X-linked hypophosphatemic rickets: from diagnosis to management

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Abstract

X-linked hypophosphatemia (XLH) is the most common cause of hypophosphatemic rickets, affecting one in 20,000 people. Although conventional therapy for XLH has been introduced for approximately four decades, temporary replacement of oral phosphate salts and activated vitamin D cannot completely control chronic hypophosphatemia, leaving patients with incomplete healing of rickets, residual skeletal deformity, risk of endocrine abnormalities, and adverse drug reactions. However, understanding the pathophysiology has led to the development of a targeted therapy, burosumab, a fibroblast growth factor-23 inhibitor, which was recently approved for the treatment of XLH in Korea. In this review, we provide insight into the diagnosis, evaluation, treatment, and recommended follow-up for a typical case of XLH and review the pathophysiology of this condition.

Keywords: Rickets, Hypophosphatemic, X-linked hypophosphatemia,

Key Message

- X-linked hypophosphatemia (XLH) is the most common cause of hypophosphatemic rickets, affecting one in 20,000 people.
- A loss-of-function mutation of the PHEX gene causes XLH.
- The main pathogenesis of XLH is the elevation of a fibroblast growth factor-23 (FGF23).
- Burosumab, FGF23 inhibitor, was developed in the early 2000s for the treatment of XLH.
- Burosumab was approved in Korea in 2020 for XLH patients aged 1 year or older with radiographic evidence of bone disease.
Introduction

The kidney tubules reclaim the majority of nutrients filtered by glomerular filtration into the urinary space through diverse mechanisms. When the reabsorption of filtered phosphate is impaired by acquired tubular damage or genetic defects in sodium-phosphate cotransporters or their regulators, significant hypophosphatemia occurs. If such an impairment persists, rickets, a failure to mineralize growing bones, develops in children because phosphate is required along with calcium (Ca) to form hydroxyapatite to mineralize the bone.\(^1\) The common cause of rickets is the nutritional deficiency of vitamin D or calcium intake, previously denoted as calcipenic rickets, while phosphopenic or hypophosphatemic rickets is relatively rare and often has a genetic cause.\(^2\)

X-linked hypophosphatemia (XLH, Mendelian Inheritance in Man # 307800) is the most common cause of hypophosphatemic rickets, comprising 90% of familial cases and 70% of sporadic cases, affecting one in 20,000 people in the general population.\(^2\)\(^-\)\(^3\) It has been known as vitamin D-resistant rickets since 1937, and its inheritance pattern of X-linked disorders was elucidated in 1958. Since female carriers of pathogenic variants are also affected, this is an X-linked dominant disorder.\(^4\) In 1972, the nature of this condition as an inborn error of phosphate transport in the disease was revealed, and the causative gene \(PHEx\) (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) was discovered in 1995.\(^5\)\(^-\)\(^6\)

Although conventional therapy for XLH has been introduced for approximately four decades, temporary replacement of oral phosphate salts and activated vitamin D cannot completely control chronic hypophosphatemia, leaving patients with incomplete healing of rickets, residual skeletal deformity, risk of endocrine abnormalities, and adverse drug reactions.\(^7\)

However, understanding the pathophysiology has led to the development of a targeted therapy,
burosumab, a fibroblast growth factor-23 (FGF23) inhibitor, which was recently approved for the treatment of XLH in Korea. In this review, we provide insight into the diagnosis, evaluation, treatment, and recommended follow-up for a typical case of XLH and review the pathophysiology of this condition.8)

