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Reports and Recommendations

Current Practices in Monitoring Children and Adults With X-linked Hypophosphatemia: A Global Survey of Expert Experience

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Abstract

This report provides recommendations for X-linked hypophosphatemia (XLH) monitoring based on current monitoring practices of experts in the management of XLH in children (<18 years) and adults. We surveyed 43 international experts in XLH to determine their monitoring practices for children and adults with XLH, including pregnant and lactating women. In the initial evaluation of children and adults with XLH, experts consistently obtain a family history of XLH or hypophosphatemia, a history of fractures and dental infections, and assess pain through age-appropriate clinical interviews or caregiver reports. They measure height, weight, and blood pressure and conduct DNA analysis of multiple genes associated with hypophosphatemia including the *PHEX* gene. For children follow-up, experts arrange follow-up every 3 to 6 months assessing height, weight, and blood pressure and examining for skeletal deformities. Laboratory tests in children include serum phosphorus, corrected total/ionized calcium, alkaline phosphatase, renal function, and PTH and spot morning urine for calcium, creatinine, and phosphorus. During adult follow-up, experts assess patients every 6 to 12 months, with a clinical examination focused on skeletal deformities and joint involvement. The laboratory profile is completed at least once a year. In the presence of bone pain, experts conduct X-rays both in children and adults to evaluate for fractures or joint damage. With respect to nephrocalcinosis, renal ultrasound is suggested on an annual basis or less frequently when monitoring children and adults with XLH. Experts conduct a dental assessment at baseline and then every 6 to 12 months for all patients with XLH. The findings of the survey inform practice for assessing new patients with XLH, monitoring existing patients, and identifying areas for future research. All recommendations based on these practices are weak with very low-quality evidence.

Summary of GRADEd (weak) recommendations

Recommendations for initial assessment and follow-up are provided if 80% or more of the respondents undertook the practices 80% or more of the time in 80% or more of their patients. Box 1 and Box 2 summarize the practices recommended by the expert panel. These are applicable in all individuals (children and adults) receiving treatment, with either burosumab or conventional therapy, or without active treatment unless otherwise specified.

Key Words: X-linked hypophosphatemia, XLH, monitoring practice, GRADEd recommendations, survey, expert experience

Box 1. Summary of GRADEd practice recommendations for newly diagnosed patients with XLH

Children (Infants to Adolescents)

THE PANEL SUGGESTS

History and Physical Examination—Key Points to Document

- Obtain a detailed family history to identify instances of XLH or hypophosphatemia.
- Assess pain through age-appropriate clinical interviews and caregiver reports.
- Document history of fractures or pseudofractures (in older children).
- Document history of dental abscesses or maxillofacial cellulitis.
- Measure and document head circumference as an age- and sex-matched percentile* (children ≤2 years old).**
- Record recumbent length as a percentile* (children ≤2 years old).**
- Measure standing height as a percentile* (children >2 years old).
- Record weight as a percentile.*
- Measure and express blood pressure as a percentile for age, sex, and height to screen for hypertension.

Biochemistry

- Conduct a comprehensive panel of laboratory tests including, serum phosphorus,* total calcium (corrected for albumin), ionized calcium, ALP,* 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D, kidney function (creatinine, eGFR), PTH, spot*** urine calcium/creatinine ratio (or a 24-hour urine calcium excretion adjusted for weight; normal <4 mg/kg/day may supplement spot testing in complex cases), morning spot urine phosphorus/creatinine for calculation of TRP or TmP/GFR. (For laboratory testing, we prefer morning, fasting for at least 2 to 3 hours, with serum and urine samples drawn at the same time or within 2 hours of one another.)
- Perform genetic testing for variants in the genes**** resulting in hypophosphatemia, including *PHEX*, in order to confirm the underlying diagnosis and guide family screening and counseling.

Imaging

- Obtain baseline X-rays of long bones (e.g., AP lying lower extremity imaging for children unable to stand and standing lower extremity views for children able to stand).
- Perform baseline renal ultrasound to screen for nephrocalcinosis.

Dental and Oral Care

- Complete a baseline dental assessment with bitewings and/or periapical X-rays or, for children ≥6 years old, orthopantomogram, to screen for enlarged pulp chambers, prominent pulp horns, and pulp necrosis.

The following are discretionary and are not suggested routinely in children:

- Baseline fundoscopy examination to exclude papilledema in children ≤ 2 years old. (Fundoscopy is recommended in the presence of concerning symptoms such as headache, vomiting, loss of developmental milestones.)

- Baseline trans-iliac bone biopsy for histomorphometry.
- X-rays for longitudinal determinations of RGI-C, for serial follow-up.

Adults

THE PANEL SUGGESTS

History and Physical Examination—Key Points to Document

- Obtain a detailed family history to identify instances of XLH or hypophosphatemia.
- Document history of fractures or pseudofractures.
- Document history of dental infections (abscesses, periodontitis, etc. and related treatments).
- Measure standing height, weight, and BMI.
- Perform a musculoskeletal examination to assess bony tenderness and range of movement.

Biochemistry

- Conduct a comprehensive panel of laboratory tests including serum total calcium (corrected for albumin), phosphorus, ALP, 25-hydroxyvitamin D, kidney function (creatinine, eGFR), PTH, 24-hour urine calcium/creatinine (or spot urine calcium/creatinine), 24-hour urine phosphorus/creatinine, TmP/GFR.
- Perform genetic testing for variants in the genes**** resulting in hypophosphatemia, including *PHEX*, in order to confirm the underlying diagnosis and guide family screening and counseling.

Imaging

- Perform a baseline BMD assessment$^{\Lambda}$.

Dental and Oral Care

- Perform a baseline dental assessment with periapical X-rays or orthopantomogram to screen for enlarged pulp chambers, pulp necrosis, and periapical bone loss.

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*Compared to appropriate age- and sex-matched normative data.

**Appropriate for the patient's ethnicity, region, and/or country, as available.

***Normal <0.2 mg/mg (or <1.4 mmol/mmol in some laboratories) in children; age-adjusted norms apply for infants/toddlers.

****Gene panel includes *PHEX, FGF23, SKG3* (uncertain FGF23 status), *ENPP, DMP1, ENPP1, FAM20C, KLOTHO, FGFR1, INPPL1, RAS, GNAS, SLC34A1, SLC34A3, CLCN5, CTNS, NHERF1.*

Λ Despite DXA limitations in XLH, BMD assessment may be of value in adults with skeletal mineralization abnormalities. In such individuals, serial assessment may be of value in the presence of hypogonadism or other conditions that can affect bone density, such as superimposed postmenopausal osteoporosis.

