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Consensus

Expert consensus on evidence-based recommendations for the diagnosis, treatment, and follow-up of X-linked hypophosphatemic rickets (XLH)

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Abstract

Introduction: X-linked hypophosphatemic rickets is a hereditary condition causing disruptions in bone mineral homeostasis. The morbidity associated with this condition has exhibited variability in previous decades, possibly stemming from variations in case definitions and diagnostic confirmation procedures.

Objective: Our aim was to generate evidence-informed recommendations for the diagnosis, treatment, and follow-up of patients with suspected or diagnosed XLH.

Methodology: Integration of a literature review with a modified Delphi method, guided by expert consensus.

Results: Following the screening and selection of 1041 documents, 41 were chosen to address the queries posed by the developer group. Experts, consulted through a modified Delphi consensus, endorsed 97 recommendations on the diagnosis, treatment, and follow-up of patients with suspected or diagnosed XLH. Notably, the quality of the evidence was deemed to be low.

Conclusions: The recommendations proposed here will allow early and timely diagnosis of X-linked hypophosphatemic rickets, while optimizing resources for its treatment and follow-up. In addition, it will help clarify the burden of the disease and improve health outcomes for this population.

Keywords: Rickets, Hypophosphatemic, Fibroblast Growth Factor-23, Diagnosis, Therapeutics, Consensus.

Consenso de expertos sobre recomendaciones basadas en la evidencia para el diagnóstico, tratamiento y seguimiento del raquitismo hipofosfatémico ligado al cromosoma X (XLH)

Resumen

Introducción: el raquitismo hipofosfatémico ligado al cromosoma X es una enfermedad hereditaria que provoca alteraciones en la homeostasis mineral ósea. La morbilidad de este cuadro ha mostrado variabilidad en décadas anteriores e incluso contradicciones, posiblemente debido a la definición del caso y la confirmación diagnóstica.

Objetivo: elaborar recomendaciones fundamentadas en evidencia para el diagnóstico, tratamiento y seguimiento de pacientes con sospecha o diagnóstico de XLH.

Metodología: revisión de la literatura y consenso de expertos mediante el método Delphi modificado.

Resultados: después de llevar a cabo el proceso de tamización y selección de 1,041 documentos, se incorporaron 41 para abordar las preguntas planteadas por el grupo desarrollador. Se obtuvieron 97 recomendaciones sobre el diagnóstico, tratamiento y seguimiento de pacientes con sospecha o diagnóstico de XLH, las cuales fueron aprobadas por expertos consultados mediante un consenso Delphi modificado. Cabe destacar que la calidad de la evidencia fue baja.

Conclusiones: las recomendaciones propuestas aquí posibilitarán el diagnóstico temprano y oportuno del raquitismo hipofosfatémico ligado al cromosoma X. Al mismo tiempo, optimizarán la asignación de recursos destinados a su tratamiento y seguimiento, contribuyendo así a dilucidar la carga de enfermedad y a mejorar los resultados de salud en esta población.

Palabras clave: raquitismo, hipofosfatemia, factor de crecimiento de fibroblastos-23, diagnóstico, terapéutica, consenso.

Introduction

X-linked hypophosphatemic rickets (XLH) or X-linked hypophosphatemia is a hereditary disease that generates alterations in bone mineral homeostasis. It represents the most prevalent form among hereditary hypophosphatemic rickets. Its inheritance pattern is X-linked dominant, being mostly transmitted from one of the parents (inherited) and on some sporadic occasions, secondary to *de novo* mutations. The figures for the morbidity of the condition have been variable in previous decades and even contradictory, probably due to the definition of the case and the diagnostic confirmation. It has a global incidence of 3.9 to 5 cases per 100,000 live births and a prevalence between 1.7 and 4.8 per 100,000 people among children and adults [1].

XLH is caused by altered function in the phosphate regulating gene homologous to endopeptidase on chromosome X (PHEX), located on chromosome Xp22.1. The encoded protein is predominantly expressed in osteoblasts, osteocytes, odontoblasts, and cementoblasts (teeth) [2–5]. Studies in animals indicate that PHEX deficiency results in increased secretion of phosphaturic hormone or fibroblast growth factor 23 (FGF23). As a result, there is an increased renal loss of phosphate, attributed to the downregulation of sodium-dependent phosphate cotransporters NPT2a and NPT2c in the proximal convoluted tubule, along with an elevated catabolism of active vitamin D (1,25 (OH)2D3), due to the decrease in 1α-hydroxylase and the increased activity of the enzyme 24-hydroxilase in the subsequent alteration in the synthesis of 1,25 (OH)2D3, also called calcitriol [6]. The renal loss of phosphorus generates chronic hypophosphatemia, altered skeletal mineralization, and rickets/osteomalacia, causing the clinical and radiological signs characteristic of the condition [7–9].

The characteristics and severity of XLH vary from patient to patient with a wide range of signs and symptoms, which differ not only between pediatric and adult patients, but also between cases within the same age group, and even within the same family, a particularity that delays diagnosis and generates variability in treatment, influencing the incidence of complications and affecting the quality of life for both the patient and their family. Taking this into account, our aim was to generate evidence-based recommendations for the diagnosis, treatment, and follow-up of patients with suspected or diagnosed XLH.

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Materials and methods

The recommendations are founded on a thorough review of the evidence, enabling the resolution of clinical questions of interest as proposed by the developer group, involving Colombian specialists in pediatric and adult population: ten nephrologists (nine pediatric and one adult), four endocrinologists (two pediatric and two adult), two pediatric orthopedists and two clinical geneticists, who have been working in either public universities or private hospitals.

Literature review

The search for information that supported the recommendations was carried out based on MeSH, entry and free terms, consulting the specialized databases Pubmed and Embase, development and compiler agencies of clinical practice guidelines (CPG). The search was expanded in Google and Google Scholar and consultation with clinical experts. The inclusion criteria encompassed documents involving patients with clinical suspicion or a confirmed diagnosis of XLH between 2011 and 2021, with publications in English or Spanish. No restrictions were imposed on the study type.

The screening and selection of the information was initially carried out independently by two reviewers (clinical expert and a methodologist), disagreements were resolved by consensus between them. The processes of documents included are presented in a PRISMA diagram (Figure 1). The quality of evidence was assessed according to AGREE II for CPG, AMSTAR-2 for SLR, RoB for clinical trials and the Joanna Briggs Institute tools for observational studies (cohorts or cases and controls), diagnostic tests and case series or case reports.

Expert consensus

The recommendations were socialized and agreed into a panel of external clinical experts that included different specialists in pediatric and adult populations: two pediatric nephrologists, three endocrinologists (one pediatric and two adult), one pediatric orthopedist and one specialist on bone metabolism. The experts that participated in the consensus have worked in Argentina, Brazil, Chile, Colombia, Mexico and Spain. The majority of them worked in university hospitals.

The expert consensus was achieved through the application of the modified Delphi methodology. An online tool was employed containing the 95 recommendations, and the expert panel cast their votes between February 01 and 08, 2022. For recommendations, a cut-off point of at least 80total number of experts responding to each recommendation as the denominator.

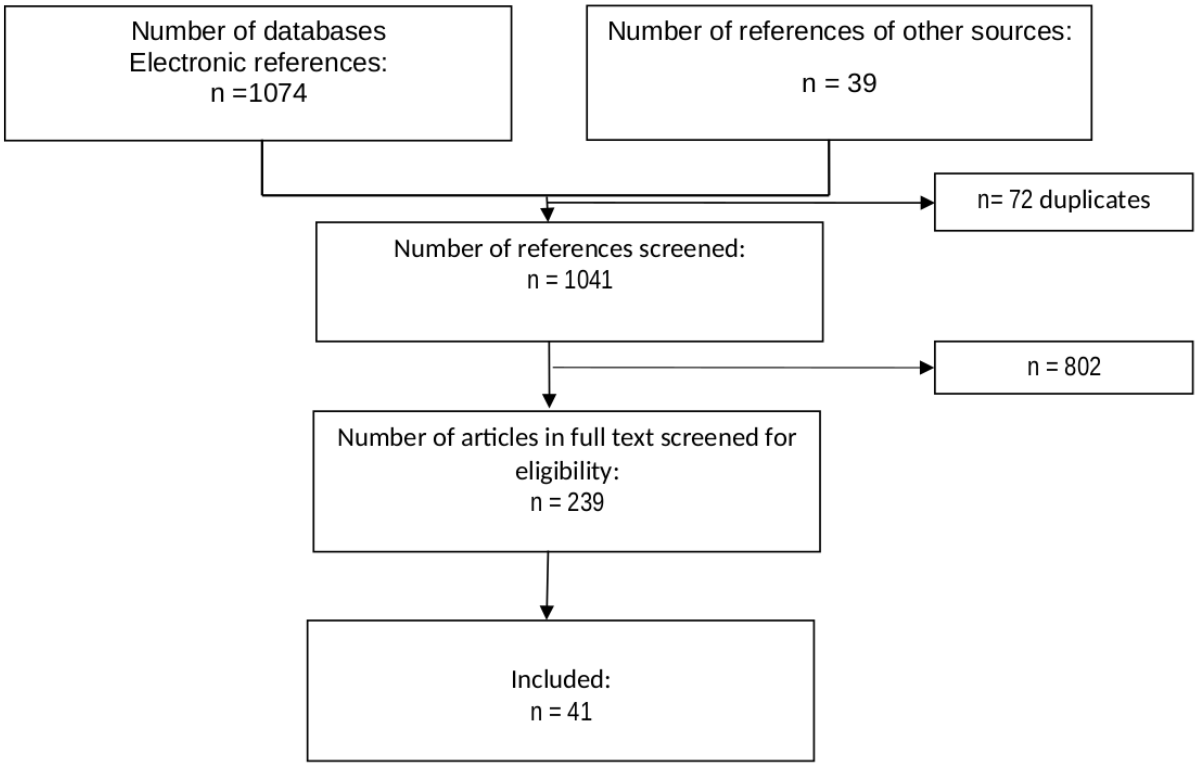

Figura 1. Flow chart – Prism

Source: Own elaboration.