Presentation and evaluation

Clinical vignette part 1

A 25-month-old girl visited the outpatient clinic because of growth impairment. Her perinatal and family histories were unremarkable, and she was receiving vitamin D supplementation. Upon examination, her height was 77.6 cm (< third percentile), and her weight was 9.8 kg (fifth to the tenth percentile). Her laboratory test results were unremarkable [serum calcium (Ca) 9.8 mg/dL and creatinine (Cr) 0.39 mg/dL] except for elevated alkaline phosphatase (ALP, 1087 IU/L) and hypophosphatemia [serum phosphorus (P), 2.4 mg/dL]. Radiograms of the hand and knee revealed metaphyseal fraying and widening of growth plates, suggesting rickets (Fig. 1). Additional workup for rickets showed normal urine Ca/Cr (0.04) with elevated urine P (75.2 mg/dL), low tubular reabsorption of phosphorus (TRP, 69%), and a low ratio of tubular maximum reabsorption of phosphorus to glomerular filtration rate [TmP/GFR, 1.65 (reference range 3.25-5.51)]. Serum 25-hydroxy (OH) vitamin D and parathyroid hormone (PTH) levels were within the normal range (45.47 ng/mL and 67.8 pg/mL, respectively), and 1,25-dihydroxy vitamin D [1,25(OH)2D] levels were elevated (99.95 ng/mL). Genetic diagnosis of XLH was made by identifying loss-of-function mutations in the PHEX gene.
XLH usually presents as typical rickets, but its symptoms vary according to age at presentation and severity of the disease. Short stature, bowing of the legs, difficulty walking from deformity and weakness (waddling gait), and unusual shape (dolichocephaly, frontal bossing) of the skull from craniosynostosis are common chief complaints. Family history may be significant in X-linked dominant patterns for disproportionate short stature, leg deformities, dental abscess, periodontal diseases, and hearing loss, along with osteoarthritis, enthesopathy, and (pseudo)fractures. Upon examination, typical findings of rickets, namely widening of the wrists and metaphysis and valgus or varus deformities of the legs, were noted. Often, the children of an affected female patient visit the clinic and are diagnosed through laboratory tests before the disease develops. Laboratory characteristics of XLH include hypophosphatemia, normocalcemia, hyperphosphaturia (low TRP and TmP/GFR), and inappropriately normal 1,25(OH)2D levels. While normal PTH is a typical finding of XLH, if the patient was taking vitamin D supplementation, PTH might be mildly elevated, as well as 1,25(OH)2D, as shown in the vignette.

**Pathophysiology**

To understand the pathophysiology of XLH, it is necessary to understand the regulatory mechanisms of calcium and phosphate (Fig. 2). When serum P is decreased, intestinal absorption and tubular reabsorption of P are increased through the sodium-coupled phosphate cotransporters NaPi2b (intestine), NaPi2a, and NaPi2c (kidney), which are upregulated by the increased production of 1,25(OH)2D. With hyperphosphatemia, the phosphaturic hormone, fibroblast growth factor-23, is activated. Then, it lowers serum P by decreasing renal tubular reabsorption of phosphate through the downregulation of NaPi2a and NaPi2c and suppresses
the activity of renal 25(OH)D3 1α-hydroxylase to reduce the production of 1,25(OH)2D.15-19
In the case of hypocalcemia, PTH is upregulated to increase serum Ca by mobilization of Ca
from the bone, increasing the production of 1,25(OH)2D to absorb/reabsorb more calcium from
the intestine and kidney, and downregulating kidney tubular reabsorption of P.20) In XLH, the
level of FGF23 is increased regardless of the serum P level, causing phosphaturia and decreased
or inappropriately normal 1,25(OH)2D levels, which is the main pathogenic mechanism in
XLH (Fig. 2).21) However, the mechanism by which FGF23 is increased in XLH has not yet
been elucidated.22-24) Additionally, other regulators of bone mineralization, such as osteopontin
and acid serine aspartate-rich-MEPE-associated protein peptides, are also known to increase in
XLH.24-25) On the other hand, such an increase in FGF23 leading to phosphaturia is not unique
to XLH. Still, other genetic conditions affecting FGF23, or its regulators have a similar
pathophysiology (Table 1, Fig. 3). In recent studies, the detection rate of PHOX mutations has
been reported from 33.0% to 83.3% when patients with phosphopenic rickets were screened
by targeted next-generation sequencing.26-28) Therefore, a confirmative diagnosis of XLH is
usually obtained only after a genetic diagnosis.

Differential diagnosis

The typical clinical picture of hypophosphatemic rickets can be found in conditions other than
XLH such as dietary phosphate deficiency, including very low birth weight infants absolutely
breastfed, infants fed elemental or hypoallergenic formulas, and patients receiving parenteral
nutrition, as well as impaired phosphate bioavailability due to overuse of P binders and
gastrointestinal disorders.2, 28-30) Other conditions, such as primary renal tubulopathies, may
resemble XLH, including hereditary hypophosphatemic rickets with hypercalciuria, Dent


disease 1, cystinosis, other hereditary forms of Fanconi syndrome, and iatrogenic proximal tubulopathy.³⁰)

Treatment

Clinical vignette part 2

The patient was prescribed alfacalcidol 0.25 µg once a day and potassium phosphate/sodium phosphate 125 mg (Phospha 250 Neutral 0.5 tablet) four times a day. She will be followed up every month until normalization of her ALP level, then quarterly until 5 years of age, and every 3-6 months till puberty, and more frequently during puberty, according to the guidelines.³¹) Growth, neurological signs, and metabolic control were monitored for normal ALP, PTH, and normocalciuria. Blood pressure and dental examination twice a year, renal ultrasonography, and orthopedic examination once a year, and yearly hearing tests from 8 years will be performed. When available, burosumab and anti-FGF23 will be prescribed until growth is complete.