Abbreviations: ALP, alkaline phosphatase; AP, anteroposterior view; BMD, bone mineral density; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate, *PHEX* gene, phosphate regulating endopeptidase homolog X-linked gene; RGI-C, Radiographic Global Impression of Change; TmP/GFR, tubular maximum phosphate reabsorption adjusted for glomerular filtration rate; TRP, tubular reabsorption of phosphorus; XLH, X-linked hypophosphatemia.

Box 2. Summary of GRADEd monitoring practice recommendations for follow-up of patients with XLH

Children (Infants to Adolescents)

THE PANEL SUGGESTS

History and Physical Examination

Perform the following *every 3 to 6 months*:

- Record weight as percentile*.
- Record recumbent length as a percentile* (children $\leq$ 2 years old).
- Measure standing height as a percentile* (children > 2 years old).
- Measure and document head circumference as an age- and sex-matched percentile* (children $\leq$ 2 years).
- Measure and express blood pressure as a percentile for age, sex, and height.
- Perform a clinical physical examination for skeletal deformities (e.g., genu varum, genu valgum, tibial torsion, spinal lordosis/kyphosis/scoliosis) in all children $\geq$ 6 months old.
- Measure growth velocity in children up to age 16 for females and 18 for males.

Biochemistry

Perform the following lab tests *every 3 to 6 months*:

- Morning fasting (preferred) or random phosphorus.*
- Total calcium (albumin corrected) or ionized calcium.
- ALP.*
- Creatinine and eGFR.
- PTH.
- Spot urine calcium/creatinine ratio.
- Spot urine phosphorus/creatinine.

Perform the following lab test *at least once a year*:
- 25-hydroxyvitamin D.

Imaging
Perform the following imaging *annually or less frequently*:
- Renal ultrasound.

Perform the following imaging *as clinically indicated:*
- Knee/hand-wrist X-rays to evaluate for rickets or rachitic changes.

Perform the following imaging *in the presence of localized leg or foot pain:*
- X-rays to assess for fractures or joint involvement.

Dental and Oral Monitoring Tool
Perform the following *every 3 to 6 months:*
- Document history of dental infections or maxillofacial cellulitis.

Arrange for the following *every 6 to 12 months:*
- Dental visit in all children $\geq$ 1 year old.

The following are discretionary and are not suggested routinely in children:
- Mobility assessment with 6MWT, unless symptoms are present.
- QoL assessment in children between 2 months and 18 years.
- Fundoscopy examination in children $\leq$ 2 years old in the absence of symptoms.
- 24-hour urine calcium to creatinine measurements.
- Assessment of RGI-C in children $\geq$ 6 months old.
- BMD measurements in children.

Adults
THE PANEL SUGGESTS
History and Physical Examination
Every 6 to 12 months:
- Perform clinical examination for skeletal deformity, osteoarthritis, and joint restriction.

At least once a year:
- Perform pain assessment.
- Perform a clinical assessment for fractures through history-taking and physical examination, with an emphasis on evaluating tenderness and swelling.
- Measure weight, standing height, and BMI.
- Measure blood pressure.

In the presence of neurological deficit:
- Perform a comprehensive neurologic clinical examination.

Biochemistry
Perform the following lab tests *at least once a year:*
- Morning (fasting) phosphorus.*
- Total calcium (albumin corrected) or ionized calcium.
- ALP.*
- Creatinine and eGFR.
- PTH.
- 25-hydroxyvitamin D.
- Spot urine phosphorus/creatinine.
- Spot urine calcium/creatinine ratio.

Imaging
Perform the following imaging *annually or less frequently:*
- Renal ultrasound.

Perform the following imaging *annually in the presence of bone pain:*
- Skeletal survey (X-rays or other specific imaging) to screen for fractures or pseudofractures.

Dental and Oral Monitoring Tools
- Dental assessment every 6 to 12 months.

Perform the following *at least once a year:*
- Documentation of dental infections or periodontitis history.

The following are discretionary and are not suggested routinely in adults:
- Sitting height measurements.
- QoL assessment.

Pregnancy and Preconception
THE PANEL SUGGESTS
History and Physical Examination
- Provide genetic counseling to all women of childbearing age, including adolescents, regarding the inheritance of XLH and the risk of transmission.

- Counsel women of childbearing age, including adolescents, treated with burosumab or conventional therapy** about the limited evidence on the risks and benefits of these treatments.

In the presence of neurological deficit*:*

- Conduct a comprehensive neurological clinical examination for patients presenting with neurological deficits.

Biochemistry

- Measure serum total calcium (albumin-corrected) or ionized calcium once every trimester for all pregnant women.
- Monitor serum creatinine and eGFR monthly for pregnant women receiving medical therapy.
- Check fasting serum phosphorus at least once during pregnancy for all women.

The following are discretionary and are not suggested routinely in pregnancy:

- Mobility assessment with 6MWT during pregnancy.
- QoL assessment in all women.
- Renal ultrasound to screen for nephrocalcinosis during pregnancy.

*Compared to appropriate age- and sex-matched normative data.
**Conventional therapy (phosphate salts and active vitamin D).
Abbreviations: 6MWT, 6-minute walk test; ALP, alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; eGFR, estimated glomerular filtration rate, QoL, quality of life; RGI-C, Radiographic Global Impression of Change; TmP/GFR, tubular maximum phosphate reabsorption adjusted for glomerular filtration rate; XLH, X-linked hypophosphatemia.

Overview of XLH in Children (< 18 Years)

X-linked hypophosphatemia (XLH) in children causes rickets, defined as inadequate mineralization of growth plates, structures no longer present in adults. This is important, as rickets can be quantified radiographically, thereby providing an objective measure of disease severity and treatment efficacy. XLH also affects linear growth, in both prepubertal and pubertal phases. There are, however, complications seen across all age groups. For instance, osteomalacia may develop in older children with XLH, and skeletal abnormalities are not limited to growth plate abnormalities. Other manifestations in older adolescents may include enthesopathy, dental anomalies, hearing loss, and fatigue (1).

Current Monitoring Tools for XLH in Children (<18 Years)

Clinical assessment

After diagnosis, children with XLH on conventional therapy (phosphate salts and active vitamin D) or burosumab, a recombinant human monoclonal antibody targeting fibroblast growth factor 23 (FGF23), are examined at each clinic visit to assess improvement in linear growth and lower limb deformities and to screen for complications of craniosynostosis, pseudofractures, and dental defects. Linear growth may be monitored by assessing length/height growth velocity on standard pediatric growth curves and by tracking height SD scores over time. Lower limb deformities associated with weight-bearing can be assessed on physical exam by measuring the upright intercondylar distance with heels together (varus deformity) and intermalleolar distance with knees together (valgus deformity) (2). For children with a "windswept" deformity of the lower extremities, the same measurements may be helpful but can be correlated with radiographic measures of the tibiofemoral angle.

