the first 2 years of life; however, as the spectrum of symptoms can vary, the diagnosis may be made after age 2 years and even during adulthood, especially for de novo cases [9, 28].

The main biochemical features of XLH are low fasting serum phosphorus levels, inappropriately low or normal 1,25-dihydroxyvitamin D levels, reduced ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate, and elevated or inappropriately normal serum FGF23 levels [9, 26, 33, 34] (Table 1). Fasting serum phosphorus levels should be monitored, given that normal ranges of postprandial phosphorus levels will sometimes be exhibited. Importantly, normal serum phosphorus range varies with age, as children have higher serum phosphorus levels than adults [9]. Furthermore, serum phosphorus appears to vary inversely with age among children [35], with a wide range of levels reported in younger children compared with older children: 4.8 to 8.2 mg/dL (age 0-5 days), 3.8 to 6.5 mg/dL (age 1-3 years), 3.7 to 5.6 mg/dL (age 4-11 years), 2.9-5.4 mg/dL (age 12-15 years), and 2.7 to 4.7 mg/dL (age > 15 years) [9]. Clinical laboratories do not always report age-specific phosphorus ranges, which can contribute to delayed or incorrect diagnoses [36]. Additional biochemical features of XLH include serum alkaline phosphatase (ALP) and PTH levels that may be elevated or within the normal range [9] (Table 1). Because the biochemical and clinical features of XLH may be similar to those of other renal phosphate-wasting disorders, family history or genetic testing may be necessary to diagnose XLH [9]. However, genetic testing is typically not necessary, particularly when there is an appropriate family history and radiographic and biochemical findings consistent with XLH. Family members of affected patients can be screened for XLH by testing fasting serum phosphorus and ALP levels (ALP is elevated in pediatric patients, but may be elevated or normal in adult patients) [9, 36]. Between 20% and 30% of cases are considered spontaneous and therefore have no family history [37-39].

Table 1. Biochemical features of X-linked hypophosphatemia [9, 25, 33]

Parameter	Feature
Serum phosphorus	↓
$1,25(OH)_2D$	↓ or inappropriately normal
TmP/GFR	↓
FGF23	↑
ALP	↑[a]
PTH	↑ or normal

Abbreviations: $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; ALP, alkaline phosphatase; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; TmP/GFR, ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate.
[a]ALP is elevated in pediatric patients but may be elevated or normal in adult patients.

When evaluating patients for suspected XLH, it is important to consider other possible causes of hypophosphatemia, including vitamin D deficiency or resistance, refeeding syndrome in malnourished patients with alcoholism or anorexia nervosa, treatment of diabetic ketoacidosis or nonketotic hyperglycemia, prolonged use of antacids, primary hyperparathyroidism, or Fanconi syndrome, which can be the result of an underlying genetic mutation or acquired, such as from treatment with tenofovir in patients with HIV. Details about other common causes of hypophosphatemia are reviewed elsewhere [40-42].

Early diagnosis of XLH is essential because early treatment of affected children may help to maximize growth and minimize lower-extremity deformity and dental abnormalities [28, 43-45]. Unfortunately, adult patients with XLH may not seek medical care, as some patients do not exhibit serious manifestations (eg, lower-extremity deformity) and their current symptoms are not recognized as being due to their childhood diagnosis of XLH or the absence of the diagnosis in childhood [46, 47]. In a study of 3 large families, a diagnosis of XLH was confirmed in 57 of 234 (24%) family members (50 participants were older than 18 years). Although 61% of the individuals with XLH had complained of bone or joint pain to their physicians, only 23% had been diagnosed with rickets or osteomalacia before the study. Screening family members of patients with XLH may help identify previously undiagnosed individuals [47].

X-Linked Hypophosphatemia Clinical Manifestations

Children

The principal manifestations of XLH in children are rickets and osteomalacia, which lead to lower-extremity deformity and diminished height (Figs. 2 and 3) [8, 9]. In a survey including 90 pediatric patients, bowing was reported in the tibia and/or fibula in 65 (72%), femur in 57 (63%),

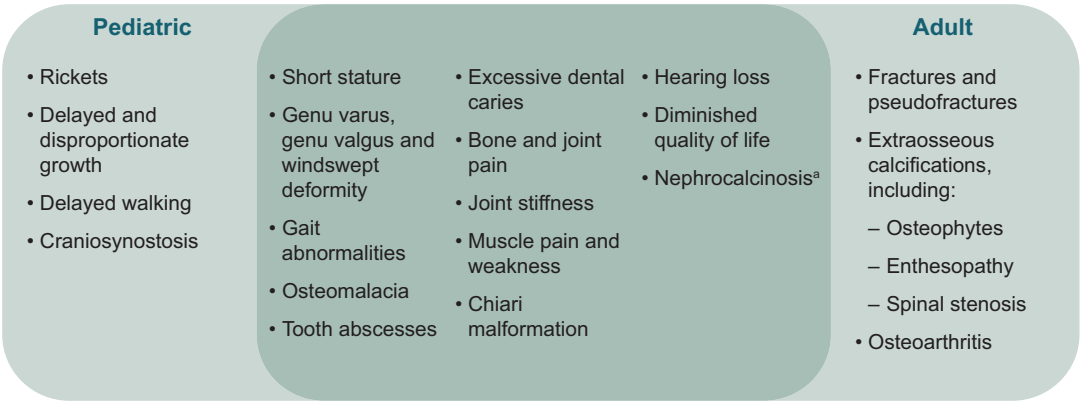

Figure 2. Clinical manifestations of X-linked hypophosphatemia (XLH), a lifelong disease with manifestations that begin in childhood and persist into adulthood. Adults suffer from the consequences of childhood disease and ongoing disease processes. [a]Nephrocalcinosis is typically associated with conventional therapy.