Traditionally, XLH has been managed with oral phosphate supplementation and activated vitamin D (calcitriol or alfacalcidol) to offset renal loss. The recommended doses of each medication are listed in Table 2.³¹-³³) Once provided with phosphate and active vitamin D, rickets symptoms are usually ameliorated, and patients grow better and complain of less bone pain.³⁴-³⁶) However, the efficacy of such management is often insufficient, the skeletal deformity progresses relentlessly, and osteotomy becomes necessary in many cases.³⁷-³⁸) In addition, a large amount of phosphate is necessary to normalize serum P levels, and excessive
amounts of P inhibit intestinal Ca absorption, leading to secondary hyperparathyroidism and
aggravating bone resorption and phosphaturia.\textsuperscript{39} However, excessive calcitriol dosage may
cause hypercalciuria and nephrocalcinosis. Nephrocalcinosis is a common complication of
XLH, not from the disease itself, but from the replacement therapy for XLH.\textsuperscript{40-41} Therefore,
clinicians need to well titrate and balance the dosage of phosphate supplementation and active
vitamin D to maintain normal PTH levels and normocalciuria.

The target of XLH management is the recovery from rickets with the normalization of serum
ALP levels but not the normalization of serum P levels. Another problem with classical
treatment is poor compliance owing to gastrointestinal problems caused by phosphate
supplementation.

\textbf{Anti-FGF23 treatment}

As an increase in FGF23 is the main pathogenic mechanism of XLH, thus the inhibition of
FGF23 may be an ideal approach. Burosumab, a fully humanized monoclonal IgG1 antibody
that neutralizes FGF23, was developed in the early 2000s and has shown efficacy and safety in
a series of clinical trials in adults and children.\textsuperscript{42-48} This targeted medicine increases serum P
levels and improves physical function.

\textbf{In an open-label, phase 2 trial of XLH children, 52 patients between 5 and 12 years of age were
randomly assigned to receive burosumab either every 2 weeks or every 4 weeks for 64 weeks.}
Every 2 weeks dosing improved TRP with more stable serum P levels than every 4 weeks
dosing and resulted in substantial healing of rickets in nearly all the children who had severe
rickets. These results indicate that administration of burosumab every 2 weeks is an appropriate
regimen for children with XLH.\textsuperscript{44} In an active-controlled, open-label, phase 3 trial of XLH
children, 61 patients between 1 and 12 years of age were randomly assigned to receive either
burosumab (subcutaneously every 2 weeks) or conventional therapy for 40 weeks. Rickets severity and height Z score in the burosumab group improved significantly better than in the conventional therapy group. Another open-label, phase 2 trial for children with XLH between 1 and 4 years of age, 13 patients received burosumab every 2 weeks for 64 weeks. In this study, burosumab increased serum P levels, improved rickets, and prevented early decline in height Z score.

Additional benefits of this targeted therapy include the removal of the burden of frequent medication dosing, side effects of conventional medications of gastrointestinal discomfort, secondary hyperparathyroidism, hypercalciuria, and nephrocalcinosis. In clinical trials of XLH children, most patients who received burosumab experienced an adverse effect, but most of them were mild or moderate in severity with the most common being injection site reactions, hypersensitivity, headache, cough, vomiting and pyrexia. As a result, burosumab was approved for the treatment of XLH and tumor-induced osteomalacia in patients older than 1 year, with radiographic evidence of bone diseases, in the United States, Europe, and Japan in 2018, followed by Korean approval in 2020. It is expected to be available in early 2023 in Korea.

