

Exploring the Exercise and Physical Activity Experiences of Adults with X-Linked
Hypophosphatemia

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Background: X-linked hypophosphatemia (XLH) is a rare hereditary phosphate-wasting disorder, marked by mutations in the PHEX gene on the X chromosome. Mutations result in renal phosphate wasting and decreased 1,25-dihydroxyvitamin D, leading to rickets in children and osteomalacia in adults. XLH contributes to significant physical impairments including lower limb deformities, reduced height, bone pain, stiffness, early osteoarthritis, and fractures, which collectively hinder mobility, physical functioning, and quality of life. Despite pharmaceutical treatments, mobility and physical functioning deficits remain inadequately addressed. Currently, there is not a strong understanding of how physical activity and exercise can affect health outcomes for people with XLH. XLH brings unique challenges to mobility and physical functioning which could bring its own barriers to exercise making it an important topic to explore to create interventions for the XLH population.

Objective: The objective of the study was to understand the experiences of people with XLH when participating in physical activity and exercise. I looked to identify how having XLH affects participation in physical activity and exercise, the barriers to and facilitators of exercise and physical activity, and the health outcomes that are most important for people with XLH when making treatment decisions with medications, and exercise.

Methods: Using a phenomenological approach from a post-positivism point of view, semi-structured interviews were conducted with adults diagnosed with XLH. The interview guide was designed using the COM-B model of behavior to reveal how capability, motivation and opportunity affects people with XLH's exercise and physical activity behaviors. Data was analyzed using reflexive thematic analysis to understand the experiences during exercise and physical activity, the barriers to and facilitators of exercise, and the outcomes prioritized by participants. A content analysis was done to understand the most frequent modes of exercise being completed, and the patient important outcomes most prioritized to participants.

Results: Semi-structured qualitative interviews, and two content analyses with 17 adults who have XLH were conducted. Pain, stiffness, and fatigue were identified as major barriers to both a person with XLH's capability and motivation to participate in exercise and physical activity. Pain and stiffness created mobility limitations challenging a person's capability. Fatigue and overexertion led to increases in pain and stiffness. The exacerbation of pain and stiffness from fatigue led to a fear of worsening symptoms affecting people's reflective motivation to exercise. While fatigue

worsens symptoms and discourages activity, participants described that when they were able to find the right balance of physical activity and exercise with rest they found improvements in pain, stiffness, mobility and overall physical functioning. Walking, stretching, swimming/water aerobics and strength training were completed most frequently by participants. Key facilitators to exercising were strategizing movement to manage fatigue, and tailoring exercise for mobility impairments.

The study also highlights the importance of identifying patient important outcomes. Similar outcomes were identified for treatment with medications and exercise (pain, fatigue, strength mobility and physical functioning). But physical functioning and its individual components, such as strength, were more highly prioritized for exercise, versus pain for treatment with medications. Regardless of the context, improving functional outcomes and progression of the disease in the long-term was of the highest priority.

Conclusion: While pain, stiffness, and fatigue pose substantial barriers to motivation and capability to participation in physical activity and exercise, the findings reveal that appropriately tailored and balanced exercise can lead to improvements in physical functioning, mobility, and symptom management. Participants emphasized the need for tailored approaches that account for their unique physical limitations, and for the management of fatigue. Crucially, the study underscores the significance of centering interventions around patient-prioritized outcomes which are often underrepresented in current clinical approaches. The findings lay the foundation for developing informed, person-centered physical activity guidance and exercise interventions that address both the physical and psychological challenges of living with XLH, ultimately aiming to improve quality of life and long-term health outcomes.

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Table of Contents

Author’s Declaration.....	ii
Abstract.....	iii
Acknowledgements.....	v
List of Figures.....	viii
List of Tables.....	ix
List of Abbreviations.....	x
1.0 Background.....	1
1.1 X-Linked Hypophosphatemia.....	1
1.1.1 Physical Consequences of XLH.....	1
1.1.2 Psychological Effects of XLH.....	6
1.1.3 Qualitative Experience Living with XLH.....	7
1.1.4 Management Guidelines.....	8
1.1.5 Efficacy of Treatment.....	10
1.2 Physical Activity and Exercise.....	12
1.2.1 Exercise and XLH.....	13
1.2.2 Physical Activity and Similar Conditions.....	19
1.3 Behavioral Change.....	23
2.0 Objective.....	26
3.0 Study Design and methodology.....	27
4.0 Methods.....	28
4.1 Recruitment and Screening.....	29
4.2 Interview Guide and Interview Process.....	30
4.3 Data Analysis.....	30
5.2 Content Analysis: Patient Important Outcomes.....	51
5.2.1 Addressing symptoms of XLH.....	52

5.2.2 Ability to maintain a healthy status and independence	55
6.0 Discussion	57
6.1 Exercise Experience: Barriers and Facilitators	57
6.2 Patient important outcomes.....	65
6.4 Strengths and Limitations	69
6.5 Conclusion	70
References.....	72
Appendices.....	84
Appendix A: Demographic Survey.....	84
Appendix B: Semi-Structured Interview Guide.....	87

List of Figures

Figure 1. Thematic map of patient experiences and barriers to and facilitators of exercise.

Figure 2. Identified barriers to physical activity and exercise for people with XLH and applicable intervention functions, according to the BCW.

Figure 3. Patient important outcomes identified in content analysis of treatment with medications.

Figure 4. Patient important outcomes identified in content analysis of exercise.

List of Tables

Table 1. Collection of exercise recommendations and statements made in clinical practice guidelines for the treatment of XLH.

Table 2. Description of the exercise pilot completed by Kanamalla et al. (2022).

Table 3. Characteristics of participants.

Table 4. Self-reported XLH treatment and history of symptoms and complications.

Table 5. Results of IPAQ, WOMAQ, and BPI-SF questionnaires

Table 6. Physical activities that participants reported engaging in, according to content analysis.

List of Abbreviations

5XSTS – Five Times Sit to Stand
6MWT – Six-minute Walk Test
ABC – Activity-specific Balance Confidence
ADL – Activities of daily life
ALP – Alkaline phosphatase
BBS – Berg Balance Scale
BCW – Behavioral Change Wheel
BMD – Bone mass density
BOS – Base of support
BPI – Brief Pain Index
BPI-SF – Short Form-Brief Pain Index
COM – Centre of Mass
FGF23 – Fibroblast growth factor 23
GBFT - Gait, balance, and functional tasks
IPAQ - International Physical Activity Questionnaire
LEFS – Lower Extremity Function Scale
OA - Osteoarthritis
OP – Osteoporosis
PT - Physiotherapy
PTH – Parathyroid hormone
QOL – Quality of life
ROM – Range of motion
SOAP – Subjective, objective, assessment, and plan
TUG – Timed Up and GO
WOMAC – Western Ontario and the McMaster Universities Osteoarthritis
XLH – X- linked hypophosphatemia

1.0 Background

1.1 X-Linked Hypophosphatemia

X-linked hypophosphatemia (XLH) is an X-linked dominant disease caused by mutations in the PHEX gene. XLH is the most common hereditary phosphate wasting disorder with a prevalence estimated to be 1.7 to 4.8 per 100,000 people.¹⁻³ The pathogenesis of XLH is not well understood but studies with Hyp mice, an XLH mouse model, show that the mutation in the PHEX gene causes overproduction of fibroblast growth factor 23 (FGF23).^{4,5} Increased FGF23 leads to renal phosphate wasting and decreased 1,25-dihydroxyvitamin D production resulting in decreases in serum phosphate.^{6,7}

Clinical symptoms of XLH normally develop within the first or second year of life.⁵ Clinical features of XLH include osteomalacia (accumulation of unmineralized bone tissue) in adults, and rickets (deficient mineralization of the cartilage at growth plates) in children, growth retardation, bone pain, lower limb deformities including genu varum/valgum, abnormal (waddling) gait, pseudofractures and spontaneous fractures, enthesopathies (the calcification of tendons and ligaments at the insertion into bone), stiffness, muscle weakness, early osteoarthritis (OA) and decreased mobility.^{1,5,8-11} Other symptoms include persistent dental abscesses, hearing loss, and tinnitus.^{7,12} XLH is a chronic and progressive disease meaning symptoms tend to worsen over time, especially if the patient is not being managed correctly.

1.1.1 Physical Consequences of XLH

Reduced serum phosphate leads to skeletal deformities, fractures, and pain as the primary consequences of XLH. Phosphate is the most abundant anion in the body constituting 1% of total body weight. The majority of phosphate is within the bones and teeth (90%) where it is primarily

complexed with calcium as hydroxyapatite crystals.^{13,14} In children, reduced serum phosphate leads to rickets. The growth plate is a region found at the end of long bones where chondrocytes proliferate, hypertrophy, and go through apoptosis. Osteoblasts are then formed to create primary ossification centers for the creation of bone; a process known as endochondral ossification. The growth plates of Hyp mice have been shown to be wider and disorganized, with irregular mineralization compared to control.^{6,15} Further, phosphate mediates chondrocyte apoptosis, a critical step in the process of mineralization and the growth of bones via endochondral ossification.¹⁶⁻¹⁸ Reduced serum phosphate causes a reduction in chondrocyte apoptosis, hindering bone development and leaving an accumulation of hypertrophic chondrocytes and hypomineralization, a bone manifestation known as rickets.¹⁸

Rickets leads to reduced growth and severe skeletal deformities. The primary skeletal deformities are of the lower limb, particularly genu varum or valgum (64% and 35% respectively).¹⁹ Genu varum is the lateral deviation of the knee, and genu valgum is the medial deviation of the knee. If lower limb deformities are left untreated they will continue and possibly worsen into adulthood; 53% of adults with XLH have genu varum and 26% have genu valgum.¹⁹ The lower limb deformities commonly experienced by people with XLH and rickets lead to an abnormal gait which is referred to as a “waddling” gait. In children, due to lower limb deformities, performance of the Six Minute Walk Test (6MWT) is 80% of what it is projected to be.²⁰ Adults perform the 6MWT 38% lower than normative values.²¹ Due to the effect that lower limb deformities can have on mobility and quality of life, orthopedic surgery is very common to correct and straighten the legs of people with XLH (60%).^{5,11}

Phosphate not only mediates the endochondral ossification process but contributes to the structure of bone as a component of hydroxyapatite, which provides strength and rigidity. Bone,

both in childhood and adulthood, is going through a constant remodelling process where osteocytes sense bone stress and damaged bone tissue then signal for osteoclasts to resorb bone tissue. Osteoblasts lay down new matrix which will then be mineralized with hydroxyapatite crystals. Due to reduced serum phosphate, formation of hydroxyapatite is insufficient, resulting in areas of low and unmineralized osteoid, an outcome known as osteomalacia.^{22,23} Additionally, areas of low or unmineralized bone are consequently filled with highly disordered bone matrix.²² Due to a lack of phosphate, the ion is frequently substituted by carbonate ions in hydroxyapatite.²² The differences in bone structure in areas of low mineralized bone is likely caused by the differences in charge and size of the carbonate ion compared to the phosphate ion.²² Collectively, the changes XLH causes to the material properties and structure of bone leads to bone pain, and a very high risk of fractures.

Osteomalacia creates pockets of unmineralized bone leading to poor bone quality resulting in a high risk of fracture.^{24,25} Additionally, osteomalacia leads to pseudofractures or looser zones. Pseudofractures are not caused by trauma and are therefore not considered to be classical fractures. Pseudofractures occur from the accumulation of unmineralized bone tissue and appear on X-rays as linear, transverse abnormalities that look similarly to fractures, yet they occur from different mechanisms and should therefore not be treated the same, despite frequently being mistaken for them.^{26,27} Pseudofractures cause pain, but can also progress into complete fractures.^{27,28} In the largest burden of disease survey completed among people with XLH, 44% of adult respondents indicated a history of fractures, particularly in the lower limbs which is a common fracture location for people with osteomalacia.¹¹ Of the adults who reported a history of fracture, 42% reported at least three fractures.¹¹ Osteomalacia also causes people with XLH to suffer from delayed fracture healing, causing the pain to remain for longer.⁵

While XLH is primarily recognized as a metabolic bone disorder, it also affects tendons and joints. Enthesopathies are prolific affecting nearly 100% of adults with XLH.^{10,29-31} The enthesis is a fibrocartilaginous unit at the insertion site of a tendons, ligaments, or joint capsules.³² At a cellular level, the enthesis has 4 zones organized in a hierarchy transitioning from elastic to more stiff materials: the elastic connective tissue tendon, uncalcified fibrocartilage, calcified fibrocartilage, and finally the zone of stiff connective tissue consisting of mineralized bone.³³ The fibrocartilaginous enthesis acts to buffer forces across materials ranging in stiffness to decrease the level of stress seen at the anchor into bone.^{33,34} In the case of a person with XLH, the enthesis shows increased ALP positive chondrocytes, also known as hypertrophic chondrocytes.³³ Furthermore, the anchoring point of the enthesis is comprised of soft osteomalacic bone.³³ Due to osteomalacic bone being less strain resistant, the enthesopathy may contribute to maintain the transfer of force through the enthesis into bone. At the insertion point of tendons, Hyp mice show equal levels of stress and strain as control when the enthesopathy is present, versus significantly higher levels when the enthesopathy is not.³³ However, that response is not shown until six to eight months of life in Hyp mice.³³ Liu et al provide evidence that enthesopathies are inherent to the pathogenesis of XLH.³³ Bone morphogenetic protein (BMP) and Indian hedgehog (IHH) signaling promote chondrogenesis, and regulate enthesis development.³⁵ In Hyp mice entheses growth/differentiation factor 5 (GDF5) is increased by day 14 of a mouse's life, before the enthesis has matured; GDF5 induces BMP signaling and regulates chondrocyte maturation by inducing chondrocyte hypertrophy.^{35,36} Therefore, studies in Hyp mice show a mechanism that support enthesopathies being inherent to XLH and not only a mechanical adaptation.