Subsequently, eight recommendations were identified for a synchronous consensus session, during which experts analyzed, discussed, adjusted, and approved them through a round of voting.

Results

A total of 1041 documents were identified. Following the screening and selection process, 38 documents were deemed suitable for addressing the questions posed by the developer group. The types of studies included were institutional clinical guidelines, SLR, rapid technology assessment (Mini-HTA), narrative reviews with and without recommendations, informal expert consensus, documents of recommendations, clinical trials, cohorts of patients, case series and clinical cases. In general, the quality of the evidence was assessed as low.

Diagnosis

The available evidence emphasizes the importance of relating the clinical, radiological and biochemical findings in patients with suspected XLH [7–10]. In this sense, in the pediatric po-

pulation, the recommendation considers clinical and radiological findings, changes in growth rate, serum phosphorous levels lower than reference level for age, renal phosphate loss, and absence of vitamin D deficiency and/or hypocalcemia. In adults, the recommendation considers lower limb deformities, clinical and radiographic signs of osteomalacia, serum phosphorous levels lower than reference range for age along with renal phosphate loss [7].

What is the clinical presentation of XLH?

Recommendations

1. **Strong in favor.** The clinical characteristics of XLH rickets in the pediatric population include asymmetric short stature, bone deformities such as *genu varus, genu valgum*, or rotational deformities of the lower limbs, Chiari malformations and craniosynostosis, gait alterations, dental abscesses, bone pain, muscle weakness and limitation of mobility, which are manifested at an early age. In adults, the deformities described in childhood persist, in addition to osteomalacia, pain, stiffness, enthesopathies, arthrosis, delayed fracture consolidation, and hypoacusia.

2. **Strong in favor.** It is advisable to compile a comprehensive medical history that includes anamnesis, family antecedents of XLH or suggestive signs, review of systems, and a comprehensive physical exam with evaluation of the general condition, anthropometry, measurement of body segments and skeletal deformities.

3. **Strong in favor.** It is recommended to individualize clinical approaches, taking into account the distinct presentations of the disease in both pediatric and adult population.

4. **Strong in favor.** It is recommended to conduct an anthropometric evaluation that includes measurements of weight, height, and head circumference. In pediatric patients, plot the data on graphs referencing tables specific to the general population, categorized by age and gender (consult the reference tables for Colombian population in https://www.growthxp.com/co/).

5. **Expert opinion. Weak in favor.** In cases of *genu varus* after 2 years of age or *genu valgum* after 6 years of age, it is recommended to refer to an orthopedic specialist.

6. **Strong in favor.** It is recommended that the evaluation of the lower extremities includes the measurement of the intercondylar distance in search of the genu varus and the intermalleolar distance for the *genu valgum* and to compare them with the reference tables according to age (Table 1).

7. **Weak in favor.** In the adult population, when there is a suspicion of a change in alignment, it is recommended to refer the patient to orthopedics with a panoramic radiograph of the lower extremities.

Table 1. Normal values of the intercondylar distance (ICD) and intermalleolar distance (IDM) according to age for the definition of the genu varus or valgum

Age	Genu Valgum (IMD)	Genu varus (ICD)
6 months	0-2 cm	0-5 cm
12 months	0-2 cm	0-4 cm
2 years	<6 cm	0-2 cm
3-4 years	<6 cm	0-2 cm
7 years	<6 cm	0-2 cm

Source: Own elaboration based on [11].

Evidence

XLH is characterized by an excess of fibroblast growth factor 23 (FGF23), leading to the loss of renal phosphate [12] that reduces serum phosphate levels. This can cause vitamin D deficiency due to the alteration of renal synthesis of 1,25(OH)2D3 (8), and a decrease in intestinal calcium absorption [13]. Furthermore, it increases levels of alkaline phosphatase (ALP) [7] and parathyroid hormone (PTH) [14].

Bone deformities are common in up to 80 % of patients with XLH [12], including torsional deformities, in the *varus* or *valgum* and shorter length of the limbs with respect to height in a sitting position, especially of the lower extremities [15] that cause *varus* or *valgum* deformity and torsion. There is also an expansion observed in the distal metaphysis of the wrist and the neck of the foot, thickening of the costochondral junctions (Harrison's sulcus), dolichocephaly [7], flattening of the skull base that favors Chiari malformations (25 and 50 % of the children) and craniosynostosis [16]. Abnormal gait is a frequent manifestation in about 70 % of the cases, as well as short stature for age (standard deviation -2.3 + 1.4 in Chinese young people and -4.6 + 2.1 in Chinese adults) and stunted height growth [12–17]. There are cases of dental diseases such as abscesses (30-60 %), bone pain (18 %), fractures (16 %), and muscle weakness [8–10].

In adults, the following clinical and biochemical characteristics of suspected rickets have been documented: short stature, osteomalacia, bone pain, osteoarthritis or arthrosis (55 %), hypophosphatemia, high or normal alkaline phosphatase [13], hypoacusia (adults 48-82 %, children 9 %) [1, 7], high blood pressure (27 %), overweight, obesity, and mobility

limitations [8, 10, 18]. Concerning the radiological findings, they encompass: bowing of the lower limbs, *valgum* or *varus* knees , spinal stenosis, osteoarthritis of the spine, enthesopathies, ossification of the paraspinal ligaments, thickening of the lamina, calcification of the intervertebral disks, hypertrophy of the facet joint, widening of the iliac bones, trapezoidal distal femoral condyles, shortening of the neck of the astragalus, flattening of the talar dome, root dysplasia and enlarged pulp cavities [1], pseudofractures and fractures with delayed consolidation or pseudoarthrosis [13].

The signs or symptoms of the disease can appear between 6 months and 26 years of age, as depicted in descriptive studies of patients with the condition [12].

What biochemical studies are useful for diagnosing XLH?

Recommendations

1. **Strong in favor.** It is recommended to perform biochemical tests such as serum and urinary levels of phosphorus and creatinine, to calculate GFR, tubular phosphorus reabsorption (TPR) and maximum tubular phosphate reabsorption for GFR (TmP/GFR), in addition to calcium, alkaline phosphatase, PTH, 25 (OH) vitamin D3 and 1,25(OH)2D3 (reference values in Table 2 and Table 3).

2. **Expert opinion.** Not graded. Considering that vitamin D deficiency can modify biochemical results, it is recommended to carry out a previous measurement.

3. **Weak in favor.** It is recommended to calculate the TmP/GFR using Equation 1 [22], which is based on the Walton-Bijvoet nomogram [23]:

$$TmP/GFR = Pp - (Up \times \frac{PCr}{UCr}) \quad (1)$$

   Where Pp corresponds to the plasma phosphate concentration, Up is urinary phosphate, PCr is plasma creatinine and UCr is urine creatinine. The normal value ranges between 2.8 and 4.0. A reabsorption below 2.8 is considered low.

4. **Expert opinion. Not graded.** Although the measurement of FGF23 was not widely available and standardized in Colombia until the date of the achievement of consensus, its execution is suggested depending on the availability in the context.

Table 2. Normal values of calcium, phosphorus, and alkaline phosphatase according to age

Age	Calcium (mg/dL)	Phosphorus (mg/dL)	Alkaline Phosphatase (IU/L)	
			Male	Female
0 to <1 month	8.7 - 11	5.6 – 10.5	90 - 273	90 - 273
1 month to <1 year	8.9 – 10.9	4.8 – 8.4	134 - 518	134 - 518
1 year to 3 years	8.9 – 10.5	4.3 – 6.8	156 - 369	156 - 369
4 to 6 years	8.9 – 10.2	4.1 – 5.9	156 - 369	156 - 369
7 to 9 years	8.9 – 10.2	4.1 – 5.9	156 - 369	156 - 369
10 to 12 years	8.9 – 10.2	4.1 – 5.9	141 - 460	141 - 460
13 to15 years	8.8 – 10.1	3.2 – 5.5	127 - 517	62 - 280
16 to <18 years	8.6 – 10.1	2.9 – 5.0	59 - 365	48 - 128
>18 years	8.5 – 10.5	2.5 – 4.5	40 - 150	40 - 150

Source: Own elaboration based on [19, 20].

Table 3. Reference ranges of TmP/GFR, according to age and sex

Years	Sex	Range (mg/dL)	Range (mmol/L)
Birth	Both	3.6 – 8.6	1.43 – 3.43
3 months	Both	3.7 - 8.25	1.48 – 3.30
6 months	Both	2.9 – 6.5	1.15 – 2.60
2-15 years	Both	2.9 – 6.5	1.15 – 2.44
25-35 years	Male	2.5 – 3.4	1.00 – 1.35
25-35 years	Woman	2.4 – 3.6	0.96 – 1.44
45-55 years	Male	2.2 - 3.4	0.90 – 1.35
45-55 years	Woman	2.2 - 3.6	0.88 – 1.42
65-75 years	Both	2.0 - 3.4	0.80 – 1.35

Source: Translated and adapted from [21].

Evidence

FGF23 is a promising biomarker for diagnosing XLH rickets. The latest available evidence suggests that patients with this disease have increased serum levels of FGF23 [7, 12, 24]. However, the diagnosis of XLH does not rely solely on this marker. Low serum phosphorus levels coupled with elevated alkaline phosphatase (ALP), increased or normal PTH, and a deficiency in 1,25(OH)2D3 levels are also taken into consideration in more than half of the cases, regardless of age. In addition, a decrease in the re-absorption of phosphorus in the kidney is taken into account [12].

