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

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Abstract

Background: X-linked hypophosphatemic rickets is a hereditary disease that generates alterations in bone mineral homeostasis. The morbidity of the condition has been variable in previous decades and even contradictory, probably due to the definition of the case and the diagnostic confirmation. Our propose was to generate evidence-informed recommendations for the diagnosis, treatment, and follow-up of patients with suspected or diagnosed XLHR.

Results: After the screening and selection process for 1041 documents, 38 were included to answer the questions raised by the developer group. 97 recommendations about the diagnosis, treatment, and follow-up of patients with suspected or diagnosed XLHR were approved by the experts consulted through modified Delphi consensus. The quality of the evidence was 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 and help clarify the burden of disease and improve health outcomes for this population.

Background

X-linked hypophosphatemic rickets (XLHR) or X-linked hypophosphatemia is a hereditary disease that generates alterations in bone mineral homeostasis. It is the most frequent 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 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).

XLHR is caused by altered function in the phosphate regulating gene with homologies to endopeptidases on chromosome X (PHEX), located on chromosome Xp22.1. The encoded protein is predominantly expressed in osteoblasts, osteocytes, odontoblasts, and cementoblasts (teeth) (3–6). Studies in animals indicate that PHEX deficiency results in increased secretion of phosphaturic hormone or fibroblast growth factor 23 (FGF23). As a consequence of this, there is a greater renal loss of phosphate, due to a downregulation of the sodium-dependent phosphate cotransporters NPT2a and NPT2c in the proximal convoluted tubule and an increased 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 with the subsequent alteration in the synthesis of 1,25 (OH)2D3, also called calcitriol (7). The renal loss of phosphorus generates chronic hypophosphatemia, alteration in skeletal mineralization and rickets/osteomalacia, giving rise to the clinical and radiological signs characteristic of the condition (8–10).

The characteristics and severity of XLHR 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 groups, 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 of the patient and his/her family (8, 10).

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

Results

1041 documents were found from the search, of these, after the screening and selection process, 38 documents were included to answer the questions raised by the developer group. The types of studies included are institutional clinical guidelines, SLR, rapid technology assessment (Mini-HTA), narrative reviews with recommendations, narrative reviews, informal expert consensus, documents of recommendations, clinical trials, cohorts of patients, case series and clinical cases. In general, the quality of the evidence was low; details are presented in Annex D.

Diagnosis

The available evidence emphasizes the importance of relating the clinical, radiological and biochemical findings in patients with suspected XLHR. (8, 9, 12). In this sense, in the pediatric population they recommended to consider the clinical and radiological signs, alterations in the growth rate, serum phosphorus levels lower than the reference levels for age, associated with renal phosphate loss and in the absence of deficit of vitamin D or calcium; while for the adults, the identification of lower limb deformities, clinical and radiological signs of osteomalacia, with serum phosphorus levels lower than the reference levels for age associated with renal phosphate loss was recommended (8).

1. What is the clinical presentation of XLHR?

XLHR is characterized by an excess of fibroblast growth factor 23 (FGF23), which conditions the loss of renal phosphate (13) and with that, a reduction in serum phosphate levels, vitamin D deficiency due to alteration of the renal synthesis of 1,25(OH)2D3 (9), decreased intestinal calcium absorption (14), increased levels of alkaline phosphatase (AP) (8) and parathyroid hormone (PTH) (15).

Bone deformities are common in up to 80% of the patients with XLHR (13), including torsional deformities, in varus or valgum and shorter length of limbs with respect to the height in a sitting position, especially of the lower limbs (16) that causes varus or valgum deformity and torsion. There is also widening of distal metaphysis in the wrist and the neck of the foot, thickening of the costochondral junctions (Harrison's sulcus), dolichocephaly (8), flattening of the skull base that favors Chiari malformations (25 and 50% of the children) and craniosynostosis (17). 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 (13, 18). There are cases with dental diseases such as abscesses (30–60%), bone pain (18%), fractures (16%) and muscle weakness (9, 12, 13).

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 (14), hypoacusia (adults 48–82%, children 9%) (1, 8), high blood pressure (27%), overweight, obesity, and mobility limitations (9, 12, 19). Regarding the radiological findings, they include: bowing of 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 (14).

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 (13).

Recommendations

- The clinical characteristics of XLHR 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.

Strong in favor

- It is recommended to make a complete medical history that includes anamnesis, family antecedents of XLHR 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.

Strong in favor

- It is recommended to individualize the clinic, considering the presentation of the disease in the pediatric and the adult population.

Strong in favor

- It is recommended that the anthropometric assessment includes measurement of weight, height and head circumference. In pediatric patients, graph in reference tables of the general population according to age and gender (consult the reference tables for Colombian population in https://www.growthxp.com/co/).

Strong 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.

Expert opinion. Weak in favor

- Is it recommended that the evaluation of the lower extremities include the measurement of the intercondylar distance in search of *genu varus* and of the intermalleolar distance for *genu valgum* and compare them with the reference tables according to age (Table 1).

Strong in favor

- In the adult population, when there is a suspicion of alteration in the alignment, it is recommended to refer the patient to orthopedics with a panoramic radiography of the lower limbs.

Weak in favor

Table 1
Normal values of intercondylar distance (ICD) and intermalleolar distance (IDM) according to age for the definition of 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 (21).

2. What biochemical studies are useful to diagnose XLHR?

FGF23 is a promising biomarker in the diagnosis of XLHR rickets, the latest available evidence suggest an increase of serum levels of FGF23 in patients with this disease (8, 13, 22), however, the diagnosis of XLHR is not based exclusively on this marker. Low serum phosphorus levels with alkaline phosphatase (AP) usually above the reference levels in the young population, increased or normal concentration of PTH and levels of deficiency of 1,25(OH)2D3 are also considered in more than half of the cases, without distinction of age, as well as a decrease in the reabsorption of phosphorus in the kidney (13).

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 (8, 9, 23).