Calcification of the enthesis creates significantly reduced range of motion (ROM) in the spine, hips, and ankle.^{10,31} Enthesopathies on the spine lead to hyperkyphosis, or excessive forward

flexion of the thoracic spine, which shifts a person's center of mass (COM) forwards in the base of support (BOS) leading to balance, mobility issues and increased fall risk.^{10,37}

Early onset OA adds to mobility and flexibility deficits caused by enthesopathies; of 232 adults, 54% report having OA and 40% have vertebral spondylosis, a degenerative OA of the spine.^{11,31} Articular cartilage is hyaline cartilage composed of primarily water, collagen and proteoglycans, with chondrocytes distributed sparsely throughout the cartilage. Articular cartilage is comprised of 4 zones: the superficial zone, the middle zone, the deep zone, and the calcified zone. The zones of cartilage range in stiffness and like the enthesis of tendons, promote the transition of forces through unmineralized, into mineralized zones to reduce stress at the interface between the cartilage and subchondral bone.³⁸ Normally, OA arises when breakdown of the cartilage exceeds synthesis. In XLH the mechanism appears to be different.^{39,40} While it appears that abnormal wear and tear due to the uneven loading of joints caused by genu varum and genu valgum likely contributes to OA, Macica et al. demonstrated that it may be inherent to the XLH pathophysiology. In their study, Macica et al. found that taking therapy for XLH improves structural stiffness and normalizes the mineralized zone of articular cartilage in Hyp mice.⁴⁰ Their results support a role of the phosphate-wasting environment in the etiology of OA in people with XLH.⁴⁰

Adults with XLH score 50.3 in the stiffness domain and 40.8 in the physical functioning domain of the Western Ontario and McMaster Universities Osteoarthritis (WOMAC), which is notably higher than the population norm of 20.1 and 15.4 respectively.^{10,11} Advanced arthritis and enthesophytes are reported in load bearing joints and shoulders of people with XLH.¹⁰ The advanced degeneration of joints creates challenges in completing activities of daily living (ADL) for people with XLH, reducing their QOL.¹⁰

Osteomalacia, lower limb deformities, enthesopathies, OA, and fractures all add up to create the most common experiences for someone with XLH, bone and joint pain. In the self-reported survey by Skrinar et al. (2019) 97% of 232 adults and 80% of the 90 children report bone and joint pain. 67% say that the pain is enough to require the use of medication at least once a week.¹¹ Despite use of pain medications, the Brief Pain Index (BPI) indicated that the pain they are experiencing is of moderate severity, interfering with functions of daily life, and is significantly higher than normative data according to the pain domain of the WOMAC.¹¹ Patients describe the pain in qualitative analyses: *“It’s like...that constant dull ache that never goes away....I’m used to it...it’s when you’re walking and your knee gives way and you get a sharp, shooting pain, that is the worst and you just want to cry because it’s so painful, it feels like someone’s stabbed you in the knee”*.⁴¹ Pain is a constant in people with XLH’s life, so much so that as a coping mechanism people tend to get used to it.⁴² Pain is described as the most salient symptom of XLH affecting all aspects of life including physical functioning, social life, and psychological well-being.^{41–43}

1.1.2 Psychological Effects of XLH

For many people with XLH the psychological burden begins as adolescents when they begin to understand the realities of having a rare genetic bone condition. Stress and anxiety comes from coming to terms with what their future could look like due to aging with a progressive bone disorder, and the fact that they will be passing the condition onto their children.^{41,43} Additionally, people with XLH tend to be shorter, with leg deformities, and can experience bullying, anxiety and a lack of confidence due to their deformities.⁴³ Moving into adulthood many of the same stresses continue, but as pain and stiffness worsen it begins to weigh more heavily on one’s psyche. Chronic pain and stiffness affects almost every aspect of their life and therefore has massive psychological effects: *“It impacts my mental well-being, it’s depressing... it’s extremely tiring*

having pain all the time."⁴¹ Even though people with XLH tend to score normally on balance scales such as the Berg Balance Scale (BBS), fear of falling is a common theme for people with XLH, especially after previous falls that have caused injury.^{11,12} A fear of falling commonly causes individuals with XLH to stay home more often and to less frequently engage in social events.¹²

A final theme of psychological burdens from having XLH is lack of credence in the healthcare system. Due to the rarity of the disease, people with XLH have difficulties finding physicians who understand the condition and their struggles.¹² Because of the lack of knowledge of the disease, patients will have doctors that do not give credence to their symptoms which gives the perception of the patient being an unreliable narrator of their own pain or irresponsibly searching for drug prescriptions.¹² The rotation of healthcare providers and lack of support leads patients to be frustrated, angry, and lose confidence in their healthcare. It either leads them to a provider who does not have experience in the condition, but will attempt to understand their symptoms, or they will stop honestly reporting symptoms.¹²

1.1.3 Qualitative Experience Living with XLH

The physical symptoms caused by XLH create reductions in physical functioning and mobility which greatly affect the lived experience of an individual with XLH. When looking at qualitative analyses, most address the disease burden caused by XLH. The most prevalent symptoms interfering with the experience of an individual living with XLH are pain, stiffness, and lower limb deformities; fatigue is commonly expressed to be a factor as well.^{12,41-44} Stiffness and pain primarily occurs in the lower limbs which cause issues with mobility. Individuals with XLH describe that stiffness and pain creates difficulty with walking, noting that they walk slowly, standing for long periods of time, and movements that require flexibility (sometimes including selfcare).^{41,44} Due to their limitations, people with XLH struggle completing many ADLs including

house work, dressing themselves, shopping and running errands, doing laundry, getting in and out of cars and the bath or shower.⁴⁴ Fatigue is expressed as a symptom of XLH itself, while also being caused by the impact that pain can have on an individual's sleep, which can limit the time and energy people can put into activity during their daily lives such as housework, playing with their children, running errands, or going to health care appointments.^{12,41-43} Further to this, chronic pain directly impacts choices made regarding career paths and can be a driving factor for early retirement.¹² Overall, pain, stiffness, fatigue and mobility deficits impact almost every aspect of a person's experience living with XLH, greatly reducing their QOL. No qualitative analyses have been conducted to look at the experience of people with XLH during physical activity or exercise, and therefore guidance cannot be made surrounding those activities for individuals with XLH.

1.1.4 Management Guidelines

XLH is a lifelong progressive disease, where a patient should be followed by a multidisciplinary team throughout the entire lifespan consisting of orthopedic surgeons, audiologists, physiotherapists, and dentists.^{5,7,45-51} The team should be led by an endocrinologist or nephrologist with experience treating metabolic bone diseases. Follow-up periods with the endocrinologist or nephrologist should be every three to six months for children and three to twelve months for adults.^{5,7,45-50} The length between follow-up is dependent on the stability and severity of the person's condition.

Currently, there are two treatment methods for XLH. The first, and most common, is known as "conventional therapy". Conventional therapy consists of taking oral phosphate supplements to increase serum phosphate levels, and active vitamin D (calcitriol) to increase absorption of phosphate in the gut. Phosphate is recommended to be taken in smaller doses and as many times as possible per day because large doses of phosphate will increase parathyroid

hormone (PTH) levels, eventually inducing secondary hyperparathyroidism.^{52,53} Conventional therapy should begin once serum phosphate levels begin to fall after birth; serum phosphate normally decreases at approximately six months of age.⁵⁰ On average, it is recommended to take phosphate three to five times per day and calcitriol one to two times per day. Vitamin D3 is also added to treatment as needed. The second treatment method is known burosumab. Burosumab is a human monoclonal antibody which inhibits FGF23 activity, as such it treats the cause of decreased serum phosphate (increased FGF23), unlike conventional treatment. Burosumab will normalize serum phosphate concentrations without the need for other drugs. Burosumab is a new drug that was approved in Canada in 2019.^{54(p)} It can be used in children starting at six months old. The medication is a subcutaneous injection given every two to four weeks.

One area where there is a lack of consensus is whether adults with XLH should receive treatment or not. In children there is almost complete agreement in favour of treatment to improve rickets and optimize growth, regardless of symptoms.^{5,45-48,50,55,56} For adults, due to some of the more serious side effects of conventional therapy, there is the thought that if symptoms are not serious or progressing, treatment is not needed as it does not appear that conventional therapy has a strong benefit.^{5,51,57} Since the release of burosumab, systematic reviews for adults and children support the use of burosumab over no therapy.^{5,47,51,56} As more evidence comes for burosumab the opinion that no treatment is acceptable for adult patients is beginning to fade. The opinion that burosumab is better than no treatment is supported by the recent reimbursement criteria draft released by the Canadian Agency for Drugs and Technologies on June 13 2024, and the draft guidelines released by the National Institute for Health and Care Excellence released on June 21 2024, supporting the reimbursement of burosumab, not just for children, but for adults.^{58,59}

1.1.5 Efficacy of Treatment

The goal of treating XLH in children is to heal rickets and therefore improve growth and limit lower limb deformities.⁵ In adults the goal is to heal osteomalacia, improve fracture healing, and reduce pain and mobility deficits.⁵ Improved bone health is not marked by normalizing phosphate, but instead by serum alkaline phosphatase (ALP).^{5,60} ALP acts as a biomarker for skeletal response and is elevated before treatment.⁶⁰ Treatment with phosphate and calcitriol effectively brings ALP down to a normal range.⁶⁰ Early treatment in childhood and ongoing normalization of ALP improves rickets, promotes growth, reduces bone pain, reduces effects of leg deformities, promotes dental health, and improves fracture healing.^{5,45,50,55} While symptoms are improved with normalization of ALP, they are not fully resolved. Furthermore, there is no evidence that conventional therapy is able to prevent or reduce occurrence of enthesopathies, OA, or reduce fracture risk.^{5,30,45,50,51,61} Given that enthesopathies, OA, and fractures are major sources of pain and reductions of mobility, physical functioning, and QOL for people with XLH, conventional therapy is not particularly efficacious at treating XLH in the long-term.¹⁰ Furthermore, conventional therapy has negative side effects. Calcitriol and phosphate treatment promote nephrocalcinosis (calcium deposits in the kidneys) and high doses of phosphate lead to gut irritation and diarrhea.^{5,50,62} As mentioned previously, secondary hyperparathyroidism can be induced from long-term phosphate supplementation which, if left untreated, will lead to tertiary hyperparathyroidism and require a parathyroidectomy.^{5,20,52,53} Treatment of XLH via calcitriol and phosphate will also increase circulating FGF23 creating a negative feedback loop which could reduce the efficacy of treatment overtime.⁶³

Burosumab is the second treatment option for people with XLH. As a new treatment there is no long-term data but in 64 week, randomized, active-controlled, open label phase 3 trial in 61

children and adolescents aged one to twelve years old comparing burosumab to conventional therapy, burosumab showed to be superior.²⁰ Burosumab normalized serum phosphate, and serum ALP and was better at improving growth, lower limb deformities, and mobility than conventional therapy.²⁰ In adults, a 24 week phase 3 randomized, double blind, placebo-controlled trial showed burosumab's effectiveness at normalizing serum phosphate and healing osteomalacia, improving fracture healing, and statistically significantly reducing stiffness based on the WOMAC index.⁶⁴ There were statistically significant effects on pain and physical functioning, but only in the long-term follow up at 48 weeks, not in the originally designed 24-week study.^{64,65} In the short-term, burosumab seems to be more effective at treating many of the symptoms that come with XLH, including stiffness and pain. Due to its efficacy balanced with the reduced negative side effects, it is now recommended over conventional therapy especially if patients are experiencing the detrimental effects of conventional treatment.^{5,66,67} Unfortunately, there is no long-term data to be able to judge its impact on OA, enthesopathies, and mobility, which are three large contributors to reductions in health outcomes for people with XLH. Burosumab is generally well accepted and has few adverse side effects. Due to no longer needing to take large doses of phosphate and calcitriol none of the side effects of conventional therapy affect people taking burosumab. Reported adverse effects include injection-site reactions, headaches, pain in the extremities, and increased occurrence of dental abscesses in children.^{5,20,64,65}

Even though burosumab is technically a second treatment option for people with XLH and it has a superior ability to improve bone pain, osteomalacia, heal fractures, and improve general QOL compared to conventional therapy, in practice it is not an option for many Canadians. In Canada, burosumab is only covered for children who have yet to have closure of their epiphyseal plates; it is not covered for adults.⁶⁸ The price is incredibly expensive, costing hundreds of

thousands of dollars a year.⁶⁹ Due to the prohibitive cost and the lack of coverage for adults, burosumab is not a treatment option for most Canadians.

Despite pharmaceutical treatments, mobility and physical functioning deficits remain inadequately addressed. Based on the efficacy of either treatment option to treat the long-term effects of XLH other interventions should be considered to help people with XLH manage their disease.

1.2 Physical Activity and Exercise

The Canadian 24-Hour Movement guidelines highlight the importance of daily physical activity for adults aged 18 – 64.⁷⁰ The guidelines recommend 150 minutes per week of moderate to vigorous aerobic exercise, and muscle strengthening activities at least twice a week.⁷⁰ The movement guidelines are the same for people above the age of 64, with the additional recommendation to include physical activities that challenge balance.⁷⁰ The recommendations come from evidence of the many positive health outcomes that can come from physical activity and exercise. Moderate to vigorous physical activity is correlated with reduced cardiovascular mortality, all-cause mortality, and reductions in the incidence of stroke, cardiovascular disease, and heart failure.⁷¹ Resistance training is associated with 21% lower risk of all cause mortality, improved strength and physical functioning in adults over 65 years of age, and 23% reduction in fatal coronary heart disease.^{70,72–75} In adults aged over 65 years of age, balance and functional training reduces rate of falls, fall-related fractures, and improves physical functioning.^{70,76} In summary, adhering to the Canadian 24-Hour Movement guidelines, which recommend regular aerobic and muscle-strengthening activities, along with balance exercises for older adults, significantly enhances overall health by reducing mortality rates and improving physical

functioning. The Canadian 24-Hour Movement guidelines are recommendations for the general population, but what about people with XLH?

1.2.1 Exercise and XLH

XLH causes mobility and physical functioning deficits that likely creates additional barriers to exercise and physical activity, thus people with XLH may need different recommendations or extra information to support physical activity. When examining current clinical guidelines for the treatment of XLH most guidelines make a weak, unspecific recommendation at best (Table 1). The most comprehensive recommendation comes from Laurent et al. (2021). While no formal guidance exists, they make recommendations based on those made for OA. They recommend that physiotherapy (PT) and exercise should be done with the intention to prevent and improve muscle weakness, back and joint pain, stiffness and limited mobility through resistance training in combination with swimming, yoga, and Pilates.⁴⁸ Gonzalez-Lamuno et al. (2022) make a similar recommendation highlighting resistance training.⁶⁶

Table 1. Collection of exercise recommendations and statements made in clinical practice guidelines for the treatment of XLH.