Baseline imaging may be completed in infants to screen for premature fusion of the sagittal (and other) sutures, together with examination for ridging along suture lines and abnormal head shape, especially frontal bossing and failure of posterior widening (scaphocephaly). At each visit in the first 3 to 4 years, head circumference may be measured at the widest forehead-occiput position to screen for frontal bossing or suboptimal growth of the overall cranial vault; babies can be assessed for unusual irritability, neck discomfort, and gross motor function. For those with suspected craniosynostosis, raised intracranial pressure, or Chiari 1 malformation, appropriate cranial imaging and assessment for papilledema by an ophthalmologist is advised.

After the age of 3 to 4 years, monitoring shifts to screening for subtle signs of raised intracranial pressure from undiagnosed craniosynostosis, Chiari 1 malformation, and syringomyelia (occipital headache, vomiting, back pain, or lower tract neurologic symptoms). These findings should prompt fundoscopy and imaging studies. Unexplained pain in the lower extremities may warrant X-rays to identify pseudofractures. Inspection of teeth for overt caries should prompt referral to a dentist to optimize oral hygiene and monitor for dental complications including abscesses. Blood pressure can be assessed annually in children.

Biochemical assessment

At each clinic visit on conventional therapy, biochemical assessment begins with a measure of serum phosphorus. Ideally, this can be timed to capture the peak (about 1 hour after the morning oral doses of phosphate and calcitriol) or trough (about 4-6 hours after oral dosing) in a consistent manner. During the growth period, alkaline phosphatase (ALP) is useful to monitor as an index of rickets severity. While a high ALP may reflect insufficient dosing of phosphate and calcitriol, it may also reflect a failure of such therapy, given that higher doses might increase the risk of other complications. It is important to ensure that age-appropriate ALP reference ranges are utilized in the interpretation of results due to the physiological variations in ALP levels during the different phases of growth (3). Excess phosphate or inadequate calcitriol may induce secondary hyperparathyroidism, which is best evaluated by assay of intact PTH and ionized or total serum calcium adjusted for albumin at each visit. Excess calcitriol dosing is initially reflected by increased urinary calcium excretion (as assessed by either a 24-hour urine or spot

calcium/creatinine ratio). With persistent excess dosing or if administered in the presence of parathyroid autonomy, calcitriol may contribute to hypercalcemia. Measurements of FGF23, tubular maximum phosphate reabsorption adjusted for glomerular filtration rate (TmP/GFR), or 1,25 dihydroxyvitamin D are not helpful for adjusting conventional therapy at clinic visits.

On burosumab treatment, similar biochemical parameters are measured, but timing of the blood and urine sampling is more flexible and is preferably completed just prior to dosing (trough), and peak values can be obtained day 7 to 11 after dosing (4). As standard FGF23 ELISA assays cannot measure endogenous hormone in the presence of burosumab (exogenous antibody), FGF23 measurement during burosumab therapy is not useful.

Radiological assessment

Rickets can be assessed qualitatively on X-rays of upper and/or lower extremity growth plates or quantitatively using the Rickets Severity Score (RSS). The RSS is calculated using bilateral wrist and knee X-rays according to specific criteria and has been validated in children with XLH (5). The RSS ranges from 0 (no rickets) to 10 (severe rickets), with most patients with XLH harboring scores less than 5 to 6 in the absence of treatment. The RSS was popularized in XLH when selected as an outcome and entry criterion for the clinical trial program of burosumab (6). An RSS $\geq$2 is considered mandatory by many health authorities for determining access to burosumab (thereby mimicking the eligibility criteria of the phase 3 trial). This approach has raised concern among pediatricians due to the need for additional radiation when using the standardized bilateral wrist and knee RSS (as opposed to a single wrist and/or knee being adequate for treatment monitoring). Of the 2, the knee appears to best reflect rachitic activity. The Radiographic Global Impression of Change (RGI-C) was developed during clinical trials of hypophosphatasia and compares serial X-rays for change in rickets severity over time (7). This 7-point ordinal scale ranges from −3 (severe worsening) to 0 (no change) to +3 (complete healing) and was used as the primary outcome in the randomized controlled trial of burosumab vs conventional therapy in children (6). In practical terms, neither the formal RSS nor the rickets RGI-C are recommended as part of routine clinical care; rather, periodic X-ray assessments for changes in rickets severity at the wrists and/or knee are sufficient. Standing lower extremity X-rays should also be completed periodically in children with XLH with significant or worsening lower limb deformity to evaluate the need for guided growth by hemi-epiphysiodesis in those with genu varum and/or valgum. In-toeing is also frequently observed in children with XLH, with surgical decisions made based on physical examination findings. If rotational malalignment is clinically significant and interfering with mobility, a low-dose computed tomography scan or low-radiation bipolar X-ray imager may be considered for assessment. Craniosynostosis, Chiari 1 malformation, and syringomyelia are also comorbid in children with XLH (8).

Limitations of Current Monitoring Tools in Children (<18 years)

Current monitoring tools in children are adequate to allow the clinician to determine the severity of the disease (mild, moderate, or severe) at baseline and whether the child's disease manifestations are improving, stable, or worsening. While hypophosphatemia is a hallmark feature of XLH, the serum phosphorus level does not appear to provide the best gauge of a child's overall disease trajectory. Other biochemical indicators (ie, ALP) plus structural and functional outcomes (growth velocity, lower limb deformity, rickets severity) provide more robust evidence for disease severity and evolution with therapy.

Overview of XLH Diagnosed in Adults

XLH is usually diagnosed in childhood, but a small proportion of individuals may initially be diagnosed in adulthood. This may be due to earlier misdiagnosis or the presence of mild disease that was identified only after the birth of an affected child, prompting family testing, or after symptomatic presentation in adulthood (9). The diagnosis should be suspected with a clinical and biochemical phenotype consistent with osteomalacia in the presence of hypophosphatemia, often with lower limb deformities, dental manifestations, enthesopathy, and spinal stenosis. Renal phosphate wasting is confirmed with a low TmP/GFR and elevated or inappropriately normal FGF23 (where this assay is available) in the setting of hypophosphatemia.

Current Monitoring Tools for XLH in Adults

The goals of monitoring an adult patient with XLH are to determine the need for and choice of treatment, to evaluate the efficacy of treatment, and to manage long-term complications of XLH. The therapeutic challenge is to maintain skeletal and oral health and quality of life (QoL) without increasing the risk of hyperparathyroidism or renal impairment due to nephrocalcinosis (9). The frequency of follow-up visits should be increased with changes in therapy, around the time of surgical interventions, in pregnancy, and in the case of evolving complications.