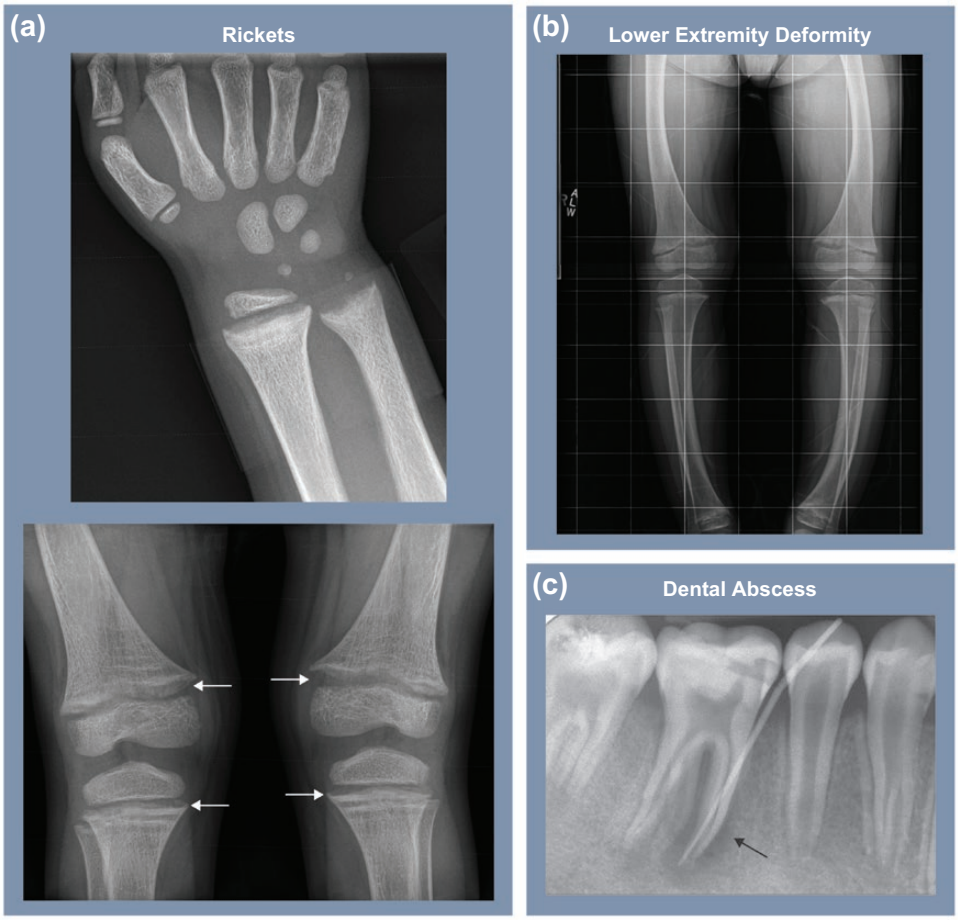

Figure 3. Clinical findings in pediatric patients with X-linked hypophosphatemia (XLH). A, Pediatric patients typically demonstrate rickets with metaphyseal flaring and fraying of the distal femur and proximal tibia and fibula (arrows). Rickets may also be demonstrated in the distal radius and ulna. B, Lower-extremity deformity is common, which can lead to disproportionate short stature, decreased physical functioning, and pain. C, Periapical radiograph in a patient with XLH shows a sterile abscess with a sinus tract in the right lower molar (arrow). Adapted from Lee BN, et al. [48] with permission from the Korean Academy of Conservative Dentistry under the Creative Commons Attribution 4.0 International Public License (https://creativecommons.org/licenses/by/3.0/).

and genu valgum in 29 (32%), and short stature was reported in 72 (80%) children [49]. In a separate study, the median height *z* score in a cohort of 21 pediatric patients (age 0-18) with confirmed XLH was –1.2 (range, –6.5 to 1.0) [17]. Impaired growth with XLH appears to manifest early, as the mean (±SD) height *z* score was –1.4 (±1.2) in

a group of 13 patients age 1 to 4 years [50]. Children with XLH often have a defective gait and/or leg-length abnormalities and an unusual gait or way of walking/running [20, 49], and approximately 40% of children with XLH eventually require surgery to correct bone deformities [36, 51, 52].

Dental abscesses and caries, which may result from defects in enamel, dentin, and cementum, are also common in children with XLH (Figs. 2 and 3) [36, 52]. Severe infections such as maxillofacial cellulitis spreading from an abscess focus have been reported [53]. Among 14 patients with XLH age 4 to 26 years, 7% had dental abscesses, 43% had enlarged pulp chambers, 57% had enamel hypoplasia, and 14% had dentin hypomineralization [54]. Other studies have reported dental abscesses in 25% to 51% of children age 1 to 22 years [49, 55].

Children with XLH may also exhibit cranial abnormalities, such as craniosynostosis, Chiari malformations, and syringomyelia, which may lead to headache, vertigo, and intracranial hypertension [9, 36, 53]. In a retrospective study of 44 children with XLH, 59% had a complete or partial fusion of the sagittal suture and 25% had protrusion of the cerebellar tonsils [56]. Fibroblast growth factor receptor 2 (FGFR2) and FGFR3 overexpression affects both intramembranous and endochondral ossification in the skull, and it has been proposed that cross-binding FGF23 with FGFR2 and FGFR3 at the cranial sutures contributes to craniosynostosis; however, the effect of blocking FGF23 on the skull is unknown [57]. Hearing loss is typically sensorineural or conductive but may occur because of osteosclerosis and thickening of the petrous bone [9, 47, 57-59]. The prevalence of hearing loss varies—16% to 76% depending on age and cohort selection criteria—and it has been reported as early as age 11 years (Fig. 2) [47, 57, 58].

There are unfortunately no published data for mobility, pain, fracture rate, or QoL measures in pediatric patients with XLH compared with age-matched healthy controls. However, a recent survey including 90 pediatric patients found that nearly all the children (80%) reported having experienced bone or joint pain, 38% reported restricted range of motion, and 30% reported muscle weakness [49]. Scores using the Pediatric Outcomes Data Collection Instrument for transfers/basic mobility, sports/physical function, and pain/comfort domains were 1 to 2 SDs below normal scores for the US general population. Health-related QoL, as measured by the SF-10 physical health summary score, was also 1.5 SDs below normal.

Adolescents and Adults

XLH is a lifelong progressive disease, and adults suffer from both the consequences of childhood disease (lower-limb deformities and short stature) as well as ongoing disease manifestations (Fig. 2) [18]. Notably, osteomalacia, which persists into adolescence and adulthood as a result of chronic hypophosphatemia [6, 12, 14], has been associated with bone pain (reported in 45% of patients) and an increased risk of pseudofractures [14, 20, 48]. Pseudofractures (also called Looser zones) are focal regions of lucency extending through the cortices [60]. Radiographically, osteomalacia is identified by pseudofractures, coarsened trabeculation, and rarified areas and/or nonunion fractures (Fig. 4) [20]. Between 45% and 60% of adult XLH patients have fractures or pseudofractures [12-14, 49].

Enthesopathy, or mineralization of tendon or ligament insertion sites, often begins to manifest in the second and third decade. Recent data from preclinical studies suggest that enthesopathy is most likely not due to FGF23, but rather the result of impaired 1,25-dihydroxyvitamin D activity [61-63]. Enthesopathy occurs in 30% to 45% of patients younger than 30 years and 100% of patients older than 30 years; it commonly occurs at the spine, hips, or ankles and contributes to progressive joint pain and stiffness (Figs. 2 and 4). Between 2% and 5% of patients with XLH develop spinal stenosis, which can result in spinal cord compression, and consequently, muscle weakness and pain [11, 12, 14, 18, 64, 65]. Notably, hypermineralization of the spinal ligaments due to enthesopathy can render spine dual-energy x-ray absorptiometry scans invalid (Fig. 4).

Degenerative arthropathy or osteoarthritis occurs in 55% of patients younger than 30 years, likely as a consequence of ongoing weight-bearing on misaligned joints [12, 14, 18], and likely contributes to stiffness and joint pain [47]. In addition, patients with XLH experience decreased range of motion and muscle weakness [18, 47] likely due to muscle phosphate depletion and/or decreased physical activity associated with lower-limb deformity [10, 66]. In a mixed pediatric and adult group (age 6-60 years) of patients with hypophosphatemic rickets, 22 of 34 with confirmed *PHEX* mutations, lower-leg muscle density and function were lower than in healthy controls [10]. In a subgroup of patients with straight legs, although muscle function was decreased compared with controls, it was higher than in patients with extensive leg deformities. The authors concluded that muscle weakness may have been a clinical feature of XLH that was exacerbated by low muscle quality and limb deformities.

In a survey including 232 adults with XLH, 80% reported bone or joint pain and 63% reported muscle pain, with 67% using pain medication at least once per week. Joint stiffness and muscle weakness were reported in 91% and 60% of patients, respectively. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function domain score was notably