The biochemical studies reported in the literature with diagnostic purposes in patients with suspected XLH rickets include: serum and urine phosphorus levels (in a partial urine sample), serum and urine creatinine (in a partial urine sample) and the glomerular filtration rate (GFR), to calculate the tubular maximum reabsorption of phosphorus corrected for GFR (TmP/GFR)

where <2.8 corresponds to abnormal phosphate loss by urine and the tubular reabsorption of phosphate (TRP) above 80 % is normal, other tests that should be requested are: PTH, calcium, ALP, and 1,25(OH)2D3 [7, 8, 22].

What initial radiological studies are recommended to be performed in patients with XLH?

Recommendations

1. **Strong in favor.** Comparative AP and lateral radiographs of the wrists and knees are recommended for the diagnosis of XLH, to look for signs of alterations compatible with phosphocalcic metabolism disorders, such as metaphyseal irregularity that shapes the image of a cup with concavity toward the epiphyseal side, increased physis size, presence of growth arrest lines (Harris) in sites of rapid growth, such as the distal femur and the distal radius.

2. **Expert opinion.** Not graded. In adults, it is suggested to perform an AP radiograph of the pelvis and a lateral radiograph of both hips, bilateral AP and lateral of the femur at the time of diagnosis to assess signs of pseudofracture, as well as AP and lateral panoramic of the spine to evaluate calcification of paravertebral ligaments. Additional radiographs are recommended in cases with a history of fracture to evaluate the consolidation status and identify sites of pseudofracture. Similarly, they are warranted in instances of angular or rotational limb deformities.

3. **Weak in favor.** To evaluate the severity of the disease and monitor the response to medical treatment, it is recommended to employ the RSS score (Figure 2). This scoring system is based on the radiographic findings of the wrist and knees on the most affected side.

4. **Strong in favor.** If the patient clinically presents *genu varus* or *genu valgum*, it is suggested to perform a panoramic X-ray of the lower limbs for the diagnosis and location of the deformity.

5. **Strong in favor.** In patients with persistent headache, suspicion of intracranial hypertension or cranial deformity, it is suggested to perform a simple nuclear magnetic resonance of the skull and cervical spine, in search of craniosynostosis, Chiari malformation, and syringomyelia.

6. **Strong in favor.** It is suggested to perform a skull X-ray in the first evaluation for the diagnosis of craniosynostosis. If the first consultation takes place before one year of age

and craniosynostosis is ruled out at that time, it is suggested to repeat it according to clinical evolution.

7. **Strong in favor.** In cases of diagnostic uncertainty with radiographic findings, slow growth of the head circumference or skull deformity, and following prior evaluations by neurosurgery and neuropediatrics, it is advisable to order a computed tomography scan (CT scan) with a bone window and 3D skull reconstruction.

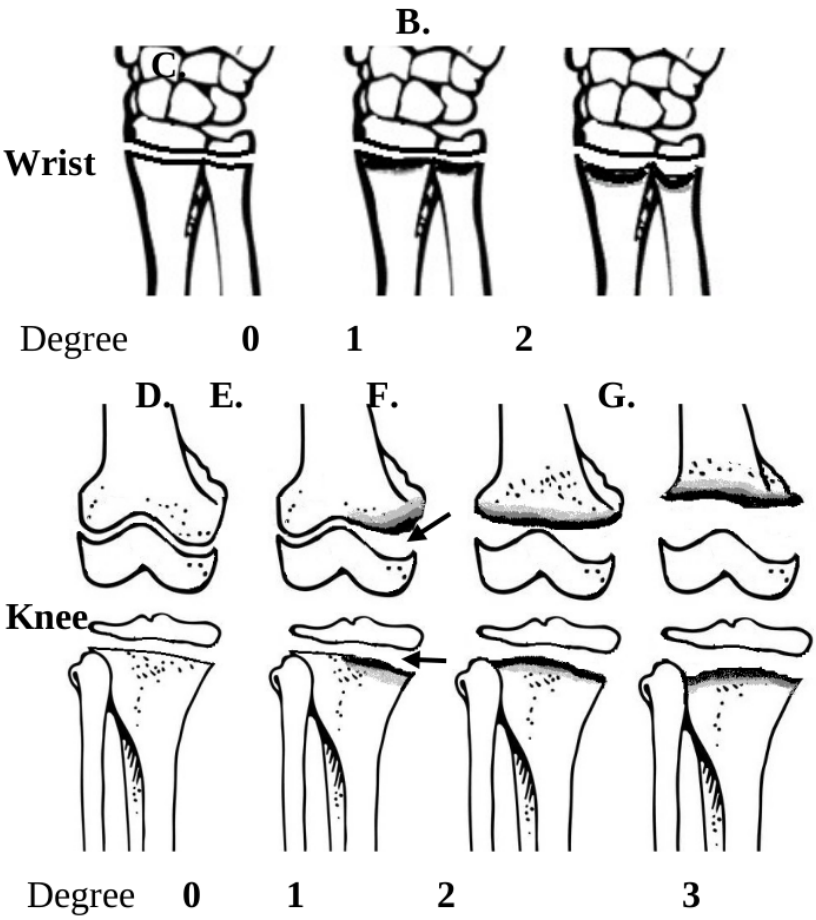

Figura 2. Thacher RSS severity score by grade and segment

Note: A: normal wrist; B: irregularity and widening of the growth plate, but without concave cupping; C: concave metaphyseal cupping and frayed margins. D: normal knee. E: only the medial portion of the femoral and tibial metaphysis is affected. There is partial lucency of the metaphysis, but the margins are clearly visible (arrows). F: partial lucency of the metaphysis, but the margins are not clearly defined. However, the areas of provisional calcification are not completely lucid and have some calcification. G: complete lucency of the provisional calcification area. The epiphyses appear far apart from the distal metaphysis.
Source: Taken and translated from [26].

Evidence

Considering the distinctive bone deformities associated with XLH, X-rays of the knees, wrists, and ankles play a crucial role in elucidating the diagnosis in the pediatric population. The identification of metaphyseal widening and defects in these radiographs [10] are considered the gold standard for diagnosis [25]. After establishing the diagnosis, an anteroposterior (AP) and lateral panoramic radiograph of the lower extremities in standing position, as well as renal ultrasound, evaluation of the ocular fundus, and magnetic resonance are indicated if there is any suspicion of craniosynostosis or signs of increased intracranial pressure. Dental orthopantomography has been recommended after 5 years of age [7].

The Thacher Rickets Severity Score (RSS) (Figure 2) was established based on the observations from wrist and knee X-rays. This scoring system serves as a metric for monitoring the response to treatment in the pediatric population. Although the score considers the metaphyseal concavity and irregularity (fraying or teasing) and the proportion of the growth plate affected, it does not consider the deformities characteristic of rickets, which is why its scores are low. The scoring system consists of a scale of 10 categories that are evaluated from 0 to 4 for the wrist and from 5 to 10 for the knee, always considering the unilateral evaluation of the segment most affected by the disease according to the clinical criteria for the findings of the wrist [21, 23, 25].

In the radiological follow-up of patients, how often are images performed and how useful is bone densitometry (BMD)?

Recommendations

1. **Weak in favor.** It is recommended to assess the severity of the disease through radiographs of the wrists and knees at least once a year in children with an inadequate response to management or in those experiencing a progression of bone deformities despite medical treatment.

2. **Expert opinion.** Not graded. In adults, it is suggested to perform an annual or biannual assessment with an AP radiograph of the pelvis and a lateral of both hips, particularly following the initiation of the treatment. This study is always indicated in the event of increased pain.

3. **Strong in favor.** It is suggested to perform an annual panoramic radiograph of the lower extremities, to follow up the bone deformities, verify the alignment of the extremities, or when a surgical intervention is necessary.

4. **Weak in favor.** For patients undergoing conventional therapy or receiving monoclonal antibodies (Burosumab), it is recommended to undergo a renal ultrasound every two years is for individuals without nephrocalcinosis and annually for those with nephrocalcinosis or diagnosed hypercalciuria.

5. **Strong in favor.** It is advisable to perform a dental orthopantomography at the age of 5 and in adults with recent manifestations, with consideration given to repeating it on an individualized basis as needed.

6. **Strong against.** Routine BMD for bone health assessment is not recommended in patients with XLH.

Evidence

Wrist and knee radiographs are recommended in the pediatric population in cases of persistent clinical or biochemical signs despite adequate treatment. They are also indicated in situations of poor response to treatment, progression of bone deformities, need for orthopedic surgery, presence of unexplained bone pain, and during the transition from childhood to adulthood [7].

Between 30 and 70 % of XLH patients who receive conventional treatment have nephrocalcinosis [10]. It has been recommended to perform a renal ultrasound every two years in patients without nephrocalcinosis, and once this condition is identified, it should be performed annually [7].

Haffer *et al.*, 2019, do not recommend the use of dual energy X-ray absorptiometry (DXA) or peripheral quantitative CT for assessing bone health. This is because these techniques cannot diagnose osteomalacia and are associated with a high rate of false- negative results due to the presence of enthesopathy and ligamentous calcifications in the hip and spine, which can lead to the mistaken detection of abnormally high bone density [7].

Magnetic resonance imaging (MRI) presents itself as a viable imaging alternative for the follow-up of patients with rickets. This option offers the advantage of not exposing individuals to radiation and provides greater accuracy in measuring physeal widening and transverse extension of the widening [14]. It is worth noting that, in some cases, general anesthesia may be required, and the procedure can be relatively expensive.

In which patients is genetic testing indicated to confirm XLH?