Clinical assessment

A detailed history should include a structured assessment of pain using standardized tools, for example the Numeric Rating Scale, where patients rate their pain intensity on a scale from 0 to 10, suitable for adults and older children. Evaluation of stiffness by documenting its presence or absence, as well as the duration of morning stiffness. Fatigue should be assessed by inquiring about its severity, frequency, and impact on daily activities. Muscle weakness can be evaluated through patient-reported difficulties in performing tasks requiring strength such as climbing stairs, standing from a seated position, walking long distances, or carrying objects. The history should also include assessment of joint pain and mobility by asking about joint-specific discomfort, range of motion, and limitations in daily activities. History of fractures or pseudofractures (with or without interventions) should be obtained as well as any new or progressive bony deformity, dental complications (dental infections and periodontal disease), or neurological symptoms. Additional parameters include a history of previous orthopedic surgery, symptoms and signs of Arnold Chiari and spinal disease, mental health issues, hearing loss, and functional status.

A focused examination includes but is not limited to vital signs and oral, neurological, and musculoskeletal (including deformity and gait) assessment. Hypertension has been reported as a complication in adults and children with XLH

(10). Hearing loss is reported in 16% to 76% of XLH patients, with mixed sensorineural and conductive deficits, attributed to hypomineralization of the auditory ossicles, as also observed in *Hyp* mice (11). The frequency of audiometric evaluation has not been established (11).

The well-being of patients with XLH should be assessed through patient history and supported by the use of general QoL measures. While various measures designed for rheumatologic conditions have been employed in trials and observational studies of XLH, many of these tools have not been specifically validated for use in the XLH population. In contrast, the Western Ontario and McMaster Universities Arthritis (WOMAC) Index and the Brief Pain Inventory Short Form (BPI-SF) have been validated in patients with XLH (12).

Biochemical assessment

Biochemical assessment includes disease-specific measures such as serum phosphorus, ALP, FGF23, and TmP/GFR and monitoring for potential complications including serum creatinine, estimated GFR (eGFR), calcium, PTH, and urine calcium excretion. Biochemical assessment will be more extensive when the diagnosis is being established and more focused during disease monitoring. The goal of treatment with conventional therapy is to normalize bone-specific alkaline phosphatase (BsALP) and not necessarily normalize serum phosphorus. Avoiding elevations in PTH and serum and urine calcium is advised. Please refer to Table 1 for optimal laboratory assessment practices.

Radiological assessment

Dual-energy X-ray absorptiometry (DXA) has limited clinical utility in the assessment of osteomalacia in XLH due to falsely elevated results in association with ligamentous ossification and lamina thickening in the spine. Thus, the diagnostic value of a hip bone mineral density (BMD) may be greater than that of a spine BMD. In addition, the cross-sectional area of the bones is increased in XLH resulting in an increase in areal BMD in both children and adults (19-21). Despite limitations, DXA is used in adults with XLH by panel members to assess for the possibility of superimposed conditions of low bone mass. Declines in areal BMD as measured by DXA raise the possibility of an additional secondary cause for bone loss such as the development of secondary or tertiary hyperparathyroidism, suboptimal treatment, or an additional skeletal insult such as estrogen deficiency. Whole lower extremity X-rays are used to assess for bony deformity. Focused X-rays help evaluate joint damage of hips and knees, spinal involvement, enthesopathy, and pseudofractures. Renal ultrasound is suggested for monitoring nephrocalcinosis. Magnetic resonance imaging of the brain (Chiari malformation) or spine (spinal stenosis, syringomyelia) is indicated in the presence of neurological symptoms and signs. A postauthorization safety study of burosumab (NCT03193476), the International XLH Registry, is further evaluating the utility of echocardiography, electrocardiography, and hearing assessments in adults with XLH (22).

Limitations of Current Monitoring Tools in Adults

Monitoring practices should be individualized for each patient, recognizing the wide spectrum of manifestations of XLH. Currently, there are limited data on the natural history of the disease, making it difficult to provide evidence-based recommendations on monitoring frequency. Furthermore, the serum marker we follow most closely, serum phosphorus, does not always correlate with symptoms.

The guidance for follow-up of patients on burosumab therapy is based on clinical trial protocols. Bone-specific ALP represents a smaller proportion of adult total ALP (~50%) in comparison to children (90%). It is recommended that BsALP be utilized for follow-up of adult XLH patients if available.

Stiffness is a feature of XLH and a prominent complaint by patients; however, measures such as the WOMAC Index stiffness subscale show poor retest reliability in osteoarthritis (23). Retest reliability was not reported in XLH (12).

Overview of XLH in Pregnancy and Lactation

During pregnancy, physiological changes occur in the calcium-regulating hormones affecting calcium and phosphorus homeostasis. These changes ensure that the fetal mineral demands are met with adequate mineralization of the fetal skeleton. In the setting of XLH, these changes may alter the serum calcium and phosphorus response to conventional therapy or burosumab, possibly predisposing to hypercalciuria, hypercalcemia, or hyperphosphatemia compared to the nonpregnant state, thereby requiring greater monitoring and counseling of patients regarding risk.

Current Monitoring Tools of XLH in Pregnancy

Clinical, biochemical, and radiological assessment

Clinical assessment of childbearing women with XLH should involve genetic counseling on the inheritance pattern of XLH and the risk of transmission to the offspring. It is also important to counsel those undergoing medical therapy on the potential risks and benefits associated with treatment. It is prudent to note that as a monoclonal IgG antibody, burosumab can cross the placenta based on animal data, and its effects on the developing fetus are not yet known (24). Calcitriol and phosphate salts are classified as Food and Drug Administration pregnancy category C, indicating that risk has not been excluded (25, 26). Although satisfactory studies in pregnant women are lacking, animal studies have demonstrated potential risks to the fetus. However, the potential benefits may outweigh these risks (27). In addition, the risks of hypercalcemia or hypercalciuria to the mother from calcitriol use may increase due to physiological changes of pregnancy, such as elevated levels of $1,25(OH)_2D$ and enhanced gut calcium absorption, and this should be closely monitored. A review of a woman's current medications should be undertaken to ensure safety during pregnancy.

There is no published evidence to guide optimal biochemical monitoring during pregnancy and lactation. However, given the physiologic changes in mineral metabolism during pregnancy, biochemical monitoring during pregnancy may need to be more frequent than when nonpregnant. Radiographic imaging should be minimized, taking into consideration the benefits vs risks of exposure to radiation during pregnancy.

