



Review

Complications and Treatments in Adult X-Linked Hypophosphatemia

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Abstract: X-linked hypophosphatemia (XLH) is a rare inherited disorder involving elevated levels of fibroblast growth factor (FGF) 23, and is caused by loss-of-function mutations in the *PHEX* gene. FGF23 induces renal phosphate wasting and suppresses the activation of vitamin D, resulting in defective bone mineralization and rachitic changes in the growth plate and osteomalacia. Conventional treatment with combinations of oral inorganic phosphate and active vitamin D analogs enhances bone calcification, but the efficacy of conventional treatment is insufficient for adult XLH patients to achieve an acceptable quality of life. Burosumab, a fully human monoclonal anti-FGF23 antibody, binds and inhibits FGF23, correcting hypophosphatemia and hypovitaminosis D. This review describes a typical adult with XLH and summarizes the results of clinical trials of burosumab in adults with XLH.

Keywords: burosumab; FGF23; hypophosphatemic rickets; XLH



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1. Introduction

X-linked hypophosphatemia (XLH) is caused by loss-of-function mutations in the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (*PHEX*) [1]. XLH was first described in 1937 as a type of rickets resistant to physiologic doses of natural vitamin D [2]. XLH is the most frequent cause of inherited hypophosphatemic rickets, with an incidence of 3.9 per 100,000 live births and a prevalence of 4.8 per 100,000 persons [3–5].

Fibroblast growth factor 23 (FGF23) is an osteocyte-derived hormone that regulates phosphate and vitamin D homeostasis. Elevated circulating FGF23 causes renal phosphate wasting and suppresses the production of activated vitamin D, resulting in hypophosphatemia and impaired bone mineralization [6–10]. Physiologically, FGF23 is important in calcium-phosphate homeostasis, as well as in regulating parathyroid hormone (PTH) and dihydroxy vitamin D levels [11]. Mutations in *PHEX* enhance circulating FGF23 levels, resulting in hypophosphatemic rickets [12,13]. Hypophosphatemic rickets/osteomalacia caused by excessive FGF23 activity has also been observed in individuals with autosomal dominant hypophosphatemic rickets [14], tumor-induced osteomalacia [12,13], fibrous dysplasia with McCune-Albright syndrome [15], sporadic fibrous dysplasia [16], and repeated intravenous iron infusion [17,18].

Conventional treatment for hypophosphatemic ricket/osteomalacia consists of combinations of active vitamin D analogs and multiple daily doses of oral inorganic phosphate [19]. However, both active vitamin D and phosphate enhance FGF23 secretion [11]. Clinical trials have shown that burosumab, a humanized monoclonal anti-FGF23 antibody, is safe and effective in pediatric patients with XLH [20–22].

This review will first describe an adult XLH patient, enabling an understanding of the complications that frequent occur in these patients. This review will also focus on the effects of treatment, comparing conventional treatments with burosumab.

2. Case Presentation

A 48-year-old woman was referred to our hospital for incidental hypophosphatemia at a medical checkup. She was short in stature (119.5 cm), with a body weight of 32.5 kg and bowed legs. She could not walk alone until age 5 years. She had been diagnosed with malnutrition of unknown causes and did not receive any treatment for her rickets. Her mother was also short in stature with bowed legs, but her father and five brothers did not exhibit short stature or bone abnormalities. Her serum phosphate concentration was 0.8 mg/dL, and she was diagnosed with XLH. She was started on treatment with alfacalcidol and inorganic phosphate, resulting in a gradual reduction of alkaline phosphatase levels. Her renal function was normal (serum creatinine 0.5 mg/dL). Analyses at age 58 years showed that her intact FGF23 level was 38.7 pg/mL and her tubular maximal reabsorption of phosphate to glomerular filtration rate (TmP/GFR) was 1.28 mg/dL, indicating a diagnosis of FGF23-related hypophosphatemia [23].