Recommendations

1. **Strong in favor.** For every patient with clinical, biochemical, and radiological findings compatible with XLH rickets and with a family history that follows an X-linked pattern of inheritance, it is recommended to perform the PHEX gene sequencing and the duplication/deletion analysis.
2. **Strong in favor.** In atypical cases or in those with a negative family history of XLH, it is recommended to perform the genetic analysis using the NGS panel for specific genes and with a CNV (copy number variation) analysis.
3. **Weak in favor.** To expand the family study in the index case with an already defined mutation, punctual analysis of the pathogenic variant is recommended.
4. **Strong in favor.** In patients in whom the genetic study was initiated with a panel with or without a CNV study, a negative result does not rule out the diagnosis of XLH. It is suggested to complement it with the deletion/duplication study for the PHEX gene.
5. **Expert opinion.** Not graded. Biochemical studies for the diagnosis of newborns with a family history of XLH can be falsely abnormal, as in the case of phosphorus; therefore, it is suggested to perform a molecular study using a sample of peripheral blood, umbilical cord, oral sample or filter paper.
6. **Strong in favor.** It is suggested to adhere to the algorithm proposed by the developer group for the genetic confirmation of the diagnosis of XLH rickets (Figure 3).

Evidence

The diagnosis of XLH relies on the association of clinical, radiological, and biochemical findings. However, for molecular confirmation, genetic testing is recommended to facilitate genetic counseling and identify other affected individuals, offering various available alternatives.

In the case of a clinical, paraclinical, and familial diagnosis compatible with XLH in the pediatric and adult population, it has been proposed to study the PHEX gene by means of next-generation sequencing (NGS) and a deletion/duplication study. Up to 90 % of patients clinically diagnosed with XLH will show a PHEX mutation [8]. In case of suspicion of other types of hypophosphatemic rickets or absence of positive family history, gene-specific panels (NGS), exome sequencing or whole genome sequencing are available [7, 10].

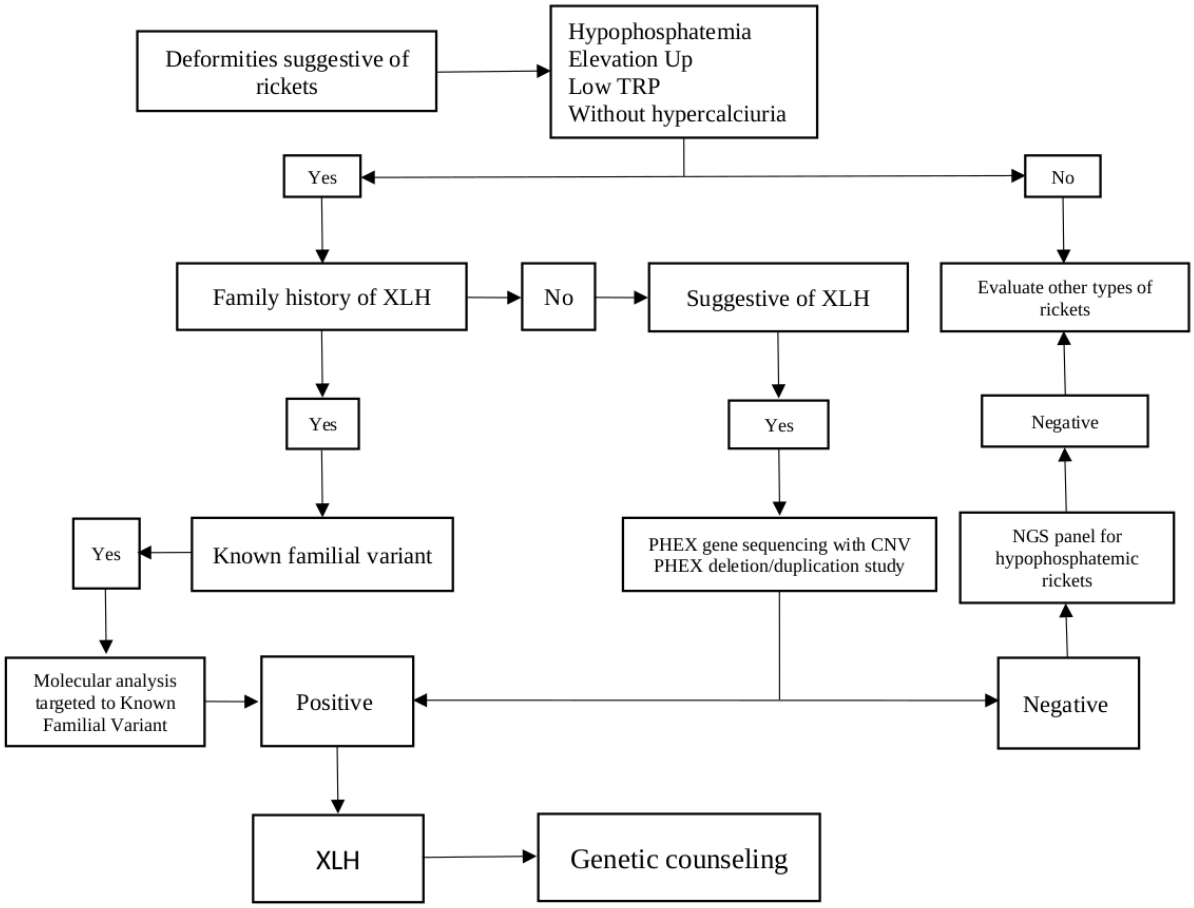

Figura 3. Algorithm for genetic diagnosis

Source: Own elaboration.

Negative results of the NGS panel or of the single sequencing of the PHEX gene do not completely exclude the diagnosis of XLH. It is recommended to carry out the MLPA study (Multiplex Ligation-dependent Probe Amplification) study for the PHEX gene [27].

In the absence of availability of genetic analysis, the diagnosis should be guided by elevated plasma levels of FGF23 and/or a family history positive for XLH. On the contrary, in cases with atypical clinical manifestations and negative genetic analysis, a comprehensive analysis of the patient has been proposed considering biochemical and radiological findings to establish a diagnosis [7].

Genetic counseling is encouraged in cases of genetic confirmation of index case, during transition from childhood to adulthood, and for families planning pregnancy [7], even before obtaining genetic results [8].

What constitutes the standard treatment for individuals diagnosed with XLH, and at what point should this treatment be initiated?

Recommendations

1. **Strong in favor.** In pediatric patients with XLH rickets, it is suggested to initiate conventional treatment at the time of diagnosis.
2. **Expert opinion.** Not graded. No-magisterial formulas are preferred over the magisterial ones, to ensure a standardized composition.
3. **Strong in favor.** In cases involving conventional treatment (Table 4), it is recommended to initiate therapy with phosphate salts at a dose of 20 mg/kg/day and gradually titrating to prevent exceeding the maximum daily dose of 80 mg/kg/day. Dose adjustments should be based on the patient's clinical and biochemical response.
4. **Strong in favor.** Administer the phosphate in several doses (4 to 6 times/day) during the beginning of the therapy and decrease the frequency (3 to 4 times/day) when the biochemical and clinical goals are reached (refer to the section addressing the objectives of conventional treatment).
5. **Weak in favor.** In addition to phosphate, add active vitamin D analogs, such as alfacalcidol, in a daily dose between 0.5 - 3 μg/kg/day or calcitriol 0.02 μg/kg/day up to 1 μg/kg/day adjusting according to the age and needs of the patient.
6. **Weak in favor.** It is recommended to suspend the administration of active vitamin D analogs during extended periods of prolonged immobilization, such as in orthopedic surgeries and fractures.
7. **Strong in favor.** It is recommended to associate nonactive vitamin D analogs with treatment when vitamin D deficiency has been documented.
8. **Expert opinion.** Not graded. Although there is not enough evidence for conventional treatment in adults, it can be considered in symptomatic patients and/or with biochemical and/or radiological evidence of active osteomalacia, monitoring the presence of adverse events such as nephrocalcinosis, hypercalciuria, and hyperparathyroidism.
9. **Weak in favor.** In special conditions such as pregnancy and lactation, conventional phosphate therapy is recommended, the suggested dose is between 0 and 2000 mg/day administered in two doses plus an intake of alfacalcidol 1.5 μg/day or less.
10. **Strong in favor.** It is recommended to consider the preferences of patients and relatives in the choice of the treatment.

Table 4. Scheme of conventional treatment by age

Age group	Dose of oral phosphate	Type of vitamin D and dosage	References
Any pediatric age	35 - 70 mg/kg/day in 3 – 4 doses	Alfacalcidol 1-3 μg/day	Linglart, 2014 [33]
Any pediatric age	20 – 60 mg/kg/day in 3 – 4 doses	Alfacalcidol 0.5 – 1.5 μg/day	Haffner, 2019 [8]
			Imei, 2019 [17]
	20 – 40 mg/kg/day in 3 – 5 doses	Calcitriol 0.02 – 0.03 μg/kg/day in two doses	Carpenter, 2012 [35]
Infants	55 – 70 mg/kg/day in 4 doses	Alfacalcidol 1.5-2 μg/day	Linglart, 2014 [33]
	20–60 mg/kg/ day in 3 – 4 doses	Calcitriol 0.02 – 0.05 μg/kg/day in two doses	Haffner, 2019 [8]
			Juraibah, 2021 [12]
School-age children	45 – 60 mg/kg/day in 3 doses	Alfacalcidol 1-2 μg/day	Linglart, 2014 [33]
Adolescents	35 – 50 mg/kg/day in 3 doses	Alfacalcidol 1.5-3 μg/day	Linglart, 2014 [33]
Adults	750 - 1200 mg/day in 2 doses	Alfacalcidol 0.75-1.5 μg/day	Lecoq, 2020 [36]
	250 – 1000 mg/day in 3 – 4 doses	Calcitriol 0.5-0.75 μg/ day in two doses	Carpenter, 2012 [35]
Pregnancy and menopause	0 – 2000 mg/ day in two doses	Alfacalcidol <1.5 μg/day	Linglart, 2014 [33]

Evidence

The conventional treatment for the management of patients with XLH consists in the combined use of oral phosphate and vitamin D analogs [8, 14]. Some authors also include healthy lifestyle practices, such as maintaining a calcium-rich diet, engaging in regular physical activity, and avoiding smoking and obesity, into the conventional treatment regimen [8]. The physical activity should be subject to and adapted to the functionality and the degree of limitation of the patient, without restriction for any sport but favoring aerobic activities [7].

