



BUROSUMAB – CHANGING THE TREATMENT PARADIGM FOR PEDIATRIC XLH

Professor Thomas Carpenter, MD

Professor of Pediatrics (Endocrinology)
and of Orthopaedics and Rehabilitation
Director, Yale Center for X-Linked Hypophosphatemia
Medical Director, Hospital Research Unit

Rickets and its classification

Rickets is the disordered proliferation and under-mineralization of hypertrophic chondrocytes leading to physical deformities such as bowed legs and expansion of the wrist at the growth plate (Figure 1).¹

It is seen radiographically as the frayed edge of the metaphysis as it approximates the growth plate. This is known as cupping deformity (Figure 2).¹

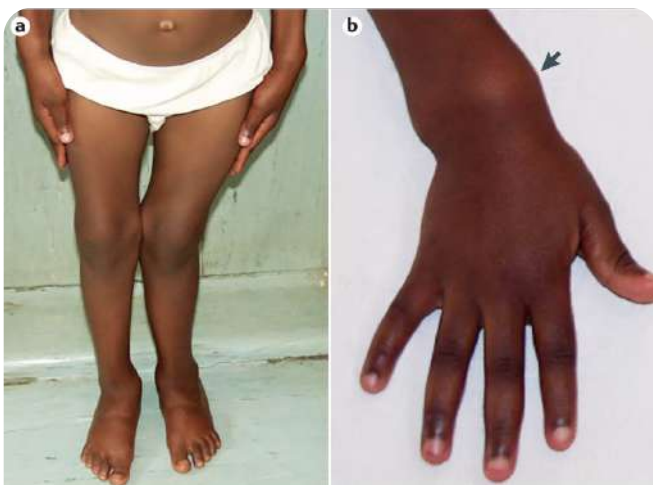


Figure 1. Bowed legs and wrist deformity in rickets.¹

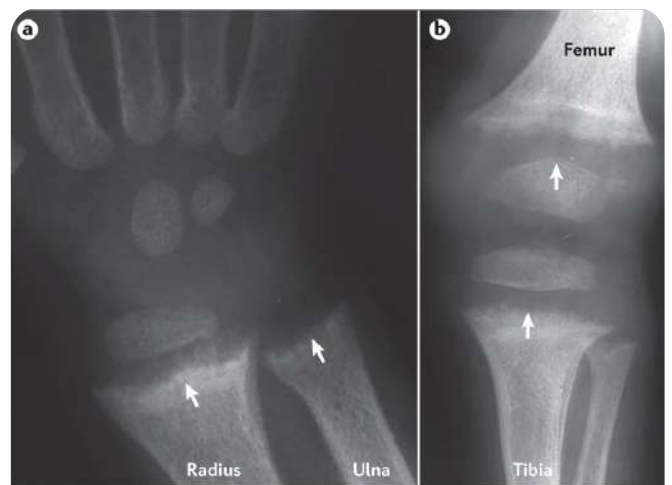


Figure 2. X-ray of severe leg deformity in a patient with rickets.¹

When one has rickets, there is an accompanying lesion of the bone called osteomalacia. Osteomalacia is the deficient mineralization of the bone matrix (osteoid), which makes one vulnerable to cortical fractures (Figure 3). Figure 3 shows the difference between normal bone and osteomalacia. The top layer (pink) represents the osteoid while the layer below it is the new bone (blue). There is an increase in osteoid in osteomalacia. This is represented by the pink layer/pink stain, which is visibly greater in the bone with osteomalacia.

Figure 3. Normal bone vs. osteomalacia.