Overview of XLH and Dental Monitoring

Dental complications are commonly seen in XLH and include spontaneous dental infections (abscesses, pulp necrosis, tooth loss, and, less frequently maxillofacial cellulitis) and, in adults, frequent periodontal disease (1, 28-33). These infections are a direct consequence of the impaired

Table 1. Laboratory assessment best practice

Test	Method of testing
Alkaline phosphatase (13, 14)	Random serum sample (compared to age- and sex-matched normative data)
Calcium (total) corrected for albumin	Random serum calcium and albumin samples Calculation (mg/dL): [0.8 × (normal albumin − patient's albumin in g/dL)] + serum calcium (mg/dL) Calculation (mmol/L): [0.02 × (normal albumin − patient's albumin in g/L)] + serum calcium (mmol/L)
Calcium ionized (corrected for pH) (15)	Fasting serum sample (4- to 6-hour fast) To be collected in red-top tube, gel-barrier tube, or green-top (lithium heparin) tube Sample to be analyzed within 30 minutes of blood draw Do not use oxalate, EDTA, or citrate plasma in the collection tube Do not store it on ice or expose it to air
Fibroblast growth factor-23 (16)	Serum sample (fasting preferred but not required) Sample to be frozen upon collection then sent for biochemical analysis
Kidney function (creatinine, eGFR)	Random serum/plasma sample
PTH (17)	Random serum/plasma sample
Phosphorus- serum	Fasting serum/plasma sample (compared to age-matched normative data)
Phosphorus- urine	24-hour urine collection: overnight fast First urine void is discarded 24-hour urine collection starts The following day, first urine void is collected, concluding the 24-hour collection Sample to be refrigerated within 4 hours of collection Spot urine collection: overnight fast In the morning: collect the second urine void
TRP (tubular reabsorption of phosphorus)	Calculation: 1− phosphate-to-creatinine clearance = 1− [(urine phosphorus (mmol/L) × serum creatinine (mmol/L)) / (urine creatinine (mmol/L) × serum phosphorus (mmol/L))]
TmP/GFR calculation (18) Children • Spot urine phosphorus • Spot urine creatinine • Fasting serum creatinine + phosphorus collected simultaneously to urine sample Adults • 24-hour urine phosphorus • 24-hour urine creatinine • Fasting serum creatinine + phosphorus collected simultaneously to urine sample	1. Phosphate-to-creatinine clearance = (urine phosphorus (mmol/L) × serum creatinine (mmol/L)) / (urine creatinine (mmol/L) × serum phosphorus (mmol/L)) 2. TRP = 1− (phosphate-to-creatinine clearance) 3. TmP/GFR = Serum phosphorus (mmol/L) × TRP
Spot urine calcium/creatinine (for infants and small children)	Random urine sample
24-hour urine calcium/creatinine (for older children and adults)	Overnight fast First urine void is discarded 24-hour urine collection starts The following day, first urine void is collected, concluding the 24-hour collection Sample to be refrigerated within 4 hours of collection
25-hydroxyvitamin D	Random serum/plasma sample
1,25-dihydroxyvitamin D	Random serum/plasma sample

mineralization of dental and periodontal tissues (32, 34, 35). Dental complications negatively affect the patient's QoL (36-38).

Current Monitoring Tools for Dental Complications

Clinical assessment

A history of dental infections in patients with XLH should be recorded at all clinic visits as well as a review of the patient's preventative dental hygiene including avoiding culprit drinks, method and frequency of tooth brushing and flossing, and type of toothpaste. At the time of diagnosis, a baseline dental examination should be performed by a dentist on all patients (above 1 year of age in children). During patient follow-up, dental visits should be performed at least annually or biannually, or more frequently if necessary, depending on the severity of dental manifestations (1, 30, 31, 33).

Radiological assessment

At the time of diagnosis, a dental orthopantomogram (radiograph of the upper and lower jaw and teeth) should be performed in all patients above 6 years old in order to obtain a global view of the patient's dentition and to detect any periapical bone infection. This exam should be repeated based on individual needs during follow-up (31).

Methods

To assess how patients with XLH are monitored globally and reach a consensus on common practices pertaining to patient-important outcomes, we adapted a clinical practice survey from a recently published practice survey on initial assessment and monitoring of patients with chronic hypoparathyroidism (39). We divided our patient population into 4 groups: children under 18 years old, adults 18 years old and older, pregnant and lactating women, and children and adults with dental complications. The survey questions addressed clinical practices relevant to each patient group. We used a web-based software, SurveyMonkey (https://www.surveymonkey.com/), to distribute the survey, record the responses, and generate the analysis. We sent the survey to all members of the International Working Group (IWG) (40) in March 2023 using a web link and followed up with reminder emails. We contacted respondents individually if they had missing information and asked them for completion. We provided respondents with the option to complete relevant sections of the survey pertaining to their clinical practice and the patient population they routinely treat. We collected all responses confidentially, and we presented the results of the survey reporting in both averages and proportion format.

Demographic Data

The survey collected demographic data, practice location, specialty, years of experience treating XLH, number of patients with XLH followed in each practice, and types of patients being followed (such as adults, children, pregnant women, and patients with dental manifestations). We also collected data on the percentage of patients being treated with burosumab, conventional therapy, or chronic pain medications.

Assessment of New Patients With XLH (Adults and Children)

In this section, we asked respondents to answer questions addressing clinical practice for newly diagnosed patients, both adults and children, with XLH. We defined a new diagnosis in adults as one made or confirmed during adulthood. The questions covered clinical, biochemical, and radiological aspects of monitoring of these patients. We asked the respondents to use a sliding tool to indicate the percentage of new patients for whom they performed the indicated assessment (ranging from 0% to 100%). For respondents answering the adult section, we instructed them to choose 0 for questions addressing new diagnosis in adults if their patients were diagnosed in childhood and transitioned to adult care. We defined consensus as when 80% or more of respondents performed any of the clinical, biochemical, or radiological assessments in 80% or more of their patients 80% or more of the time.

Assessment of Follow-up Practice in Patients With XLH (Adults and Children)

In this survey section, we asked respondents about their follow-up practices for both adults and children with XLH. We further divided the patient groups into those receiving burosumab, those receiving conventional therapy, and those not receiving any medical treatment. Respondents chose the option closest to their clinical practice, and if none of the provided responses fit their practice, they chose "other" and provided a written explanation of their practice routine. For patients receiving burosumab, we asked respondents to select "not applicable" if their patients were currently receiving the drug only as part of an ongoing approved study protocol, as we wanted to capture real-time clinical practice behaviors. The questions in this section addressed clinical, biochemical, and radiological aspects of follow-up for patients with XLH. We defined consensus as being reached in this section when 80% or more of respondents performed the monitoring parameter on patients in any 1 of the treatment groups (burosumab, conventional therapy, or not on therapy) at different time intervals.

Assessment of Follow-up Practice in Pregnant and/or Lactating Women

We asked respondents in this section how often they conduct specific clinical, biochemical, and radiological tests during pregnancy and lactation in women with XLH. Additionally, we included questions about preconception counseling, education, and the use of contraception in patients receiving medical therapy. As with previous sections, we instructed respondents to select the closest response to their clinical practice or indicate if none were applicable, in these cases providing more detailed information. We defined consensus as being reached in this section when 80% or more of respondents performed the monitoring parameter on patients in any 1 of the treatment groups (burosumab, conventional therapy, or not on therapy) at different time intervals.