Regarding the management with phosphate salts (oral phosphorus) and vitamin D analogs (calcitriol or alfacalcidol), there is variability in the recommended doses. However, it is important to individualize the therapy and its dosage, considering the age of the patient, the severity of the phenotype and special cases such as pregnancy or menopause [7, 28].

When the phosphate combination is made with alfacalcidol, the dose varies between 1-3 μg/day and the phosphate between 35 and 70 mg/kg/day, depending on the age of the child [28]. Another alternative corresponds to the combination of alfacalcidol at doses of 0.5-1.5 μg/day with phosphate between 20 [8] and 60 mg/kg/day [16]. Some authors have distinguished the dosage by age group. In infants, it has been suggested a daily dose of phosphate of 55-70 mg/kg/day in 4 divided doses, in combination with one dose of 1.5-2 μg/day of alfacalcidol; in school-age children, phosphate between 45-60 mg/kg/day in 3 doses and alfacalcidol 1-2 μg/day; in adolescents is proposed a dose of alfacalcidol between 1.5-3 μg/day and phosphate 35-50 mg/kg/day in three daily doses. In adulthood, pregnancy, lactation, and menopause, the total dose of phosphate ranges from 0 to 2000 mg/day administered in two doses plus an intake of 1.5 μg/day or less of alfacalcidol [28]. Other authors recommend for adults a dose of elemental phosphorus of 750 - 1600 mg/day and alfacalcidol 0.75-1.5 μg/day.

If the combination of phosphate salts is made with calcitriol, Haffnner et al., recommend elemental phosphorus 20–60 mg/kg/day in infants and preschoolers with calcitriol at an initial dose of 0.02 μg/kg/day, or in children older than 12 months, the empirical dose of calcitriol can start between 0.5-1 μg/day with progressive adjustments according to the clinical response [7, 10].

Alongside the suggestion to administer frequent phosphate intakes (between 4-6 times a day), it is essential to exercise caution not to exceed the maximum daily dose of 80 mg/kg/day [7], since it can produce undesirable gastrointestinal symptoms such as: diarrhea, abdominal pain and hyperparathyroidism. Progressive titration of oral phosphate may be useful at the beginning of treatment to avoid gastrointestinal effects, which are considered one of the limitations of adherence and continuation of therapy [16]. In addition, the association with active vitamin D analogs facilitates the development of hypercalcemia, hypercalciuria, formation of kidney stones and nephrocalcinosis [7, 8, 16]. Other treatment-related alterations include arterial hypertension and hyperkalemia.

A controversial issue in the literature revolves around the discontinuation of conventional treatment in children upon the completion of the height growth stage, with a subsequent recommencement solely upon the reappearance of signs and symptoms associated with XLH rickets [16]. In this sense, different authors agree that conventional treatment is indicated in the presence of symptoms and routine administration of treatment in asymptomatic adults is discouraged [7, 28]. Other indications suggested for temporary suspension are prolonged immobilization in order to avoid hypercalciuria, hypercalcemia, and increased PTH, but with rapid initiation when the patient begins to walk [7].

Re-initiation of treatment is contemplated in the presence of active osteomalacia or associated conditions [16], as well as in situations of an increase in the basal requirements of phosphate and calcium such as in pregnancy and lactation. Inactive vitamin D supplements (cholecalciferol or ergocalciferol) are only indicated for vitamin D deficiency [28].

Despite the established efficacy of conventional therapy supported by FGF23 findings, there is ongoing discussion in some literature about the potential of vitamin D analogs and phosphates to stimulate FGF23 levels. This stimulation could have an effect on the renal loss of phosphate and could reduce the effectiveness of the therapy against XLH rickets, as well as favor the development of hyperparathyroidism [7–16].

On the other hand, a lower risk of loosening the prosthetic joint has been mentioned in patients receiving conventional treatment [29, 30], between 3 and 6 months before the procedure and up to 9 months after surgery [30].

What are the objectives of conventional treatment and how to assess them?

Recommendations

1. **Strong in favor.** In cases of pediatric patients with a diagnosis, but without clinical manifestations, the objective of the treatment is to prevent bone involvement.
2. **Strong in favor.** The objectives of conventional treatment in pediatric patients with XLH rickets are:
    a. To improve the quality of life.
    b. To reduce bone pain.
    c. To improve the growth rate and final height of the patient.
    d. To improve the radiographic alterations and bone mineralization, as well as the periodontal disease.
    e. To minimize the complications associated with conventional treatment, such as secondary hyperparathyroidism and nephrocalcinosis.
    f. To normalize the levels of biomarkers such as alkaline phosphatase and PTH. Given the potential complications of conventional treatment and the limitations therein, it is not sought to normalize phosphorus.
    g. To avoid the recurrences of lower limb deformities after surgical management.

3. **Strong in favor.** The objectives of conventional treatment in adult patients with XLH rickets are:

    a. To reduce musculoskeletal pain.

    b. To prevent the development of osteomalacia and pseudofractures.

    c. To improve oral health (periodontitis, dental abscesses).

    d. To improve mobility and functionality.

    e. To avoid joint stiffness.

    f. To improve fracture consolidation.

Evidence

Conventional therapy should aim to normalize altered biochemical markers in XLH rickets, such as ALP and FGF23 [14]. Likewise, conventional treatment seeks to improve quality of life and functionality by maintaining range of motion, reducing bone pain, optimizing the growth rate and final height, reducing periodontal disease, and strengthening muscle tone, all in order to avoid or delay the need for surgical treatments and minimize bone deformities [7, 8]. In adults, treatment objectives should aim at the prevention or healing of pseudofractures and fractures, pseudoarthrosis, and improvement of osteomalacia [2].

Achieving treatment objectives relies on a combination of biochemical and clinical monitoring, enabling informed decision-making in the management of patients with XLH [7,10]. The clinical response to treatment is assessed by stature growth, comparing standing and sitting measurements, head growth, improvement in lower limb deformities, and an assessment of gait, muscle function and frequency of appearance of dental abscesses. Plain knee radiographs every 6 months are a useful tool in follow-up of therapy effectiveness, and annual or biannual measurement of intermalleolar and intercondylar distances can support adjustments in therapy [10]. On the other hand, measurement of serum levels of calcium, phosphorus, creatinine, ALP, PTH, as well as determination of calcium and creatinine in isolated urine or 24-hour urine collection, are biomarkers used for the evaluation of therapy, especially with respect to its safety with regard to the development of hyperparathyroidism or nephrocalcinosis [16]. Regular ultrasound monitoring of the renal parenchyma every two years is recommended for the early detection of nephrocalcinosis/lithiasis associated with conventional treatment [10]. It has been suggested that the frequency of biochemical analyzes should be 2 weeks after the start of treatment and then every 3 months during childhood [10, 28], every 6 months during puberty, and every 6 months or annually in adults [28].

When should monoclonal antibody treatment start in patients with a diagnosis of XLH rickets?

Recommendations

1. **Weak in favor.** Initiation of Burosumab is recommended in pediatric patients aged one year or older, with severe rickets and with at least one of the following manifestations: nephrocalcinosis, hyperparathyroidism, craniosynostosis, or growth retardation of more than 2 standard deviations in stature.

2. **Weak in favor.** Switching from conventional therapy to targeted therapy with monoclonal antibodies is recommended in the pediatric population in case of not achieving therapeutic objectives, severe intolerance, lack of adherence to treatment and in the presence of significant adverse events, 6 months after the start of the conventional therapy.

3. **Weak in favor.** The use of monoclonal antibodies is recommended for adult patients with a confirmed diagnosis of XLH, supported by radiographic evidence of bone disease, persistent bone, and joint pain, osteomalacia that affects functionality and activities of daily living, pseudofractures, fractures, insufficient or refractory response to conventional therapy or with need of orthopedic surgery such as osteotomies for limb alignment, management of delayed consolidations, or joint replacements.

4. **Strong in favor.** Initiation of monoclonal antibody treatment in pediatric patients with XLH rickets is recommended at doses of 0.8 to 2 mg/kg every 2 weeks and in adult patients at 1 mg/kg every 4 weeks with a maximum dose of 90 mg per dose.

5. **Expert opinion.** Not graded. For patients transitioning from childhood to adulthood, it is advisable to undergo assessment by an interdisciplinary medical board. This evaluation aims to redefine therapeutic objectives and consider potential adjustments the monoclonal antibody dose, considering the opinion of both, the patient and their family.

6. **Strong in favor.** It is recommended to discontinue the management with monoclonal antibodies when serum phosphorus levels surpass the age-normalized values. Subsequent follow-up within 2 to 4 weeks is advised to define the resumption of the therapy. In such instances restarting treatment is recommended at half the prescribed dose before the suspension.

7. **Strong against.** Adjusting the dose of monoclonal antibody in periods shorter than 4 weeks is not recommended.

8. **Strong in favor.** The use of monoclonal antibodies concomitantly with conventional treatment is not recommended, neither in the case of evidence of serum phosphorus va-

lues higher than the minimum normal levels for age, nor in patients with stage 5 chronic kidney disease.

9. **Expert opinion.** Not graded. Individualized follow-up and adjustment of phosphorus intake in the diet is recommended in patients receiving monoclonal antibodies, especially in those with CKD in advanced stages.

10. **Strong in favor.** In women of childbearing age who are receiving monoclonal antibody treatment, education and prescription of contraceptive methods is recommended.

11. **Strong in favor.** Given the lack of evidence of the use of monoclonal antibodies in cases of pregnancy or lactation, it is recommended to suspend monoclonal antibody therapy and to consider starting conventional therapy in these periods, at least while new information on safety and efficacy in this group of patients becomes available.

Evidence

Burosumab is the anti-FGF23 monoclonal antibody approved for its use in patients with XLH after the first year of life. Its development and inclusion as therapy for the management of XLH rickets in some European and American countries is recent (2018) [10, 32].