The dosage of burosumab is usually titrated to achieve a lower age-related normal range of serum P levels. For growing children, its starting dosage is 0.8 mg/kg every 2 weeks subcutaneously (not to exceed 90 mg; after completion of growth, 1 mg/kg every 4 weeks subcutaneously) and increased by 0.4 mg/kg (up to 2.0 mg/kg) every 4 weeks to raise fasting serum P levels within the lower end of the normal reference range for the age. Burosumab should be withheld if fasting serum P level 7 to 11 days post-injection is above the upper range of normal and can be restarted at approximately half of the previous dose when serum P concentration is below the normal range. Assess TmP/GFR is recommended to confirm
improvement in renal phosphate wasting.

Follow-up evaluation

Recommendations on follow-up intervals and evaluations are listed in Table 3. In addition to disease activity and growth, treatment-associated side effects such as hypercalciuria, nephrocalcinosis, nephrolithiasis, abnormal PTH levels (high or low) in patients receiving conventional treatment, and hyperphosphatemia or hypervitaminosis D (1,25(OH)2D) in patients receiving burosumab treatment can be observed. Since XLH is accompanied by complications encompassing orthopedics, neurosurgery, dentistry, and otolaryngology, careful evaluation of these conditions is also needed. Notably, the majority of adult and children with XLH experience bone, joint and/or muscle pain. Craniosynostosis can be observed in about one-third of patients with hypophosphatemia, a strict monitoring of head circumference and skull shape during the early years of life is essential. The possibility of increased intracranial pressure, headache, neck pain from craniosynostosis, type 1 Chiari malformation or syringomyelia needs to be considered. Also, approximately two-thirds of patients with XLH suffer from dental and periodontal lesions, regular dental examinations to screen for delayed dentition and tooth abscesses are necessary. Hearing problem is rarely seen in children with XLH, but various degrees of hearing loss can occur in adult XLH, so it is recommended to start the evaluation whether symptoms of hearing loss appear at the age of 8.

Radiographic evidence of bone diseases can be quantitatively assessed by the Rickets Severity Score (RSS) using radiographs of the wrists and knees (Table 4, Fig. 4). RSS is a validated measure of rickets severity ranging from 0 (no rickets) to 10 (severe rickets) based on the "degree of metaphyseal fraying and concavity, and the proportion of the growth plate affected
Prognosis

Upon completion of growth, the requirement for calcium and phosphate decreases with the spontaneous amelioration of hypophosphatemia, albeit with incomplete resolution. The final height of the XLH depends on the timing and mode of intervention.\textsuperscript{25,54} The efficacy of growth hormone treatment is uncertain, especially in those with less optimal metabolic control.\textsuperscript{54-58} Residual lower leg deformities are often debilitating, and about half of the patients require surgical corrections, corrective osteotomies for those who attain their adult height, and epiphysiodesis for those who are still growing.\textsuperscript{31,37,38,49} Optimal metabolic control is a prerequisite of surgery. In addition to deformities, osteophytes, enthesopathies (ossification of the tendon), osteoarthritis, (pseudo)fractures, and spinal stenosis may occur, resulting in pain and/or immobility.\textsuperscript{7,31,59,60} Supplementation of phosphate and active vitamin D may relieve the symptoms.\textsuperscript{61,62} Dental care is important for patients with XLH because dental abscesses, poorly mineralized dentin, and periodontitis are common. Although conventional treatment with oral phosphate and active vitamin D may ameliorate this problem, the efficacy of burosumab remains unclear.\textsuperscript{4,61}

Conclusion

Although rare, XLH is a clinically significant disease because short stature and debilitating deformity may result from delayed management. Especially as a targeted therapy based on pathophysiology is now available, suspicion and early diagnosis of XLH in every case with
short stature and hyperphosphaturic hypophosphatemia is necessary.

Acknowledgments

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### Tables

**Table 1.** Phosphopenic rickets with renal tubular phosphate wasting due to elevated fibroblast growth factor-23 levels and/or signaling in comparison to calcipenic rickets with vitamin D-dependent rickets.