Publication	Exercise Statements
Khan et al. (2025) ⁵¹	“Early referral to the spinal team with physiotherapy in cases of spinal scoliosis”
Seefried et al. (2023) ⁶⁷	“It is preferable to have a lead clinician, ideally with expertise in metabolic bone diseases, to lead and coordinate the care of a person living with XLH, working with ... physiotherapists and neurologists, as and when required.”

<p>Munns et al. (2023)⁴⁷</p>	<p>“(Referral to) A physiotherapist and occupational therapist for improvement in muscle strength, stiffness, pain, mobility, gait, and optimal school participation, especially after orthopedic surgery”</p>
<p>González-Lamuno et al. (2022)⁶⁶</p>	<p>“We suggest insisting on the importance of resistance exercise supervised by qualified personnel, maintenance of joint range, and maximizing strength and endurance.”</p> <p>“We recommend that physical activity for XLH patients be encouraged and adapted to the patient’s ability. All sports are allowed unless there are individual contraindications; aerobic activities are preferred because anaerobic activities can cause too much stress on the skeleton”</p> <p>“We recommend interventions aimed at reducing bone and joint pain, deformity, stiffness, muscle weakness and improving walking distance and physical activity. These interventions include general measures such as the use of analgesics... physical therapy, rehabilitation, physical activity and non-pharmacological treatment of pain and the assessment of orthopaedic surgery according to progression and functional limitation.”</p>

<p>Sandy et al. (2022)⁴⁵</p>	<p>“Regular reviews by physiotherapists and occupational therapists are essential to achieving these (improvement of physical functioning) aims. There is evidence that physiotherapy programs improve motor function in patients with XLH.”</p>
<p>Laurent et al. (2021)⁴⁸</p>	<p>“We recommend that exercises and physiotherapy should aim to prevent or improve muscle weakness, back and joint pain, stiffness and limited mobility, by targeting muscle strength, core stability, joint range and general mobility, e.g. by resistance exercise training in combination with swimming, yoga, Pilates, dancing etc.</p> <p>Participation in leisure or professional sport activities is encouraged, with an emphasis on sports with lower risk of trauma.”</p> <p>“Local and/or systemic non-steroidal anti-inflammatory drugs (NSAIDs; with gastroprotection if necessary) in combination with physical therapy (aiming for a good balance between exercise and rest, warmth or ice application, etc.) are considered first-line therapies (for musculoskeletal pain).”</p>
<p>Al Juraibah et al. (2020)⁵⁰</p>	<p>“Members of the multidisciplinary team should include orthopedic surgeons, dentists, physiotherapists, and occupational therapists.”</p>

<p>Haffner et al. (2019)⁵</p>	<p>“Physiotherapy (in terms of a general strengthening and/or a gait education programme) might be helpful, especially after surgery.”</p> <p>“We recommend interventions aimed at reducing bone and joint pain, deformity, stiffness, muscular weakness and improving walking distance and physical function. These interventions include... physiotherapy, rehabilitation, physical activity and non-pharmacological treatment of pain”</p> <p>“We do recommend physiotherapy following surgery or in case of decreased range of movement, muscle weakness, fatigue, instability or physical deconditioning.”</p> <p>“This multisystem disease evolves over time, and multidisciplinary care of patients with XLH is needed, involving physicians, physiotherapists, dentists and social workers and liaison with patient group representatives.”</p>
<p>Linglart et al. (2014)⁴⁶</p>	<p>“Individualized exercises and adapted physical activity should be proposed to improve physical function and reduce the metabolic consequences of XLHR.”</p>

Carpenter et al. (2011) ⁵⁵	NA
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“NA” indicates that the guideline did not include any statements about exercise, physical activity, or physical therapy.

One of the main reasons for a lack of exercise recommendations is the lack of evidence. Research for XLH has been focused on pharmaceutical treatments, especially since the introduction of burosumab. As of May 2024, there has only been one pilot exercise intervention done among people with XLH; the design and outcomes measured are outlined in Table 2. Two participants, one female aged 65 (participant A) and one male aged 54 (participant B), successfully completed the program with minimal difficulty and no reported injuries. At the end of the intervention subjective, objective, assessment, and plan (SOAP) notes revealed lessened pain and increased confidence, agility, functional ability, and ROM. The participants felt more confident walking on uneven terrain, changing directions while walking, and were able to reach lower with less pain; previously they were unable to reach the ground due to pain and fear of falling. Balance was improved in both participants subjectively shown by improved confidence in unstable environments and improved ability to complete ADLs, and objectively with improved scores in the BBS and ABC. The BBS improved by 6 and 9 for participants A and B respectively and scores for the ABC improved by 17% and 19.5% respectively. Strength and physical functioning improved in each person shown by their improved scores in the timed up and go (TUG), Five times sit to stand test (5XSTS), and lower extremity function scale (LEFS). TUG times decreased by 2.8 and 4.3 seconds in subject A and B respectively. 5XSTS times decreased by 8.4 and 2.4 seconds and LEFS improved by 8 and 12 points for participants A and B respectively.⁷⁷

Table 2. Description of the exercise pilot completed by Kanamalla et al. (2022).⁶⁵

Study Design	Outcomes Studied	Assessment Tools
<p>Goal: To assess the potential benefit and efficacy of a PT program at addressing physical and function limitations common for people with XLH.</p> <p>12-week telehealth PT program completed 3 times weekly involving resistance, balance, and mobility exercises.</p> <p>Functional progress was compared to baseline at 4 weeks, 8 weeks, and 12 weeks.</p>	<p>Lower extremity function</p> <p>Mobility</p> <p>Fall risk</p>	<p>Lower extremity function scale</p> <p>Five times sit to stand test</p> <p>Timed up and go</p> <p>Activity specific balance confidence scale</p> <p>Berge balance scale</p>

The study completed by Kanamalla et al. (2022) demonstrates the possible benefits of exercise for people with XLH, but a twelve-week study with two participants is not enough to make any conclusions or create interventions that can be widely implemented. Furthermore, their objective was to create evidence-based recommendations for physical therapists but included no methodology to complete said goal. Another study recorded physical activity participation for

people with XLH. 26 adults completed the International Physical Activity Questionnaire (IPAQ), a clinically validated 27 item self-reported survey with four domains: during transportation, at work, during household and gardening tasks, and during leisure time.⁷⁸ The results showed that most people with XLH (73%) completed low levels of physical activity.²¹ While an analysis has not been done to look directly at exercise, the results from the IPAQ coincides with findings in burden of disease studies where patients expressed their inability to run or take part in high-impact sports; motivation, skeletal deformities, fatigue, pain, and stiffness were all listed as reasons they were unable to participate.^{5,12,41,42} Yet, when asked about what types of things people with XLH do to improve their stiffness and pain, most participants stated that they used movement as a tool to overcome stiffness; examples given were general movement, stretching, walking, yoga, and water based exercise.^{41,42} Despite pain some participants report forcing themselves to exercise in the hopes of lessening future pain and have had questions about the role of exercise in the management of XLH.^{12,41,42} Overall, although limited, the understanding of the relationship between exercise and XLH suggests that exercise could be an effective intervention. However, the relationship between exercise and people with XLH is complex. Preliminary data and patient experiences indicate benefits, yet the elevated risk of fractures and significant disability associated with XLH complicate the approach to exercise. Due to the complications, a better understanding of the experience of people with XLH when participating in physical activity and exercise will help better understand how to adapt and create guidelines and interventions in a way to facilitate participation in physical activity for people with XLH.

1.2.2 Physical Activity and Similar Conditions

Due to the sparse evidence on how exercise can affect people with XLH we can look at comparable conditions to XLH and leverage their knowledge. Understanding the relationship

between physical activity and exercise with other conditions will provide more evidence as to why exercise is worth pursuing in XLH and act as a starting point to progress research in XLH faster.

Osteoporosis (OP) is a musculoskeletal disease characterized by low bone mineral density (BMD), and damaged microarchitecture causing susceptibility to fractures. In 2019 - 2020 OP was reported to affect approximately 2.5 million Canadians according to data from Canada's Chronic Health Reporting System.⁷⁹ Although OP typically develops later in life leading to reduced BMD, while XLH is a genetic condition in which individuals tend to have normal BMD, the two conditions share similarities. Both XLH and OP cause similar fracture rates; 40% women and 20% of men with OP, and 44% of people with XLH experience fractures.^{11,80} Heightened fracture rate creates an increased fear of falling in people with OP and XLH putting restrictions on ADLs.^{12,81} Like XLH, hyperkyphosis is a contributor to increased fall risk and mobility deficits for people with OP.⁸² While hyperkyphosis occurs in non-osteoporotic older adults, OP increases or worsens spinal flexion due to fractures.^{82,83} Despite their distinct etiologies and manifestations, OP and XLH have similar outcomes of heightened fracture rate, reduced mobility and physical functioning. Insights from OP research, particularly in safe exercise practices and hyperkyphosis, can potentially enhance care strategies for individuals with XLH.

When analyzing physical activity and exercise research in OP, the benefits are clear. In the 2023 clinical practice guidelines for the management of OP and fracture prevention, strong recommendations are made for balance and functional training at least twice a week and a conditional recommendation is made for resistance training at least twice weekly.⁸⁴ In meta-analyses, exercise interventions reduce the rate of falls by 23% (95% confidence interval (CI) 0.71 to 0.83) when compared to control.⁷⁶ Balance and functional exercise alone reduces the rate of falls by 24% (95% CI 0.70 to 0.81), but multiple types of exercise at once (commonly resistance,

balance, and functional training) reduce the rate by 34% (95% CI 0.50 to 0.88).⁷⁶ Looking at functional outcomes, resistance training alone has been shown to improve performance of the TUG test with a mean difference of -1.24 seconds (95% CI -1.67 to -0.82), and combined with other interventions by -0.90 seconds (95% CI -1.01 to -0.78).⁸⁵ Varahra et al. (2018) completed a meta-analysis to assess the effects of exercise interventions on functional outcomes for people with OP. Their analysis assessed 28 studies with a total of 2113 participants aged 55 to 89. The data was heterogeneous, and it was not possible to establish a single optimal exercise program. While multicomponent exercise appears to be favored for benefits to physical functioning, a conclusion cannot be made before more in depth analyses are completed.⁸⁶ A consistent part of the most effective exercise programs includes re-learning, or practice, of basic movement patterns for dynamic activities through gait, balance, and functional tasks (GBFT), including walking on uneven surfaces, avoiding obstacles and changing speed/direction.⁸⁶ Adding GBFT aspects to training more effectively decreases fear of falling, and directly influenced participation in social activities.⁸⁶ As we deepen our understanding of XLH, adopting an approach that includes safe exercise could mitigate risks and improve physical functioning for people with XLH, as it does for people with OP. However, we do not currently have a strong enough understanding of the risks and barriers associated with exercise for people with XLH making it challenging to design recommendations and interventions that can be widely implemented.

OA is a degenerative joint condition and is one of the most common chronic health conditions in Canada. In 2017 it was the second most prevalent chronic disease, behind hypertension, affecting 37.9% of Canadians aged 65 and older.⁸⁷ OA is a progressive disease that most commonly affects weight bearing joints such as the knee and hip.⁸⁸ Major symptoms of OA include inflammation and joint pain, which reduce mobility and QOL.⁸⁹ OA is a clear comparison

for XLH because, as established earlier, OA is a side effect of XLH.^{5,10-12} In a case study, all 8 people with XLH had radiological findings of OA at the hip or knee, and in burden of disease self-reported surveys 50% of adults reported to have OA.^{10,11} Independent of XLH, OA causes a fear of movement, balance limitations, pain, and reduced mobility.⁹⁰ In a cross sectional study of 70 patients with hip and knee OA the average time to complete the TUG was 22.3 seconds; longer than 13.5 seconds is considered to put a person at a high risk of falling and is an indicator of reductions in mobility and physical functioning.⁹⁰ Like XLH, people with OA see reductions in ROM in the knee and hip (depending on the site of OA) which is an important determinant of disability for patients with OA.^{10,91} Overall, individuals with OA and XLH share an experience of joint pain, reduced ROM in the knees and hip, and reductions in mobility and physical functioning. The fact that OA is a side effect of XLH makes research in OA a valuable resource to be applied to the XLH population.

OA research on exercise is much more extensive than that of XLH. Looking at clinical practice guidelines for the treatment of OA, recent guidelines recommend exercise.⁹²⁻⁹⁵ When considering all types of exercise, meta-analyses demonstrate the significant benefit to pain immediately after training; equal to 12 points on a 0 to 100 point scale (95% CI 10 to 15 points).⁹⁶ Exercise was still found to have a significant benefit to pain two to six months after the exercise intervention.⁹⁶ In 44 RCTs involving 3900 patients, exercise had a moderate immediate effect on physical functioning, being equal to an improvement of 10 on a 100-point scale (95% CI 8 to 13 points).⁹⁶ Physical functioning's response to exercise lasted over six months and was therefore better sustained than that of pain relief.⁹⁶ Across 14 trials with 956 participants, strength training improved the 6MWT and TUG by a mean difference of 32.15 (95% CI 19.44 to 44.85) and 1.92 seconds (95% CI 0.41 to 3.43) respectively.⁹⁷ It does not appear that there is one single form of

exercise that is most effective at treating the symptoms and impairments of OA, but multicomponent exercise including functional and balance training is beneficial to pain, mobility, and physical functioning.

XLH presents unique challenges to skeletal health stemming from its genetic origins and widespread impact on the body. Given the dearth of research specific to exercise for XLH, evidence from other musculoskeletal conditions like OP and OA offers valuable insights that can guide management strategies for XLH. However, at the current moment we do not understand if there are additional barriers to exercise and safety aspects that must be accounted for individuals with XLH. Before creating an intervention, identifying the experiences of completing exercise and physical activity directly from people with XLH will help to understand what their specific barriers to and facilitators of exercise are to help take recommendations for diseases like OP and OA and adapt them as needed.