The available presentations are 10, 20 or 30 mg/ml for subcutaneous administration [33]; the treatment dose ranges between 0.8 mg/kg and 2 mg/kg (up to 90 mg per dose) every two weeks in pediatric population [34] and 1 mg/kg every 4 weeks in adults [33].

The findings from studies that evaluated the drug's efficacy in individuals with XLH indicate an improvement in the serum phosphorus levels, ALP and TmP/GFR, in addition to reduction in the severity of the disease measured through the rickets severity score, reduction in lower limb deformities, and an improvement in growth and mobility [8, 10, 34].

In the pediatric population, notable improvements were observed serum phosphorus and ALP levels, growth rate, reduction of the deformities, attenuation of rickets, severity and enhance mobility [2, 35].

In the available studies examining Burosumab in adults, improvements were observed in phosphorus levels and in TmP/GFR, along with the normalization of 1,25(OH)2D3 levels. In addition, there was a significant reduction in stiffness, as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale, enhanced fracture consolidation, and notable improvements in pain, functionality well-bwing, and, osteomalacia [2, 35].

Regarding the indication for Burosumab use, it has been suggested in different documents to start treatment when XLH is confirmed, with radiographic evidence of bone disease in children aged one year or older, with serum levels of phosphorus lower than those expected for the age measured with a minimum of 4 hours of fasting [9] and those in the growth stage [9, 10, 16]. Furthermore, according to Haffner et al., 2019, it is recommended to start Burosumab therapy in the pediatric population in the presence of radiographic evidence of bone disease resistance to conventional therapy, evidence of associated complications, or when the patient faces challenges in adhering to conventional therapy. Adequate follow-up is advised in such cases [7].

In the European Union in the year 2020, the indication for initiating the drug was accepted, specifically in cases presenting radiographic evidence of bone disease [8]. For this age group, other authors have proposed starting therapy with Burosumab in cases of persistent bone and joint pain, osteomalacia impacting functionality and daily activities, pseudofractures, fractures, insufficient or refractory response to conventional therapy [7]. It is worthwhile to mention that in the clinical trials that evaluated treatment with monoclonal antibody vs. placebo, 99 % of patients presented radiographic findings of enthesopathies, 69 % of the adult patients had a history of orthopedic surgery, 72 % had a worst pain score higher than 6 in a pain scale of 10, had received analgesic medication and 22 % opioids [2], for which in some cases it has been suggested to consider targeted therapy in patients with an indication for orthopedic surgery [36].

It is important to note that the administration of Burosumab should be discontinued in cases of high serum phosphorus levels beyond the age-normalized range. Follow-up evaluations four weeks after the suspension are essential in order to make the decision to restart therapy in the event of persistently low levels for the patient's age [33]. In case you consider restarting therapy, it has been recommended to do so with half the dose [7]. Furthermore, discontinuation is advised in cases of pregnancy. The initiation of antibody therapy has not been recommended in women of childbearing age without a contraceptive method. Therefore, it has been suggested to initiate contraception prior to the initiation of treatment [36]. In Europe, it is advisable to consider discontinuation of treatment in cases of reduction in growth rate of less than 2 cm/year [9]. Similarly, Burosumab is contraindicated in patients with stage 5 chronic kidney disease (CKD), concomitant conventional treatment, and hypersensitivity to the drug [32].

How is the response to monoclonal antibody treatment evaluated?

Recommendations

1. **Weak in favor.** Clinical follow-up is recommended in patients with XLH receiving monoclonal antibody treatment at each medical visit, through the measurement of head circumference, standing and sitting height, evaluation of lower limb deformities, presentation of abscesses, loss of teeth, requirement of dental procedures, estimation of muscle strength, presence and severity of pain, stiffness, motility and management required (Table 5).

2. **Strong in favor.** In patients with XLH receiving monoclonal antibody treatment, it is suggested to perform the 6-minute walk test once a year (Table 5).

3. **Weak in favor.** Once monoclonal antibody treatment is started in patients with XLH, it is recommended to perform paraclinical evaluation with serum phosphorus levels every 2 or 4 weeks until reaching the lower limit of the expected values for age. Measurement of serum creatinine, calcium and phosphorus (in blood and isolated urine), alkaline phosphatase, PTH, albumin (for calculation of corrected calcium) and TmP/GFR is also suggested every 3 or 4 months and of 1.25(OH)2D3 between 6 and 12 months (Table 5).

4. **Expert opinion.** Not graded. In pediatric patients with XLH rickets in the growth stage and under treatment with monoclonal antibody, it is suggested to perform knee X-rays every six months and until stability of treatment is achieved to assess improvement in disease signs (Table 5).

   In favor. Strength to be defined by consensus.

Table 5. Follow-up and periodicity of the treatment with monoclonal antibody

Monitoring of patients with X-linked hypophosphatemic rickets						
Category	**Previous /Initial**	**2-4 weeks**	**Month 3**	**Month 6**	**Month 9**	**Month 12**
Clinical Control						
Weight	X		X	X	X	X
Standing and sitting height	X		X	X	X	X
Head circumference	X		X	X	X	X
Lower limb deformity	X		X	X	X	X
Dental abscesses and/or losses	X		X	X	X	X

Functional status (strength, pain, need for treatment)	X		X	X	X	X
Adherence to treatment	X		X	X	X	X
Tolerability/adverse events	X		X	X	X	X
Laboratory tests						
Serum calcium	X		X	X	X	X
Fasting serum phosphorus	X	X	X	X	X	X
Alkaline Phosphatase	X		X	X	X	X
PTHi	X		X	X	X	X
Creatinine	X		X	X	X	X
Albumin	X		X	X	X	X
1,25 (OH) Vitamin D	X			X		X
FGF23	X			X		X
Calcium in occasional urine	X		X	X	X	X
Phosphorus in occasional urine	X		X	X	X	X
Creatinine in occasional urine	X		X	X	X	X
Images						
X-rays of knees	X		Every 6 months until treatment stability is achieved			
Kidney ultrasound	X					X
Test						
6-minute walk test	X					X
WOMAC	X					X

Source: Own elaboration based on [28].

Evidence

Once treatment with Burosumab has been started, dose optimization is based on the findings of serum phosphorus values every 2 weeks in the first month and every 4 weeks for the following two months until reaching the lower limit of the expected values of this biomarker according to the age of the patient [10], starting with a dose of 0.4 mg/kg to 0.8 mg/kg [34] until reaching the maximum dose of Burosumab of 2mg/kg or 90 mg/dose [7, 9]. In children under 5 years of age, monthly follow-up of the therapy has been recommended during the three first months [9, 32, 33], in adolescents every 3 months and in adults every 6 months [7].

After achieving the stabilization of serum phosphorus, the available evidence suggests a clinical follow-up approach that includes monitoring the head circumference, sitting and standing height, and lower limb deformity in children. Starting with dental eruption, biannual dental visits to the dentist are recommended to detect caries, dental abscesses, tooth loss, and the need for procedures. The proposal involves conducting the 6-minute walk test semiannually. Additionally, assessing muscle strength, presence and severity of pain, evidence of joint stiffness and fatigue is recommended at each patient visit, occurring every 3 to 6 months in pediatric age and every 6 to 12 months in adults. Finally, biochemical follow-up is performed with serum phosphorus and occasional urine sample, serum and urine creatinine (to calculate TmP/GFR), calcium in serum and isolated urine, alkaline phosphatase, PTH, and 1,25 OH2D3 [10].

The hearing evaluation is carried out from the age of 8 years, and the frequency of this evaluation will depend on the presentation of symptoms [7].

The Thacher Rickets Severity Score was initially designed to assess the response to Burosumab treatment [25, 26]. Similarly, the radiographic impression of the change score allows the evaluation of the treatment results. This involves a comparative analysis of baseline and follow-up radiographs to identify changes or differences between them, which are scored on a scale of 7 points, graduated between -3 and 3. Negative scores indicate deterioration, while positive scores indicate improvement in rickets severity. The score of -3 corresponds to the category of highest severity while a score of 3 corresponds to complete improvement.

What are the risks of starting monoclonal antibody treatment?

Recommendations

1. **Strong in favor.** Follow-up, surveillance, and reporting of possible adverse effects associated with monoclonal antibody therapy previously described in the literature, such as pain at the administration site, headache, pain in the extremities, skin rash, dental pain, myalgia, and dizziness, are recommended.

Evidence

In patients with XLH rickets treated with Burosumab, the following associated adverse effects have been reported over a time horizon of 64 weeks: pain at the application site (57 %), headache (54 %), pain in the extremities (42 %), reduction in the concentration of 1,25 $(OH)_2D3$ (28 %), skin rash (23 %), dental pain (19 %), dental abscesses (14 %), myalgia (14 %) and dizziness (11 %) [9,37]. Considering the recent incorporation of this new therapy into the XLH treatment

landscape, it is likely that the current accumulated follow-up time has not yet provided a comprehensive assessment of complications associated with the antibody. Ongoing studies are anticipated to furnish detailed information on these aspects in the future.

When and how is orthopedic surgical treatment indicated in XLH?

Recommendations

1. **Weak in favor.** To address deformities correctly, it is recommended that the disease be under metabolic control for at least one year, due to the high risk of recurrence.

2. **Weak in favor.** The follow-up and evaluation of angular deformities should be performed with AP and lateral panoramic radiographies of the lower limbs, ideally every year, unless the patient has no changes for 3 consecutive years, in which case it is suggested to do it every two years.

3. **Strong in favor.** It is recommended to employ guided growth techniques for correcting angulations, particularly in patients with open physis, where the apex of the deformity is located close to the epiphyses.

4. **Weak in favor.** It is recommended to perform correction for angulations with one or several apexes in the diaphysis with osteotomies and intramedullary fixation with a telescopic nail.

5. **Strong in favor.** In the adult population, the correction of the deformities will depend on the patient's age, the comorbidities, the location of the deformity and joint involvement.