Assessment of Monitoring Practice From a Dental Perspective

We collaborated with a dental expert (C.C.) from the IWG to develop this section of the survey, which is intended for respondents who treat dental complications associated with XLH. The objective is to emphasize significant practice considerations concerning dental diseases and complications associated with XLH and to evaluate the frequency of performing dental visits. We defined consensus as being reached in this section when 80% or more of respondents performed the monitoring parameter.

Results

Demographics Data

All 43 members of the IWG completed the survey, resulting in a response rate of 100%. Table 2 displays the demographic data of the respondents. The IWG demonstrated global representation, with respondents practicing on 4 different continents. The distribution of specialties showed nearly identical proportions for adult and childhood practitioners (41.8% vs 53.4%). About 25.5% of respondents reported having fewer than 5 patients with XLH, while 37.1% were following more than 15 patients with XLH.

Table 2. Demographic data of XLH survey respondents

Demographic parameter	n = 43 (%)
Practice	
North America	21 (48.8)
Europe	18 (41.8)
Asia	3 (6.9)
South America	1 (2.3)
Female	23 (53.4)
Specialty	
Adult endocrinology	15 (34.8)
Pediatric endocrinology	9 (20.9)
Pediatric nephrology	7 (16.2)
Dentists or oral surgeons	5 (11.6)
Adult rheumatology	3 (6.9)
Geneticists	2 (4.6)
Adult and pediatric endocrinology	1 (2.3)
Metabolic bone disease	1 (2.3)
Years of following patients with XLH	
0-5	9 (20.9)
6-10	6 (13.9)
11-15	8 (18.6)
16-20	8 (18.6)
More than 20	12 (27.9)
Number of patients with XLH in current practice	
Fewer than 5	11 (25.5)
5-15	16 (37.2)
16-25	6 (13.9)
More than 25	10 (23.2)
Number of respondents treating patient group[a]	
Children and adolescents	18 (41.8)
Adults	23 (53.4)
Pregnant	17 (39.5)
Dental	5 (11.6)

Abbreviation: XLH, X-linked hypophosphatemia.
[a]Some respondents treat all age groups, including pregnant women (3/43).

Initial Assessment of Children With XLH

Inquiring about a family history of XLH, history of fractures, pain assessment, and history of dental infections is carried out by 100%, 91%, 92.3%, and 94% of respondents respectively, in 80% or more of their patients. Head circumference and recumbent length measurements in children ≤2 years are performed by 88% of respondents. For children >2 years old, standing height is done by 83% of respondents, as well as blood pressure in children of all ages. All respondents measure weight.

Regarding practices that did not reach our consensus threshold but were done by 50% or more of respondents, approximately 72% perform a baseline musculoskeletal examination for bony tenderness and range of motion in 80% or more of their patients. Our group members commonly report anthropometric parameters [eg, height, recumbent length, and body mass index (BMI)] in percentiles. However, 72%, 78%, and 57% of members expressed a preference for using Z-scores for these measurements, respectively.

Supplementary Fig. S1 (41) displays the biochemical and radiological tests requested by ≥80% of respondents at the initial evaluation. Supplementary Fig. S2 (41) displays the parameters that did not reach consensus.

Follow-up Assessment of Children With XLH

As part of the clinical assessment, >80% of respondents measure blood pressure, weight, recumbent length, and head circumference (in children ≤2 years old) every 3 to 6 months. In children older than 2 years, standing height is measured every 3 to 6 months, with only those on therapy meeting consensus criteria (92% on burosumab, 86% on conventional therapy). Over 80% of respondents perform a clinical examination for skeletal deformities every 3 to 6 months in children ≥6 months old. Supplementary Fig. S3 (41) displays the results for biochemical parameters commonly ordered by the IWG.

More than 80% of respondents order renal ultrasound annually or less frequently to screen for nephrocalcinosis, with repeat scans at the same interval, irrespective of whether nephrocalcinosis is present or absent in the previous scan. Similarly, ≥80% of respondents order X-rays to assess fractures or joint involvement in the presence of bone pain and order knee/hand-wrist X-rays to evaluate for rickets or rachitic changes, as clinically indicated.

Radiological tests not routinely ordered by ≥80% of respondents, unless warranted by symptoms, include foot/ankle X-rays to monitor for enthesopathy in children ≥2 years and X-rays of the upper extremity (excluding hand/wrists) to monitor for signs of osteomalacia or skeletal deformity. Additionally, BMD assessment in children is not routinely conducted.

Initial Assessment of Adults With XLH

In our survey, 94% of respondents conduct an initial assessment, documenting the family history of XLH, personal history of fractures or pseudofractures, and history of dental infections in 80% or more of their patients. Over 90% of respondents measure weight, standing height, and BMI. Additionally, 87% of respondents measure blood pressure, and 82% perform a musculoskeletal clinical examination to assess for bony tenderness and range of movement.

Supplementary Figs. S4 and S5 (41), respectively, show the parameters that reached and did not reach consensus for clinical, biochemical, and radiological tests. Several respondents indicated their inclusion of iron studies (for iron deficiency) as well as use of procollagen type I intact N-terminal propeptide (PINP)—chosen over BsALP as a marker of bone formation—within the initial laboratory parameters when assessing new adults with XLH. Other members recommend evaluating bone microarchitecture with high-resolution peripheral quantitative computed tomography (HR-pQCT), if available; however, these questions were not part of the survey.

Follow-up Assessment of Adults With XLH

More than 80% of respondents monitor adults with a clinical physical examination for skeletal deformity, osteoarthritis, and joint restriction every 6 to 12 months, in addition to a comprehensive neurological examination if neurological deficits are present. At least once a year, ≥80% of respondents measure weight, standing height, and BMI as well as assess for pain and fractures. Supplementary Fig. S6 (41) summarizes the biochemical and radiological tests that ≥80% of respondents order. At least 80% of respondents measure blood pressure at least once a year in adults.

Follow-up Assessment of Pregnant and/or Lactating Women With XLH

The majority (80-90%) of respondents conduct genetic counseling on the inheritance pattern of XLH and the risk of transmission in all women of childbearing age (including adolescents). For those undergoing medical therapy (burosumab or conventional therapy), 80% to 85% of respondents counsel women on the risks and benefits associated with these treatments. However, several members of the group performed practices that did not meet consensus criteria, including assessing blood pressure and weight once every trimester. The lack of consensus on these parameters was due to the fact that, in many practices, weight and blood pressure measurements are routinely performed by maternal-fetal medicine or obstetric clinics. In addition, 92% and 84% of respondents check serum total corrected calcium/ionized calcium once every trimester in patients on conventional therapy or no treatment, respectively. All respondents check kidney function (eGFR and creatnine) every month in those receiving medical therapy. At least once during pregnancy, 84% and 83% of respondents check fasting serum phosphorus in women on conventional therapy or no treatment, respectively. Radiological studies are not routinely ordered during pregnancy or lactation.