<table>
<thead>
<tr>
<th>Disorder (Abbreviation; OMIM#)</th>
<th>Gene (location)</th>
<th>Ca</th>
<th>P</th>
<th>ALP</th>
<th>UCa/Crea</th>
<th>UP/Crea</th>
<th>TmP/GFR</th>
<th>FGFR23</th>
<th>PTH</th>
<th>25(OH)D*</th>
<th>1,25(OH)2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked hypophosphatemia (XLH; OMIM#307800)</td>
<td>PHEX (Xp22.1)</td>
<td>N</td>
<td>↓</td>
<td>↑, ↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>AD hypophosphatemic rickets (ADHR; OMIM#193100)</td>
<td>FGFR3 (12p13.3)</td>
<td>N</td>
<td>↓</td>
<td>↑, ↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>AR hypophosphatemic rickets 1 (ARHR1; OMIM#241520)</td>
<td>DMP1 (4q22.1)</td>
<td>N</td>
<td>↓</td>
<td>↑, ↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>AR hypophosphatemic rickets 2 (ARHR2; OMIM#613312)</td>
<td>ENPP1 (6q23.2)</td>
<td>N</td>
<td>↓</td>
<td>↑, ↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>Raine syndrome-associated (ARHR3; OMIM#259775)</td>
<td>FAM20C (7q22.3)</td>
<td>N</td>
<td>↓</td>
<td>↑, ↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>Fibrous dysplasia (FD; OMIM#174800)</td>
<td>GNAS (20q13.3)</td>
<td>N, ↓</td>
<td>↓</td>
<td>↑, ↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>Tumor-induced osteomalacia (TIO)</td>
<td>NA</td>
<td>N</td>
<td>↓</td>
<td>↑, ↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>Cutaneous skeletal hypophosphatemia syndrome (SFH; OMIM#163200)</td>
<td>NRAS (1p13.2)</td>
<td>N</td>
<td>↓</td>
<td>↑, ↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>Hypophosphatemic rickets and hyperparathyroidism (OMIM#612089)</td>
<td>KRAS (1p13.2)</td>
<td>N</td>
<td>↓</td>
<td>↑, ↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>Osteoglophonic dysplasia (OGD; OMIM#612089)</td>
<td>FGFR1 (8p11.23)</td>
<td>N</td>
<td>↓</td>
<td>↑, ↑</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>Hypophosphatemic rickets</td>
<td>KLOTHO (13q13.1)</td>
<td>N</td>
<td>↓</td>
<td>↑, ↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
</tr>
</tbody>
</table>

**Rickets and/or osteomalacia with high PTH levels (calcipenic rickets)**

| Nutritional rickets | D-dependent rickets | N |↓| N |↓| ↑| ↑| ↓| Varies | N |↓| ↑| ↑| ↓| ↑| ↑| N |Varies |

N=normal; ↑=elevated; ↑↑=very elevated; (↑↑)=may range widely; Ca, serum levels of calcium; P, serum levels of phosphate; ALP alkaline phosphatase; UCa/Crea, urinary calcium to creatinine ratio; UP/Crea, urinary phosphate to creatinine ratio; TmP/GFR=maximum rate of renal tubular reabsorption of phosphate normalized to the glomerular filtration rate; FGFR23=fibroblast growth factor 23; PTH=parathyroid hormone; 1,25(OH)2D=1,25-dihydroxyvitamin; 25(OH)D=calcifediol; NA=not applicable; *=cave: prevalence of vitamin D deficiency was reported to be up to 50% in healthy children; **=normal after restoration of Pi, but falsely reduced before restoration; ‡=PTH may be moderately elevated; Modified from Haffner, D. et al. Rickets guidance: part I—diagnostic workup. Pediatr Nephrol 37, 2013–2036 (2022).2 | Creative Commons license http://creativecommons.org/licenses/by/4.0/.
Table 2. Dosage of conventional medications for X-linked hypophosphatemia.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphatea given in 4–6 doses</td>
<td>Elemental P 20–60 mg/kg/day (0.7–2.0 mmol/kg/day)</td>
</tr>
<tr>
<td></td>
<td>Maximum 80 mg/kg</td>
</tr>
<tr>
<td>Calciotrob given in 1–2 doses</td>
<td>20–30 ng/kg/day, Alternatively, 0.5 μg² (age &gt; 12 months)</td>
</tr>
<tr>
<td>Alphalcaldio³ (ng/kg) given once daily</td>
<td>30–50 ng/kg/day, Alternatively, 1 μg² (age &gt; 12 months)</td>
</tr>
<tr>
<td>Vitamin D2 or D3</td>
<td>In case of vitamin D deficiency</td>
</tr>
<tr>
<td>Age-appropriate daily calcium intake</td>
<td>≥ 500 mg Ca in children &gt; 12 months</td>
</tr>
</tbody>
</table>


Table 3. Recommended follow-up interval and evaluations in patients with rickets.