6. **Strong in favor.** It is suggested that the follow-up of the deformities and the performance of the surgical procedure should be carried out by an interdisciplinary team with experience in metabolic bone diseases.

Evidence

The presence of angular and rotational deformities of the lower limbs secondary to XLH rickets is common. Initial management is focused on adequate treatment of bone metabolic alteration, but on some occasions the deformities persist and at this point surgical treatment is indicated. Surgical treatment is frequent in more than half of adult patients with XLH rickets. Osteotomy (63 %), knee replacement (12 %) and hip replacement (8 %) have been reported among the most common procedures [18].

In the cohort of patients described by Gizard *et al.*, in 2017, it was reported that 65 % ($n = 32$) of the patients had *genu varus* and the rest of them ($n = 17$) *genu valgum*. The most frequent surgical procedure (94 %) was osteotomy with correction and fixation for bone alignment purposes. Deformity recurrence was reported in 29 % of the operated patients, with a lower incidence observed in patients who underwent surgeries after the age of 15 or after growth completion. The complications presented by the patients were: absence of postoperative consolidation, fractures, infection, osteitis, early arthrosis, and hypoesthesia in the area of the tibial nerve [38]. Guided growth has also been documented in the pediatric population to avoid increased angulation or to correct to correct for deformities [39].

Corrective surgery has been indicated in cases of significant deformities of the lower extremities that affect functionality or imply long-term joint involvement [38]. In addition, surgery is justified after unsatisfactory medical treatment, that is, when the bone deformities in the lower limbs and bone pain persist [28, 39]. Surgical treatment should be delayed until the completion of growth and physis closure, aiming to avoid recurrence of deformities and therefore the need for new interventions [28]. Nevertheless, there is a special emphasis on early follow-up of the *varus* or *valgum* knee and analysis of the proximal joints, anticipating potential complications like future deformities such as the foot and ankle *valgum* or femoral antecurvatum [39]. Elective surgical treatment has been recommended in the pediatric population with intensive medical treatment for at least 12 months [7], including guided growth in cases of persistence of deformities despite the medical management [40].

The surgical decision should consider the age of the patient, the potential for growth, and the location and severity of the deformity. Relevance of surgery should be considered in cases of persistent deformity (axis deviation Zone 2 or greater) [7].

How are the follow-up and clinical and paraclinical controls of patients with XLH carried out?

Recommendations

General considerations for follow-up:

1. **Strong in favor.** It is recommended that the follow-up of all the patients should be carried out by a multidisciplinary team, with an emphasis on the management of the needs of the patient and the optimization of his/her quality of life. The goal is to anticipate, detect and early and appropriately treat complications associated with the disease and its treatment.

2. **Strong in favor.** It is recommended to focus on the psychological treatment of the patient and his family, both due to the impact of the disease itself, as well as the feelings of guilt that may arise in some parents of affected children.

3. **Strong in favor.** At each control, it is recommended to compile a comprehensive clinical history, considering the current disease, review by systems, presentation of symptoms, musculoskeletal pain, medications used, dosage, and tolerance. Additionally, the evaluation and anticipation of potential complications should be a focal point.

4. **Weak in favor.** It is recommended to perform the 6-minute walk test and assessment of quality of life (for adults the WOMAC Scale and for children the PROMIS-Patient-Reported Outcomes Measurement Information System scale) in patients over 5 years of age, every year by trained professionals.

5. **Strong against.** Routine bone biopsy is not recommended. However, its performance is subject to the clinical criteria of the treating specialist.

6. **Strong in favor.** Evaluation and management by dentistry is recommended at least every 6 months, and more frequently, depending on the presentation of complications and the need for treatment.

7. **String in favor.** It is recommended to perform the following laboratories in each control: serum calcium and phosphorus, total AP, serum creatinine, evaluation of calciuria (UCa/Ucreat or calcium in 24-hour urine) and phosphaturia (tubular reabsorption of phosphate and maximum tubular transport of phosphate).

8. **Weak in favor.** It is suggested to perform a bone-specific PA test in adults when available in the context, considering that it is not an essential biomarker for diagnosis or follow-up and that it can be replaced by total PA in the absence of liver or kidney disease or obesity.

9. **Weak in favor.** The six-monthly evaluation of parathyroid hormone and $1,25(OH)_2D3$ is recommended, the latter of special interest in patients treated with specific therapy.

10. **Strong in favor.** In patients receiving conventional treatment, strict laboratory monitoring is suggested to detect hypercalciuria, nephrocalcinosis, and chronic kidney disease. In cases of insufficient treatment, the possibility of tertiary hyperparathyroidism should be evaluated.

11. **Strong in favor.** In patients under treatment with monoclonal antibody, evaluation of serum phosphorus and TMp/GFR is recommended every 2 weeks during the first month

of treatment, then every 4 weeks for two months and then, after stabilization of serum phosphorus levels, in each routine control.

Serum phosphorus should be measured 4 weeks after each dose adjustment. Periodic dose adjustments are recommended based on changes in body weight, growth rate, and skeletal mineralization.

12. **Weak against.** Routine quantification of FGF23 levels is not recommended.

13. **Strong in favor.** Suggesting an evaluation by both pediatric and adult orthopedics is recommended for all patients, particularly those with significant limb deformities. This aims to facilitate imaging evaluation and a comprehensive treatment.

The recommendations for follow-up by age group are summarized in Table 6: Follow-up of patients with XLH rickets by age category.

Patients in pediatric age:

14. **Strong in favor.** Individualized follow-up is recommended for each patient, initially at least every 3 months. In patients who are in the phase of adjustment of pharmacological treatment, controls are suggested every 2 to 4 weeks.

15. **Strong in favor.** In patients under treatment with monoclonal antibody, with clinical and drug dose stability, it is suggested to have controls every 3 to 6 months.

16. **Strong in favor.** It is recommended to carry out a complete physical examination, recording the anthropometric data of weight, height, body mass index, growth rate, and head circumference for the detection or follow-up of craniosynostosis. Ocular fundus examination is suggested every 6 months until 3 years of age and then annually in the search for signs of intracranial hypertension.

17. **Strong in favor.** Evaluation of intermalleolar and intercondylar distance, psychomotor development, muscle function, bone and joint pain, complete examination of the spine (lordosis, kyphosis, or scoliosis) and blood pressure record are suggested at each consultation.

18. **Strong in favor.** Hearing evaluation by an otorhinolaryngologist is recommended according to the presentation of symptoms in this regard.

Patients in adult age:

19. **Strong in favor.** Follow-up in adult patients is suggested every 6 to 12 months depending on their individual needs.

20. **Strong in favor.** Stricter controls are recommended if the patient is in the phase of medication adjustment.

21. **Strong in favor.** It is recommended to perform a complete physical exam, recording anthropometric data of weight, height, body mass index, evaluation of intermalleolar and intercondylar distances, muscle function, bone and joint pain, complete examination of the spine (lordosis, kyphosis or scoliosis), alcohol consumption, and record of blood pressure at each visit, as well as evaluation of the ocular fundus annually.

22. **Weak in favor.** Hearing evaluation by an otorhinolaryngologist is recommended at least once a year.

Table 6. Follow-up of patients with XLH rickets by age category

Category	**Under 18 years of age**					**Adults**	
Periodicity	**Initial /Previous**	**Month 3**	**Month 6**	**Month 9**	**Month 12**	**Month 6**	**Month 12**
Clinical Control							
Weight	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X
Lower limb bowing	X		X		X		X
Head circumference (up to 5 years)	X						
Functional status	X	X	X	X	X	X	X
Assessment by dentistry	X		X		X		X
Hearing evaluation by		According to clinical evolution					
Blood							
Total calcium	X	X	X	X	X	X	X
Phosphorus	X	X	X	X	X	X	X
Alkaline Phosphatase	X	X	X	X	X	Bone phosphatase[£]	Bone phosphatase[£]
Creatinine	X	X	X	X	X	X	X
PTHi	X		X		X	X	X
1,25(OH)2D3	X		X		X		X
Urine (*) (**)							
Calcium in urine*	X	X	X	X	X	X	X
Phosphorus in urine*	X	X	X	X	X	X	X
Creatinine in urine*	X	X	X	X	X	X	X
UCa/Ucr ratio	X	X	X	X	X	X	X
TPR	X	X	X	X	X	X	X
TmP/GFR	X	X	X	X	X	X	X

Calcium in 24-hour urine	X	X	X	X	X	X	X
Images							
X-rays (Knees, Wrists, etc.)	X	According to clinical evolution					
Adherence to treatment		X	X	X	X	X	X
Tolerability/adverse events		X	X	X	X	X	X

Note: *In an isolated urine sample. **In 24-hour urine. Schwartz formula; TRP: Tubular reabsorption of phosphate; TmP/GFR: maximum tubular reabsorption of phosphates for the glomerular filtration rate; $\mathcal{L}$: In cases of availability, perform bone ALP, otherwise request ALP.
Source: Own elaboration based on [28].

Evidence

The available evidence advocates for regular follow-up at least every 3 months during childhood and puberty, for patients with XLH rickets or following the initiation. These follow-ups should involve multidisciplinary teams, headed by an expert in metabolic bone diseases. Once patients have a favorable response to treatment or are stable, follow-up could be performed biannually. In the case of adults, follow-up has been proposed every 6 months to assess response to treatment or annually when they do not receive pharmacological treatment [7, 8].

Regarding the clinical follow-up of the pediatric population, the evidence indicates that measurement of height, weight, head circumference (up to five years of age), intercondylar and intermalleolar distances, blood pressure, estimation of the body mass index (BMI) and annual growth rate should be included in each visit; as well as the evaluation of the shape of the head, presence of signs of intracranial hypertension, dental abscesses, bone pain, fatigue, functionality, and search for hearing alterations and spinal deformities [7, 8]. Furthermore, bone age should be assessed in children older than 5 years of age with growth retardation. In the case of bone deformities, orthopedic follow-up has been recommended [7].