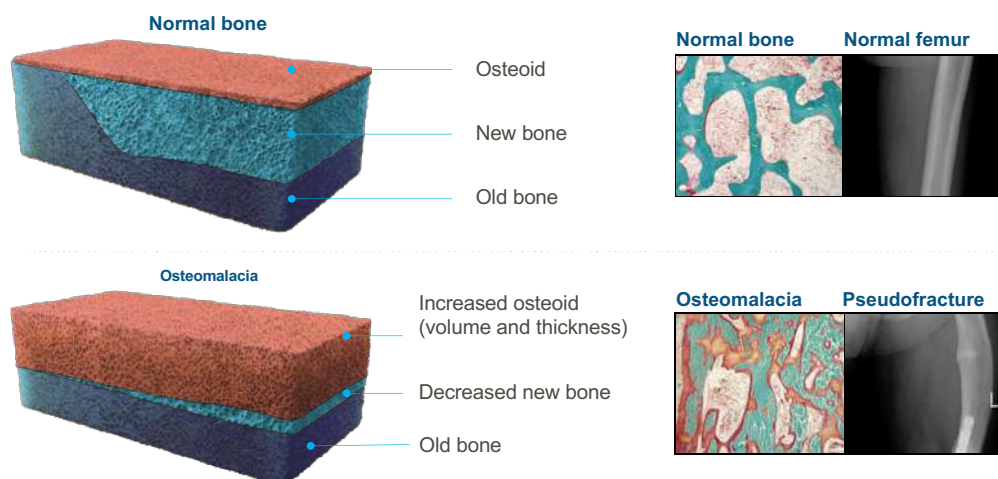


Image courtesy of Dr. Anthony Portale

Rickets is classified as calciopenic or phosphopenic.¹ The availability of calcium and phosphorus to the skeleton are major regulators of both growth plate mineralization and bone mineralization.¹ Phosphopenic rickets can occur rarely from nutritional causes but is most commonly due to disorders of transport.¹ Disorders of transport are generally divided into two categories: XLH (x-linked hypophosphatemia) type, which has been shown to be hypophosphatemia that is mediated by excess fibroblast growth factor 23 (FGF23) activity and other transport disorders that are not mediated by FGF23.¹

X-linked Hypophosphatemia: Diagnosis and treatment

XLH is the most common heritable cause of rickets and is due to renal phosphate wasting.¹ Manifestations of XLH include rickets and osteomalacia, which are often the presenting features, skeletal deformity and short stature, dental abscesses, and craniosynostosis.¹ The biochemical findings of XLH include low blood phosphate level (hypophosphatemia), decreased fractional tubular reabsorption of phosphate (TRP) and ratio of maximum tubular reabsorption of phosphate to glomerular filtration rate (TmP/GFR), and low circulating levels of 1,25 dihydroxyvitamin D (1,25 (OH)2D).¹

The treatment of XLH has evolved over the years. It was initially recognized as “Vitamin D-resistant rickets” when vitamin D therapy did not treat the disease.² When phosphate-wasting was eventually identified, phosphate was used for treatment. However, while phosphate therapy led to a healing effect on the bones, it also led to markedly elevated parathyroid hormone secretion. This led to combination therapy using phosphate and vitamin D, which produced better outcomes but required very high doses of vitamin D often leading to vitamin D toxicity. This combination therapy continued to be used until approximately 1980 when the active vitamin D metabolite calcitriol was used instead of vitamin D.² For the past 40 years, the use of 1,25(OH)2D3 (calcitriol) together with phosphate has been the standard of care.³ Complications of this kind of therapy include hyperparathyroidism, nephrocalcinosis, hypercalciuria/hypercalcemia, and soft tissue calcification in other sites.⁴