1.3 Behavioral Change

To design truly effective interventions or physical activity recommendations for people with XLH they must be designed with implementation in mind from the beginning. Behaviour change interventions can be defined as coordinated activities designed to change specific patterns of behaviours.⁹⁸ Successful interventions need a multi-level approach that is systematic, but many interventions are designed without evidence of going through any scrutiny.⁹⁸ Using a systematic method to incorporate an understanding of the nature of a behaviour assists in assessing the circumstances that make different interventions most effective, forming a basis for intervention design.⁹⁸

The COM-B is a framework for understanding behaviour. Michie et al. designed the COM-B to be “useful”. They defined the criteria of a useful framework to be coherent in all categories,

both in the type and level of details, comprehensive (i.e., it should apply to all interventions), and finally it should link to an overarching model of behaviour.⁹⁸ After defining what is considered useful, they assessed what the minimum number of additional factors were needed to be accounted for to create change in a targeted behaviour. Using sources from US law they were able to narrow down three necessary factors that built the COM-B: capability, opportunity, and motivation.⁹⁸ According to COM-B capability is an individual's capacity to engage in an activity. Motivation is the brain processes that direct behaviour. Opportunity is the factors that lie outside the individual making behaviour possible.⁹⁸ Within the three categories it is possible to develop further subdivisions (e.g., physical and psychological capabilities). Each category has its own effect on a given behaviour and a single intervention might change one or more components in the behaviour system. While the COM-B is a model of behaviour, it also provides a basis for designing interventions aimed at behaviour change.⁹⁸ When applying it to intervention design the task is to consider what the behavioural target is, and what components of the behaviour system would need to be changed to achieve said target.⁹⁸ The COM-B is the basis of the behavioural change wheel (BCW), a theory- and evidence-based tool used to design and select interventions according to an analysis of the nature of the behaviour.⁹⁸ The BCW approach draws from a single unifying theory of motivation in context, and the theoretical understanding of behaviour from the COM-B. Starting from the theory of motivation in context, the BCW can determine what needs to change in order for the behavioural target to be achieved, and what intervention functions are likely to be effective to bring about that change.⁹⁸ Using the COM-B we can better understand the behaviour behind the experiences of people with XLH when it comes to exercise, to later apply it to the BCW to help create more effective interventions in the future.

Currently, while we understand the burdens that XLH causes, there is a lack of information regarding XLH and exercise, and how their burdens apply in the context of exercise and physical activity. In conditions such as OP and OA, that pose similar challenges to mobility, fractures, and physical functioning as XLH, multicomponent exercise, especially those including strength and functional training, has beneficial effects on mobility, fall risk, physical functioning, pain relief and QOL. Despite the best pharmacological management individuals with XLH face severe challenges caused by pain, stiffness and mobility deficits which can severely limit physical functioning and QOL. Due to evidence of positive effects of exercise and physical activity at reducing mortality and cardiovascular comorbidities in the general population, and to pain, stiffness and physical functioning in diseases like OP and OA, non-pharmacological interventions, such as exercise, should be considered. The starting point of intervention design is behaviour in context.⁹⁸ By understanding people with XLH's current experiences during physical activity and exercise we can have a stronger understanding of the usefulness of physical activity to allow future interventions to be developed in a way to effectively address the needs of individuals with XLH.

2.0 Objective

People with XLH struggle with pain and mobility deficits causing reduced physical functioning and QOL despite being on treatment. Not enough is known about people's experiences living with XLH, specifically how it affects their participation during physical activity and exercise and what health outcomes are important to them, to allow effective design of interventions and educational resources to support participation in physical activity and exercise. My objective is to understand the experiences of people with XLH and how XLH affects a person's participation in exercise and physical activity. To understand the perspectives of people with XLH, I aim to generate answers to the following questions:

- How does having XLH influence physical activity and exercise participation?
- What are the barriers to and facilitators of physical activity and exercise specific to people with XLH?
- What health outcomes are important to people with XLH?

3.0 Study Design and methodology

I took a phenomenological approach from a post-positivism point of view to understand the experiences of people with XLH completing exercise and physical activity, the barriers to and facilitators of exercise and physical activity, and the important outcomes to participants when it comes to making treatment decisions with medication, and with exercise. Phenomenology is a qualitative research strategy that is particularly useful to understand the essence of a phenomenon through the exploration of the experiences of individuals. Data comes from in-depth conversations regarding the connections between a person, things, events and their experiences, explaining a phenomenon through the perspective of a person who has experienced it.

The goal of conducting a qualitative analysis via a phenomenological approach is to highlight and understand the experiences and perspectives of the participants, but meaning does not reside in the data and emerge from it. The researcher plays an active role in identifying and interpreting meaning from the data making it important to be reflective throughout the entire research process. Understanding the effects of positionality and how the intersection of identities can affect it, I consistently worked to consider the dynamic nature of social interactions both within myself, the participants, and within the research team. I have identified myself as a white, male, middle-class, English speaking, Canadian graduate student experienced in exercise and kinesiology who has XLH. Due to having XLH, I have an interesting perspective that not many analyses of a similar kind have. Throughout the project, I used my own personal experience as a tool to connect with and understand the participants. Simultaneously, constant reflection was used to limit personal bias being transposed onto the participants and the project.

4.0 Methods

The primary method used to complete my research objectives were semi-structured qualitative interviews. To design effective interventions, it is crucial to understand behaviour in context, therefore the semi-structured interview guide was developed using the COM-B framework.⁹⁸ The goal of using COM-B was to elicit answers to understand how a XLH affects person's capabilities, opportunities, and motivations to participate in physical activity and exercise. By understanding how each factor of the COM-B affects a person's behavior, we can better target the features that are perceived have the largest effect on their behavior for the development of an intervention.⁹⁸

To understand the transferability of the sample I collected demographic data, information regarding history of XLH and treatment, information regarding the participants' activity level, and disease severity (see appendix). Surveys were completed online using Qualtrics XM™. Disease severity was collected via the WOMAC and the short form Brief Pain Inventory (BPI-SF) as they have been the most widely used and are the only surveys that have been validated in the XLH population.⁴⁴ The WOMAC scores for stiffness and function are reported; in the survey stiffness scores range from 0 to 8 with a higher score representing a higher amount of stiffness and function scores range from 0 to 68 with higher scores representing lower levels of function. However, to maintain consistency with previous literature in XLH, both the stiffness and function scores were normalized to a 0 to 100 scale. The BPI-SF was used to report pain severity rating, a score ranging from 0 to 10 with higher scores representing worse pain severity, and pain interference, a score ranging from 0 to 10 with higher scores representing higher levels of pain interference in multiple domains of life. Reporting follows the "Standards for Reporting Qualitative Research" O'Brien et al. (2014).⁹⁹

Interviews took place virtually on Zoom™. The Zoom™ recording feature was used, and the audio file was uploaded onto the lab drive then imported into Microsoft Word to complete word for word transcription. The transcription was then reviewed and corrected by me. During each interview, note taking was completed in a reflective journal to determine tone and context of conversations that may not be clear in the transcript otherwise. Immediately after interviews active reflection was also completed using the reflective journals. In the journal I reflected on how I perceived the interview went including the participants and my own mindset and emotions throughout, the sections of the interview where I felt my line of questioning was effective versus the sections I felt were less effective, and any answers that stood out to me throughout the interview. The journals acted as a strategy to check bias and improve rigor.

4.1 Recruitment and Screening

Recruitment and interviews were conducted from October 2024 to March 2025. Only adults, aged 18 or older, who are English speaking, and have a self-reported diagnosis of XLH were included. Meaning is generated through interpretation of the data, and it is impossible to estimate in advance the number of participants required.¹⁰⁰ As recommended by Braun and Clarke a pragmatic initial sample size estimate of 10-15 was selected based on previous qualitative research done with XLH.^{41,44,100,101} Final decisions on sample size were based on the adequacy of the data for addressing the research question.

Recruitment was done through multiple means to sample a wider range of people. I reached out to patient advocacy groups to spread the study advertisement on social media. With permission from admins, I posted the study poster on public Facebook groups. Finally, Dr. Aliya Khan, an expert in metabolic bone disease, contacted her patients to inform them of the study; if interested they reached out to me via email.

Once a person contacted the team regarding their interest in participating in the study they were briefed on the eligibility criteria, the objective, and the procedure to participate in the interview. After reading the informed consent form, confirming they were eligible to participate, and agreeing to participate, the interview was scheduled and their personal link to the survey was sent. Participants were asked to fill out the survey before the interview.

4.2 Interview Guide and Interview Process

The interview guide (see appendix) was designed in a way to elicit detailed data. All participants completed the survey before the interview and written consent was gained for the collection of data via a question in the survey. The interviews took place virtually one-on-one with participants who have been diagnosed with XLH. Each interview started with introductions of myself, the goals of the study, and an introduction from the participant to support increased trust and rapport before going into the interview. Verbal consent to collect and use the data was then gained before the recording began. Participants were also given the opportunity to ask any questions before beginning the interview. While the interview guide was used in each interview it was fluid, so the questions and the prompts were adapted, and follow-up questions were asked to dig deeper into certain topics that were beneficial to answering my research questions.

4.3 Data Analysis

Reflexive thematic analysis was completed guided by work done by Braun and Clarke to understand the experiences of adults with XLH during physical activity and exercise, the barriers to and facilitators of physical activity and exercise and to understand the outcomes prioritized.¹⁰² Two researchers, myself and NT, conducted the thematic analysis and iteratively consolidated themes through discussion. The steps to this process occurred as follows: Step 1 involved

transcription of the interviews where I reviewed the transcription with the audio of the interview to ensure it was 100% accurate. Step 2 included familiarization of the data where I and NT reread and listened to the interviews to allow a better understanding. Step 3 involved coding of the first two transcripts individually where each researcher read the transcript and highlighted/labeled sections based on our own interpretation of the importance and meaning of the quote. In step 4 NT and I met and developed the initial analytical framework by discussing and comparing codes. We came to a consensus on the codes that will be included, and their definitions. The initial framework was then used to code the next two subsequent interviews, and we met again for step 5. In step 5 any new codes and the use of the current framework were discussed. The analytical framework was finalized to move forward coding the remaining transcripts. The remaining transcripts were coded by me. The final step involved interpretation of the data using a thematic map. In the thematic map, the codes or themes from the analytical framework were extracted and a pattern was identified. The map was then brought to NT to confirm the validity in relation to the data, and whether the map was consistent and representative of the data set. Each researcher reviewed the transcript and created codes based on the data. The codes were used to develop themes, thus the approach to thematic analysis was inductive.

Throughout the interview and coding process peer debriefing occurred with LG to improve credibility and trust, and to reduce bias. During the interviews, peer debriefing was used to review the interview process and the interview guide, changes were made to the interview guide to ensure open questions and leading questions were not being asked. During coding, the coding framework was reviewed and quotes within to ensure the data is representative of the quotes from another perspective as a strategy to limit bias. Once the thematic map was finalized peer debriefing occurred with LG to ensure the ideas were clear to someone who was not immersed in the data.

A content analysis was completed to count the frequency of codes related to the modes of exercise currently being completed by each participant using the ProFANE taxonomy.¹⁰³ A content analysis was also done to identify and count the participants who acknowledged each patient important outcome for both treatment with medication and exercise.¹⁰³ Important outcomes were identified inductively. Data analysis, both content and thematic analysis, was done using Nvivo 15.0.0. The demographic, WOMAC and BPI-SF data was not directly analysed, but calculated as a count, percent, mean or standard deviation and only used to speak about transferability of the sample.

During the consent process participants were informed they were not required to answer all questions in the surveys or the interview meaning participants were not contacted regarding any missing data. In the demographic data there was no missing data. For the BPI-SF and WOMAC data processing guidelines were followed when applicable for missing data, and if there was no guidance then the participant was not given a score or included in the results for the section. Data processing guidelines were followed for the IPAQ as well, in some cases participants gave a range of values instead of a discrete number which is not covered in the guidelines. In those cases, the lowest value was chosen.

5.0 Results

21 adults with XLH reached out interested in the study and 17 were screened and recruited to participate. The 4 participants who were not included in the sample reached out via email interested in participating, but contact was lost during scheduling and no reason was given for their loss of interest in participation. Data saturation was achieved following interviews and analysis of 15 participants, all of whom were female. Due to the imbalance in sex, new advertisements targeted toward males were sent out. After interviewing, and coding the data of two males, no additional codes or contradictory data was added, and therefore analysis proceeded.

The participants' ages range from 22 to 76 years with a median age of 41 (Table 3). The sample reflected individuals with a range of scores in the chosen assessments of symptoms and physical functioning (Table 3). Scores for the WOMAC stiffness domain range from 25.00 – 87.50 with a median score of 50.00 and function scores range from 0 – 73.53 with a median score of 25.53. BPI-SF pain severity ranged from 0.25 to 8.50 with a median score of 3.50, and pain interference scores ranged from 0.83 to 9.14 with a median score of 3.71.

Table 3. Characteristics of participants.

Participants (<i>n</i> = 17)	
Age (mean ± SD)	43 ± 14.83
Sex (<i>n</i>)	
Female	15 (88%)
Male	2 (12%)

Country (*n*)

Canada	9 (53%)
Finland	1 (6%)
Netherlands	1 (6%)
USA	6 (35%)

Self-reported ethnicity

Afro Latino	1 (6%)
Caucasian	11 (61%)
Italian	1 (6%)
Middle Eastern	2 (11%)
Portuguese	1 (6%)
South Asian	2 (11%)

Education (*n*)

College	4 (24%)
High school equivalent	1 (6%)
Graduate school (e.g., MSc or PhD)	3 (18%)
University	8 (47%)
Professional school (e.g., MD)	1 (6%)

Table 4. Self-reported XLH treatment and history of symptoms and complications.

Characteristic	
Treatment (<i>n</i>)	
Burosumab	12 (71%)
Conventional ^a	5 (29%)
History of fracture (<i>n</i>)	
History of fracture (<i>n</i>)	8 (47%)
History of knocked knees ^b (<i>n</i>)	3 (17%)
History bowed legs ^b (<i>n</i>)	13 (76%)
Enthesopathies (<i>n</i>)	7 (41%)
Osteoarthritis (<i>n</i>)	9 (56%)

^a Taking, individually or in combination, phosphate supplements and calcitriol. ^b History of knocked knees and bowed legs includes anyone who was diagnosed but had them surgically corrected.