The lack of general consensus on monitoring practices during pregnancy as opposed to in nonpregnant adults reflects the lack of certainty and need for research focused on pregnancy in XLH.

Dental and Oral Health

All dental panelists order periapical X-rays to screen for enlarged pulp chambers and pulp necrosis as part of the initial evaluation of both children ≥6 years of age and adults. During the monitoring of children with XLH, >85% of respondents inquire about history of dental infections every 3 to 6 months. More than 80% of respondents recommend dental visits to occur at 6- to 12-month intervals in both age groups (children and adults).

Discussion

At this time, the number of published clinical guidelines/consensus statements providing recommendations on the monitoring of XLH is limited (31, 42-44).

The objective of the current survey-based consensus report is to convey XLH disease monitoring practice patterns of international experts and in doing so help clinicians in providing both evidence-based and expert-based care to their patients with XLH.

The results of our survey reflect the differences in clinical practices amonng international experts managing XLH in various regions of the world. We observed that certain practices did not achieve the consensus threshold (eg, FGF23 measurement) or had lower percentages of adoption among respondents. The reasons for these lower percentages are multifactorial and include lack of standardized recommendations for some aspects of XLH management and heterogeneity in practice patterns among experts—stemming from differences in regional healthcare systems, resource availability, and individual clinical experiences, as well as variations in methods of measurement and assessment tools available.

Main Findings

Initial assessment in children with XLH

When initially assessing children for XLH, our IWG suggest historical elements that are consistent with published guidelines (31, 44). The clinical examination suggested includes measuring height/recumbent length and weight to assess growth in children, as 1 of the initial presentations of XLH in children is short stature and reduced growth velocity, observed in up to 90% of affected individuals (45). Measurement of head circumference (for skull deformities and craniosynostosis) in children ≤2 years of age as well as blood pressure in all children is suggested by the IWG and endorsed by other published guidelines (31, 43). The biochemical testing that our IWG commonly order are also congruent with published guidelines and consensus statements (31, 43, 44). Our recommendations for imaging (eg, X-rays to assess lower limb deformities and renal ultrasound for nephrocalcinosis) are consistent with published guidelines (31, 43, 44). With dental complications being diagnosed in more than 70% of children, often with recurrent dental abscesses (21, 45-47) and maxillofacial cellulitis, our dental experts recommend periapical X-rays or orthopantomogram in children ≥6 years of age for screening, diagnosis, and prompt treatment of dental infections, if present.

Several pertinent areas of heterogeneity in practice patterns have been identified through our survey. While several panel members assess gait on their initial evaluation of children due to the high prevalence of gait abnormalities in children, especially in the first 2 years of life (48), this practice did not reach our consensus threshold (72.2%). Concerning biochemical testing, only 50% of respondents measure circulating FGF23 during the initial visit. This may be attributed to the limited availability of FGF23 assay in certain institutions or the perception that it might not be necessary when other parameters already indicate a diagnosis of XLH. According to the 2019 European guidelines, measurement of FGF23 can assist in diagnosing FGF23-dependent renal phosphate wasting, most commonly XLH, when genetic analysis or family history is not available (31). For imaging, published guidelines advise performing hand X-rays to evaluate for rickets, however; only 69% of respondents order 1 in 80% or more of patients at the initial visit, and thus it did not reach the consensus threshold (31, 43, 44). However, our IWG orders knee or hand-wrist X-rays as clinically indicated to monitor healing/recurrence of epiphyseal features of rickets. Baseline BMD measurement did not reach the consensus threshold in children.

During the initial assessment of children for XLH, our IWG advises excluding other causes of hypophosphatemia, such as Fanconi syndrome and other non-FGF23-dependent renal phosphate wasting disorders. Screening for iron deficiency (known to increase FGF23 expression) is also of value, given that in autosomal-dominant hypophosphatemic rickets (ADHR), FGF23 is resistant to cleavage. Thus ADHR may be unmasked as a diagnosis due to the FGF23 excess observed in the presence of iron deficiency (49, 50). Genetic testing for the other conditions in the differential diagnosis may be useful unless there is a documented family history of a *PHEX* gene variant.

Follow-up assessment in children with XLH

The IWG agrees on monitoring children with XLH every 3 to 6 months with clinic visits focused on anthropometric measurements, blood pressure measurements, and clinical musculoskeletal examination to assess for skeletal deformities. When measuring growth velocity, the IWG assesses females

up to age 16 years and males up to age 18 years. The biochemical parameters are consistent with published guidelines. The correlation between spot and 24-hour urinary calcium measurements has been an area of ongoing debate. Studies suggest that the spot urine calcium-to-creatinine ratio can serve as a reliable measure to detect hypercalciuria in children, particularly when adjusted for age and body weight (51). However, spot measurements may have limitations in certain scenarios, such as highly variable dietary calcium intake or hydration status, which should be considered when interpreting results.

The IWG suggests screening for nephrocalcinosis with a renal ultrasound at yearly or less frequent monitoring intervals, in line with the recommendations of the 4 published guidelines, regardless of the presence or absence of nephrocalcinosis (31, 42-44). While 58% to 66% of our respondents order routine monitoring X-rays of the lower extremities, such a practice did not meet the consensus threshold. Specifically, the IWG suggest ordering X-rays when there are symptoms of pain or worsening deformity. This approach aligns with previously published guidelines that advise performing these X-rays only when clinically indicated, aiming to minimize radiation exposure in children (31, 43, 44). Mobility testing with a 6-minute walk test, used to assess physical function, is recommended by the Asian-Pacific and European guidelines every year if resources are available, whereas the British guidelines give no clear time interval (31, 42, 44). The IWG does not suggest the routine assessment of the 6-minute walk test unless warranted by children's symptoms. The IWG also does not suggest the routine use of the RSS or RGI-C (which involve radiographs of both wrists and both knees serially) in children 6 months or older being treated with conventional therapy or burosumab, primarily due to the additional radiation involved as noted previously.

On review of the published guidelines, a strong suggestion to optimize the follow-up care of children with XLH is to assemble a multidisciplinary team of providers, preferably led by a metabolic bone disease expert, to manage those children with follow-up intervals individualized per patient. Where our panel suggests 3- to 6-month clinic visits, the published guidelines recommend visits as frequent as every 3 months during periods of rapid growth (infancy, puberty) or after initiation of therapy and subsequently tailoring the visits depending on the therapy and severity of the disease (31, 33, 43, 44). The purpose of follow-up visits is not only the monitoring of patient symptoms and response to therapy but also the assessment for potential treatment-related complications including hypercalcemia, hypercalciuria, nephrolithiasis, nephrocalcinosis with possible progression to chronic kidney disease, hypertension, as well as secondary and tertiary hyperparathyroidism. Therefore, close monitoring is critical to minimize these complications.