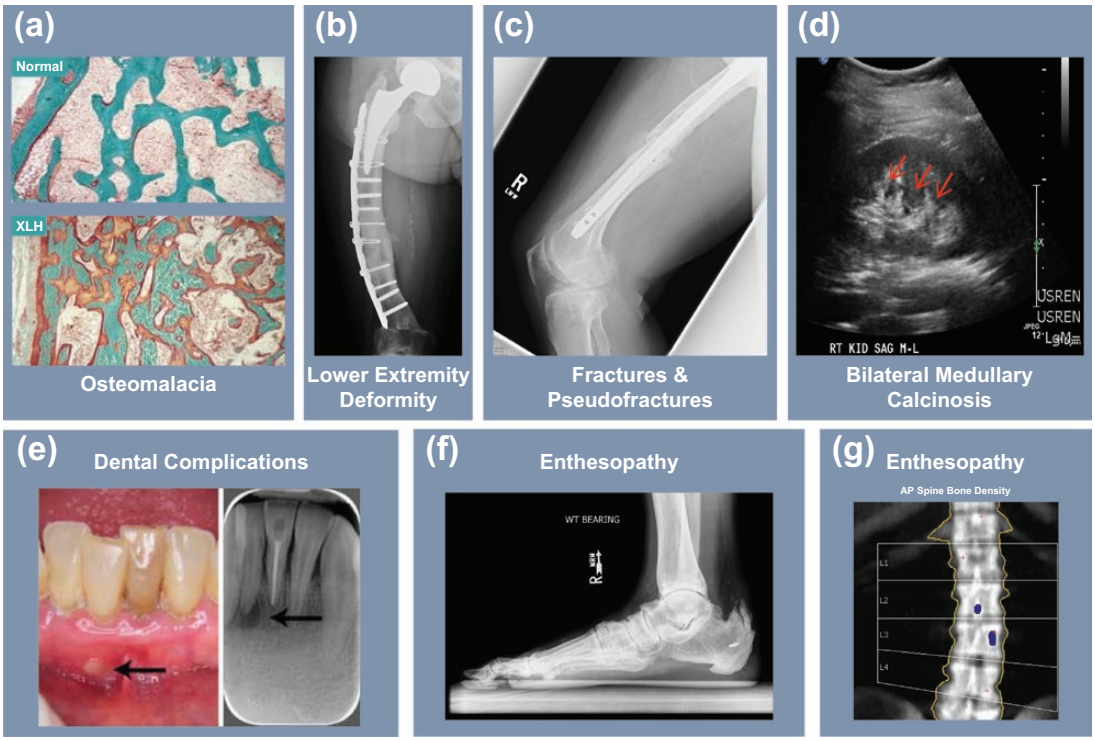

Figure 4. Clinical findings in adult patients with X-linked hypophosphatemia (XLH) [28]. A, Undecalcified Goldner-stained iliac bone samples in a patient with untreated XLH. Mineralized bone is shown in green; unmineralized osteoid is shown in orange. The layer of unmineralized osteoid is thicker and covers a larger percentage of bone surface in XLH compared with a normal control. B, Bipolar hemiarthroplasty of the right hip of a 45-year-old woman with XLH. There is a lytic focus or "brown tumor" in the setting of this patient's known hyperparathyroidism and renal osteodystrophy and a healing pathologic fracture in the midshaft of the femur, which has undergone plate and screw fixation and bone grafting. Background features include bowing of the femoral shaft and diffuse osteosclerosis. C, Osteotomy in a 54-year-old woman with XLH in which the mid shaft of the right femur has been transfixed with an intramedullary rod; note the bowing deformity. D, Renal ultrasound of a 28-year-old woman with XLH showing increased echogenicity of the renal pyramids bilaterally, indicating bilateral medullary calcinosis. E, Intraoral view and x-ray of endodontic infection (arrows) in the intact central right lower incisor in a 35-year-old patient with XLH. F, Right foot and ankle images from a 35-year-old-man with XLH showing large, posterior heterotopic ossification enthesophyte formations post reconstruction. G, Dual-energy x-ray absorptiometry scan of a 49-year-old man with XLH showing increased lumbar spine bone density due to calcifications of spinal ligaments. The bone density of the spine (L1-L4) was 2.748 g/cm^2 with a T score of +12.2 and a *Z* score of +12.4.

worse compared with the population normative score of (40.8 vs 15.4), and the SF-10v2 physical component summary score was reduced to 37.0, at greater than 1 SD below the normal of 50 [49]. In a study by Che et al, age, female sex, musculoskeletal fatigue, and enthesopathies were associated with a reduced QoL defined using a composite score [3]. The observation of worsened QoL in female patients is noteworthy considering the trend toward more significant manifestations in male patients. Despite low levels of depression reported for adults with XLH in existing studies [12, 67], in our experience, depression and anxiety are not uncommon [68].

As in children, adults with XLH often have recurrent dental abscesses, reported in 40% to 55% of patients [11, 18, 47, 52]. Studies in predominately adult XLH cohorts have reported both a sensorineural and conductive hearing loss in 29% to 76% of patients (Figs. 2 and 4) [47, 58].

X-Linked Hypophosphatemia Management and Treatment

The goals of treatment for XLH in children are to normalize hypophosphatemia, and thereby heal rickets and osteomalacia and prevent the outcomes of these abnormalities, such as bowing of the lower extremities and impaired growth. In contrast, the goals of treatment of XLH in adults are normalization of serum phosphorus, healing of

osteomalacia, prevention and/or healing of pseudofractures and nonunion fractures, and relief of bone pain.

Multidisciplinary Evaluation

Following diagnosis of XLH, the patient may benefit from evaluation by a multidisciplinary team potentially consisting of endocrinologists, nephrologists, orthopedic surgeons, rehabilitation physicians, physical therapists, dentists, and primary care providers [32, 53, 69]. Neurologists, neurosurgeons, orthodontists, ophthalmologists, social workers, and/or psychologists may be required based on individual needs. Management of XLH may include pharmacological treatment, orthopedic interventions, physical therapy, dental care, genetic counseling, treatment for hearing loss, and prevention of primary or secondary complications.

Conventional Therapy

Historically, pediatric patients with XLH have been treated with multiple daily doses of phosphate and active vitamin D analogues in an attempt to replete serum phosphorus [2, 28]. In some children with XLH, treatment with phosphate salts or phosphate and/or calcitriol results in improvement of osteomalacia and healing of rickets [28, 70]. Although this management approach aims to counteract the downstream effects of excess FGF23, it may not correct the underlying pathogenesis or normalize fasting serum phosphorus [2, 20, 71, 72]. After oral administration of phosphate, serum levels increase rapidly but return to baseline within 1.5 hours; therefore, phosphate should be administered frequently—potentially as often as 4 to 6 times per day [2, 28, 32].

Early management (ie, beginning when patients are age < 1 year) with conventional therapy can improve rickets and osteomalacia, decrease lower leg deformity, and improve growth [44]. However, persistence of hypophosphatemic rickets and diminished height are common in pediatric patients with XLH despite long-term conventional therapy initiation at a young age [7, 51]. In a retrospective study of 19 patients with well-controlled XLH, among those who began management at age younger than 1 year, height *z* scores at prepuberty (age 9 years) were −1.3 compared with −2.0 among those who initiated management at age 1 year or older [44]. Likewise, rickets severity among patients who began management at age younger than 1 year was +4.0 on a scale of 0 (normal) to 6 (severe) compared with +5.0 in those who initiated management after age 1 year. Even with closely monitored management, 40% of patients with XLH eventually require surgery to correct bone deformities [51].

In adults with XLH, clinical data on the use of conventional therapy are limited, including data on improvement in bone pain and healing of pseudofractures and nonunion fractures. Current recommendations are to consider conventional therapy for symptomatic patients, such as those with spontaneous insufficiency fractures, pending orthopedic procedures, biochemical evidence of osteomalacia, dental issues, or disabling skeletal pain [32]. Although there is no association between conventional therapy and prevention or promotion of enthesopathy, it has been associated with a lower risk for dental disease [73].

Conventional management is associated with adverse events (AEs), including hypercalcemia, hypercalciuria, nephrocalcinosis, and hyperparathyroidism [20, 28, 74]. Rarely, cardiovascular abnormalities and hypertension have been reported and may be secondary to conventional therapy and/or increased renal sodium reabsorption associated with increased FGF23 [57]. Conventional therapy requires frequent monitoring and dose adjustments to balance improvements in bone mineralization with the risk of AEs [2, 32]. Frequent dosing (phosphate is dosed 3 to 5 times per day and activated vitamin D 1-3 times per day), tolerability issues (which, in our experience, include diarrhea, abdominal pain, and bitter taste), and the need for regular monitoring (every 3 to 5 months) may decrease adherence to conventional therapy and lead to reduced therapeutic benefit [2, 9, 20]. Lastly, obtaining insurance coverage may be challenging for conventional therapies not approved by the US Food and Drug Administration for XLH (eg, calcitriol).

Burosumab

Burosumab, a fully human immunoglobulin G1 monoclonal antibody to FGF23, is approved in the United States, Canada, and Brazil for the management of XLH in patients age 6 months or older [75, 76] and in Europe for the management of XLH with radiographic evidence of bone disease in children age 1 year or older and in adolescents with growing skeletons [77].