Recommendations

- It is recommended to perform biochemical tests such as: serum and urinary levels of phosphorus and creatinine, for the calculation of the GFR, the tubular phosphorus reabsorption (TPR) and the maximum tubular reabsorption of phosphate for the GFR (TmP/GFR), in addition to calcium, alkaline phosphatase, parathyroid hormone, 25(OH)Vitamin D3 and 1,25(OH)2D3 (Reference values in Tables 2 and 3.

Strong in favor

- Consider that the vitamin D deficiency can modify the biochemical results; hence, it is recommended to carry out a previous measurement.

Expert opinion. Not graded.

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 (24, 25)

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 (26).

- It is suggested to calculate the TmP/GFR with the Eq. 1 (23), which is based in the Walton-Bijvoet nomogram (27):

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

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.

Weak in favor

- 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.

Expert opinion. Not graded

3. Which initial radiological studies are recommended to be performed in patients with XLHR?

Given the bone deformities characteristics of XLHR, X-rays of the knees, wrists and ankles allow to clarify the diagnosis in the pediatric population, when they show changes of metaphyseal widening and defect (12) and are considered the gold standard for diagnosis (28). After establishing the diagnosis, an anteroposterior (AP) and lateral panoramic radiograph of the lower limbs in standing position are indicated, as well as renal ultrasound, evaluation of the ocular fundus and magnetic resonance if there is suspicion of craniosynostosis or signs of increased intracranial pressure. Dental orthopantomography has been recommended after 5 years of age (8).

Based on the findings of the wrist and knee X-rays, the Thacher rickets severity score (RSS) was defined to follow-up 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 (28–30).

Recommendations

- Comparative AP and lateral radiographs of the wrists and knees are recommended for the diagnosis of XLHR, to search for signs of alterations compatible with phosphocalcic metabolism disorders such as metaphyseal irregularity shaping the image of a cup with concavity towards the epiphyseal side, increased size of the physis, presence of growth arrest lines (Harris) in sites of rapid growth such as the distal femur and the distal radius.

Strong in favor

- 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. Other

radiographs are indicated when there is a history of fracture to assess the state of consolidation and sites of pseudofracture or in cases of angular or rotational limb deformities.

Expert opinion. Not graded

- To assess the severity of involvement of the disease and the response to the medical treatment, the application of the RSS score based on the findings of the wrist and knees radiographs of the most affected side is recommended

Weak 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.

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.

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

Strong in favor

- It is recommended to request a computed axial tomography (CAT) with a bone window and 3D reconstruction of the skull in cases of diagnostic doubt with the radiograph, slow growth of the head circumference or skull deformity, previous assessment by neurosurgery and neuropediatrics.

Strong in favor

Taken and translated from (29).

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

Wrist and knee X-rays have been indicated in the pediatric population with persistent clinical or biochemical signs despite adequate treatment, also in the face of poor response to treatment, progression of bone deformities, requirement for orthopedic surgery, or presence of unexplained bone pain, and during the transition from childhood to adulthood (8).

Between 30 and 70% of patients with XLHR who receive conventional treatment have nephrocalcinosis (12). 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. (8).

Haffer et al, 2019, do not recommend dual-energy X-ray absorptiometry (DXA), nor the peripheral quantitative computed tomography for the assessment of bone health, since they cannot diagnose osteomalacia and

because of the high presence of false negatives associated with the enthesopathy (8).

Magnetic resonance could be an imaging alternative for the follow-up of patients with rickets, with the advantage of not generating radiation and being more accurate in the measurement of physeal widening and transverse extension of the widening (15), however, general anesthesia is required in some cases and it is an expensive procedure.

Recommendations

• Is recommended to assess the severity of the disease by radiographs of the wrists and knees at least once a year in children with an inadequate response to management or in those in whom the bone deformities worsen despite medical treatment.

Weak in favor

• In adults, it is suggested to perform an AP radiograph of the pelvis and a lateral of both hips annually or biannually after the treatment has been started. In case of increase in pain, this study is always indicated.

Expert opinion. Not graded

• It is suggested to perform a panoramic radiograph of the lower limbs annually, to follow-up the bone deformities, verify the alignment of the extremities or when a surgical intervention is necessary.

Strong in favor

• In patients who receive conventional therapy or under treatment with monoclonal antibodies (Burosumab), a renal ultrasound every 2 years is recommended in patients without nephrocalcinosis and annually in those with nephrocalcinosis or with diagnosed hypercalciuria.

Weak in favor

• It is suggested to perform a dental orthopantomography at the age of 5 years and in adults with recent manifestations, considering repeating it on an individualized basis.

Strong in favor

• Routine BMD for bone health assessment is not recommended in patients with XLHR.

Strong against

4. In which patients is it indicated to perform genetic tests to confirm XLHR?

The diagnosis of XLHR is based on the association of clinical, radiological, and biochemical findings; however, with the interest of confirm it molecularly, provide genetic counseling and seek other affected individuals, different alternatives are available.

In the case of a clinical, paraclinical and familial diagnosis compatible with XLHR 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 the patients clinically diagnosed with XLHR will show a PHEX mutation (9). 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 (8, 12).

Negative results of the NGS panel or of the single sequencing of the PHEX gene do not completely rule out the diagnosis of XLHR and it has been suggested to carry out the MLPA (Multiplex Ligation-dependent Probe Amplification) study for the PHEX gene (31).

In the absence of availability of the genetic analysis, the diagnosis should be guided by elevated plasma levels of FGF23 and/or a family history positive for XLHR. 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. (8).

Genetic counseling has been promoted in cases of genetic confirmation of index case, transition from childhood to adulthood, and families planning pregnancy (8), even before obtaining the genetic results (9).

Recommendations

• For every patient with clinical, biochemical, and radiological findings compatible with XLHR 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.

Strong in favor

• In atypical cases or in those with a negative family history of XLHR, is recommended to perform the genetic analysis using the NGS panel for specific genes and with a CNV (copy number variation) analysis.