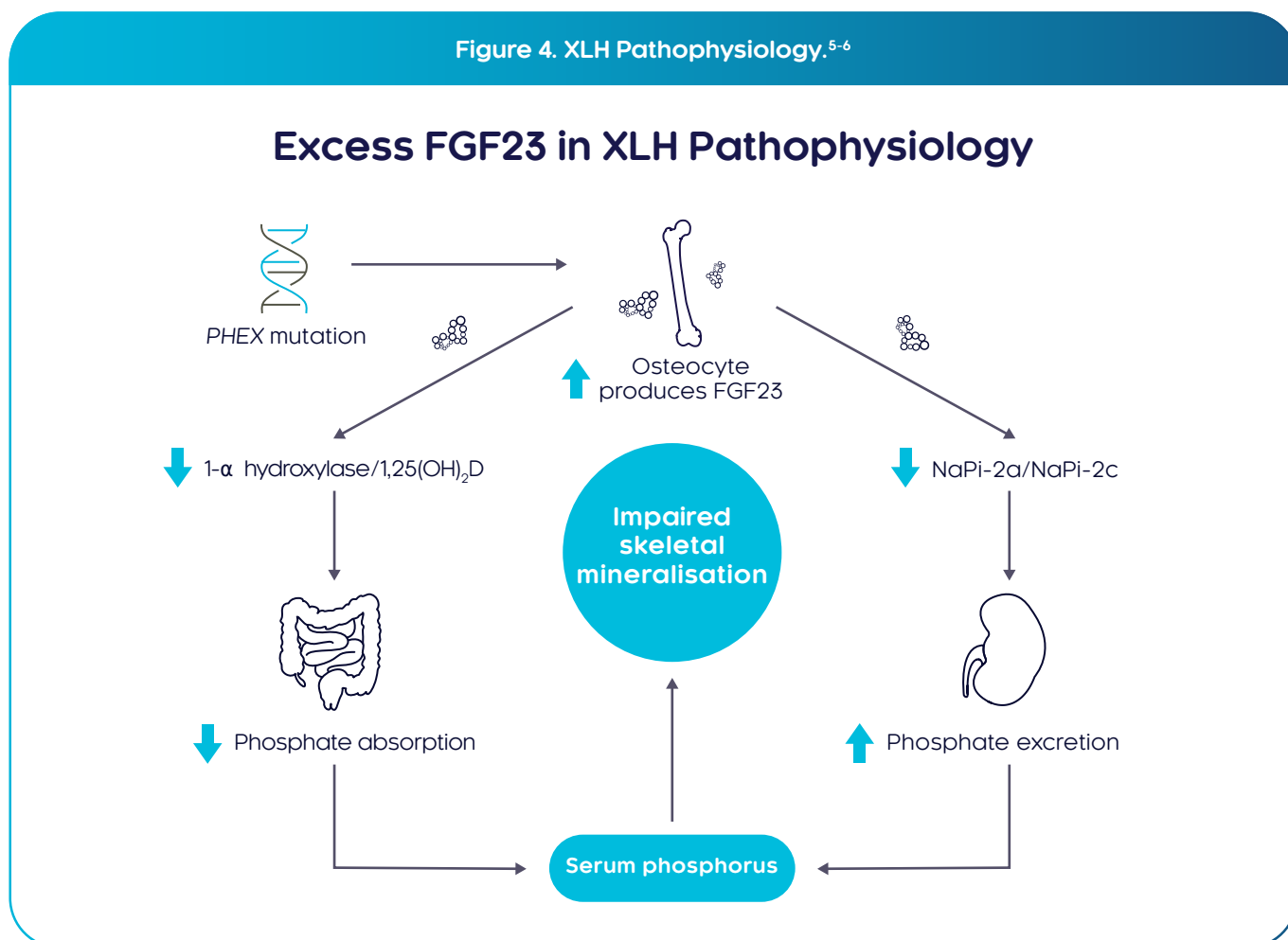
What mediates hypophosphatemia?

It was discovered that FGF23 was the mediator of hypophosphatemia.⁵⁻⁶ It is secreted excessively by osteocytes that harbor the phosphate regulating endopeptidase homolog on the X chromosome (PHEX) mutation that are responsible for XLH.⁵⁻⁶

XLH pathophysiology and novel treatment

Renal tubular cells have fibroblast growth factor (FGF) receptors and also have the enzymes that convert 25-hydroxyvitamin D to 1,25-hydroxyvitamin D.⁵⁻⁶ They also have Sodium-dependent Phosphate Cotransporter (NaPi2) in the apical surface of the cell.⁵⁻⁶ The cells also express the necessary co-receptors for FGF23. In XLH, the PHEX mutation results in the oversecretion of FGF23 leading to reduced expression of transporters, increased excretion of urinary phosphate resulting in decreased serum phosphorus, which in turn impairs skeletal mineralization. Increased FGF23 secretion likewise leads to impaired 1,25(OH)₂D production and impaired phosphate production again resulting in low serum phosphorus, which contributes to impaired skeletal mineralization (Figure 4).⁵⁻⁶

Figure 4. XLH Pathophysiology.⁵⁻⁶



Burosumab, a fully human monoclonal antibody inhibits FGF23 allowing transporter abundance to be restored, phosphate excretion to be corrected, correction of the serum phosphorus, and ultimately improvement of skeletal mineralization. It would also allow for upregulation of 1-alpha-hydroxylase, enhanced phosphate absorption, and correction of serum phosphorus, which contributes to improved skeletal mineralization.⁵⁻⁶

The goals of treatment in paediatric XLH are to prevent rickets, enhance growth, and minimize pain.⁴

Burosumab in children: Clinical trial data

One clinical trial on burosumab involved children ages 5-12 at enrollment who were randomised to every 2-week versus every 4-week dosing schedule of subcutaneous burosumab. The doses were titrated upward over the first 16 weeks. Primary outcome was assessed at 64 weeks and the children were followed up in the extension phase through 160 weeks.⁷