Pediatric patients. Three clinical studies have investigated burosumab in children with XLH: a phase 2 trial in 52 participants aged 5 to 12 years who received subcutaneous burosumab every 2 weeks (Q2W) or every 4 weeks (Q4W); a phase 2 trial in 13 participants aged 1 to 4 years who received subcutaneous burosumab Q2W; and a phase 3 randomized, open-label trial of burosumab in 61 participants aged 1 to 12 years who received subcutaneous burosumab Q2W or conventional therapy [7, 50, 72].

Despite having received conventional therapy before trial initiation, enrolled participants had persistent rickets, lower-extremity deformities, functional impairment, and short stature at baseline. Many children younger than 4 years also had nephrocalcinosis at baseline (Table 2).

In the phase 2 trial that included participants between age 5 and 12 years, burosumab Q2W led to a sustained normalization of serum phosphorus levels, whereas Q4W dosing resulted in levels below the lower limit of normal between doses [7]. Given this observation and the superior improvements in rickets, Q2W dosing was deemed to be appropriate for children. By week 40, participants in both groups demonstrated improvements in rickets assessed using the Thacher Rickets Severity Score. At week 64, modest healing of rickets was observed using the Radiographic Global Impression of Change global score (RGI-C), as well as sustained increases in serum phosphorus and 1,25-dihydroxyvitamin D levels and a decrease in serum ALP (Table 3). Similar results were observed in another phase 2 study of younger individuals aged 1 to 4 years with XLH, in which all of the 13 children who received burosumab Q2W demonstrated substantial healing of rickets by week 40 [50].

A randomized, open-label, phase 3 study assessed the efficacy and safety of burosumab Q2W vs conventional therapy in children aged 1 to 12 years [72]. Mean phosphorus levels normalized rapidly and remained normal among individuals who received burosumab but remained below normal among those who received conventional therapy. At week 64, serum 1,25-dihydroxyvitamin D levels were increased (but remained within the normal range) and ALP levels decreased among participants who received burosumab compared with conventional therapy. Eighty-seven percent of participants who received burosumab achieved substantial healing of rickets (RGI-C ≥ 2.0) at week 64 vs 19% of those who received conventional therapy (see Table 3). Mean RGI-C lower-limb deformity scores at week 64 were also significantly higher with burosumab compared with conventional therapy (least squares mean [LSM] +1.3 [SE, 0.2] with burosumab vs +0.3 [SE, 0.1] with conventional therapy). At week 64, increases in height *z* score were greater among participants who received burosumab (LSM change, +0.17; SE, 0.7) vs conventional therapy (LSM, +0.02; SE, 0.04). Mobility assessed using the 6-minute walk test in children age 5 years or older was improved among individuals who received burosumab (LSM change, 9%; SE, 2) vs conventional therapy (LSM change, 2%; SE, 3).

In the 3 clinical studies of burosumab in children with XLH, the most frequent treatment-emergent AEs were consistent with common childhood illnesses, underlying disease pathology, and/or injection site reactions related to treatment with a monoclonal antibody (Table 4) [7, 50, 72]. There were no occurrences of hyperphosphatemia. One

Table 2. Participants treatment history, baseline height, and baseline nephrocalcinosis in burosumab trials [7, 13, 50, 72]

	Open-label, phase 2 burosumab Q2W (N = 13)	Open-label, dose-finding phase 2 burosumab Q2W or Q4W (N = 52)	Randomized, double-blind, placebo-controlled phase 3		Randomized, active-controlled, open-label, phase 3 burosumab Q4W (N = 134)
			Conventional therapy (n = 32)	Burosumab Q2W (n = 29)	
Age, y	1-4	5-12	1-12		≤ 18
Treatment history					
Conventional therapy, n (%)	13 (100)	50 (96)	32 (100)	29 (100)	181 (98)
Mean (SD) duration of conventional therapy, y	1.3 (1.2)	6.9 (2.4)	4.3 (3.0)	3.3 (3.1)	16.5 (10.4)[a] 18.2 (11.0)[b]
Mean (SD) age when conventional therapy was initiated, y	1.7 (1.5)	2.1 (91.3)	NR	NR	10.9 (81)[c]
Baseline height					
Mean (SD) *z* score	–1.4 (1.2)	–1.9 (1.0)	–2.1 (0.9)	–2.3 (1.2)	–2.3 (1.3)
Mean (SD) percentile for age and sex	18 (25)	8.7 (11.5)	NR	NR	6.8 (12.5)
Baseline nephrocalcinosis					
Grade > 0,[d] n (%)	0	18 (34)	9 (28)	5 (17)	73 (55)

Abbreviations: NR, not reported; Q2W, every 2 weeks; Q4W, every 4 weeks.
[a]Among individuals with any prior use of phosphate.
[b]Among individuals with any prior use of vitamin D metabolites or analogs.
[c]n (percentage, %) of individuals who received conventional therapy before age 18 years.
[d]Values range from 0 (normal) to 4 (stone formation).

Table 3. Effect of burosumab on select laboratory values and Rickets Severity Score in pediatric clinical trials [7, 50, 72]

	Open-label, phase 2 burosumab Q2W (N = 13)	Open-label, dose-finding phase 2 (N = 52)	Randomized, double-blind, placebo-controlled phase 3	
			Conventional therapy (n = 32)	Burosumab Q2W (n = 29)
Mean (SE) change from baseline in fasting serum phosphorus, mg/dL	0.89 (0.11) (week 40)	0.84 (NR) (week 64)	0.21 (0.06) (week 64)	0.91 (0.08) (week 64)
Mean (SE) change from baseline in $1,25(OH)_2D$, pg/mL	12 (3) (week 40)	18 (NR) (week 64)	1 (3) (week 64)	10 (2) (week 64)
Mean (SE) change from baseline in ALP	–213 U/L (14) (week 40)	–90 U/L (NR) (week 64)	–33% (13[a]) (week 64)	–5% (21[a]) (week 64)
Least squares mean (SE) change from baseline in total RSS	–2.0 (0.1[a]) (week 64)	–0.92 (0.7) (week 64)	–1.0 (0.2) (week 64)	–2.2 (0.1) (week 64)
Patients with substantial healing of rickets (RGI-C ≥ 2.0), %	100 (week 40)	54 (week 64)	19 (week 64)	87 (week 64)

Abbreviations: $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; ALP, alkaline phosphatase; NR, not reported; Q2W, every 2 weeks; RGI-C, radiographic global impression of change; RSS, Rickets Severity Score.
[a]SD reported.

participant had serious AEs (fever and myalgia) assessed as possibly related to burosumab. Four participants had serious AEs (tooth abscess, craniosynostosis, viral infection, and migraine) considered not related to burosumab. No patients discontinued treatment, resulting in a 100% participant continuation rate that was maintained through the extension studies.

Adult patients. A randomized, double-blind, phase 3 study investigated subcutaneous burosumab vs placebo Q4W for 24 weeks in 134 adults with XLH, nearly all (98%) of whom had previously received conventional therapy (81% before age 18 years) [13]. The overall group sex-specific percentile for height was 6.8% ± 12.5% (see Table 2). Although most participants had received prior conventional therapy, most had osteoarthritis, previous surgery, or enthesopathy at baseline (Fig. 5). Radiographic skeletal surveys revealed a large number of active fractures (including fractures and pseudofractures) at baseline (Table 5) [13].

Among adults who received burosumab, 94% achieved a mean serum phosphorus concentration above the lower limit of normal averaged across the midpoints between monthly doses compared with 7.6% of participants who received placebo [13]. Furthermore, renal tubular phosphate reabsorption increased among individuals who received burosumab compared with placebo, and serum 1,25-dihydroxyvitamin D levels remained normal. Therapy with burosumab led to significant decreases in stiffness using the WOMAC stiffness subscale and was associated with greater fracture healing compared with placebo (see Table 5). The odds of complete fracture healing at week 24 were 17-fold greater among participants who received burosumab group compared with placebo. Bone pain and physical function appeared to improve with burosumab compared with placebo but the reductions did not reach statistical significance. In our experience, patients reported increased activity and sense of well-being, with no patients wishing to stop therapy.