Strong in favor

• To expand the family study in the index case with an already defined mutation, punctual analysis of the pathogenic variant is recommended.

Weak 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 XLHR. It is suggested to complement it with the deletion/duplication study for the *PHEX* gene.

Strong in favor

• The biochemical studies for diagnosis in newborns with a family history of XLHR may be falsely abnormal, as in the case of phosphorus; therefore, it is suggested to carry out a molecular study using a sample of peripheral blood, umbilical cord, oral sample, or filter paper.

Expert opinion. Not graded

• It is proposed to follow the algorithm proposed by the developer group for the genetic confirmation of the diagnosis of XLHR rickets (Fig. 2).

Strong in favor

5. **What is the conventional treatment for patients with a diagnosis of XLHR? and when should it be started?**

The conventional treatment for the management of patients with XLHR consists in the combined use of oral phosphate and vitamin D analogs (9, 15). Some authors also include in the conventional treatment healthy habits with a diet with an adequate amount of calcium, physical activity, avoiding smoking and obesity (9). 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 (8).

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 (8, 33).

When the combination of the phosphate is made with alfacalcidol, a dose that varies between 1–3 µg/day and of phosphate between 35 and 70 mg/kg/day, according to the age of the child (33). 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 (17). 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 1.5-2µg/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 f35-50 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 (33). 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 0.5–1µg/day with progressive adjustments according to the clinical response (8, 12).

In addition to the recommendation to give frequent intakes of phosphate (between 4–6 times a day), caution should be taken not to exceed the maximum daily dose of 80 mg/kg/day (8), 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 (17). In addition, the association with active vitamin D analogs facilitates the development of hypercalcemia, hypercalciuria, formation of kidney stones and nephrocalcinosis (8, 9, 17). Other treatment-related alterations include arterial hypertension and hyperkalemia.

A controversial issue in the literature is the suspension of conventional treatment in children once the stage of height growth ends and its restart only when signs and symptoms of XLHR rickets reappear (17). In this sense, different authors agree that conventional treatment is indicated in the presence of symptoms and the routine

administration of treatment in asymptomatic adults is discouraged (8, 33). Other indications suggested for temporary suspension are prolonged immobilization in the interest of avoiding hypercalciuria, hypercalcemia, and increased PTH, but with a rapid initiation when the patient begins to walk (8).

Re-initiation of treatment is contemplated in the presence of active osteomalacia or associated conditions (17), as well as in situations of 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 (33).

Despite the fact that conventional therapy is well positioned, with the findings of FGF23, in some documents it has been discussed the possibility that the vitamin D analogs and phosphates have to stimulate the FGF23 levels which would have an effect on the renal loss of phosphate, would reduce the effectiveness of the therapy against XLHR rickets and favor the development of hyperparathyroidism (8, 17).

On the other hand, it has been mentioned a lower risk of loosening of the prosthetic joint in patients who receive conventional treatment (34, 35), between 3 and 6 months before the procedure and up to 9 months after the surgery (35).

Recommendations

• In pediatric patients with XLHR rickets, it is suggested to initiate conventional treatment at the time of diagnosis.

Strong in favor

• No-magisterial formulas are preferred over the magisterial ones, to ensure standardized composition.

Expert opinion. Not graded

• In cases with conventional treatment (Table 3), is recommended:

o Start with phosphate salts at a dose of 20 mg/kg/day and progressive titration avoiding exceeding the maximum daily dose of 80 mg/kg/day. The dose adjustment should be made according to the clinical and biochemical response.

Strong in favor

o 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 (see question 6: objectives of conventional treatment).

Strong in favor

o It is recommended to associate to treatment with phosphate, 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 requirements of the patient.

Weak in favor

• It is suggested to suspend the administration of active vitamin D analogs during periods of prolonged immobilization, such as in orthopedic surgeries and fractures.

Weak in favor

• It is recommended to associate non-active vitamin D analogs with treatment when vitamin D deficiency has been documented.

Strong in favor

• Although there is not enough evidence of 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.

Expert opinion. Not graded

• 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 one intake of alfacalcidol 1.5 µg/day or less.

Weak in favor

• It is recommended to consider the preferences of patients and relatives in the choice of the treatment.

Strong in favor

Table 3
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	Linglart2014(33)
Any pediatric age	20–60 mg/kg/day in 3–4 doses	Alfacalcidol 0.5–1.5 µg/day	Haffner2019 (8) Imei2019 (17)
	20–40 mg/kg/day in 3–5 doses	Calcitriol 0.2–0.3 µg/kg/day in two doses	Carpenter 2012 (35)
Infants	55–70 mg/kg/day in 4 doses	Alfacalcidol 1.5-2 µg/day	Linglart2014(33)
	20–60 mg/kg/ day in 3–4 doses	Calcitriol 0.02–0.5 µg/kg/day in two doses	Haffner2019 (8) Juraibah 2021 (12)
School-age children	45–60 mg/kg/day in 3 doses	Alfacalcidol 1–2 µg/day	Linglart2014(33)
Adolescents	35–50 mg/kg/day in 3 doses	Alfacalcidol 1.5-3 µg/day	Linglart2014(33)
Adults	750–1200 mg/day in 2 doses	Alfacalcidol 0.75–1.5 µg/day	Lecoq2020 (36)
	250–1000 mg/day in 3–4 doses	Calcitriol 0.50–0.75 µg/ day in two doses	Carpenter 2012 (35)
Pregnancy and menopause	0–2000 mg/ day in two doses	Alfacalcidol < 1.5 µg/day	Linglart2014(33)

Source: Own elaboration

6. What are the objectives of conventional treatment? And how to assess them?

Conventional therapy should be aimed at normalizing the altered biochemical markers in XLHR rickets, such as ALP and FGF23 (15). Likewise, conventional treatment seeks to improve the quality of life and functionality by maintaining the range of motion, reduce bone pain, optimize the growth rate and final height, reduce periodontal disease and strengthen muscle tone, all in order to avoid or delay the need for surgical treatments and minimize bone deformities (8, 9). In adults, in addition, treatment should be aimed at the prevention or healing of pseudofractures and fractures, pseudoarthrosis and improvement of osteomalacia (3).