<table>
<thead>
<tr>
<th>Examination</th>
<th>0-5 years</th>
<th>5 years-start of puberty (9-12 years)</th>
<th>Puberty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of visits</td>
<td>Monthly-3 monthly</td>
<td>3-6 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Height, weight, IMD, ICD⁴</td>
<td>V</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>Head circumference and skull shape</td>
<td>V</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Presence of rickets, pain, stiffness, fatigue, muscle weakness, gait pattern</td>
<td>V</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>Neurological examination⁵</td>
<td>V</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>Orthopedic examination</td>
<td>Once in a year in the presence of significant leg bowing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental examination</td>
<td>Twice-yearly after tooth eruption</td>
<td>Twice-yearly</td>
<td>Twice-yearly</td>
</tr>
<tr>
<td>Hearing test</td>
<td>Not feasible</td>
<td>From 8 years: hearing evaluation if symptoms of hearing difficulties</td>
<td></td>
</tr>
<tr>
<td>Serum levels of ALP, Ca, Pi, PTH, Crea, eGFR</td>
<td>V</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>25(OH) vitamin D levels</td>
<td>After 3-4 weeks in nutritional rickets, yearly in other rickets forms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,25(OH), vitamin D levels</td>
<td>Every 3-6 months in patients on burosumab treatment, those on active vitamin D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCa/Crea TmP/GFR</td>
<td>Every 3-6 months in patients on active vitamin D or burosumab treatment. Initially, at every visit in patients on burosumab treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Twice yearly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney ultrasonography</td>
<td>Every 1-2 years on phosphate, active vitamin D or burosumab treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left wrist and/or lower limbs radiographs</td>
<td>- If leg bowing does not improve upon treatment</td>
<td>In adolescents with persistent lower limb deformities when they are transitioning to adult care</td>
<td></td>
</tr>
<tr>
<td>Dental orthopantomogram</td>
<td>Not feasible</td>
<td>Based on clinical needs</td>
<td></td>
</tr>
<tr>
<td>Funduscopy and brain MRI</td>
<td>If aberrant shape of skull, If recurrent headaches, declining school/cognitive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
headaches, or neurological symptoms

IMD, intermalleolar distance; ICD, intercondylar distance; NA, not applicable; ALP, alkaline phosphatase; Ca, calcium; Pi, phosphorus; PTH, parathyroid hormone; Crea, creatinine; eGFR, estimated glomerular filtration rate; U, urine; TmP/GFR, maximum rate of tubular reabsorption of phosphate per glomerular filtration rate; TmP/GFR is calculated by entering the fasting urine and plasma concentrations, in the same concentration units, into the following equation: \( TmP/GFR = \frac{Pp}{Pcr} - \frac{Up}{Ucr} \times Pcr. \)

*a In the presence of significant leg bowing. b Consequences of craniosynostosis and spinal stenosis. Modified from Haffner, D. et al. Rickets guidance: part II—management. Pediatr Nephrol 37, 2289–2302 (2022). Creative Commons licence http://creativecommons.org/licenses/by/4.0/.
Table 4. Rickets Severity Score (RSS) using the radiographs of the wrist and knee.

<table>
<thead>
<tr>
<th>Grade definitions for radius &amp; ulna</th>
<th>Grade definitions for femur &amp; tibia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Normal growth plate without changes of rickets</td>
<td>0 Normal growth plate without changes of rickets</td>
</tr>
<tr>
<td>0.5 Lucency of metaphyseal margin without fraying or irregularity</td>
<td>1 Partial Lucency, smooth margin of metaphysis visible</td>
</tr>
<tr>
<td>1 Widened growth plate, irregularity of metaphyseal margin. But without concave cupping</td>
<td>2 Partial Lucency, smooth margin of metaphysis NOT visible</td>
</tr>
<tr>
<td>1.5 Partial metaphyseal concavity or incomplete fraying of metaphyseal margin</td>
<td>3 Complete Lucency, epiphysis appears widely separated from distal metaphysis</td>
</tr>
<tr>
<td>2 Metaphyseal concavity with fraying of margins</td>
<td></td>
</tr>
</tbody>
</table>

| Grade radius | 0 | 0.5 | 1 | 1.5 | 2 |
| Grade ulna | 0 | 0.5 | 1 | 1.5 | 2 |

Radius grade + Ulna grade = Total wrist

| Grade femur | 0 | 1 | 2 | 3 |
| Grade tibia | 0 | 1 | 2 | 3 |

Femur & tibia multiplier 0.5 if ≤ one condyle or plateau affected 1 if ≤ two condyle or plateau affected