During the study, most AEs were mild or moderate and there were no discontinuations due to AEs in either treatment group; the most frequently occurring AEs were similar to those in the pediatric studies (Table 6) [13]. AEs of interest with a difference between treatment groups (burosumab vs placebo) were hyperphosphatemia (6% vs 0%) and restless legs syndrome (12% vs 8%). AEs of interest with similar incidences between treatment groups were injection site reaction, hypersensitivity, and ectopic mineralization. In total, 2 patients had serious AEs, neither of which were considered to be related to the study treatment. Postbaseline antidrug antibodies were not detected.

Given the potential abnormalities in bone secondary to *PHEX* mutations that influence bone mineralization and are

Table 4. Summary of common (occurring in ≥ 20% of participants) treatment-emergent adverse events in pediatric clinical trials of burosumab [7, 50, 72]

Open-label, phase 2 burosumab Q2W (N = 13)	n (%)	Open-label, dose-finding phase 2 (N = 52)	n (%)	Randomized, double-blind, placebo-controlled phase 3	Conventional therapy (n = 32) n (%)	Burosumab Q2W (n = 29) n, (%)
Cough	11 (85)	Injection site reaction	30 (58)	Pyrexia	6 (19)	16 (55)
Pyrexia	9 (69)	Headache	26 (50)	Cough	6 (19)	15 (52)
Upper respiratory tract infection	9 (69)	Cough	23 (44)	Arthralgia	10 (31)	13 (45)
Tooth abscess	7 (54)	Nasopharyngitis	21 (40)	Vomiting	8 (25)	12 (41)
Rhinorrhea	6 (46)	Pain in extremity	21 (40)	Nasopharyngitis	14 (44)	11 (38)
Vomiting	6 (46)	Upper respiratory tract infection	18 (35)	Pain in extremity	10 (31)	11 (38)
Nasal congestion	5 (38)	Vomiting	18 (35)	Headache	6 (19)	10 (34)
Diarrhea	4 (31)	Arthralgia	17 (33)	Injection site erythema	0	9 (31)
Pain in extremity	4 (31)	Pyrexia	16 (31)	Dental caries	2 (6)	9 (31)
Streptococcal pharyngitis	4 (31)	Rash	13 (25)	Tooth abscess	3 (9)	8 (28)
Arthralgia	3 (23)	Seasonal allergy	13 (25)	Injection site reaction	0	7 (24)
Arthropod bite	3 (23)			Rhinorrhea	2 (6)	7 (24)
Nasopharyngitis	3 (23)			Diarrhea	2 (6)	7 (24)
Oral pain	3 (23)			Vitamin D decrease	1 (3)	6 (21)
Skin abrasion	3 (23)					

Abbreviation: Q2W, every 2 weeks.

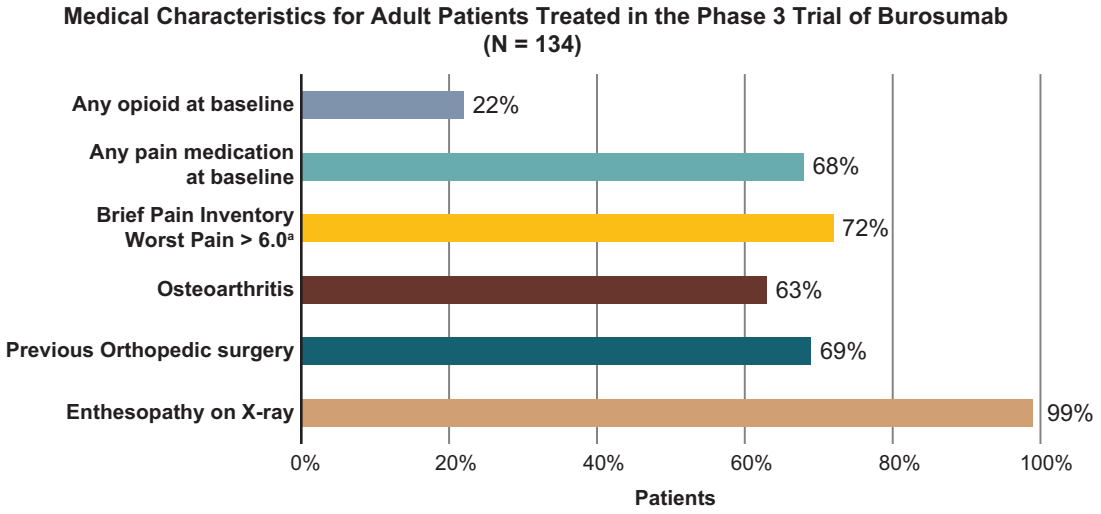

Figure 5. Baseline clinical characteristics of adult patients with X-linked hypophosphatemia (XLH) treated in a randomized, active-controlled, open-label, phase 3 study of burosumab. Although the majority of patients in the study received prior conventional therapy, most had pain, osteoarthritis, previous surgery, or enthesopathy at baseline (13). [a]Brief Pain Inventory worst pain score for the 7 days preceding the baseline visit.

independent of FGF23 and phosphorus [31], burosumab may be partially inadequate to address factors independent of FGF23 and phosphorus. In an open-label, phase 3 study in 14 adults who had not received conventional therapy within 2 years of enrollment and had extensive osteomalacia, all osteomalacia-related histomorphometric measures had improved significantly after 48 weeks of treatment with burosumab, and 3 of 4 active pseudofractures detected at baseline were healed, including 2 that healed completely and 1 that partially healed [78]. Therapy with burosumab was also associated with significant improvements in patient-reported pain and fatigue. Longitudinal follow-up is required to determine whether osteomalacia persists because of an inability to normalize mineralization dynamics or if healing of osteomalacia occurs and is a time-dependent variable.

Managing Today's Patients

Updated recommendations for the management of patients with XLH were published in 2019 [32]. Notably, these new

Table 5. Fracture healing in phase 3 trial of burosumab in adults [13, 79])

	Placebo (n = 66)	Burosumab (n = 68)
Baseline		
Participants with fractures, n (%)	38 (58)	32 (47)
Fractures, n	91	65
Fractures healed, n (%)		
Week 12	7 (8)	13 (20)
Week 24	7 (8)	28 (43)
Week 48	32 (35)[a]	41 (63)

[a]Switched to burosumab at week 24.

Table 6. Summary of common (occurring in ≥ 10% of participants) treatment-emergent adverse events in a phase 3 study of burosumab in adults with X-linked hypophosphatemia [13]

Treatment-emergent AEs, n (5)	Placebo Q4W (n = 66)	Burosumab Q4W (n = 68)
Back pain	6 (9)	10 (15)
Nasopharyngitis	6 (9)	9 (13)
Tooth abscess	5 (8)	9 (13)
Headache	5 (8)	8 (12)
Nausea	6 (9)	7 (10)
Dizziness	4 (6)	7 (10)
Arthralgia	16 (24)	6 (9)
Pain in extremity	10 (15)	5 (8)
Oropharyngeal pain	7 (11)	1 (2)

Abbreviations: AE, adverse events; Q4W, every 4 weeks.

guidelines were issued before the publication of the phase 3 study assessing the efficacy and safety of burosumab vs conventional therapy in pediatric patients with XLH. Our review of the guidelines for monitoring patients does not include detailed treatment recommendations.