Table 5. Results of IPAQ, WOMAQ, and BPI-SF questionnaires

Questionnaire	
IPAQ (<i>n</i>)	
Low	5 (29%)
Medium	4 (24%)
High	8 (47%)

WOMAC (mean \pm SD)

Stiffness^a 47.8 \pm 19.38

Function^b ($n = 16$) 28.5 \pm 19.95

BPI-SF (mean \pm SD)

Worst pain^c 5 \pm 2.66

Severity^c ($n = 16$) 3 \pm 2.38

Pain interference^d 4 \pm 3.08

^a Higher scores represent higher levels of experienced stiffness. ^b Higher scores represent lower levels of physical functioning. ^c Higher scores represent higher levels of pain. ^d Higher scores represent higher levels of interference due to pain.

Table 6. Physical activities that participants reported engaging in, according to content analysis.

Exercise type	
Endurance (n)	3
Swimming	1
Treadmill walking	2
Flexibility training	8
General stretching	3
Yoga	5
Toning tables	1

General physical activity (<i>n</i>)	12
Cycling	3
Dancing	1
Karate	1
Pole dancing	1
Snowboarding	1
Swimming	4
Tennis	1
Walking	8
Others (<i>n</i>)	
Physical therapy	3
Strength training (<i>n</i>)	8

5.1 Thematic Analysis: Exercise experiences

Four main themes were identified to describe how XLH affects a person's experience when completing exercise and physical activity, highlighting the barriers to and facilitators of exercise and physical activity participation: 1) People with XLH are unable to or uncomfortable participating in impact exercise; 2) too much exercise or physical activity causes fatigue and exacerbates pain and stiffness; 3) exercise is a tool to improve symptoms of XLH and function in the long term; 4) strategizing movement and tailoring exercise is essential to exercise participation.

The thematic map (Figure 1) highlights barriers to and facilitators of exercise and how they affect the experience of a person with XLH.

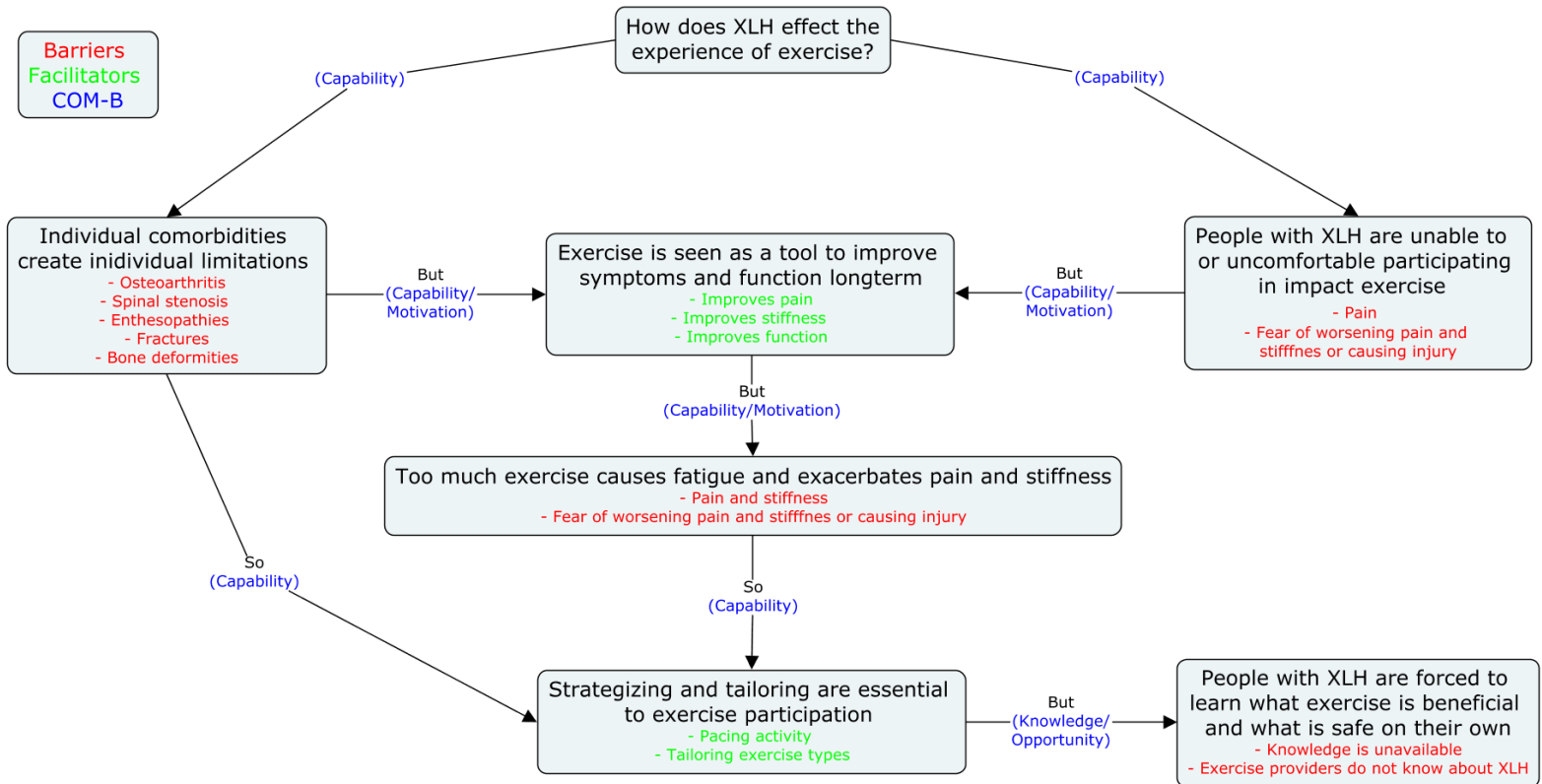


Figure 1. Thematic map of patient experiences and barriers to and facilitators of exercise.

Capability		Motivation	Opportunity
Physical	Psychological	Reflective	Social
Pain Stiffness Fatigue Bone deformity	Knowledge of safe and effective exercise	Fear of worsening symptoms Fear of fracture, injury or joint degeneration	Access to exercise providers knowledgeable on XLH Uncomfortable in group exercise situations
Intervention Function		Intervention Function	Intervention Function
Training Enablement	Education Training Enablement	Education Persuasion Inventivisation Coercion	Restriction Environmental restructuring Enablement

Figure 2. Identified barriers to physical activity and exercise for people with XLH and the applicable intervention functions, according to the BCW.

5.1.1 People with XLH are unable to or uncomfortable participating in impact exercise

When discussing their experiences with exercise, participants described pre-existing pain and stiffness as the leading causes of their functional limitations, affecting their capability and representing barriers to a range of types of exercise. Pain and stiffness also affect motivation as the fear of worsening their symptoms leads to avoidance of exercise.

“More like the achiness the stiffness and um, the exasperation of what already is there. You know, I have random knee pain that is just a random and I’ll, you know, need a cane for a little while. You know, I don’t use a cane all the time, but I do go into these moments where I will randomly hurt with my knee and my hip. And you know, so I avoid, you know, some what avoid too much of it (exercise) just because of that.” (P06, age 47)

While the nature of the participants' limitations and the types of exercise it led them to avoid varied by the individual, concerns with impact exercise were consistent. Participants described how impact exercise causes pain in the lower limbs, joints, or spine attributing the pain directly to the physical impact.

“No, I do not run. I can jog, but honestly, I can probably like speed walk faster than jogging and I just find like that extra weight on your knees, like when you're jogging like the weight shifting hurts like it just impacts my knee. So no, I don't run.” (P04, age 39)

Fear of worsening symptoms or causing an injury was a key barrier to impact exercise as well. Participants describe how impact exercise not only causes immediate pain, but it also causes concerns related to long-term health including joint degeneration, worsening pre-existing tendinopathies, and causing fractures. From their perspective, impact exercise has the potential to worsen pre-existing comorbidities and lead to long term pain and further debilitation. Therefore, even in the absence of injury, participants frequently reported that they avoid impact exercise.

“Yeah, you know from XLH the higher impact stuff you're more prone to having a lot of joint degeneration. So, wearing of like your cartilage and then especially if you have osteoarthritis. You're also at a higher risk for fractures. And that's something I knew, like at a very young age.” (P11, age 41)

Not all participants were unable to partake in impact exercise throughout their life. While some participants said they have never been able to run or participate in impact exercise, others described periods of their life where they were able to engage in impact activities like jogging but eventually had to limit and adjust due to evolution of their symptoms.

“I was quite a keen runner but you know I found on my joints and like over time, I could feel the impact quite significantly. So, I have had to taper them types of exercises back. The things that I found, you know, were very good for my mental health, very beneficial for my physical health as well. You have to restrict yourself at a certain point to not be a detriment.”

(P07, age 32)

5.1.2 Too much exercise or activity causes fatigue and exacerbates pain and stiffness

The interviewees described how completing too much of any type of exercise, or physical activity in general, would cause fatigue, and worsen pain and stiffness; the locations and causes of pain and stiffness were variable. Participants described fatigue as a complete loss of energy sometimes causing an inability to complete the activity they are participating in.

“I don't know about most difficult, but I would say like pain, stiffness and also feeling like I get very tired. I just feel like my body just loses all the energy. Like for example, I feel like it's very common for me when I'm walking my dog and then suddenly during the walk I feel like I just can't walk home anymore. Like I have no energy left like it feels like my body is really heavy and it's really hard to move. I kind of like lose all the energy and I find that very hard because sometimes that also happens at the gym. I'm doing a set and then I just feel like I don't like, I don't know, my muscles don't get enough like I don't know, I don't remember, is it ATP that they work on?” (P03, age 27)

Fatigue was described as a significant barrier to exercise that was not only triggered by exercise, but the cumulative activity throughout the day including running errands or doing chores; activities involving long periods of walking were described frequently to cause fatigue. The onset of fatigue, prior to or during, could make it impossible to participate in exercise at all, acting as a barrier by

affecting their capability to exercise. Knowing that, participants described how the anticipation of fatigue would lead them to forgo any unnecessary activity, including exercise, if they know they had an event in the following days, also creating a motivational barrier.

“I have more fatigue. I've always fatigued, but I'm like more fatigued (than previously). I have less active days than I do active days. It's just harder for me to get moving and get going. I can either go grocery shopping or I can clean my house. I can't do both in the same day. I can either Christmas shop and walk around a couple stores for a little while, or I can go home, decorate, cook, do all these things. I can't be that person that does multiple active things in a day. If I go traveling, if we go to SeaWorld, I am shot for like maybe two days.” (P06, age 47)

Participants reported that fatigue contributed to pain and stiffness. People with XLH described that fatigue would take the pain and stiffness they were already experiencing and exacerbate it to a point that it was debilitating. The exacerbation of pain and stiffness would limit mobility and function further affecting their capability to exercise.

“Oh, the pain goes from moderate to extreme or severe. There's no amount of, you're totally exhausted... I have days where I just can't function. I might get to the shower and, you know, make it to my recliner and that's just the end of the day. But I try not to do that. Um, but sometimes I just can't. I just have those days.” (P19, age 54)

Participants also described fatigue as a lack of endurance. Comparing themselves to family members or friends who do not have XLH they explained their inability to sustain exercise as long or keep up with them. Additionally, they also found they would be in more pain and stiffness comparatively.

“For sure, one the endurance. Probably the pain level too, it's hard to know because this is me and I don't know anything different, but when I look at my other healthy friend, she weighs a lot more than me, but she's able to go longer, faster, more endurance, less stops. That kind of thing. And I don't think she feels the same amount of pain at the end.” (P04, age 39)

5.1.3 Exercise as a tool to improve symptoms and function in the long term

Despite the experience of fatigue and the debilitating pain and stiffness it causes, participants described themselves frequently motivated to push their boundaries when it comes to exercise. Individuals with XLH explained that while exercise could lead to more pain and stiffness, the right balance of exercise and activity improved their pain and allowed for an overall improved quality of life. However, finding that balance was very challenging.

“But it's also like on top of the tiredness, the exhaustion I have a lot of pain. So that's also like a big part, and my pain gets worse the more active I am. But also, if I'm not active enough, it gets worse. So I have to find the balance and I find that very hard. So I often fall over the edge of doing too much because I just don't wanna, I don't like sitting still... So I often just do too much and then it causes a lot of issues. It takes days to recover, and then I'm just feeling really bad. I feel like the balance is one of the hardest parts to find for me, like the right balance of where I'm active enough and not too much.” (P03, age 27)

Participants described that even though exercise could cause increased pain acutely, in the long-term the level of pain they experienced improved when they were able to exercise consistently. Generally, staying active was described as a strategy to improve pain but specific types of physical

activity or exercise that people with XLH perceived improve their pain included: walking, swimming/water aerobics, strength training, and stretching/yoga.

“And I find like although you might be trying hard the day you're exercising, a few days later I will feel better generally, like pain and the swelling or the inflammation. I feel like everything is better long term when I'm consistently exercising.” (P05, age 40)

“Continually hearing that messaging of like ‘movement is helpful’ and once I started doing aquatic and then also increasing walking, increasing strength, it's like ohh yeah this does actually help prevent the pain.” (P02, age 36)

“I found yoga to have such a strong benefit for me... To anyone with joint stiffness, bone pain, XLH specifically. I find stretching, like very low impact type of exercises overtime just has yielded very strong benefits for myself... In terms of flexibility, I'd say in terms of pain management too, it definitely eases the pain that I sometimes feel in my ligaments and joints” (P07, age 32)

Along with pain, participants described that exercise improved stiffness. Participants explained that general movement would help warm them up and improve stiffness, but stretching and yoga were frequently described to benefit stiffness and led to gains in mobility and flexibility.

“So when I'm feeling stiff and achy, like before I get out the bed and when I first get out the bed, I will stretch and do some things and it does help. I actually really like yoga and it does help when I'm feeling up to doing it.” (P06, age 47)

Interview participants described the gains in strength that exercise like strength or resistance training could have. Improvements in strength and mobility or stiffness were consistently connected to improvements in ease of completing ADLs. Participants described how training,

whether it be at home, with a personal trainer, or through physiotherapy, improved their strength and helped them gain function and the ability to do movements they were once unable to complete.