Initial assessment in adults with XLH

The initial assessment of adults with XLH with respect to history taking and biochemical tests are similar to that of children. A musculoskeletal clinical examination for bone tenderness and range of motion is commonly done by the IWG, a recommendation noted in the Belgian guidelines in both adults and children (43). Up to 80% of adult patients with XLH develop joint damage with subsequent joint stiffness in addition to muscle weakness, making a musculoskeletal evaluation prudent (46).

Baseline BMD measurement is suggested in the adult group as part of the initial visit by 80% of respondents, despite lack of data on fracture risk prediction. Indeed, some guidelines recommend against obtaining a BMD in XLH, due to the sclerosing nature of the disease, the expected false increase in BMD due to the size artefact (19) and mineralization of spinal ligaments, and its inability to differentiate osteoporosis from osteomalacia (31, 43, 44). However, BMD assessment with DXA may still be of value, especially in postmenopausal women who have superimposed osteoporosis. Baseline renal ultrasound and X-rays of the lower extremity, while recommended in both European and Belgian guidelines (31, 44), are only performed by 78% and 68% of respondents, respectively, and thus did not achieve the consensus threshold.

Follow-up assessment in adults with XLH

The monitoring of adult patients with XLH is based on the cumulative experience of our IWG. Clinic visits involve a clinical physical examination for skeletal deformities, joint swelling, and joint restriction in all patients every 6 to 12 months. Height, weight, and BMI measurements, endorsed by published guidelines at 6- to 12-month intervals, are also performed by >80% of respondents at least once a year (31, 43, 44).

Biochemical markers commonly ordered during follow-up are done so at a frequency of at least once a year, with great variability in the measurement intervals between biochemical tests and between respondents. When compared to published guidelines, the European guidelines advise for more frequent testing with fasting serum phosphorus and TmP/GFR every 2 weeks for the first month of starting burosumab therapy then every 4 weeks for the following 2 months and as appropriate thereafter (31). The British guidelines follow a less intensive pattern with 6 monthly lab intervals (42). In patients on burosumab, only 40% of respondents check serum fasting phosphorus every 3 months, 7 to 11 days after the burosumab injection in those with injections every 4 weeks.This significant heterogeneity is likely due to the novelty of burosumab and in some cases the lack of burosumab availability in some countries for adults as well as the individualization of therapy in adults with XLH.

With respect to QoL, more than 80% of respondents reported not routinely assessing this parameter in adults.

Follow-up Assessment in Pregnant and/or lactating women with XLH

The results from our survey show significant heterogeneity in the clinical and biochemical evaluation of these patients. Both the published guidelines and the IWG recommend genetic counseling for women of childbearing age and discussion of risks and benefits associated with therapy (31, 43, 44). The IWG suggests assessment of serum creatinine and eGFR every month in those on medical therapy. If on conventional therapy or no therapy, the IWG recommends serum albumin-corrected calcium/ionized calcium measurements every trimester and serum fasting phosphorus at least once during pregnancy.

The IWG developed the monitoring survey and also developed non-GRADEd recommendations on the management of XLH during pregnancy. These recommendations include monitoring blood pressure at every prenatal visit and initiating treatment for hypertension when indicated, in accordance with local guidelines for hypertension in pregnancy.

Optimization/normalization of serum calcium and vitamin D levels preconception, during pregnancy and while breastfeeding, is also proposed. During pregnancy and lactation, the panel also proposes measuring serum phosphorus, calcium corrected for albumin, and renal function at least every 2 months. With regard to medical therapy, there is limited data on the use of burosumab during pregnancy, which is currently not recommended (22). Similarly, it is not known if burosumab is excreted in breast milk and if there are any implications for the breastfed infant (24). This is consistent with our observation that several members of the IWG who manage pregnant women with XLH do not administer burosumab to such patients.

Considering the mode of inheritance and the 50% likelihood of transmitting XLH to the offspring, screening all infants of affected mothers is advised.

Limitations

We recognize several limitations to these consensus recommendations. Survey-based consensus is based on expert opinion and hence of very low certainty evidence. In addition, because the present survey is based on practice patterns, significant heterogeneity can exist among physicians practicing in different parts of the world that may not reflect the optimal practice pattern but rather limitations in their practicing healthcare systems. This can result in several pertinent practices not meeting the threshold for consensus. We acknowledge there is underrepresentation of clinicians from South America and Asia and the absence of representation from Africa in our survey, and we hope to address this in future recommendations. Lastly, despite our panel's vast knowledge and expertise in managing patients with rare metabolic bone disorders, recall bias must be accounted for in the setting of the epidemiologically low number of existing cases (only 23% of respondents reported more than 25 patients with XLH in their practice).

Implications for Clinical Practice

Due to the paucity of guidelines and recommendations to aid clinicians in the initial assessment and monitoring of patients with XLH, the present consensus statement can serve as a valuable tool to assist in the monitoring of this condition. It also sheds light on the importance of having such resources available, pending more evidence to guide the development of updated guidelines. Due to the known risk of complications including nephrocalcinosis, renal disease, hyperparathyroidism, and skeletal deformities, timely and close follow-up and titration of therapy is crucial to avoid long-term irreversible comorbidities. This survey results will hopefully assist in advancing the care provided to patients with XLH globally.

Suggestions for Future Research

There are a number of areas in XLH monitoring that warrant consideration in future research efforts, including barriers to successful implementation of the current guidelines on the global stage, the impact of age at conventional and burosumab therapy initiation in childhood on important clinical outcomes later in life, the effect of burosumab or conventional therapy during pregnancy and lactation on maternal-fetal health, and the merit of XLH monitoring assessments that are not currently recommended as part of the disease surveillance paradigm.

Endorsements

This manuscript has been endorsed by the Argentinian society, the Brazilian Association of Bone Assessment and Osteometabolism, the Canadian XLH Network (patient group), the Chilean Society of Osteology and Mineral Metabolism, the Endocrine Society, the European Calcified Tissue Society (ECTS), the European Reference Network on Rare Bone Diseases, the French Dental Association, the German Society of Endocrinology, the German Society of Osteology, the Irish Endocrine Society, the Japanese Society for Bone and Mineral Research, the Kuwait Academy of Rare Diseases, the Pediatric Endocrine Society, the Korean Endocrine Society, and the Korean Society for Bone and Mineral Research, and XLH Denmark (patient group).

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Data Availability

The data that support the findings in this study are openly available in PubMed, EMBASE, and the Cochrane databases. Supplementary material is publicaly available in an online repository cited in the article. Detailed survey data is available with the corresponding author upon request.

Ethical Statement

The objective of this study was to evaluate the current practices of international experts and did not require ethical committee approval.

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