She began to experience numbness in her legs at age 54 years. She was diagnosed with ossification of the posterior longitudinal ligament (OPLL) of the cervical spine. She was advised by an orthopedic surgeon to undergo recommended surgical treatment but refused it for a long time. Finally, her gait became spastic at age 64 years, and she underwent vertebral resection (Figure 1). Her symptoms, such as cervicodynia, stiff neck, and pain/paresthesia of the upper limbs, improved but not completely. She also developed hearing loss at this age.

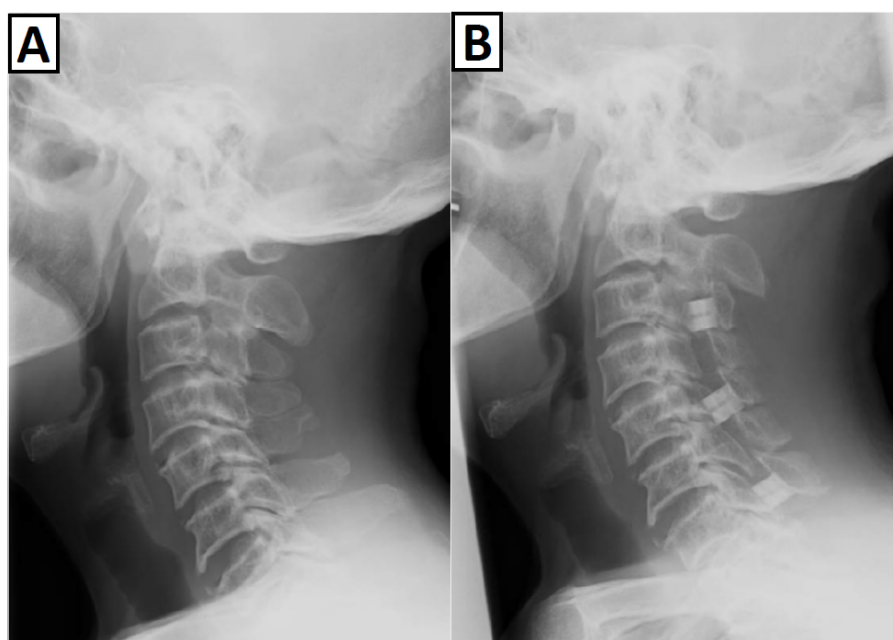


Figure 1. Cervical X-rays of the patient before (A) and after (B) vertebral resection for OPLL. After the operation, her symptoms partially improved.

At age 66 years, this patient experienced a left tibial pseudofracture and at age 67 years, she experienced pseudofractures on right tibia and left fibula. Conservative treatment of the pseudofracture of the left tibia was ineffective and intramedullary nail surgery was performed (Figure 2). After these lower limb fractures, she could not walk independently outside her house. Although her bone mineral density at age 66 years was not osteoporotic but osteopenic, both at the lumbar spine (L2–4 0.906 g/cm², T-score −0.9) and the femoral

neck (0.602 g/cm^2 , T-score -1.7), her vertebral fracture gradually progressed from this age, with multiple vertebral fractures resulting in a circle back at age 71 years.