The fulfillment of objectives is based on the biochemical and clinical follow-up which would allow to make decisions in the management of the patients with XLHR (8, 12). The clinical response to treatment is assessed by stature growth, comparing standing, and sitting measurements, head growth, improvement in lower limb deformities, and assessment of gait, muscle function and frequency of appearance of dental abscesses. Plain radiographs of the knees every 6 months are a useful tool in the follow-up of the effectiveness of the therapy

and annual or biannual measurement of the intermalleolar and intercondylar distances can support adjustments in therapy (12). On the other hand, the measurement of serum levels of calcium, phosphorus, creatinine, AP, PTH, as well as the determination of calcium and creatinine in isolated urine or in 24-hour urine collection, are biomarkers used for the evaluation of the therapy, especially with regard of its safety regarding the development of hyperparathyroidism or nephrocalcinosis (17). Monitoring the renal parenchyma with ultrasound every 2 years for timely detection of nephrocalcinosis/lithiasis associated with conventional treatment is desirable (12). It has been suggested that the frequency of biochemical analyses should be 2 weeks after the start of treatment and thereafter every 3 months during childhood (12, 33), every 6 months during puberty, and every 6 months or annually in adults (33).

Recommendations

• In cases of pediatric patients with a diagnosis, but without clinical manifestations, the objective of the treatment is to prevent bone involvement.

Strong in favor

• The objectives of the conventional treatment in pediatric patients with XLHR rickets are:

Improve the quality of life.

Reduce bone pain.

Improve the growth rate and the final height of the patient.

Improve the radiographic alterations and bone mineralization, as well as the periodontal disease.

Minimize the complications associated with conventional treatment such as secondary hyperparathyroidism and nephrocalcinosis.

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.

Avoid the recurrences of deformities of lower limbs after surgical management.

Strong in favor

• The objectives of the conventional treatment in adult patients with XLHR rickets are:

Reduce musculoskeletal pain.

Prevent the development of osteomalacia and pseudofractures.

Improve oral health (periodontitis, dental abscesses).

Improve the mobility and functionality.

Avoid joint stiffness.

Improve the consolidation of fractures.

Strong in favor

7. When t**o start treatment with monoclonal antibodies in patients with a diagnosis of XLHR rickets?**

Burosumab is the anti-FGF23 monoclonal antibody approved for its use in patients with XLHR after the first year of life. Its development and inclusion as therapy for the management of XLHR rickets in some European and American countries is recent (2018) (12, 37).

The available presentations are 10, 20 or 30 mg/ml for subcutaneous administration (38); 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 (39) and 1 mg/kg every 4 weeks in adults (38).

The results of studies that evaluated the efficacy of the drug in patients with XLHR indicate improvement in the serum levels of phosphorus, 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 improvement in growth and mobility (9, 12, 39).

Improvement in the levels of serum phosphorus and ALP, improvement in the growth rate, reduction of the deformities and the severity of rickets and improvement in mobility were observed in the pediatric population (3, 40).

In the available studies of Burosumab in the adults, improvement in the levels of phosphorus and in TmP/GFR was observed, with normalization of the levels of 1,25(OH)2D3; in addition, it was significantly less stiffness assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale and a greater consolidation of fractures. The pain, functionality and sensation of wellness also improved, as well as the osteomalacia (3, 40).

Regarding the indication for the use of Burosumab, in different documents it has been suggested to start treatment when XLHR is confirmed, with radiographic evidence of bone disease in children aged one year or older, with serum phosphorus levels lower than those expected for the age measured with a minimum of 4 hours of fasting (10) and who are in the stage of growth (12)(37). In addition, in the document of Haffner et al, 2019, it was recommended to start Burosumab therapy in the pediatric population when there is radiographic evidence of bone disease and in disease refractory to conventional therapy, evidence of related complications, or inability of the patient to adhere to conventional therapy, considering an adequate follow-up (8).

In the European Union in the year 2020, the indication of starting the drug was accepted, in cases of radiographic evidence of bone disease (9). In this age group, other authors have proposed to start therapy with Burosumab in cases of persistent bone and joint pain, osteomalacia that affects functionality and activities of daily living, pseudofractures, fractures, insufficient or refractory response to conventional therapy (8). 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 (3), for which in some cases it has been suggested to consider targeted therapy in patients with an indication for orthopedic surgery (41).

It is important to mention that management with Burosumab must be discontinued in cases of high serum phosphorus levels beyond those that are considered normal for age and follow-up four weeks after the suspension in order to make the decision to restart therapy if there are low levels for age (38). In case of considering restarting therapy, it has been recommended to do it with half the dose (8). It should also be discontinued in cases of pregnancy and the initiation of antibody therapy has not been recommended in women of childbearing age without a contraceptive method, in which case it has been proposed to initiate contraception prior to the initiation of treatment (41). In Europe, it is advisable to consider discontinuation of treatment in cases of reduction in growth rate of less than 2 cm/year (10). Likewise, Burosumab is contraindicated in patients with stage 5 chronic kidney disease (CKD), concomitant conventional treatment and hypersensitivity to the drug (37).

Recommendations

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

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.

Weak in favor

• The use of monoclonal antibody is recommended in adult patients with a confirmed diagnosis of XLHR, with 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.

Weak in favor

• Initiation of treatment with monoclonal antibodies in pediatric patients with XLHR 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.

Strong in favor

• In patients in transition from childhood to adulthood, an assessment by an interdisciplinary medical board is recommended to redefine therapeutic objectives and the need to adjust the dose of the monoclonal antibody, considering the opinion of the patient and his/her family.