Fasting serum phosphorus increased and was maintained at a steady level with the every 2-week dosing schedule.⁷⁻⁸ There was also a sustained reduction in serum alkaline phosphatase, the clinical marker used for rickets, in both dosing schedules. The level of 1,25(OH)₂D also increased in both groups and was sustained through the extension phase. There were no clinically meaningful changes in 24-hour urine calcium excretion nor serum calcium or parathyroid hormone (PTH) that occurred.⁸ There was rapid improvement in the Rickets Severity Score (RSS).⁹ Lower limb deformity likewise improved through 160 weeks, however, the bulk of the improvement was a later effect. Patient-reported outcomes in terms of global functioning were also positive.⁸

Another clinical trial involved children ages 1-4 at enrollment and all were treated every 2 weeks with no titration period. There was an abrupt rise in serum phosphorus level and this was maintained over the 64 weeks of the study. The effects on 1,25(OH)₂D, serum alkaline phosphatase, and RSS seen in the trial were similar to the initial study.¹⁰

A third paediatric trial was done comparing burosumab with conventional therapy (calcitriol and phosphate). Children were ages 1-13 at enrollment. There was improved serum phosphorus and renal phosphate reabsorption in the burosumab group. A rapid decline in serum alkaline phosphatase was likewise seen in the burosumab group. The degree of improvement in radiographic features was higher in the group treated with burosumab and this was persistent through week 64. There were also height advantages in the group who received burosumab. The group treated with burosumab also scored higher on a 6-minute walk test.¹¹

Burosumab was found to be safe with adverse effects being generally mild to moderate, not leading to discontinuation of treatment.⁷

Burosumab: Real world data

Real world data on burosumab use in children has shown significant improvements in serum phosphorus, alkaline phosphatase, PTH, fractional excretion of phosphorus without changes in the urinary calcium to creatinine ratio. Burosumab was well-tolerated with no significant adverse effects.¹²⁻¹³

Summary

- XLH is the most common inherited form of rickets.¹
- XLH is mainly due to FGF23-mediated renal phosphate losses.¹⁵
- Conventional therapy consists of oral phosphate salts and calcitriol/activated vitamin D, however it is associated with complications thus requiring frequent monitoring and dose adjustments.^{2-3,11}
- Inhibition of FGF23 is an attractive and promising treatment strategy for XLH.¹¹
- Limited term outcomes of burosumab therapy are impressive, however long-term effects are unknown at present.¹²

References

1. Carpenter, T., Shaw, N., Portale, A. et al. Rickets. *Nat. Rev. Dis. Primers* 3, 17101 (2017). <https://doi.org/10.1038/nrdp.2017.101>.
2. Ward LM et al, *JCEM* 107:e3241-e3253, 2022.
3. Albright F, Butler AM, Bloomberg E. Rickets Resistant to Vitamin D Therapy. *Am J Dis Child*, 1937.
4. Personal experience, Prof. Thomas Carpenter.
5. Razzaque MS. *Nat Rev Endocrinol* 2009;5:611-9.
6. Martin A, et al. *Physiol Rev* 2012;92:131-55.
7. Carpenter TO et al. *N Engl J Med* 2018; 378:1987-98.
8. Linglart A et al, *J Clin Endocrinol Metab* 2022;107:813-824.
9. Thomas O. Carpenter et al. Sustained Efficacy and Safety of Burosumab, an anti-FGF23 Monoclonal Antibody, for 88 weeks in Children and Early Adolescents with X-linked Hypophosphatemia (XLH). Presented at The Annual American Society for Bone and Mineral Research Meeting (ASBMR), Sept 28-Oct 1, Montreal, Quebec, Canada. Poster FRI-1020 / SAT-1020.
10. Whyte MP et al, *Lancet Diabetes Endocrinol* 2019;7:189-199.
11. Imel E et al. *Lancet* 2019;393(10189):2416-2427.
12. Paloian NJ et al. *Pediatr Nephrol* 2022, online ahead of print.
13. Martin Ramos S et al. *Front Pediatr* 2020;8:48. doi: 10.3389/fped.2020.00048.

FGF23, fibroblast growth factor 23; **NaPi**, sodium-phosphate cotransporters; **NaPi-2a**, Sodium-dependent phosphate transport protein 2A; **NaPi-2c**, Sodium-dependent phosphate transport protein 2c; **PHEX**, phosphate-regulating endopeptidase homolog on the X chromosome; **XLH**, X-linked hypophosphatemia; **1,25(OH)2D**, 1,25 dihydroxy vitamin D; **1 α hydroxylase**, 1 α -Hydroxylase.

Product is approved in selected markets and that local approved prescribing information may differ. To verify with the local approval status and local prescribing information. This material is for scientific exchange and education only.

This material is for Healthcare Professionals Only.