Additionally, follow-up in adults has been promoted in search of complications such as: enthesopathies, osteoarthritis, spinal deformity, muscle weakness, range of motion, Chiari type 1 malformation or intracranial hypertension [7].

Biochemical follow-up has been recommended for all patients regardless of age. Despite the promising results of the measurement of FGF23 in the diagnosis of XLH, its routine use for follow-up has been discouraged [7]. Although bone-specific ALP measurement in adults and total ALP in children is considered a follow-up marker that does not vary significantly during the day; in the case of children, the values must be adjusted for age and sex for correct

interpretation. Measurement of calcium in 24-hour urine or UCa/urine allows identification of hypercalciuria [8].

In the case of monoclonal antibody treatment, special emphasis is placed on the follow-up of fasting serum phosphorus and the measurement of TmP/GFR every 2 weeks during the first month of treatment and monthly from the second month of treatment or when there are therapy adjustments. For $1,25(OH)_2D3$, it is recommended to conduct measurements every 6 months, along with the measurement of urinary calcium excretion [7].

Radiographic follow-up is not widely recommended, especially in the pediatric population, considering exposure to radiation. Therefore, the main emphasis is placed on clinical and biochemical follow-up.

Bone biopsy has not been routinely recommended for the diagnosis of XLH follow-up [8].

How is comprehensive care of patients with XLH implemented?

Recommendations

1. **Strong in favor.** It is recommended that patients with XLH rickets receive comprehensive care, necessitating the formation of an interdisciplinary team led by pediatric or adult nephrology and endocrinology, depending on the patient's age. This team should include specialists in internal medicine, pediatrics, rheumatology, genetics, neurosurgery, orthopedics, ophthalmology, otorhinolaryngology, maxillofacial surgery, physical medicine and rehabilitation, in addition to the support of physiotherapy, social work, psychology, dentistry and nutrition.

2. **Strong in favor.** The creation of interdisciplinary teams that are experts in the comprehensive care of patients with bone metabolism disorders is suggested, as well as in the management of comorbidities and complications.

3. **Strong in favor.** It is recommended that the patient and their family group receive appropriate genetic counseling since confirmation of the disease.

4. **Strong in favor.** The creation of transition programs with defined and appropriate protocols for the comprehensive care of pediatric patients with XLH who reach adulthood is suggested.

Evidence

The collected evidence coincides in promoting the comprehensive care of patients with XLH rickets, with the interest of evaluating patient-centered outcomes and improving quality of life [8]. The conformation of the multidisciplinary team is expected to be led by an endocrinologist or nephrologist expert in bone metabolism disorders, and should include different specialties and professions according to the patient's needs, considering orthopedists, dentists, physical therapists, occupational therapists, clinical geneticists, audiologists, ophthalmologists, neurosurgeons, radiologists, nurses, social workers, psychologists and nutritionists [8–10]. Surgical treatment has been recommended to be implemented by surgeons who are experts in bone metabolism [7].

In addition to the multidisciplinary team, it is recommended to implement local or institutional protocols that guide the transition from pediatric to adulthood. These protocols should integrate different levels of care and involve patients, their families, and caregivers. Additionally, protocols on the disease should be established to allow primary care physicians to understand and direct the patient to an appropriate diagnosis, treatment, and follow-up [8].

What are the main complications derived from treatment in patients with XLH?

Recommendations

1. **Expert opinion.** Not graded. The complications associated with conventional treatment for XLH are: hypercalciuria, nephrocalcinosis, secondary or tertiary hyperparathyroidism, nephrolithiasis, ectopic calcification, and alterations in renal function.

   Regarding Burosumab treatment, the presentation of hyperphosphatemia, dental abscesses, and heterotopic calcifications have been described as complications. Further studies are required to clarify the long-term complications of Burosumab therapy.

2. **Strong in favor.** High doses of phosphate solution can cause side effects such as emesis, abdominal pain, and diarrhea; for this reason, it is recommended to distribute the dose throughout the day, for example, diluted in a bottle of water to be taken for several hours.

3. **Strong in favor.** To avoid side effects of the phosphate solution and improve adherence in adults and adolescents, it is recommended to distribute the daily dose in 3 to 4 doses during the day. If hypercalciuria occurs as a complication of the treatment (high doses of calcitriol and/or low doses of phosphates or lack of adherence to dietary treatment), it is recommended to reduce the dose of calcitriol and reinforce the diet. If hypercalciuria

persists or nephrocalcinosis is detected during follow-up, the suspension of the treatment should be considered, in addition to a reassessment with the treating team for its adjustment.

4. **Strong in favor.** It is recommended to treat hypercalciuria with hydrochlorothiazide (at a dose of 1 mg/kg in children and a maximum dose of 50 mg in adults) with strict monitoring of side effects such as hypotension, hypokalemia, hyponatremia, or hypomagnesemia.

5. **Strong in favor.** In case that secondary hyperparathyroidism appears in patients who are under conventional treatment, it is recommended to increase the dose of calcitriol or to reduce the dose of phosphate salts. If the condition persists despite these adjustments, it is suggested to consider discontinuing the phosphate and calcitriol solution and evaluate the treatment adjustment with the interdisciplinary team.

6. **Strong in favor.** In case that secondary hyperparathyroidism appears in patients who are under conventional treatment, it is recommended to increase the dose of calcitriol and/or to reduce the dose of phosphate salts. If the condition persists despite these adjustments, it is suggested to rule out tertiary hyperparathyroidism and consider its management with the interdisciplinary team.

Evidence

Patients with XLH rickets treated with conventional therapy have been documented to have gastrointestinal events, nephrocalcinosis, ectopic calcification, secondary or tertiary hyperparathyroidism, hypercalciuria, nephrolithiasis, and impaired renal function [10, 16].

Regarding nephrocalcinosis, it has been described as a frequent complication (45 %) of early appearance (median age 4.6 years) (18,41). In serious cases of this complication, patients are at high risk for developing CKD and high blood pressure [16].

In a cohort of patients with XLH rickets ($n = 21$), 76 % of women with a median age of 0.9 years (10.8 months) at the time of diagnosis were treated with conventional therapy. Nephrocalcinosis was developed in 45 % of cases, there was dental involvement in 43 % of the patients and persistent deformities in 62 %. Nephrocalcinosis occurred within the first 5 years of treatment, probably associated with high doses of phosphates or earlier initiation of treatment [41].

As a result of the therapy with Burosumab in patients with XLH the following adverse events have been reported in a time horizon of 64 weeks of treatment: pain in the adminis-

tration site (57 %), headache (54 %), pain in the extremities (42 %), decreased concentration of 1,25 $(OH)_2$ D (28 %), skin rash (23 %), dental pain (19 %), dental abscess (Burosumab 28 % vs. conventional 9 %), myalgia (14 %) and dizziness (11 %) [9, 16, 37]). Due to the recent inclusion of this drug in the treatment of XLH, it is likely that the accumulated follow-up time to date has not provided a comprehensive assessment of Burosumab complications. Ongoing studies are anticipated to offer detailed insights into this information in the future.

Data on carcinogenicity, teratogenicity, and mutagenicity; long-term studies are required in this regard.

Conclusion

The recommendations in our consensus will allow for an early and timely diagnosis, while standardizing the treatment and follow-up of patients with X-linked hypophosphatemic rickets (XLH). We hope to positively impact the burden of disease, and its health outcomes, including patient survival, and quality of life.

Conflict of interests

JGCA, AMO, AIMM, AR, AKSG, AMZ, GAG, JE, JCP, JPL, NMG, RBR, SN, VA, PF, MDC, MHV, MBZ, NEGH, EES and OB are speakers and have received fees from Ultragenyx. KRCA, AU, GAM, GA, JC and MFG declare that they have no competing interests.

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Authors' contributions

JGCA, RBR, KCA participated in the conception and design of the consensus. KCA performed the search, synthesis, and qualification of evidence. JGCA, AMO, AIMM, AR, AU, AKS, AMZ, GAM, GAG, JC, JE, JCP, JPL, MFG, NMG, RBR, SN, VA, and KCA reviewed the evidence and made recommendations. PF, MDC, MHV, MBZ, NEGH, EES and OB reviewed the paper

and provided valuable comments. All authors reviewed and approved the final version of the manuscript.

List of abbreviations

Abbreviations	Meaning
1,25 (OH)2D3	1,25 (OH)2 vitamin D
AGREE	Appraisal of Guidelines for Research & Evaluation Instrument
ALP	Alkaline phosphatase
AMSTAR	Assessment of multiple systematic reviews
AP	Anteroposterior
BMD	Bone densitometry
BMI	Body mass index
CT Scan	Computed tomography Scan
CKD	Chronic kidney disease
CNV	Copy number variation
CPG	Clinical practice guidelines
DXA	Dual-energy X-ray absorptiometry
ENT	Otorhinolaryngology
FGF23	Fibroblast growth factor 23
GFR	Glomerular filtration rate
ICD	Intercondylar distance
IMD	Intermalleolar distance
IU	International units
Mesh	Medical Subject Headings
Mini-HTA	Mini health technology assessment
MLPA	Multiplex Ligation-dependent Probe Amplification
NGS	Next-generation sequencing
NPT2a	2a sodium-dependent phosphate cotransporters
NPT2c	2c sodium-dependent phosphate cotransporters
Pcr	Plasma creatinine
PHEX	Phosphate regulating endopeptidase X-linked
Pp	Plasma phosphate concentration
PROMIS	Patient-Reported Outcomes Measurement Information System
PTH	Parathyroid hormone
RCT	Randomized clinical trial
Rob	Risk of bias
RSS	Rickets severity score
SLR	Systematic literature review
Tmp/GFR	Maximum tubular reabsorption of phosphate for the GFR
TPR	Tubular phosphorus reabsorption
Uca	Urinary calcium
Ucr	Urine creatinine
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
XLH	X-linked hypophosphatemic rickets

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