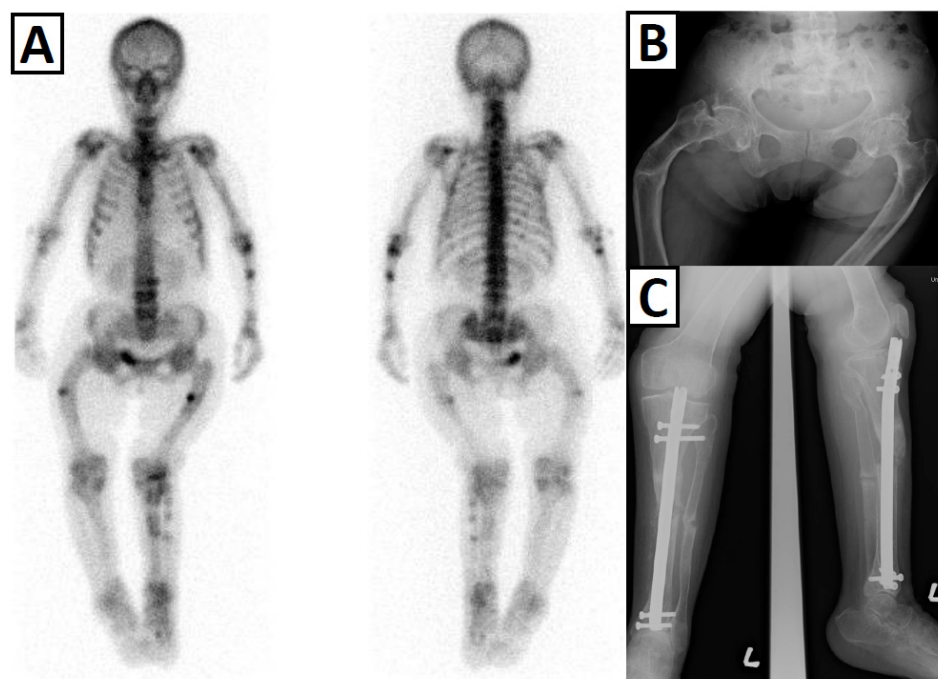


Figure 2. Bone scintigraphy of the patient at age 67 years (A). X-rays of both femurs (B) and left lower legs (C) after intramedullary nail surgery. The accumulations of radioisotope indicated fracture/pseudofracture of the left forearm, lumbar spines, and both legs. Along with bowing, beaking was observed at both femurs, findings consistent with the results of bone scintigraphy. After the surgery, she experienced partial easing of pain in her lower extremities, but calcifications of the pseudofracture regions were delayed.

Her blood pressure gradually increased during this time, and she was started on a calcium channel blocker at age 64 years. Her renal function also gradually decreased, with her serum creatinine concentration at age 75 years being above 1.0 mg/dL . Her doses of alfacalcidol and inorganic phosphate were reduced, with both stopped at age 75 years, resulting in a decrease in renal function. Because her renal function at age 79 years became very low (Cre 6.86 mg/dL , eGFR 4.98 mL/min), she was started on hemodialysis. Before starting hemodialysis, she exhibited secondary hyperparathyroidism (SHPT) with hyperphosphatemia (serum Ca 9.1 mg/dL , Pi 4.9 mg/dL , ALP (IFCC) 212 U/L , and whole PTH 821.3 pg/mL).

3. Complications in Adult XLH Patients

The patient described above had been diagnosed with adult XLH with severe complications, such as short stature, lower limb deformity and gait difficulty, OPLL, bone fragility, and hearing loss, complications often encountered in adult XLH patients. Renal insufficiency and SHPT were also observed, with these complications resulting from conventional treatment with inorganic phosphate and active vitamin D.

3.1. Short Stature

Short stature and growth retardation are typical phenotypes of XLH. At birth, patients with XLH are not abnormally small [24], but adult XLH patients are smaller than healthy subjects [25]. Despite treatment with oral inorganic phosphate and active vitamin D, including agents such as calcitriol and alfacalcidol, many patients show suboptimal growth [26]. Pubertal growth spurt is almost normal in patients with XLH [27], suggesting that some of the height deficit in treated patients results from late diagnosis and treatment onset.

Although initiating treatment in early infancy increases adult heights in patients with XLH, these heights are not completely normalized compared with healthy subjects [28]. Recombinant human growth hormone (rhGH) has also been used to improve growth velocity in pediatric XLH patients [29], with the combination of rhGH and conventional treatments in pediatric patients improving final height and bone mineral density (BMD) [30]. However, rhGH therapy is ineffective in adult XLH patients with epiphyseal line closure.