Expert opinion. Not graded

• It is recommended to discontinue the management with monoclonal antibody when the serum phosphorus levels increase beyond the values considered normal for age, and follow-up them 2 to 4 weeks later to define

the restart of the therapy. In this case is recommended to restart the treatment with half the dose prescribed before the suspension.

Strong in favor

• It is not recommended to adjust the dose of monoclonal antibody in periods shorter than 4 weeks.

Strong against

• The use of monoclonal antibody concomitantly with conventional treatment is not recommended, neither in case of evidence of serum phosphorus values higher than the minimum normal levels for age nor in patients with stage 5 chronic kidney disease.

Strong in favor

• Individualized follow-up and adjustment of phosphorus intake in the diet is recommended in patients who receive monoclonal antibodies, especially in those with CKD in advanced stages.

Expert opinion. Not graded

• In women of childbearing age who are receiving monoclonal antibody treatment, education and prescription of contraceptive methods are recommended.

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 consider starting conventional therapy in these periods, at least while new information on safety and efficacy in this group of patients becomes available.

Strong in favor

8. How is the response to treatment with monoclonal antibodies evaluated?

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 (12), starting with a dose of 0.4 mg/kg to 0.8 mg/kg (39) until reaching the maximum dose of Burosumab of 2mg/kg or 90 mg/dose (8, 10). In children under 5 years of age, monthly follow-up of the therapy has been recommended during three first months (10, 37, 38), in adolescents every 3 months and in adults every 6 months (8).

Since the stabilization of serum phosphorus, the available evidence suggests clinical follow-up that considers the head circumference, sitting and standing height, and lower limb deformity in children. From the dental eruption, visit to the dentist twice a year to detect caries, dental abscesses, tooth loss and the requirement of dental procedures is recommended. It has been proposed to perform the 6-minute walk test twice a year. It is recommended to assess the muscle strength, the presence and severity of pain, evidence of joint stiffness and

fatigue, at each patient visit, every 3 to 6 months in pediatric age and every 6 to 12 months in adults. Finally, biochemical follow-up is done with phosphorus in serum 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 (12).

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 (8).

The *Thacher rickets severity score* was initially designed to assess the response to Burosumab treatment (28, 29). In the same way, *the radiographic global impression of change score* allows the evaluation of the treatment outcomes, considering comparatively the baseline and follow-up radiographs to identify changes or differences between these, which is scored in a scale of 7 points, graduated between − 3 and 3; negative scores indicate worsening and positive scores indicate improvement of the rickets. The score of -3 corresponds to the category of highest severity while a score of 3 corresponds to complete improvement.

Table 4
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

Monitoring of patients with X-linked hypophosphatemic rickets		
WOMAC	X	X

Source: Own elaboration based on (33).

Recommendations

• Clinical follow-up is recommended in patients with XLHR 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 4).

Weak in favor

• In patients with XLHR receiving monoclonal antibody treatment, it is suggested to perform the 6-minute walk test once a year (Table 4).

Strong in favor

• Once monoclonal antibody treatment is started in patients with XLHR, 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 every 3 or 4 months and of 1.25(OH)2D3 between 6 and 12 months is also suggested (Table 4).

Weak in favor

• In pediatric patients with XLHR rickets in the growth stage and under management with monoclonal antibody, it is suggested to perform knee X-rays every six months and until treatment stability is achieved in order to assess the improvement of the signs of the disease (Table 4).

In favor. Strength to be defined by consensus

Expert opinion. Not graded

What are the risks of starting treatment with monoclonal antibodies?

In patients with XLH rickets treated with Burosumab, he following associated adverse effects have been reported over a time horizon of 64 weeks: pain in 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%) (10, 42). Given the recent inclusion of this new therapy in the management of XLHR, it is probable that the accumulated follow-up time until now has not allowed to fully evaluate the complications associated with the antibody and that the ongoing studies will allow us to know this information in detail later.

Recommendations

• Follow-up, surveillance, and reporting of possible adverse effects associated with the therapy with monoclonal antibodies previously described in the literature such as: pain in the administration site, headache, pain in the extremities, skin rash, dental pain, myalgia and dizziness are recommended.

Strong in favor

9. When and how is orthopedic surgical treatment indicated in XLHR?

The presence of angular and rotational deformities of the lower limbs secondary to XLHR rickets is common. The initial management is focused on an adequate treatment of the 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 XLHR rickets. Osteotomy (63%), knee replacement (12%) and hip replacement (8%) have been reported among the most common procedures (19).

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 purposes of bone alignment. Recurrence of deformity was reported in 29% of the operated patients, being lower in patients with surgeries after 15 years of age or after the completion of growth. The complications presented by the patients were: absence of post-surgical consolidation, fractures, infection, osteitis, early arthrosis and hypoesthesia in the area of the tibial nerve (43). Guided growth has also been documented in the pediatric population to avoid greater angulation or for correction of deformities (44).

Corrective surgery has been indicated in cases of significant deformities of the lower limbs that affect functionality or imply joint involvement in the long term (43). In addition, surgery is justified after unsatisfactory medical treatment, that is, when the bone deformities in the lower limbs and bone pain persist (33, 44). Surgical treatment should be delayed until the end of growth and closure of the physis to avoid the recurrence of deformities and therefore the need for new interventions (33), although special emphasis has been placed on the early follow-up of *varus* or *valgum* knee and analysis of proximal joints, foreseeing complications with presentation of deformities in the future such as foot and ankle *valgum* or femoral antecurvatum (44). Elective surgical treatment has been recommended in the pediatric population with intensive medical treatment for at least 12 months (8), including guided growth in cases of persistence of deformities despite the medical management (45).

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) (8).

Recommendations

• To correct the deformities, it is recommended to have achieved metabolic control of the disease for at least one year, due to the high risk of recurrence.

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.

Weak in favor

• It is suggested to perform the correction of angulations with the apex of the deformity located close to the epiphyses in patients with open physis using guided growth techniques.

Strong in favor

• It is suggested to perform the correction of angulations with one or several apexes in the diaphyses with osteotomies and intramedullary fixation with a telescopic nail.