“I had never done a lunge. You know, where you lunge out. And that was part of one of the questions from the physical therapist. And so I got through this regimen. And on the last day she's like, alright, do a lunge. And I said, I can't do a lunge. And she said do a lunge. And I did it. I could not believe it. I was like, oh my gosh, I was flipping out. I never thought like the little things that we were doing were, you know, how is this make gonna make a difference? But it did. I was blown away.” (P21, age 46)

Participants reported that improvements in strength and function increased their confidence in their ability to complete ADLs and made them less afraid of injury.

“I kind of avoided or was afraid of, you know, making things worse or certain movements to exacerbate it. But I guess nowadays now that my, you know, knees are strengthened that I feel stable and I just feel stronger in my body for various reasons I have confidence that even if I did slip on ice that, you know, I could handle it or, you know I could fall in a way that minimizes risk.” (P02, age 36)

The perceived improvement in function acted as a facilitator of exercise participation for people with XLH. Participants described that their primary motivation to exercise was to maintain their function and slow the progression of XLH.

“Because it (exercise) just makes me feel better. And that's me. And also, not wanting to lose the skills or abilities that I have, that's also a big part because I'm very scared of the disease progressing to the point where I can't like get up from the floor anymore.” (P03, age 27)

The motivation to stay active to maintain function was also reported by people who were unable or did not partake in exercise. Participants who did not exercise explain how they still try and stay active by doing chores or running errands in an attempt to maintain function and independence.

“I catastrophize. Where even though I'm having like a bad pain day and I just want to be on my heating pad, take an Epsom salt bath, lay in bed all day, I feel intense pressure to like, go out and do stuff because I don't know how much longer I have. It's sort of like being followed by the guy with the sickle, you know? Waiting to just like put me in a wheelchair. But so that's sort of hanging over my head physically.” (P01, age 44)

5.1.4 Strategizing and tailoring are essential to exercise participation

In the interviews participants described two main facilitators of exercise: 1) strategizing movement; and 2) tailoring of exercise. Strategizing movement entailed the deliberate planning and anticipation of the level of physical activity that would be required for the current and subsequent days. People with XLH described that they must strategically plan their exercise, and other activities, to avoid fatigue, and the pain and stiffness caused by overexertion.

“So, it's kind of like cumulative. But it's like if I'm very active many days in a row, it takes less to get to the point where it's too much. But it's like it can be if I have too many things. I have a dog, so I walk a lot every day with my dog and then I also have many hobbies, like physical hobbies. I have like many things, I go to the gym, I walk my dog, I have to go grocery shopping, I have to do housekeeping work like it kind of like gathers up being too much. So I kind of have to like balance on the days where I have to go like grocery shopping or something, maybe I don't go to the gym that day, or maybe I don't do that much housework that day. So, it kind of like just, it gets like worse every time I stop after an

active day... And I find that also hard like having to plan so much ahead, if I know I'm going to a concert or something tomorrow then I know that I can't do too much throughout today because then I have to like kind of like rest ahead.” (P03, age 27)

While strategizing movement was a tactic used to avoid fatigue to facilitate exercise, the constant need to plan the day around your physical abilities was described as mentally fatiguing and adds extra stress to a person with XLH's life.

Tailoring and adapting exercise was recognised as a tool to help compensate for mobility and functional impairments. The need for individualisation was linked to a diverse range of comorbidities – including knee and hip osteoarthritis, spinal stenosis, bowed or knocked knees, and weakness in the lower limbs – which contributed in varying ways to mobility limitations, thus creating distinct barriers to exercise.

“So if I would have somebody give me a program of when you rest when you do these things, more like that was actually like tailored more to me, to my life, my capabilities... Especially for people with XLH because there is a lot of different situations that people are in. Some can do more, some are like more disabled and some are like almost passing as healthy.” (P03, age 27)

“Uh, yeah, I basically I love free weights a lot more. So I do like the basic, I don't know what they call in English, like the multi joint movements like squatting, deadlifts, like bench press, stuff like that. So like the basic weightlifting, but then also like I don't really like the machines. And I also feel like they're often made for taller people, like I'm very short. So I feel Like they are made by people who are taller than me, so it's not optimal.” (P03, age 27)

“No, squats are out. Can't do the squats, my patellar tendon is now very calcified and my achilles tendon has calcified to the back of my knee. I used to have raging tendonitis as a kid all the way until I was like 25 and then one day just stopped hurting so I was like rad. I didn't know that it was like toast at that point, so I have very limited range of motion in my knees and my ankles.” (P01, age 44)

Heterogeneity in the physical presentation of XLH reinforced the need for personalized exercise planning for mobility impairments. Participants also described that it was challenging to find information on how to adapt exercise in a way to allow it to be safe and effective. Working with physical therapists and personal trainers was described as a route to receive individual support. However, along with financial reasons, people with XLH reported that they struggled to find exercise providers who are knowledgeable on the disease and that they could trust. A lack of trust of professionals was established from pre-existing feelings of frustration and dismissal from the healthcare system.

“We need physical therapists to look into us and to help us with exercises. And there should be kind of a guideline for physical therapists, how to deal with XLH patients and they would like to have some kind of standard. And when I listen to that, I always wonder. How would a physical therapist be able to give one size fits all treatment. If you are so different in your well-being, in your physical status.” (P09, age 60)

“More like a healthcare professional to learn more about it [XLH]. But of course nobody knows about XLH like especially instructors or anything like that. Like PT's know nothing like that. They've never heard of it, of course, because it's a rare disease.” (P03, age 27)

Group exercise with an instructor was considered a way to receive tailoring and adaptation for exercise but social factors created barriers to participating in group classes. When comparing themselves to people without XLH, participants who had mobility limitations often reported feeling self-conscious and uncomfortable in group situations stemming from the perspective that they are less capable.

“I absolutely hate it [exercise] as it seems to accentuate and point out and write big neon letters all over me. {participant name} can't do this, {participant name} can't do that. Um, I've wanted to maybe go to the Y and take some of those exercise classes for seniors. But there's so much I can't do and I just. I just don't. I don't wanna be in a room where other people are doing things perfectly fine and here's {participant name} who can't.” (P16, age 67)

The participants who did start exercising by themselves, or with an exercise provider like a personal trainer or physical therapist, were forced to learn from experience. Participants noted it took trial and error to find what they were capable of and that they progressed at what they perceived to be a slower rate compared to someone that does not have XLH. For some people slower progression was because they were more cautious about injuring themselves or causing fatigue, and others felt they had to simply work harder to get the same results as their peers.

“We learned quickly what I can't do. What made it easier? Time and patience. I do things at a much slower rate. I don't know if it's because I'm so cautious of not overly pushing, but it took a long time for the therapist to figure out where my limits were, and I wasn't just being stubborn.” (P01, age 44)

“So it's always, you know, if I compare to colleagues or people my age, same fitness level, I could tell I have to try much harder for a result... Even like a working out routine, if I would lift I think the same, and I'm talking for a long period of time, I find it takes me longer to build muscle, longer to get stronger. Like even when I do my physiotherapy, I find it takes multiple sessions to feel, you know, any kind of relief or any progress either with the pain or with strength.” (P05, age 40)

Participants identified other strategies that facilitated their exercise participation. A good pair of shoes, or insoles, that allowed for greater impact absorption to support longer walking durations. Education on body awareness and understanding the difference between muscle soreness and pain helped participants understand that not all pain or discomfort is inherently linked to injury. Previously any level of pain or soreness would be avoided, resulting in avoidance of exercise that causes muscle soreness.

“I couldn't determine the difference between muscle pain of like working out too hard versus like bone pain when I was a kid. And so, I would just stop, and I had to learn that for myself.” (P01, age 44)

Burosumab treatment was noted as another facilitator for exercise. Participants described how Burosumab enabled them to be capable of participating in exercise and physical activity they were once unable to. It also acted as a motivator for one participant. The following quote was an answer to what motivated them to stay physically active.

“Just taking Burosumab... The amount of change I got after taking burosumab injections. Only in two injections it changed my life.” (P13, age 33)

5.2 Content Analysis: Patient Important Outcomes

During the interview participants were asked about their treatment priorities in two different areas. The first was treatment with medications and was framed as the following: “When it comes to considering new treatments or therapies, what is most important to you?” OR “If you were to consider a different therapy or treatment to take instead of your current treatment, what would you want it to treat?”. The second context was exercise and was framed as the following: “If we were to design an exercise program for people with XLH, what would you want us to target and help improve?”. The results of the content analysis for each context are in Figures 3 and 4.



Figure 3. Patient important outcomes identified in content analysis of treatment with medications.



Figure 4. Patient important outcomes identified in content analysis of exercise.

5.2.1 Addressing symptoms of XLH

Pain emerged as the most frequently prioritized symptom for treatment among participants. It was described as one of the most challenging symptoms to work through and manage as it affected all aspects of life. Participants expressed that, while pain medications could provide some relief, they were forced to cope with ongoing discomfort caused by pain.

Even though participants expressed that stiffness affected mobility, it was not mentioned as an important outcome as frequently as pain. At its worst, stiffness was described to seriously affect mobility and a person's ability to complete ADLs. However, it was something that multiple participants mentioned could be worked through and lessened by strategies like heating and movement or stretching.

“The achiness. Um, yeah, cause I can kind of plunge through the stiffness I can like, when I feel stiff I can kind of, for lack of a better word, I can workout those kinks a little bit. Like eventually they work themselves out, but when I'm aching, when I have like that, there's like, I get this dull ache in my extremities that just hurts and it can, and it can hurt for hours, it can hurt for days. And I can't, nothing seems to help with that.” (P06, age 47)

Fatigue was mentioned frequently as an important outcome to treat. Participants described seeking interventions that could increase their energy with the intent to be less tired, allowing them to complete ADLs, especially those that involve walking or standing for extended periods. Participants also characterized fatigue as the need to “pay for” today’s activities with exhaustion the following day or days; exhaustion extended beyond reduced energy but to increased pain and stiffness that is commonly associated with fatigue for people with XLH. The constant need to plan around fatigue added to the mental weight that XLH brings and increases emotional and mental stress.

“But walking the dog like my stamina, mobility, not paying for as much the next day. My ability to like go to a museum and walk around and not sit in a wheelchair and spend 3 hours in a museum, that's a big deal to me” (P01, age 44)

The mental health of people with XLH may be affected in multiple ways and was therefore an important outcome in both contexts. Participants described needing mental health support not only for chronic pain and fatigue, but to help cope with the potential of a worsening quality of life as XLH progresses. Furthermore, they suffered from a lack of confidence due to physical deformities and pain, which impacted their emotional well-being, and their confidence to complete ADLs without injuring themselves. Finally, mental stress was added to their lives due to the number of doctor appointments they are required to attend. Participants saw treating their

symptoms was a way to help with mental health and, for some, exercise was a way to provide an outlet to do something they enjoy to lessen mental stress. Other participants noted they did not enjoy exercise.

“And I think when you go through surgical interventions because of XLH and you're living in pain, your mindset's very different, you're almost in that doom and gloom, like, what if I'm not ok? You have that pity party talk with yourself.” (P11, age 41)

“Lunges have historically been really difficult for me with my knees, but I think as I'm doing body weight lunges in different ways, different formats of that, its been really encouraging and stabilizing. Like ohh, my knees can still do these things and not hurt, cool. That's really encouraging. So you know, I guess one thing I would look for in a program is just things that are fun and feel good, but also things that are you know not just the kind of routine physical therapy.” (P02, age 36)

Improving strength was expressed as an important outcome for over 50% of participants in the context of exercise and was still noted to be important when it comes to treatment with medications. Participants connected muscle weakness primarily to weakness in the lower limbs, and how it affected their function. They discussed the compensatory actions taken due to pain and that improving strength, especially in the lower limbs, could improve their functional ability; strength was also connected to stability.

“Coming up with a better strength activity would be fantastic. I think so that it builds your muscles so that you're able to continue doing the things that you want to for activities of daily living.” (P04, age 39)

Fractures emerged as a key outcome across both contexts. Among participants discussing treatment with medications, there was a strong emphasis on the importance of identifying therapies that could prevent fractures and improve fracture healing. Such prevention would reduce the need for subsequent surgeries and lessen the requirement for more extreme interventions. In the context of exercise, addressing fractures was also important, but through the means of improving strength and mobility. Improvement of strength and mobility would support their confidence in completing ADLs and from their perspective building muscle supported their bones and prevented fractures.

“So, I saw how much it [burosumab] could help kids not feel so different, not feel so alone, not break the stuff that I broke not have to wear the leg braces, all of that. Maybe save them from osteo knee surgeries and stuff like that.” (P01, age 44)

5.2.2 Ability to maintain a healthy status and independence

When speaking about the outcomes that they would like to prioritize for treatment there was an overall desire to stay healthy and maintain independence, especially over time. The general desire to not have their disease state progress was commonly mentioned as an important outcome.

“The outcomes I'd find most important, I suppose for me, it's more looking long-term like I mentioned, I find myself having a milder case of XLH right now, but at least based on my own personal research and speaking to others with the condition, it seems to have been something that worsened over time. So that's always in the back of my head. You know, like I feel okay now, but how about the future? That is a big concern for me, especially being on conventional medication. So, if there's something you know, something that's more specifically designed for XLH and that could be more beneficial to me in the longer term. That would be of interest to me.” (P07, age 32)

From listening to doctors, stories from other people with XLH, or from their own experience, participants understood the progressive nature of XLH and that just because their health is stable now, it may not remain that way. Their recognition of the progressive nature of XLH created concerns for their health in the future and is why their priorities were not just to improve current symptoms, but to maintain their current health or slow the progression in the long-term. While individual symptoms such as pain or stiffness were important, overall, many participants prioritized how the symptoms affect their lives over the symptom itself; that is, how pain can affect a person's mobility or flexibility.

“I think people with XLH, they can go from being able to put their shirt on one year to having, you know, shoulder pain and not being able to like lift their arms over their head.”

(P11, age 41)

Maintaining physical functioning was the largest priority of 82% and 41% of participants for exercise and treatment with medication respectively. When discussing the selection of a treatment or exercise program, they emphasized the goal of being able to walk for extended periods and not requiring a wheelchair, now or in the future, completing chores and errands without experiencing fatigue, keeping up with their children or grandchildren when they play, and being able to dress themselves.