3.2. Lower Limb Deformity and Gait Difficulty

Long bone deformities, including bowing and malrotation of the lower limbs, are common in patients with XLH, with many of these patients requiring multiple surgical procedures to correct these deformities [31,32]. A cross-sectional study in East Asian patients with XLH showed that 59.4% of adult XLH patients complained walking difficulties and that 25.0% required a walking device [33]. Because of these deformities, most patients with XLH experience gait and joint problems, reducing their quality of life (QoL) [34,35]. Gait analyses with a motion capture system showed that gait quality was lower in 29 XLH patients than in healthy individuals [36]. Factors associated with poor gait quality include the severity of lower limb deformity, high body mass index (BMI > 30 kg/m²), and the presence of enthesopathies.

Poor muscle strength is also associated with gait difficulties. An analysis of calf muscle quantity and quality by peripheral quantitative computed tomography and jumping mechanography in 34 patients with hypophosphatemic rickets showed that muscle size was normal, but muscle density and peak muscle force and power were lower than in age-matched healthy volunteers [37]. Lower muscle quality and limb deformities contribute to gait difficulty. Most renal transplant recipients develop hypophosphatemia after transplantation due to the inappropriate secretion of FGF-23 and PTH in spite of improved renal function [38]. Administration of inorganic phosphate to hypophosphatemic patients after renal transplantation restored their serum phosphate levels and the composition of muscular phosphate components, such as adenosine 5'-triphosphate, and systemic acid/base homeostasis [39]. Hypophosphatemia itself may cause poor muscle quality in patients with XLH.

3.3. Spinal Complications

Spinal complications, such as ossified ligamentum flavum (OLF), posterior longitudinal ligament (OPLL), and Chiari malformation, have been observed frequently in adult XLH patients. For example, seven (11.8%) of 59 adult XLH patients were reported to have symptoms attributable to the spine clinically and/or radiologically [40]. Spinal complications observed in these patients included OLF, OPLL, Chiari malformation, cervical discectomy, cervical disc prolapse, and spinal cord syrinx. Surgical intervention (osteotomy) was frequently required. High rates of spinal ligament ossification, hip and knee osteophytes, and enthesopathy in the Achilles tendon have also been reported in Japanese adults with XLH [41].

3.4. Bone Fragility

High rates of fractures and/or pseudofractures have been reported in adult XLH patients [25,33,42]. For example, a cross-sectional survey of Japanese adults with XLH found that 34.4% had experienced a fracture, with the most commonly fractured bone being the femur (25.0%) [33]. In addition, some patients experienced more than one fracture.

BMD of the lumbar spine and hip assessed by dual-energy X-ray absorptiometry (DXA) was found to be higher in adult XLH patients than in an age-matched reference group [25,43,44]. A histologic analysis of adult patients with hypophosphatemic rickets showed that trabecular calcified and osteoid volumes were elevated, as was osteoid seam thickness [45]. Significant discrepancies between BMDs of the lumbar spine and hip have been observed in some patients, suggesting that extra-skeletal calcifications may interfere with BMD, especially of the lumbar spine. Bone microstructure is a component of bone

quality that affects bone fragility [46] and can be evaluated noninvasively in patients with osteoporosis using high-resolution peripheral quantitative computed tomography (HR-pQCT) [47]. Although DXA showed that areal BMD was higher in 37 female XLH patients than in matched healthy controls, HR-pQCT found that volumetric BMD and microarchitectural parameters were lower in the XLH patients than in controls [48]. These findings suggested that bone quality is poor in patients with XLH.