Among the updated recommendations, the guidelines for monitoring treated and untreated patients with XLH include selected laboratory and anthropometric evaluations at least every 3 months during times of rapid growth (before age 5 years and during puberty), with continued evaluation every 3 to 6 months throughout the remainder of childhood and every 6 to 12 months during adulthood (Table 7) [32]. Notably, assessing fasting serum phosphorus levels is recommended only in patients receiving burosumab (see Table 7). Furthermore, PTH levels should be monitored given the possibility of secondary hyperparathyroidism with oral phosphate use. Normalization of serum phosphorus levels may not be necessary but targeting phosphorus levels in the low end of the normal range is ideal. Given the mechanism of action of burosumab, it is unlikely that treatment of XLH will result in hypercalciuria; however, there is currently an absence of long-term clinical data. Consequently, additional recommendations include urine creatinine:calcium ratio and renal ultrasonography in patients who receive burosumab or conventional therapy (see Table 7) [32]. As long-term data on the use of burosumab in XLH become available, monitoring urine creatinine:calcium ratio may no longer be necessary for patients receiving this treatment regimen.

Regardless of treatment, the guidelines recommend left-wrist and/or lower-limb radiographs only in pediatric patients who have one or more of persistent leg bowing, indication for surgery, localized persistent pain, or short stature [32]. However, we recommend more frequent radiographic evaluation in children, particularly when rachitic findings are noted at therapy initiation. Evaluations should include repeat knee and/or wrist radiographs at diagnosis and approximately 6 months after therapy initiation and every 1 to 2 years throughout growth. In adults, we recommend hip and femur films at baseline to evaluate for subtrochanteric or femur fractures and to monitor fracture healing; these should be repeated as clinically indicated every 1 to 2 years after therapy commences or with increased pain (see Table 7). In adult patients, we also recommend considering bone densitometry at the hips and spine to evaluate enthesopathy; however, observations should be interpreted with caution because of possible spine artifact.

We agree with the recommendations for twice-annual measurement of blood pressure, twice annual dental evaluation, and hearing screens as clinically indicated [32]. In addition, consultation with a genetic counselor can be beneficial for patients at diagnosis and whenever questions arise (eg, family planning counseling). Creation of a genetic pedigree may be helpful for multiple family members.

The guidelines recommend annual 6-minute walk tests (6MWTs) in patients older than 5 years, as well as administration of age- and disease-appropriate QoL assessments every 2 years [32]. However, we prefer an annual evaluation by an experienced physical therapist and ongoing treatment as needed. The 6MWT in patients older than 5 years and timed up and go test in patients age 18 years or older have predominantly been used to quantify musculoskeletal deficiencies but may be considered in regular practice. Baseline gait videos can also be useful in assessing functional impairment. Every 1 to 2 years, we recommend annual, age-appropriate QoL measures, pain measures, and depression screening and prefer the SF-10, PROMIS Pediatric Self- and Proxy-Reported Health Measures, and Patient Health Questionnaire–9 depression module in pediatric patients and the PROMIS and WOMAC in adults. Because patients may have functional deficiencies and chronic pain that can be a burden on caregivers and other family members, caregiver burden should also be assessed through careful questioning, particularly for affected parents caring for affected children.

Table 7. Recommended evaluations for patients with X-linked hypophosphatemia[a]

Evaluation	Frequency			
	Every 1-3 mo	**Every 3-6 mo**	**Every 6-12 mo**	**Other or as indicated**
Laboratory values				
Serum calcium, iPTH, creatinine, ALP, fasting serum phosphorus	Age < 5 y	Age 5-18 y	Adults	
Urine creatinine:calcium		All patients on any treatment		
25 OH vitamin D			Annually (all patients)	
Anthropometric evaluations				
Height, weight, intermalleolar distance, and intercondylar distance		Age 5-18 y	Adults	Every 1-3 mo (age < 5 y)
Radiologic assessments				
X-rays of lower extremities and wrists to assess extent of skeletal disease				6 mo after therapy initiation; otherwise, every 1-2 y (pediatric)
Bone age measurement to evaluate growth potential				Every 1-2 y (pediatric with short stature)
X-rays of lower limbs to assess for fractures, pseudofractures, or enthesopathy[b]				At baseline and as clinically needed (adolescent and adult)
Other				
Blood pressure			Every 6 mo (all patients)	
Renal ultrasonography				Every 1-2 y (treated patients)
Orthopedic				Annually (symptomatic patients)
Craniofacial examination for signs of craniosynostosis			Annually (age < 5 y)	
Chiari malformation				Patients with clinical symptoms (eg, headache or vertigo)
Neurologic				Patients with clinical symptoms (eg, headache or papilledema)
Dental			Every 6 mo (all patients)	
Hearing				As needed (age > 8 y)
Physical therapy			Annually	
Quality of life			Every 1-2 y	
Clinical genetics and/or genetics counseling				At diagnosis, during transition to adult care, and during family planning

Abbreviations: ALP, alkaline phosphatase; iPTH, intact parathyroid hormone.
[a]Some recommendations are reflected in Haffner et al [32], whereas others are solely the recommendations of the authors of this review.

Transitioning Care From Pediatric to Adult Medical Providers

Although XLH is a lifelong, progressive disease, historically many patients have not received medical care as they progressed through adolescence and into adulthood, likely at least in part because of a lack of sufficient treatment options. Transition of care from pediatric to adult providers is an essential step for patients with XLH, and transition programs should be developed by individual institutions to enable and enhance the transition process. Patients require education about their disease, including the need for optimizing musculoskeletal health, promoting and maintaining

peak bone mass, prevention of fractures, adequate physical activity, dental hygiene, and nutrition. Young adults affected by XLH should be given the opportunity to meet with a genetic counselor before family planning. In our experience, close collaboration between pediatric and adult medical providers is beneficial.

Remaining Questions in the Field

Though our understanding of the pathophysiology of XLH has progressed substantially and has recently led to expanded treatment options, unanswered questions remain. The pathophysiology of enthesopathy is not understood, nor is it known whether there is a possibility of prevention or reversal. The development of nephrocalcinosis and secondary hyperparathyroidism, as well as dental manifestations and hearing loss, are relatively common consequences of XLH and/or its management and should be monitored closely. Further evaluation of burosumab therapy during infancy and adolescence needs to occur. The longer-term effects of burosumab treatment on final height, lower-limb deformities (and effect on need for surgical intervention), fracture prevention, craniosynostosis, dental abnormalities, pain, mobility, QoL, and disability are not yet known. It is essential to follow patients of all ages prospectively to help to determine these potential affected outcomes. A global, multicenter, long-term follow-up study of patients with XLH in a disease-monitoring program (ClinicalTrials.gov, NCT03651505) independent of their treatment status aims to answer some of these questions and can support the continued development of appropriate patient-management guidelines. The study will assess the long-term safety and efficacy of burosumab in children and adults with XLH and will characterize the longitudinal changes over time in biomarkers, clinical assessments, and patient- and caregiver-reported outcomes. Long-term safety evaluations in adults and children with XLH will include overall renal health, the presence and/or progression of nephrocalcinosis and spinal stenosis, and pregnancy outcomes. Furthermore, patient and disease data will be collected in patients regardless of burosumab treatment status.

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Data Availability: The study protocol and statistical analysis plan for the studies mentioned in this review will be available per regulatory requirement on the clinical trial registry website ClinicalTrials.gov with the tabulated results. More details about the Ultragenyx Pharmaceutical Inc data sharing commitment are available at https://www.ultragenyx.com/pipeline/clinical-trial-transparency.