“The quality of life when it comes to, like we were looking at, ok should we move and downsize? We're looking to a bungalow with no stairs. Like, am I gonna be able to walk up and down stairs the older I get? And is it going to be a challenge to get dressed? Those are the things that I think you worry about for a quality of life.” (P11, age 41)

6.0 Discussion

The study highlights a key tension experienced by adults with XLH: while physical activity and exercise were perceived as tools to manage symptoms of XLH, simultaneously the physical, psychological, and psychosocial burdens created by the disease present significant barriers to participation in physical activity. Primarily, participants discussed tangible improvements to pain, stiffness, mobility, strength and overall physical functioning from participating in different types of physical activity or exercise but also emphasized the challenges of overexertion that often led to debilitating fatigue. The paradox between beneficial and detrimental effects of exercise created a dynamic where individuals were motivated to exercise for symptom management but were constrained and could be demotivated by the same symptoms.

Many of the participants reported regularly participating in exercise including walking, swimming/water aerobics, strength training, stretching and yoga; participants also completed a range of physical activities. Two primary facilitators for exercise participation identified for people with XLH were strategizing movement and tailoring exercise. Other facilitators included good footwear or insoles to help with walking, education on body awareness and the difference between muscle soreness and pain and taking treatment such as burosumab.

6.1 Exercise Experience: Barriers and Facilitators

Despite concerns that exercise may exacerbate symptoms or increase risk of injury, participants generally perceived the correct balance and execution of exercise as a potential way to improve overall functioning in the long-term – even among those who were adverse to it. The sample had an elevated proportion of people completing high and medium amounts of physical activity according to the IPAQ. Having a relatively large proportion of highly physically active

participants represents a potential selection bias, however having XLH itself may also influence physical activity levels. Participants described frequently pushing boundaries of fatigue to complete physical activity due to the perceived beneficial effects. They explained that while fatigue would increase levels of pain and stiffness acutely, perceived improvements in pain, mobility and strength improved functional ability in the long-term and acted as reflective motivation to continue exercising. However, finding the balance of enough exercise to receive the benefits without leading to fatigue was very challenging; for some, finding balance was too challenging and led to demotivation. Hughes et al. also found that people with XLH reported forcing themselves to exercise in the hopes of diminishing future pain.¹² Further, the results from a pilot study of exercise in two people with XLH reported similar findings, in that participant's subjective notes described improvements of pain from participating in exercise.⁷⁷ Therefore, it is plausible that the perceived benefits of exercise act as reflective motivation for individuals with XLH who are able to find the correct balance of physical activity.⁹⁸ By learning more about the effects of exercise and how to more accurately dose it without leading to fatigue, we could harness the reflective motivation it creates to potentially improve management of the disease

The absence of physical activity and exercise guidance for people with XLH represents a significant gap in research and disease management. In general, physical activity, in any amount, is beneficial to overall health, maintenance of physical functioning in older adults, and reduction in the development of comorbidities such as cardiovascular disease.⁷⁰ Despite the potential benefits that could be gained by participation in physical activity, people with XLH may not be able to meet the most basic movement guidelines. The Canadian 24-hour Movement Guidelines recommend 150 minutes of moderate to vigorous aerobic physical activities per week.⁷⁰ The analysis in the current study outlined the impact that fatigue can have on people with XLH. The

findings reveal that in people with XLH fatigue limits endurance, which restricts physical capability or capacity for prolonged physical activity. Additionally, fatigue can lead to aggravated pain and stiffness which can further limit mobility and physical capability. Overexertion can be caused by more than just strenuous activity such as exercise but from doing chores or walking for extended periods of time. Therefore, fatigue may also undermine reflective motivation by encouraging avoidance of any non-essential physical activity to limit the effects of fatigue. The participants highlighted the benefits that physical activity such as walking can have on stiffness and pain. However, when people with XLH have other responsibilities, any extra physical activity may not be feasible due to the potential of fatigue, let alone 150 mins of moderate to vigorous physical activity. For that reason, adapted physical activity recommendations, guidance or targeted exercise and physical activity interventions may need to be developed for people with XLH to optimize their general health and possibly improve the management of their disease.

According to the BCW, one can overcome barriers to reflective motivation through education.⁹⁸ One key theme the study identified was that strategizing movement was an essential facilitator of exercise for people with XLH. Although not discussed in the literature for XLH, an already established strategy for chronic pain and fatigue management is pacing. Pacing is a proactive self-management strategy with the intent of achieving increased function in which individuals enhance self-efficacy by learning to balance time spent doing activity and resting.¹⁰⁴ The participants, without a formal mention of pacing, strategized their movement due to the consequences of fatigue and chronic pain. Improving communication with physicians on the importance of pacing activity for management of pain and fatigue could improve implementation of the strategy according to the BCW. The inclusion of pacing should be considered in physical

activity recommendations or guidance, and in exercise intervention design to enable people with XLH to participate.⁹⁸

The daily experience of pain, stiffness, and the mobility limitations resulting from symptoms, bone deformities and comorbidities such as OA and enthesopathies highlighted how physical impairments serve as barriers to physical activity and exercise for individuals with XLH. Participants described difficulties with an array of physical activities; running and walking or standing for extended periods of time were consistently the most challenging activities among participants. An array of activities that require movement to the end of the range of motion or high amounts of flexibility were also described to be challenging. Training and enablement are potential behavioral change techniques that could be used to address physical capability barriers.⁹⁸ Participants in the study identified learning how to tailor exercise to their mobility and functional limitations as an effective facilitator to exercise and physical activity.⁹⁸ However, XLH brings additional barriers to designing programs around the concept of tailored exercise.

One challenge that XLH creates for tailoring exercise is the heterogeneity in phenotypes seen in XLH. Clinical manifestations vary even within the same family; people with XLH experience comorbidities including but not limited to bowed and knocked knees, spinal stenosis, enthesopathies, OA and muscle weakness.¹⁰⁵⁻¹⁰⁷ Participants in the study acknowledged the variability in mobility and functional ability observed among those with XLH, and differences in the experiences of the participants in this study emphasizes the differing levels of mobility and functional abilities. The variability in their experiences reinforces the need for physical activity recommendations and exercise interventions that can be tailored to the needs of an individual.

Concurrently, participants described the difficulty of finding information on how to exercise in a safe and effective way. Participants cite personal training and physiotherapy as

effective ways to receive tailored exercise, but the cost can be prohibitive. Furthermore, because XLH is rare, finding an exercise provider knowledgeable of the disease was next to impossible. The challenge of finding knowledgeable exercise providers would be considered a barrier to social opportunities according to the BCW.⁹⁸ Additionally, due to the perspective that their symptoms are not taken seriously by doctors, many people with XLH may not feel motivated to try multiple exercise providers to find someone who fits their needs.¹² The analysis in this study found a similar frustration when people were searching for exercise providers and exercise information; patients were forced to be the expert on their disease and educate the provider causing another barrier to accessing exercise for people with XLH by impacting their social opportunity.⁹⁸

Environmental restructuring and enablement are strategies to overcome limitations to social opportunity.⁹⁸ In the case of XLH, environmental restructuring could occur using accessible educational materials made for exercise providers to inform them of the potential manifestations of XLH and how it affects mobility and function. Creating materials to inform exercise providers who are less knowledgeable about the disease could facilitate access to their services for people with XLH allowing them to participate in exercise more easily and safely.

Group exercise was discussed as a more cost-effective method of receiving personalized exercise, but many participants were uncomfortable in group exercise settings. It has been established that chronic pain impacts the emotional wellbeing of people with XLH, while physical deformities and functional limitations lead to a low self-esteem and reduced self-confidence.⁴³ The results of this study revealed that impacted emotional or psychological wellbeing can also act as a barrier to exercise by limiting social opportunity.⁹⁸ The emotional impact caused by XLH is echoed in the interviews where participants expressed discomfort in group situations due to feeling less

capable and feeling different due to mobility and physical functioning limitations caused by pain, stiffness, and deformities.

According to the BCW, environmental restructuring is a behavioral change technique that can help overcome barriers caused by a lack of social opportunities. Group exercise with other people who have XLH was seen by participants as a way to receive tailored exercise and to form a community in which they are comfortable to exercise. Unfortunately, due to the rarity of XLH developing in-person group exercise programs is likely not feasible, but an online group may be a pragmatic way to achieve a program to support exercise, and community for people with XLH.

One potential way to enable physical activity for people with XLH could be better management of the disease with medication. Initiating treatment with burosumab was described to enable participation in exercise for some participants. Clinical trials have demonstrated that burosumab can improve pain, stiffness and physical functioning.^{64,65} Participants in the current study described how taking burosumab lessened pain, stiffness, and fatigue which previously limited their ability to engage in physical activity and exercise. Improved function resulting from burosumab even acted as motivation to continue exercise participation for long-term functional maintenance of one participant. Physical activity has a well-established role in reducing mortality in the general population.⁷¹ Given the elevated risk of mortality observed in individuals with XLH relative to control, improved management of the disease with drugs such as burosumab could facilitate physical activity participation and may yield secondary benefits.¹⁰⁹

Pain was a barrier to participating in impact exercise for participants, such that people were unable or unwilling to partake in exercise such as running. Pain was directly attributed to impact exercise affecting the physical capability to participate in it. Additionally, the fear of worsening symptoms, causing injury, fracture or joint degeneration affected reflective motivation. Similarly,

previous qualitative studies attempting to better understand the burden of living with XLH have identified pain as the most burdensome symptom to people with XLH, especially to activities like walking and running.^{41,44} Despite the barrier pain creates, walking was the most common form of exercise and physical activity for the participants in the present study. Walking was frequently cited by participants to improve or maintain pain, stiffness and even mobility. In OA, walking has been shown to reduce the risk of functional limitations over a two-year period.¹⁰⁹ Weight bearing/low impact exercise is recommended as it improves cartilage volume and is seemingly protective against cartilage degradation due to the increased blood flow caused by compression of the cartilage.^{109,110} However, in XLH, some types of loading could do harm. Abnormal loading of the joints due to lower limb deformities likely plays a role in the development of OA for people with XLH.²⁹ Therefore, prescribing walking for people with severe lower limb deformities could not only cause acute pain, but progression of OA. A better understanding of the mechanisms contributing to OA in people with XLH, including the effects that lower limb deformities have on the development or progression of OA, or the magnitude and frequency of loading that is permissible may help make more accurate exercise and physical activity recommendations when it comes to impact exercise. However, if the hypothesis of Macica et al. is accurate and the low phosphate joint environment of people with XLH leads to early OA, correct management of XLH could prevent OA progression and pain, facilitating exercise participation for people with XLH. Overall, better understanding of the pathophysiology of OA in XLH will improve the physical activity recommendations that can be made for adults with XLH.

There is a similar conundrum when comparing recommendations for people with osteoporosis versus expectations for people with XLH. In osteoporosis, impact exercise is recommended as it is thought to stimulate bone turnover, and prevent bone loss or increase bone

mass.¹¹¹ But, people with XLH typically have higher rates of bone turnover, both breakdown and formation, due to osteomalacia.¹¹² The high rate of turnover, improper formation and deposition of hydroxyapatite crystals leads to the structural and functional changes of bone in XLH that cause a high risk of fracture. Without correct management of the disease, promoting impact exercise, even low impact such as walking, could further increase turnover despite not having the minerals to deposit and strengthen bone. If impact exercise does increase bone turnover in people with XLH, it could lead to a further weakening of bone and a higher fracture risk. Therefore, a clearer understanding of the relationship between bone turnover, impact activities, and XLH treatment could inform recommendations for walking and other exercises for individuals with XLH.

Participants identified stretching as a beneficial modality. Participants described using stretching along with general movement to help them lessen stiffness, allowing for improved mobility and functioning. The results of this study support previous findings surrounding the connection between stiffness and exercise. Movement and stretching has been reported by Lo et al. as a method to alleviate stiffness in people with XLH, in that their participants described stiffness as ‘going away’ once they started moving.⁴¹ In the context of an exercise intervention targeted for people with XLH, including stretching may be important to improving stiffness and mobility to allow for effective exercise participation. Enhanced understanding of the types of movements and stretches, along with the frequency and intensity, that are particularly beneficial at managing stiffness for adults with XLH would be a route to help improve the management of stiffness in individuals with XLH.

A fear of falling was not identified as a barrier to exercise, though it has been reported as a burden of XLH previously. A qualitative analysis by Hughes et al. identified fear of falling as a theme and discuss how it affected social life, impacted decision-making and was frequently

connected to a fall that led to a fracture.¹² Due to the burden fear of falling creates to daily life, I recognized its potential as a barrier to exercise and physical activity. Consequently, the interviews asked questions related to fears or patterns of avoidance to identify if it would have an impact on exercise participation. Although several participants had a history of fractures resulting from falls or spontaneous incidents, a fear of falling did not emerge as a barrier to exercise. Interviewees did mention they would not go out in poor weather due to a risk of falling and causing injury, which could create a barrier attending exercise in public, but falling was never linked to participating in exercise itself. Although it was not explicitly reported, fear of falling could still be relevant in the context of exercise, especially for balance and functional training, and the potential effects should be considered in exercise interventions and recommendations. Conversely, it did emerge that participating in exercise, especially strength training, was linked to stability, helped improve confidence in completion of ADLs and reduced their perceived risk of injury by a fall or a spontaneous event. Therefore, exercise, specifically strength training, could help people who do have a fear of falling.

6.2 Patient important outcomes

The present study serves as a foundational step to create tailored physical activity recommendations and eventually an exercise intervention to test its effects on health outcomes for individuals with XLH. To inform the process, participants were asked about important outcomes regarding treatment with medications versus exercise to understand if participants prioritize different outcomes in different contexts. It's important to note that the intention was not to make an exhaustive list of all outcomes important to individuals with XLH, but to highlight the outcomes that are of the highest priority.

Accurately understanding patient important outcomes is essential to ensure they are of relevance to the target population.¹¹³ When using patient important outcomes, previous clinical trials and clinical practice guidelines base their important outcomes on the experience of experts involved, along with the input of patient partners. For example, the clearest and most exhaustive list of outcomes directly attributed to be important to patients comes from an international working group's systematic review to assess the efficacy of burosumab versus conventional therapy.¹¹⁴ The outcomes were identified by the experts involved and a patient partner, the critical outcomes were as follows: fracture/pseudo fracture(symptomatic), fracture healing, musculoskeletal pain, treatment-related serious adverse events, and skeletal deformity.¹¹⁴ Treatment-related adverse events, mobility, stiffness, quality of life (mental, physical, and social), fatigue, dental manifestations, parathyroidectomy, corrective orthopedic surgeries, and auditory (hearing loss or tinnitus) were also considered important but not critical.^{51,114} The list provided for the systematic review is more exhaustive than the outcomes used in other clinical trials and practice guidelines and covers the majority of important outcomes that were identified in the present study. However, there are outcomes that the participants in the current study identified as important, that could be covered more effectively in the literature.