Histopathologic assessments of transiliac bone biopsy specimens from 16 adult XLH patients showed osteomalacia in almost all of these patients, including the absence of tetracycline double-labeling and increased osteoid surfaces [43]. Only 4 of 16 patients had been administered calcitriol when bone biopsies were performed, whereas 14 had previously been treated with vitamin D₂ and/or inorganic phosphate. Fifteen patients were found to have osteoid halos around their osteocytes, a finding typically observed in patients with vitamin D-resistant rickets [49]. Evaluation of the relationship between the severity of bone pain and the degree of osteomalacia, as determined by osteoid volumes, showed a clear threshold, with relative osteoid volumes > 25% being associated with bone pain. Histomorphometric evaluation of bone biopsies from patients with vitamin D-resistant rickets showed the presence of osteomalacia, even in asymptomatic patients [45]. Taken together, this evidence indicates that BMD does not reflect bone fragility.

3.5. Hearing Loss

Approximately 30% of adult patients with XLH experience hearing impairment [41,50], although otologic phenotype and age at presentation vary [50]. Hearing loss was not significantly associated with the severity of biochemical and skeletal abnormalities. These patients should therefore undergo routine otologic examinations.

4. Conventional Treatment of Patients with XLH

The goals of treatment of adult XLH patients include reducing bone pain and improving fracture and/or pseudofracture healing [19]. These symptoms, as well as osteomalacia, may be ameliorated by conventional treatments, such as active vitamin D and inorganic phosphate [51–54].

A 2-year randomized prospective study evaluated the efficacy and safety of 20 versus 40 ng/kg body weight (BW)/day of calcitriol in 68 children with XLH [55]. Higher doses had greater effects on Thacher rickets severity scores, reductions in serum alkaline phosphatase concentrations, and increases in height and serum phosphate concentrations. However, conventional treatment did not improve dental disease, arthritic complications, enthesopathy, and ligament calcification in adult XLH patients [19].

The risks of long-term conventional therapy with, for example, active vitamin D and inorganic phosphate, include hypercalcemia, hypercalciuria, nephrolithiasis, and nephrocalcinosis, all conditions that can cause chronic kidney disease (Table 1). The severity of nephrocalcinosis was shown to be significantly associated with the dose of inorganic phosphate [56]. Active vitamin D can contribute to the development of nephrolithiasis and nephrocalcinosis. Routine monitoring of serum and urinary parameters is necessary to avoid the side effects of conventional therapy.

Table 1. Problems of conventional treatments in adult XLH patients.

Poor adherence to medication
Gastrointestinal side effects
Secondary hyperparathyroidism
Ectopic calcification
Renal insufficiency
Insufficient effect

Although hyperparathyroidism has been linked to long-term oral administration of inorganic phosphate, it has also been reported in untreated patients. Hyperparathyroidism may be caused not only by inorganic phosphate administration but by FGF23 inactivation of calcitriol. PTH levels are high in more than 80% of patients with XLH [57], with an observational study in adult XLH patients showing that hyperparathyroidism was associated with disruption of the physiological regulation of PTH secretion [58]. Ten percent of these patients developed hypercalcemic hyperparathyroidism and underwent parathyroidectomy.

5. Burosumab Treatment of Adult XLH Patients

5.1. Preclinical Findings

Two types of anti-FGF23 antibodies were developed, FN1 and FC1, which recognize the amino- and carboxy-terminal regions, respectively, of FGF23 [59]. Both FN1 and FC1 inhibited FGF23 activity. Specifically, FN1 masked putative FGF receptor-binding sites in the amino-terminal domain of FGF23, whereas FC1 interfered with the association between FGF23 and Klotho by binding to the carboxy-terminal domain of FGF23. In Hyp mice, a model of human XLH, anti-FGF23 antibody, consisting of a 1:1 mixture of FN1 and FC1, improved hypophosphatemia by attenuating hyper-phosphaturia and low 1,25(OH)₂D levels, thereby improving growth and muscle strength [60,61].