Weak in favor

• In the adult population, the correction of the deformities will depend on the age of the patient, the comorbidities, the location of the deformity, and the joint involvement.

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.

Strong in favor

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

The available evidence supports the premise of regular follow-up at least every 3 months during childhood and puberty of patients with XLHR rickets or after the start of treatment, involving multidisciplinary teams headed by an expert in metabolic bone diseases. Once the patients have a favorable response to treatment or are stable, follow-up could be done biannually. In the case of adults, follow-up every 6 months has been proposed to assess the response to treatment or annually when they are not receiving pharmacological treatment (8, 9).

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 (8, 9). In addition, the bone age should be assessed in children over 5 years of age with growth retardation. In the case of bone deformities, follow up by orthopedics has been recommended (8).

In adults, additionally, follow-up 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 (8).

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 XLHR, its routine use for follow-up has been discouraged (8). While the measurement of bone-specific ALP 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. The measurement of calcium in 24-hour urine or UCa/Ucreat allows to identify hypercalciuria (9).

In the case of treatment with monoclonal antibody, special emphasis is placed on the follow-up of fasting serum phosphorus and 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 has been proposed measurement every 6 months, accompanied by measurement of urinary calcium excretion (8).

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 follow-up of XLHR (9).

R**ecommendations**

* General considerations for follow-up:

• 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, trying to anticipate, detect and treat early and appropriately the complications of the disease and its treatment.

Strong in favor

• It is recommended to make emphasis on the psychological treatment of the patient and his/her family, both due to the impact of the disease itself, as well as the feelings of guilt that may arise on some parents of affected children.

Strong in favor

• At each control, it is recommended to make a complete clinical history, considering the current disease, review by systems, presentation of symptoms, musculoskeletal pain, medications used, dose and tolerance, in addition to the evaluation and anticipation of potential complications.

Strong 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.

Weak in favor

• Routine bone biopsy is not recommended; however, its performance is subject to the clinical criteria of the treating specialist.

Strong against

• 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.

Strong in favor

• It is recommended to perform the following laboratories at 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).

Strong 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.

Weak in favor

• The six-monthly assessment of the parathyroid hormone and the 1,25(OH)2D3 is recommended, being the latter of special interest in patients treated with specific therapy.

Weak 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.

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 the body weight, growth rate, and skeletal mineralization.

Strong in favor

• Routine quantification of FGF23 levels is not recommended.

Weak against

• Evaluation by pediatric orthopedics and adult orthopedics is suggested in all patients, especially for those with significant limb deformities, for imaging evaluation and comprehensive treatment.

Strong in favor

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

*Patients in pediatric age:

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

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.

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.

Strong in favor

• The evaluation of the intermalleolar and intercondylar distance, psychomotor development, muscle function, bone and joint pain, complete examination of the spine (lordosis, kyphosis or scoliosis) and blood pressure recording at each consultation is suggested.

Strong in favor

• Hearing assessment by otorhinolaryngology is recommended according to the presentation of symptoms in this regard.

Strong in favor

*Patients in adult age:

• Follow-up in adult patients is suggested every 6 to 12 months depending on their individual needs.

Strong in favor

• Stricter controls are recommended if the patient is in the phase of medication adjustment.

Strong in favor

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

Strong in favor

• Hearing evaluation by otorhinolaryngology is recommended at least once a year.

In favor, strength to be defined in consensus

Weak in favor

11. How is the comprehensive care of the patients with XLHR implemented?

The collected evidence coincides in promoting the comprehensive care of patients with XLHR rickets, with the interest of evaluating patient-centered outcomes and improving quality of life (9). 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 needs of the patient, considering orthopedists, dentists, physical therapists, occupational therapists, clinical geneticists, audiologists, ophthalmologists, neurosurgeons, radiologists, nurses, social workers, psychologists and nutritionists (9, 10, 12). Surgical treatment has been recommended to be implemented by surgeons who are experts in bone metabolism. (8).

Complementarily to the multidisciplinary team, it has it has been proposed to implement local or institutional protocols that guide the transition from pediatric age to adulthood, integrating different levels of care and involving patients, families, and caregivers. As well as protocols on the disease that allow primary care physicians to understand and opportunely direct the patient in search of an assertive diagnosis, treatment and follow-up. (9).

Table 6
Follow-up of patients with XLHR 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

Category	Under 18 years of age				Adults	
Images						
X-rays (Knees, Wrists, etc.)	X	According to clinical evolution				
Kidney ultrasound (According to calciuria, calcium: urine creatinine)				X		X
Adherence to treatment		X	X	X	X	X	X
Tolerability/adverse events		X	X	X	X	X	X

*In an isolated urine sample. **In 24-hour urine. ¥Schwartz formula; TRP: Tubular reabsorption of phosphate; TmP/GFR: tubular maximum reabsorption of phosphates for the glomerular filtration rate; £: In cases of availability, perform bone ALP, otherwise request ALP.

Source: Own elaboration based on (8, 33)

Recommendations

• It is recommended that patients with XLHR rickets receive a comprehensive care, for which an interdisciplinary team should be created by pediatric or adult nephrology and endocrinology, depending on the age of the patient, with the participation of 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.

Strong in favor

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

Strong in favor

• It is recommended that the patient and his/her family group receive appropriate genetic counseling since the confirmation of the disease.

Strong in favor

• The creation of transition programs with defined and appropriate protocols for the comprehensive care of pediatric patients with XLHR who reach adulthood is suggested.

Strong in favor

12. **¿What are the main complications derived from treatment in patients with XLHR?**

It has been documented that patients with XLHR rickets treated with conventional therapy may present gastrointestinal events, nephrocalcinosis, ectopic calcification, secondary or tertiary hyperparathyroidism, hypercalciuria, nephrolithiasis, and impaired renal function (12, 17).

Regarding nephrocalcinosis, it has been described as a frequent complication (45%) of early appearance (median of 4.6 years) (19, 20). In serious cases of this complication, patients are at high risk of developing CKD and high blood pressure (17).