References

1. Beck-Nielsen SS, Brock-Jacobsen B, Gram J, Brixen K, Jensen TK. Incidence and prevalence of nutritional and hereditary rickets in southern Denmark. *Eur J Endocrinol.* 2009;**160**(3):491-497.
2. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res.* 2011;**26**(7):1381-1388.
3. Che H, Roux C, Etcheto A, et al. Impaired quality of life in adults with X-linked hypophosphatemia and skeletal symptoms. *Eur J Endocrinol.* 2016;**174**(3):325-333.
4. Martin A, Quarles LD. Evidence for FGF23 involvement in a bone-kidney axis regulating bone mineralization and systemic phosphate and vitamin D homeostasis. *Adv Exp Med Biol.* 2012;**728**:65-83.
5. Imel EA, Biggin A, Schindeler A, Munns CF. FGF23, hypophosphatemia, and emerging treatments. *JBMR Plus.* 2019;**3**(8):e10190.
6. Shore RM, Chesney RW. Rickets: part I. *Pediatr Radiol.* 2013;**43**(2):140-151.
7. Carpenter TO, Whyte MP, Imel EA, et al. Burosumab therapy in children with X-linked hypophosphatemia. *N Engl J Med.* 2018;**378**(21):1987-1998.
8. Pettifor JM. What's new in hypophosphataemic rickets? *Eur J Pediatr.* 2008;**167**(5):493-499.
9. Ruppe MD. X-linked hypophosphatemia. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*. Seattle, WA: University of Washington; 1993:1-22.
10. Veilleux LN, Cheung M, Ben Amor M, Rauch F. Abnormalities in muscle density and muscle function in hypophosphatemic rickets. *J Clin Endocrinol Metab.* 2012;**97**(8):E1492-E1498.
11. Chesher D, Oddy M, Darbar U, et al. Outcome of adult patients with X-linked hypophosphatemia caused by *PHEX* gene mutations. *J Inherit Metab Dis.* 2018;**41**(5):865-876.
12. Hardy DC, Murphy WA, Siegel BA, Reid IR, Whyte MP. X-linked hypophosphatemia in adults: prevalence of skeletal radiographic and scintigraphic features. *Radiology.* 1989;**171**(2):403-414.

13. Insogna KL, Briot K, Imel EA, et al; AXLES 1 Investigators. A randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of burosumab, an anti-FGF23 antibody, in adults with X-linked hypophosphatemia: week 24 primary analysis. *J Bone Miner Res*. 2018;**33**(8):1383-1393.
14. Reid IR, Hardy DC, Murphy WA, Teitelbaum SL, Bergfeld MA, Whyte MP. X-linked hypophosphatemia: a clinical, biochemical, and histopathologic assessment of morbidity in adults. *Medicine (Baltimore)*. 1989;**68**(6):336-352.
15. Endo I, Fukumoto S, Ozono K, et al. Nationwide survey of fibroblast growth factor 23 (FGF23)-related hypophosphatemic diseases in Japan: prevalence, biochemical data and treatment. *Endocr J*. 2015;**62**(9):811-816.
16. Burnett CH, Dent CE, Harper C, Warland BJ. Vitamin D-resistant rickets: analysis of twenty-four pedigrees with hereditary and sporadic cases. *Am J Med*. 1964;**36**(2):222-232.
17. Rafaelsen S, Johansson S, Ræder H, Bjerknes R. Hereditary hypophosphatemia in Norway: a retrospective population-based study of genotypes, phenotypes, and treatment complications. *Eur J Endocrinol*. 2016;**174**(2):125-136.
18. Beck-Nielsen SS, Brusgaard K, Rasmussen LM, et al. Phenotype presentation of hypophosphatemic rickets in adults. *Calcif Tissue Int*. 2010;**87**(2):108-119.
19. Mumm S, Huskey M, Cajic A, et al. *PHEX* 3′-UTR c.*231A > G near the polyadenylation signal is a relatively common, mild, American mutation that masquerades as sporadic or X-linked recessive hypophosphatemic rickets. *J Bone Miner Res*. 2015;**30**(1):137-143.
20. Carpenter TO. Primary disorders of phosphate metabolism. In: Feingold KR, Anawalt B, Boyce A, et al, eds. *Endotext*. South Dartmouth, MA: MDText.com Inc; 2000.
21. Lang F, Leibrock C, Pandyra AA, Stournaras C, Wagner CA, Föller M. Phosphate homeostasis, inflammation and the regulation of FGF-23. *Kidney Blood Press Res*. 2018;**43**(6):1742-1748.
22. Riminucci M, Collins MT, Fedarko NS, et al. FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting. *J Clin Invest*. 2003;**112**(5):683-692.
23. Gattineni J, Bates C, Twombley K, et al. FGF23 decreases renal NaPi-2a and NaPi-2c expression and induces hypophosphatemia in vivo predominantly via FGF receptor 1. *Am J Physiol Renal Physiol*. 2009;**297**(2):F282-F291.
24. Schiavi SC. Fibroblast growth factor 23: the making of a hormone. *Kidney Int*. 2006;**69**(3):425-427.
25. Fukumoto S, Ozono K, Michigami T, et al. Pathogenesis and diagnostic criteria for rickets and osteomalacia—proposal by an expert panel supported by the Ministry of Health, Labour and Welfare, Japan, the Japanese Society for Bone and Mineral Research, and the Japan Endocrine Society. *J Bone Miner Metab*. 2015;**33**(5):467-473.
26. Ichikawa S, Austin AM, Gray AK, Econs MJ. A *Phex* mutation in a murine model of X-linked hypophosphatemia alters phosphate responsiveness of bone cells. *J Bone Miner Res*. 2012;**27**(2):453-460.
27. Goretti Penido M, Alon US. Phosphate homeostasis and its role in bone health. *Pediatr Nephrol*. 2012;**27**(11):2039-2048.
28. Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect*. 2014;**3**(1):R13-R30.
29. Tiosano D, Hochberg Z. Hypophosphatemia: the common denominator of all rickets. *J Bone Miner Metab*. 2009;**27**(4):392-401.
30. Marcucci G, Masi L, Ferrarì S, et al. Phosphate wasting disorders in adults. *Osteoporos Int*. 2018;**29**(11):2369-2387.
31. Feng JQ, Clinkenbeard EL, Yuan B, White KE, Drezner MK. Osteocyte regulation of phosphate homeostasis and bone mineralization underlies the pathophysiology of the heritable disorders of rickets and osteomalacia. *Bone*. 2013;**54**(2):213-221.
32. Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat Rev Nephrol*. 2019;**15**(7):435-455.
33. Levine BS, Kleeman CR, Felsenfeld AJ. The journey from vitamin D-resistant rickets to the regulation of renal phosphate transport. *Clin J Am Soc Nephrol*. 2009;**4**(11):1866-1877.
34. Santos F, Fuente R, Mejia N, Mantecon L, Gil-Peña H, Ordoñez FA. Hypophosphatemia and growth. *Pediatr Nephrol*. 2013;**28**(4):595-603.
35. Krabbe S, Transbøl I, Christiansen C. Bone mineral homeostasis, bone growth, and mineralisation during years of pubertal growth: a unifying concept. *Arch Dis Child*. 1982;**57**(5):359-363.
36. Carpenter TO. New perspectives on the biology and treatment of X-linked hypophosphatemic rickets. *Pediatr Clin North Am*. 1997;**44**(2):443-466.
37. Beck-Nielsen SS, Brixen K, Gram J, Brusgaard K. Mutational analysis of PHEX, FGF23, DMP1, SLC34A3 and CLCN5 in patients with hypophosphatemic rickets. *J Hum Genet*. 2012;**57**(7):453-458.
38. Gaucher C, Walrant-Debray O, Nguyen TM, Esterle L, Garabédian M, Jehan F. *PHEX* analysis in 118 pedigrees reveals new genetic clues in hypophosphatemic rickets. *Hum Genet*. 2009;**125**(4):401-411.
39. Whyte MP, Schranck FW, Armamento-Villareal R. X-linked hypophosphatemia: a search for gender, race, anticipation, or parent of origin effects on disease expression in children. *J Clin Endocrinol Metab*. 1996;**81**(11):4075-4080.
40. Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. *Am J Med*. 2005;**118**(10):1094-1101.
41. Mateo L, Holgado S, Mariñoso ML, et al. Hypophosphatemic osteomalacia induced by tenofovir in HIV-infected patients. *Clin Rheumatol*. 2016;**35**(5):1271-1279.
42. Shimizu Y, Tada Y, Yamauchi M, et al. Hypophosphatemia induced by intravenous administration of saccharated ferric oxide: another form of FGF23-related hypophosphatemia. *Bone*. 2009;**45**(4):814-816.
43. Chaussain-Miller C, Sinding C, Wolikow M, Lasfargues JJ, Godeau G, Garabédian M. Dental abnormalities in patients with familial hypophosphatemic vitamin D-resistant rickets: prevention by early treatment with 1-hydroxyvitamin D. *J Pediatr*. 2003;**142**(3):324-331.
44. Mäkitie O, Doria A, Kooh SW, Cole WG, Daneman A, Sochett E. Early treatment improves growth and biochemical and radiographic outcome in X-linked hypophosphatemic rickets. *J Clin Endocrinol Metab*. 2003;**88**(8):3591-3597.
45. Rasmussen H, Pechet M, Anast C, Mazur A, Gertner J, Broadus AE. Long-term treatment of familial hypophosphatemic