5.2. Clinical Findings in Adults with XLH

Burosumab (KRN23), a recombinant human monoclonal IgG1 antibody that binds to the amino-terminal domain of FGF23, was developed for the treatment of FGF23-related hypophosphatemic rickets/osteomalacia, such as XLH [20–22,62] and tumor-induced osteomalacia (TIO) [63,64]. A phase 1 double-blind, placebo-controlled study tested the effects of a single intravenous or subcutaneous dose of burosumab in adults with XLH, finding that single doses of burosumab temporarily increased the ratio of TmP/GFR, as well as increasing serum phosphate and 1,25(OH)₂D levels [65]. Serum phosphate levels peaked 0.5–4 days after intravenous administration and 8–15 days after subcutaneous administration of burosumab. The pharmacokinetics and pharmacodynamics of burosumab in adult XLH patients [66,67] were analyzed using preclinical [60] and clinical [65] data. Because the effects of subcutaneous injection lasted longer than those of intravenous injection, subcutaneous administration was regarded as more suitable for clinical use [65].

A phase 1/2 open-label dose-escalation study evaluated the efficacy of subcutaneous burosumab in adults with XLH [68]. Twenty-eight adults with XLH participated in a 4-month dose-escalation study (0.05–0.6 mg/kg every 28 days), and 22 of 28 joined a 12-month extension study (0.1–1 mg/kg every 28 days). Burosumab administration resulted in prolonged improvements in TmP/GFR, serum phosphate, and serum 1,25(OH)₂D levels, with a favorable safety profile [68]. Moreover, burosumab was reported to improve patient perception of their physical functioning and stiffness due to their disease, as determined by the SF-36v2 Health Survey and the Western Ontario and McMaster Osteoarthritis Index (WOMAC), respectively, as well as to improve health-related QOL [69].

A large, double-blind, placebo-controlled, phase 3 trial found that burosumab improved patient-reported outcomes in 134 symptomatic adults with XLH [70]. Patients were administered burosumab 1 mg/kg or placebo subcutaneously every 4 weeks for 24 weeks, followed by open-label treatment with burosumab for an additional 24 weeks. Burosumab significantly improved WOMAC physical function and stiffness compared with placebo, and, also, accelerated active fracture healing [70]. None of the patients in this trial experienced treatment-related serious adverse events, nephrocalcinosis, or meaningful changes from baseline in serum and urinary calcium concentrations and intact PTH concentrations. During the open-label extension phase of this trial, the ability of burosumab to improve phosphate homeostasis was sustained for up to 48 weeks [71]. In addition, patient-reported outcomes, such as WOMAC, Brief Pain Inventory-Short Form (BPI-SF), and Brief Fatigue

Inventory (BFI) scores, were improved, as was ambulatory function, as measured by the 6 min walk test (6MWT), for up to 96 weeks [72].

An open-label, single-arm, international phase 3 trial evaluated the histomorphometric effects of burosumab in 14 adults with XLH [73]. Eleven of fourteen patients completed treatment with 1.0 mg/kg burosumab every 4 weeks for 48 weeks and underwent paired transiliac bone biopsies before and after burosumab treatment. Burosumab improved all osteomalacia-related histomorphometric parameters. such as osteoid volume/bone volume, osteoid thickness, osteoid surface/bone surface, and mineralization lag time [73]. Analyses of BMD distribution in these biopsied samples showed that mineralization in bones of patients with XLH is very heterogeneous and that burosumab treatment increased mineral matrix volume rather than overall mineralization [74].

6. Conclusions

XLH is a hereditary disorder with many complications. Conventional treatment consists of combined oral administration of inorganic phosphate and active vitamin D analogs. These treatments, however, do not restore normal phosphate levels, and their outcomes, including QOL, are not optimal [75].

Several clinical studies showed that burosumab was superior to conventional treatment in adults with XLH. Clinical trials showed that burosumab consistently improved phosphate homeostasis, fracture and pseudofracture healing, and patient-reported outcomes. Burosumab is a promising treatment that can improve QOL in adult XLH patients.

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