In a cohort of patients with XLHR rickets (n = 21), 76% of women with a median age of 0.9 years (10.8 months) at the time of diagnosis, 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 (20).

Result of the therapy with Burosumab in patients with XLHR; the following adverse events have been reported in a time horizon of 64 weeks of treatment: pain in the administration 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%) (10, 17, 42). Due to the recent inclusion of this drug in the management of XLHR, it is probable that the accumulated follow-up time until now has not allowed us to evaluate complications associated to Burosumab and that the ongoing studies will allow us to know this information in detail later.

There are no available data on carcinogenicity, teratogenicity, and mutagenicity; long-term studies are required in this regard.

Recommendations

• The complications associated with conventional treatment for XLHR are: hypercalciuria, nephrocalcinosis, secondary or tertiary hyperparathyroidism, nephrolithiasis, ectopic calcification, and alterations in renal function.

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

Expert opinion. Not graded

• 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.

Strong in favor

• To avoid side effects of the phosphate solution and to improve adherence in adults and adolescents, it is suggested 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 the follow-up, it should be considered to suspend treatment and reassess with the treating team for its adjustment.

Strong in favor

• It is recommended to manage the 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.

Strong in favor

• In case that secondary hyperparathyroidism appears in patients who are under conventional treatment, is recommended to increase the dose of calcitriol or 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.

Strong in favor

• In case that secondary hyperparathyroidism appears in patients who are under conventional treatment, is recommended to increase the dose of calcitriol and/or 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.

Strong in favor

Conclusion

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

Methods

Aim: To generate evidence-informed recommendations for the diagnosis, treatment, and follow-up of patients with suspected or diagnosed XLHR.

The recommendations are based on a review of the evidence that allowed to resolve the questions of clinical interest (Annex A) proposed by the developer group. They have been socialized and agreed upon by a panel of clinical experts in pediatric and adult populations of different specialties that include nephrology, orthopedics, endocrinology, pediatric rheumatology, and clinical genetics.

LITERATURE REVIEW

The search for information that supported the recommendations was carried out based on MeSH terms, Entry terms and free terms (Annex B), consulting the specialized databases Pubmed y Embase, development and compiler agencies of clinical practice guidelines (CPG). The search was expanded in Google and Google Scholar and consultation with clinical experts for documents not identified in the search. The publications were restricted to English and Spanish, from 2011 to the present, considering the objective of generating recommendations that would guide the current clinical practice.

The screening of the information was initially carried out by title and abstract independently by two reviewers: a clinical expert and a methodologist, in search of evidence, specifically oriented towards the diagnosis, treatment and follow-up of patients with XLHR. Disagreements were resolved by consensus between the reviewers. Subsequently, the documents preselected in the screening were reviewed in full text and agreed upon by consensus by the members of the clinical and methodological team.

The documents were included if they met the following criteria (The flow chart of evidence selection appears in ANNEX C):

1. Type of study: without restriction by type of study.

2. Population or condition: patients with clinical suspicion or confirmed diagnosis of XLHR.

3. Clinical aspect addressed: diagnosis, treatment, or follow-up.

4. Publication between 2011–2021

5. Language: English and Spanish

The quality of evidence for the documents included was rated according to the type of study, considering 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. This process was carried out independently by two evaluators from the methodological team.

The information collected during the evidence review is presented through narrative synthesis for each question. Subsequently, the developer group was organized into subgroups and two questions were assigned for the review and interpretation of the corresponding evidence for each question and generation of preliminary recommendations, which were then discussed in consensus sessions with the entire developer group until the final recommendations were obtained, which were consulted with an invited panel of clinical experts.

The developer group classified the recommendations according the direction and strength, giving rise to recommendations in favor or against and strong or weak, considering the quality of evidence, the balance of risks and benefits, consumption of resources or availability in the context and the observations issued by the expert collective (11).

EXPERT CONSENSUS

The recommendations presented in this document were chosen by consensus among a panel of clinical experts different from the developer group, characterized by being specialists in some area of action involved in the current clinical practice for patients with XLHR. The expert consensus was carried out using the modified Delphi methodology. Initially, a virtual consultation tool was applied among the expert panel defined by the developer group between February 01 and 08, 2022, to identify the recommendations that required a formal consensus session, based on the 95 recommendations formulated by the developer group.

Agreement was defined when the recommendation reached a vote of at least 80% in favor, considering as a denominator the total of experts responding to each recommendation. For the eight recommendations that did

not exceed the threshold of 80%, a virtual consensus session was held through the Zoom platform to discuss and approve the final recommendations.

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
CAT	Computed axial tomography
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
XLHR	X-linked hypophosphatemic rickets

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE (NOT APPLICABLE)

CONSENT FOR PUBLICATION (NOT APPLICABLE)

AVAILABILITY OF DATA AND MATERIALS (NOT APPLICABLE)

COMPETING INTERESTS

JGCA, AMO, AIMM, AR, AKSG, AMZ, GAG, JE, JCP, JPL, NMG, RBR, SN, VA, PF, MDC, MHV, MBZ, NEGH, EES and OB are speaker and has 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.