(Femur grade x multiplier) + (Tibia grade x multiplier) = Total knee

Total possible score is 10, with 4 for the wrist and 6 for the knee. Adapted from Thacher TD, et al. Reading JC. Radiographic scoring method for the assessment of the severity of nutritional rickets. J Trop Pediatr 46:132-9, 2000. Creative Commons licence http://creativecommons.org/licenses/by/4.0/.
**Figure legends**

**Fig. 1.** Hand (A) and knee (B) radiograms revealed metaphyseal fraying and widening of growth plates.

**Fig. 2.** Calcium (A) and phosphate (B) homeostasis and their regulators. 

(A) Parathyroid hormone (PTH) secretion is increased by low blood calcium (Ca) concentrations and reduced by high Ca concentration. PTH promotes renal Ca reabsorption, Ca resorption from the bone, and renal 1,25-dihydroxy vitamin D (1,25(OH)₂D) production, improving osteoclastic resorption of Ca from bone, inhibits PTH synthesis, and stimulates renal Ca reabsorption. Fibroblast growth factor 23 (FGF23) is mostly produced by osteocytes and inhibits renal 1,25(OH)₂D and PTH production. Ca and 1,25(OH)₂D promote the synthesis of FGF23. 

(B) FGF23 and PTH decrease the apical expression of the sodium-phosphate cotransporters NaPi2a and NaPi2c, hence decreasing renal tubular phosphate reabsorption. FGF23 inhibits 1,25(OH)₂D synthesis, which enhances NaPi2b expression, increasing intestinal absorption of dietary P. PTH and FGF23 production are influenced by one another in a negative feedback loop by as-yet-unidentified mechanisms. Modified from Haffner, D. et al. Rickets guidance: part I—diagnostic workup. Pediatr Nephrol 37, 2013–2036 (2022). Creative Commons license [http://creativecommons.org/licenses/by/4.0/](http://creativecommons.org/licenses/by/4.0/)

**Fig. 3.** Algorithm for the evaluation of a child with rickets presenting with hypophosphatemia. Modified from Haffner, D. et al. Rickets guidance: part I—diagnostic workup. Pediatr Nephrol 37, 2013–2036 (2022). Creative Commons license [http://creativecommons.org/licenses/by/4.0/](http://creativecommons.org/licenses/by/4.0/)
Fig. 4. Diagram showing the grading of radiographic changes in rickets.

(A) A normal wrist.

(B) Irregularity and widening of the growth plate, but without concave cupping.

(C) Concave metaphyseal cupping and fraying margins.

(D) A normal knee.

(E) Only the medial portions of the femoral and tibial metaphyses are affected. There is partial lucency of the metaphyses, but the margins are clearly visible (arrows).

(F) Partial lucency of the metaphyses, but the margins are not sharply defined. However, the zones of provisional calcification are not completely lucent and display some calcification.

(G) Complete lucency of the zone of provisional calcification. The epiphyses appear widely separated from the distal metaphyses.

Modified from Thacher TD. et al. Radiographic scoring method for the assessment of the severity of nutritional rickets. J Trop Pediatr 46, 132-139. Creative Commons license http://creativecommons.org/licenses/by/4.0/
(B)

FGF23 → Bone
Osteoclast resorption

PTH → Kidney
1,25(OH)₂D₃

P reabsorption (NaPi2a/c)

Gut
P reabsorption (NaPi2b)

Kidney
P
Urine
RICKETS

Clinical signs
Increased alkaline phosphatase
Low/normal serum levels of phosphate
X-ray changes

Measure serum levels of PTH

High
Calcipenic rickets

Normal/Low
Phosphopenic rickets

Measure urine levels of phosphate

Low
- Insufficient phosphate intake
- Decrease in gastrointestinal absorption of phosphate
- Internal redistribution
- Enhanced extra-renal removal of phosphate from the body

High
- Hereditary hypophosphatemic rickets (including XLH)
- Hereditary hypophosphatemic rickets with hypercalcemia
- Fanconi syndrome
- Acquired form of hypophosphatemic rickets due to high levels of FGF23

Genetic confirmation, unless a non-genetic cause can be proven, or in cases of a positive family history and clear clinical presentation

Measure serum bicarbonate and creatinine to exclude metabolic acidosis and chronic kidney disease