The findings indicate a high level of overlap when it comes to treatment with medications and exercise. However, the most significant distinction came from not what they prioritized, but the emphasis placed on the outcomes. When it came to exercise, a greater emphasis was placed on physical functioning (e.g., ability to complete ADLs) and its individual aspects, compared to pharmaceutical treatment. Many features make up physical functioning and how a person completes ADLs, but the most common aspects of physical functioning participants prioritized when talking about it was strength, mobility and fatigue – three concepts not well characterized or

tested in XLH. I hypothesize that individuals place a greater emphasis on outcomes based on the perceived potential of treatability with a given intervention. Overall, while the outcomes themselves may not significantly change, the emphasis placed by patients on different outcomes may and therefore the measured outcomes, and their priority, should change in research, especially clinical trials

There have been studies analyzing muscle function in people with XLH, but there has been no mechanism that has determined the cause of muscle weakness.^{115,116} Further, it is not considered an important outcome in the majority of clinical practice guidelines and clinical trials. Trials have used tests such as the 5XSTS, or 30-second chair stand but these tests tend to have ceiling effects and only effectively measure change in people who have more serious disability.^{64,77,116}

Mobility is better characterized in the literature as ROM has been tested to understand the effects of enthesopathies and OA, but there is little understanding or direct assessment of how XLH affects functional movements such as squats, and what aspects of XLH (i.e., general pain and stiffness, bone deformities, enthesopathies, or OA) are the direct cause to limited mobility.¹⁰ Participants in the study gave mixed answers with some describing they enjoy doing exercises such as squats and lunges, and other describing they would be unable to perform them due to a lack of mobility caused by deformities, or strength. Overall, there needs to be better characterization of the aspects of the disease that lead to functional limitations, and how they are caused. By characterizing the disease more accurately, interventions can be chosen that are targeted to the needs of the XLH population.

The participants primarily described fatigue as a lack of energy caused by overexertion that causes pain and stiffness leading them to be forced to rest and forgo any physical activities for the day or days following. Mental fatigue is also caused by the need to cope with chronic pain, and

the requirement of strategizing movement to avoid physical fatigue.^{41,43,44} The participants in the present study highlight fatigue as a priority when it comes to choosing treatments for XLH. But there is currently a lack of understanding of the cause of fatigue, making it difficult to create interventions targeting it. Burosumab has not shown to be effective at improving fatigue.¹¹⁷ Theodore-Oklotka et al. described that fatigue may be linked to a loss of sleep due to pain meaning resolving pain could help manage fatigue.⁴⁴ If there are to be interventions that treat the outcomes that are important to people with XLH, more research needs to be done to understand fatigue within patients with XLH to learn how to target and manage it.

It is important to highlight the prioritization of long-term health and well-being for individuals with XLH. While the participants sought to improve their present health, there is an awareness that their current experience may not reflect their future due to the progressive nature of XLH. Despite not being a direct health outcome, I included “slowed progression” of XLH as an important outcome because the concept was consistently mentioned without being connected to specific symptoms. When asked to explain further, participants described a range of outcomes, and thus “slowed progression” was included to highlight the importance of long-term health for people with XLH. Previous burden of disease studies have highlighted how the fear of symptoms worsening over time and the unknown future of a person with XLH adds to the psychosocial and psychological impact of living with the disease.⁴¹ The present study found that people’s primary concerns were how the disease and the progressive symptoms are going to affect their future function and ability to maintain independence. Understanding the impact and the importance of long-term health to people with XLH, longitudinal studies should be prioritized tracking the development of comorbidities such as OA and the impact that living with XLH has on physical functioning and QOL in the long-term. Currently, there are 10-year follow-up studies on the safety

and effects of burosumab being completed; understanding the long-term effects of a treatment will help patients with XLH make treatment decisions.^{118,119}

6.4 Strengths and Limitations

A strength of this study is that it represented a range of people in age and disease severity. The study had participants on high and low ends of the WOMAC and BPI-SF meaning it was able to gain an understanding of what the experience may be like for someone across the disease severity spectrum. Because XLH is a progressive disease, it is important to represent people at different levels of disability and understand how experiences may change as the disease progresses. To be able to more accurately adjust exercise recommendations it would be valuable for future research to understand and compare the experience of people with XLH at different stages in disease progression, and severity. Cheung et al. completed a qualitative study to understand the complication and symptom experiences across the course of life and how they change in different stages of life (across 8 age groups ranging from 1 year old to 60+).⁴² But for a topic such as exercise it may be more important to represent disease severity and its effect on function, rather than age.

While I went to great extents to collect rigorous and credible data using techniques such as reflectivity, peer debriefing, maintaining an accurate audit trail and reporting according to standards for reporting qualitative research, my study does not come without its limitations. I only required a self-reported diagnosis of XLH. The study had only 2 male participants compared to 15 female participants. XLH is an X-linked dominant disorder, so females are more likely to inherit it than males, resulting in a higher prevalence in females. However, the proportion of females in my sample exceeds the expected ratio.¹⁹

Nearly 50% of the sample participated in high amounts of physical activity, according to the IPAQ. Despite having a large percentage of people who participated in high amounts of

physical activity, the study had subjects who participate in low levels physical activity, and do not participate in exercise at all, which allowed for an understanding of different perspectives.

Finally, there were no questions in the survey surrounding dental manifestations, limiting the ability to analyze their impact and potentially overlooking an aspect of important outcomes.

6.5 Conclusion

The present study provides an in-depth exploration of the experiences of individuals with XLH when participating in physical activity and exercise. The results revealed a complex interplay of barriers and facilitators that shape participation. Pain, stiffness, and fatigue consistently emerged as significant obstacles leading to reduced mobility, and functional limitations. Within the framework of the COM-B model of behaviour, pain stiffness, and fatigue not only create barriers to a person's physical capability to exercise, but to their reflective motivation. Notably, while overexertion can exacerbate symptoms and discourage activity, appropriately balanced exercise—particularly walking, stretching, and strength training—was frequently reported to improve pain, stiffness, and overall physical functioning. Key facilitators identified included strategizing movement and tailoring of exercise programs to individual needs, reflecting the heterogeneity of XLH. Additional supports, such as footwear, education on body awareness, and the use of burosumab, were also found to enhance participation. However, challenges remain in accessing knowledgeable exercise providers to help tailor exercise and overcoming the mental barriers related to group activities.

Furthermore, the findings emphasize the importance of patient-centered outcome measures, with participants prioritizing improvements in, pain, fatigue, strength, mobility and physical functioning. Particularly strength, mobility and fatigue are outcomes that are not adequately addressed in existing research or clinical guidelines. Participants prioritized the outcomes in the

long-term, highlighting the importance of longitudinal studies to understand the effects of interventions over time.

In summary, insights from my study lay the groundwork for developing targeted physical activity recommendations and interventions for individuals with XLH. Addressing both the physical and psychological barriers to exercise, and ensuring that patient-important outcomes are prioritized, will be essential for improving QOL and long-term health outcomes for people with XLH.

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Appendices

Appendix A: Demographic Survey

Demographics		
What is your age? <hr/>		
What sex were you assigned on your original birth certificate? <input type="checkbox"/> Male <input type="checkbox"/> Female <input type="checkbox"/> I prefer not to say	Which option best describes the gender you currently identify as? <input type="checkbox"/> Man <input type="checkbox"/> Woman <input type="checkbox"/> Non-binary person <input type="checkbox"/> I prefer not to say	
What is your marital status? <input type="checkbox"/> Single <input type="checkbox"/> Married <input type="checkbox"/> Common Law <input type="checkbox"/> Divorced <input type="checkbox"/> Widowed <input type="checkbox"/> Other: _____ <input type="checkbox"/> I prefer not to say	What is your highest level of education? <input type="checkbox"/> Grade school <input type="checkbox"/> High School <input type="checkbox"/> College <input type="checkbox"/> University <input type="checkbox"/> Professional school (e.g. MD) <input type="checkbox"/> Graduate school (e.g. Msc or PhD) <input type="checkbox"/> Other: _____ <input type="checkbox"/> I prefer not to say	
What ethnicity/ethnicities do you identify as? <input type="checkbox"/> African American <input type="checkbox"/> Caucasian <input type="checkbox"/> East Asian <input type="checkbox"/> Hispanic <input type="checkbox"/> Indigenous <input type="checkbox"/> Middle Eastern <input type="checkbox"/> Native Hawaiian <input type="checkbox"/> South Asian <input type="checkbox"/> Other: _____ <input type="checkbox"/> I prefer not to say		
Do you use mobility aids (e.g., cane or wheel chair)? <input type="checkbox"/> Yes <input type="checkbox"/> No	If yes, which one(s)? <input type="checkbox"/> Cane <input type="checkbox"/> Walker <input type="checkbox"/> Wheel chair <input type="checkbox"/> Other: _____	If yes, how frequently? <input type="checkbox"/> Always <input type="checkbox"/> Sometimes <input type="checkbox"/> As needed

At what age were you diagnosed with X-linked hypophosphatemia? _____	What treatment are you on? <input type="checkbox"/> No treatment <input type="checkbox"/> Conventional therapy (Phosphate, calcitriol and vitamin D) <input type="checkbox"/> Burosumab (Crysvita)
Have you been diagnosed with Bowed legs (genu varum)? <input type="checkbox"/> Yes <input type="checkbox"/> No Notes: _____	Have you been diagnosed with knocked knees (genu valgum)? <input type="checkbox"/> Yes <input type="checkbox"/> No Notes: _____
Have you been diagnosed with enthesopathies (calcification of tendons or ligaments)? <input type="checkbox"/> Yes <input type="checkbox"/> No Notes: _____	Have you been diagnosed with osteoarthritis? <input type="checkbox"/> Yes <input type="checkbox"/> No Notes: _____
Have you been diagnosed with hyperparathyroidism? <input type="checkbox"/> Yes <input type="checkbox"/> No Notes: _____	Have you been diagnosed with nephrocalcinosis? <input type="checkbox"/> Yes <input type="checkbox"/> No Notes: _____

Pain Medication			
Medication Name	Dose	Frequency	Notes:

We want to record how much physical activity you do right now. What physical activities do you enjoy doing? (If you do not participate in any regular moderate to vigorous physical activities skip to the next question)

Moderate intensity activities may make you sweat and breathe a little harder. You may only be able to carry on a conversation in short sentences. It will feel a little like work to keep it up. Brisk walking (like when you are late!), an aerobics class, or raking are examples of moderate intensity activities.

Vigorous intensity activities will cause you to sweat and be out of breath. You will not be able to say more than a few words before stopping to catch your breath.

	How many days per week?	On average, how long did you do it for (in minutes)?	Total min/week
Brisk walking (no casual)			
Cycling			
Exercise class			
Running			
Swimming			
Heavy yard work			
Sports (e.g., golf, softball, curling):			
Physically demanding job (e.g., carrying objects over 25lb)			
Muscle strengthening (e.g., weights, elastic tubing)			
Other:			

Appendix B: Semi-Structured Interview Guide

1. Tell me a bit about yourself, and what it is like living with XLH on a daily basis? How does it influence the things you do? (Prompt: completing chores/errands; sleep; relationships with friends and family; community involvement; physical activity)
 - a. How would you describe your overall health and wellbeing? (Prompt: quality of life; pain; stiffness; muscle weakness; fatigue; fractures; lower limb deformities)
 - b. What aspects of XLH affect your quality of life the most? OR What challenges of living with XLH make your life more difficult or less enjoyable? How? Why?
 - c. What activities have you experienced that make you concerned or that you are fearful to do? (Prompt: lifting heavy objects; walking for long periods; running)
 - d. What things do you do to help manage your XLH symptoms? How helpful are these? Why?(Prompt: medications; massage; exercise)
 - e. When it comes to considering therapies or treatments for XLH, what is most important to you? What do you want your treatment to change, improve on, or prevent? (Prompt: pain management, mobility) **OR** Choose a magic pill to treat one thing for XLH, what would it be?
 - f. Why do you choose that – what would that help you do in your every day life?
 - g. When thinking about the progression of XLH, how do you know when your health has improved? Are there any outcomes you specifically track or pay attention to, and how do you track them?
2. In the survey you noted you had a history of fractures. Could you describe the fracture, and about the rehab/recovery process?
3. In the survey you noted a history of enthesopathies (or osteoarthritis). Could you describe any rehab or treatment you do for this?
4. Tell me about your experience doing exercise. (prompt: strength and resistance)
 - a. What, if anything, makes it difficult for you to participate in exercise? **OR** What challenges have you faced when it comes to doing exercise?
 - b. How does XLH affect your ability to exercise? (Prompt: maybe it makes you want to do more...)
 - c. (If person is active) What motivates you to be physically active?

- d. (If person is not active) What would motivate you to become more physically active? **OR** If we knew exercise could improve X symptoms, would that motivate you to exercise?
 - e. You mentioned that you are most affected by X, Y, Z symptoms, how do you feel about using exercise to improve those outcomes?
 - f. Tell me about any experiences you have had where someone, or something made physical activity easier or more accessible? (Prompt: a type of exercise; personal training/coach)
 - g. When it comes to physical activity or exercise, what do you feel you need to learn more about?
 - h. If you wanted to learn more about physical activity for people with XLH, what types of resources would help? For example, would you seek out an exercise professional, look for videos on the internet, read books?
 - i. Based on your experiences, what advice would you give to someone else with XLH who wants to exercise?
5. We are interested in understanding how we can use exercise to improve health outcomes for people with XLH, what would you want to get out of an exercise program?
- a. What do you think would help?
 - b. What things should we focus on improving?
 - c. What is most important to you?
 - d. Why is that important to you, how would that improve your daily life?
 - e. What have you found to be helpful in the past? (Prompt: strength, balance, functional, flexibility training)
6. Is there anything else you would like to share?