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Figures

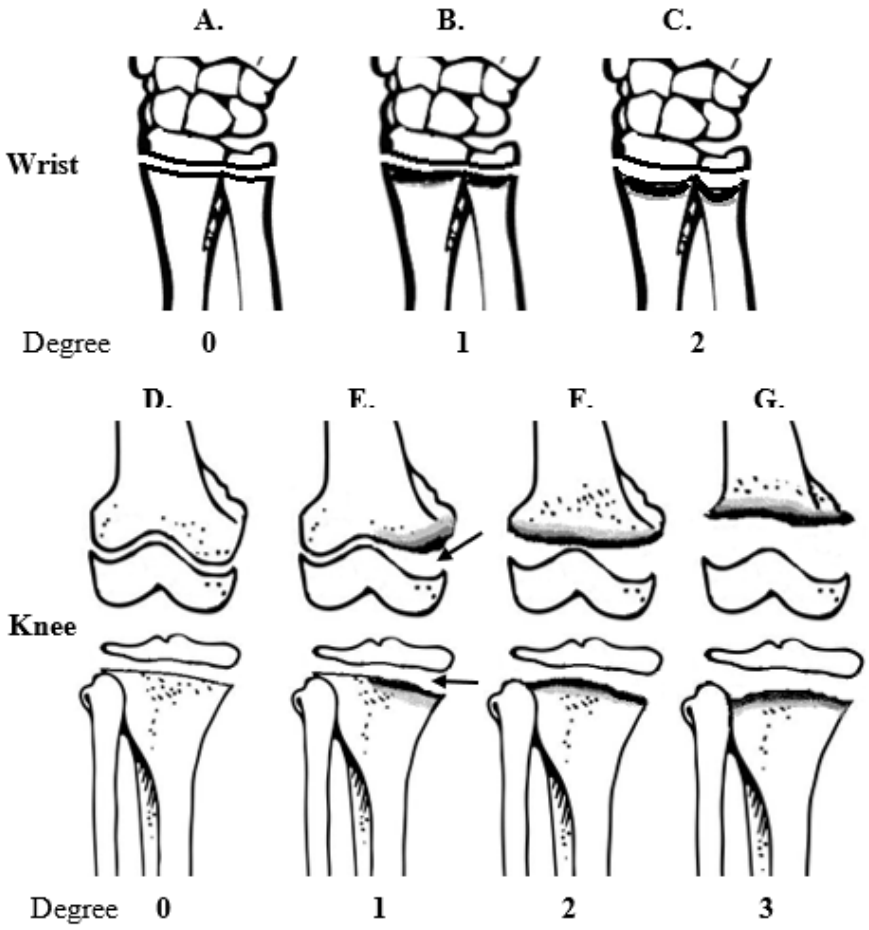

Figure 1

Thacher RSS severity score by grade and segment

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 metaphyses is 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 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.

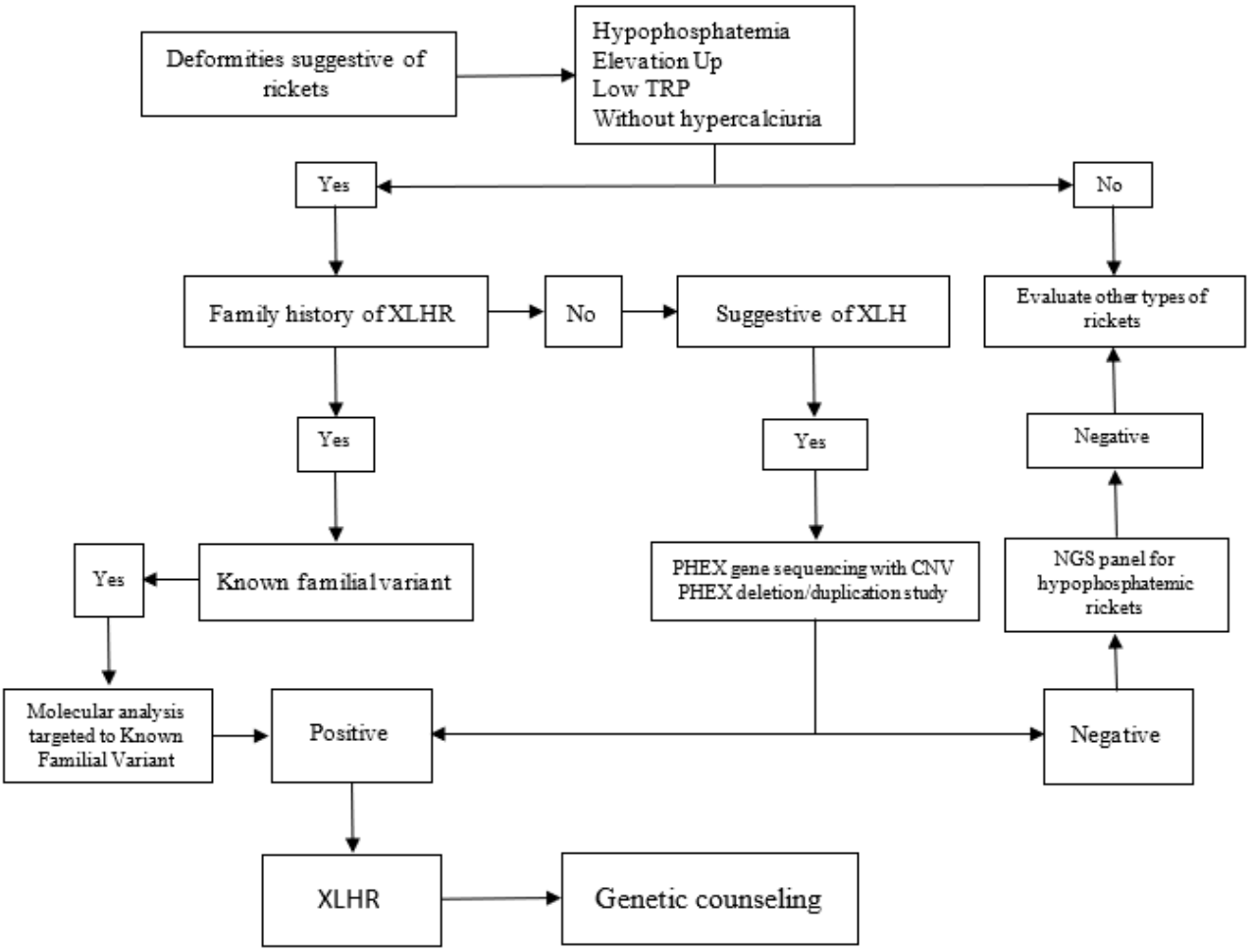

Figure 2

Algorithm for genetic diagnosis

Source: Own elaboration.