rickets with oral phosphate and 1α-hydroxyvitamin D_3. *J Pediatr.* 1981;**99**(1):16-25.
46. Econs MJ, Feussner JR, Samsa GP, et al. X-linked hypophosphatemic rickets without "rickets". *Skeletal Radiol.* 1991;**20**(2):109-114.
47. Econs MJ, Samsa GP, Monger M, Drezner MK, Feussner JR. X-linked hypophosphatemic rickets: a disease often unknown to affected patients. *Bone Miner.* 1994;**24**(1):17-24.
48. LE B-N, Jung H-Y, Chang H-S, Hwang Y-C, Oh W-M. Dental management of patients with X-linked hypophosphatemia. *Restor Dent Endod.* 2017;**42**(2):146-151.
49. Skrinar A, Dvorak-Ewell M, Evins A, et al. The lifelong impact of X-linked hypophosphatemia: results from a burden of disease survey. *J Endocr Soc.* 2019;**3**(7):1321-1334.
50. Whyte MP, Carpenter TO, Gottesman GS, et al. Efficacy and safety of burosumab in children aged 1-4 years with X-linked hypophosphataemia: a multicentre, open-label, phase 2 trial. *Lancet Diabetes Endocrinol.* 2019;**7**(3):189-199.
51. Nielsen LH, Rahbek ET, Beck-Nielsen SS, Christesen HT. Treatment of hypophosphataemic rickets in children remains a challenge. *Dan Med J.* 2014;**61**(7):A4874.
52. Foster BL, Ramnitz MS, Gafni RI, et al. Rare bone diseases and their dental, oral, and craniofacial manifestations. *J Dent Res.* 2014;**93**(Suppl 7):7S-19S.
53. Lambert AS, Zhukouskaya V, Rothenbuhler A, Linglart A. X-linked hypophosphatemia: management and treatment prospects. *Joint Bone Spine.* 2019;**86**(6):731-738.
54. Souza MA, Soares Junior LA, Santos MA, Vaisbich MH. Dental abnormalities and oral health in patients with hypophosphatemic rickets. *Clinics (São Paulo, Brazil).* 2010;**65**(10):1023-1026.
55. McWhorter AG, Seale NS. Prevalence of dental abscess in a population of children with vitamin D-resistant rickets. *Pediatr Dent.* 1991;**13**(2):91-96.
56. Rothenbuhler A, Fadel N, Debza Y, et al. High incidence of cranial synostosis and Chiari I malformation in children with X-linked hypophosphatemic rickets (XLHR). *J Bone Miner Res.* 2019;**34**(3):490-496.
57. Beck-Nielsen SS, Mughal Z, Haffner D, et al. FGF23 and its role in X-linked hypophosphatemia-related morbidity. *Orphanet J Rare Dis.* 2019;**14**(1):58.
58. Davies M, Kane R, Valentine J. Impaired hearing in X-linked hypophosphataemic (vitamin-D-resistant) osteomalacia. *Ann Intern Med.* 1984;**100**(2):230-232.
59. O'Malley SP, Adams JE, Davies M, Ramsden RT. The petrous temporal bone and deafness in X-linked hypophosphataemic osteomalacia. *Clin Radiol.* 1988;**39**(5):528-530.
60. Shore RM, Chesney RW. Rickets: part II. *Pediatr Radiol.* 2013;**43**(2):152-172.
61. Liang G, Katz LD, Insogna KL, Carpenter TO, Macica CM. Survey of the enthesopathy of X-linked hypophosphatemia and its characterization in *Hyp* mice. *Calcif Tissue Int.* 2009;**85**(3):235-246.
62. Liu ES, Martins JS, Raimann A, et al. 1,25-Dihydroxyvitamin D alone improves skeletal growth, microarchitecture, and strength in a murine model of XLH, despite enhanced FGF23 expression. *J Bone Miner Res.* 2016;**31**(5):1-10.
63. Liu ES, Martins JS, Zhang W, Demay MB. Molecular analysis of enthesopathy in a mouse model of hypophosphatemic rickets. *Development.* 2018;**145**(15):235-246.
64. Forrest G, German J, Giuffrida A, Luidens M, Dowling J. Hereditary X-linked hypophosphatemia and thoracic myelopathy. *AACE Clin Case Rep.* 2016;**2**(3):e244-e246.
65. Polisson RP, Martinez S, Khoury M, et al. Calcification of entheses associated with X-linked hypophosphatemic osteomalacia. *N Engl J Med.* 1985;**313**(1):1-6.
66. Pesta DH, Tsirigotis DN, Befroy DE, et al. Hypophosphatemia promotes lower rates of muscle ATP synthesis. *FASEB J.* 2016;**30**(10):3378-3387.
67. Forestier-Zhang L, Watts L, Turner A, et al. Health-related quality of life and a cost-utility simulation of adults in the UK with osteogenesis imperfecta, X-linked hypophosphatemia and fibrous dysplasia. *Orphanet J Rare Dis.* 2016;**11**(1):160.
68. Ferizović N, Marshall J, Williams AE, et al. Exploring the burden of X-linked hypophosphataemia: an opportunistic qualitative study of patient statements generated during a technology appraisal. *Adv Ther.* 2020;**37**(2):770-784.
69. National Organization for Rare Disorders. National Organization for Rare Disorders: Rare Disease Database—familial hypophosphatemia. Danbury, CT: National Organization for Rare Disorders; 2019.
70. Glorieux FH. Calcitriol treatment in vitamin D-dependent and vitamin D-resistant rickets. *Metabolism.* 1990;**39**(4 Suppl 1):10-12.
71. Imel EA, DiMeglio LA, Hui SL, Carpenter TO, Econs MJ. Treatment of X-linked hypophosphatemia with calcitriol and phosphate increases circulating fibroblast growth factor 23 concentrations. *J Clin Endocrinol Metab.* 2010;**95**(4):1846-1850.
72. Imel EA, Glorieux FH, Whyte MP, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. *Lancet.* 2019;**393**(10189):2416-2427.
73. Connor J, Olear EA, Insogna KL, et al. Conventional therapy in adults with X-linked hypophosphatemia: effects on enthesopathy and dental disease. *J Clin Endocrinol Metab.* 2015;**100**(10):3625-3632.
74. Schaefer M, Capuron L, Friebe A, et al. Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. *J Hepatol.* 2012;**57**(6):1379-1390.
75. CRYSVITA (burosumab-twza) [Full Prescribing Information]. Novato, CA: Ultragenyx Pharmaceutical Inc; 2019.
76. Ultragenyx Pharmaceutical Inc. Ultragenyx announces approval of Crysvita (burosumab) in Brazil for the treatment of X-linked hypophosphatemia (XLH) in adults and children. Novarto, CA: Ultragenyx Pharmaceutical Inc; 2019.
77. European Medicines Agency. Crysvita European Public Assessment Report, Summary of Product Characteristics; Amsterdamn, The Netherlands: European Medicines Agency; 2018.
78. Insogna KL, Rauch F, Kamenický P, et al. Burosumab improved histomorphometric measures of osteomalacia in adults with X-linked hypophosphatemia: a phase 3, single-arm, international trial. *J Bone Miner Res.* 2019;**34**(12):2183-2191.
79. Portale AA, Carpenter TO, Brandi ML, et al. Continued beneficial effects of burosumab in adults with X-linked hypophosphatemia: results from a 24-week treatment continuation period after a 24-week double-blind placebo-controlled period. *Calcif Tissue Int.* 2019;**105**(3):271-284.