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Clinical Research Article

An Evidence-based Physical Therapy Prescription for Adults With X-linked Hypophosphatemia

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Abstract

Context: X-linked hypophosphatemia (XLH) is a rare and progressive metabolic phosphate-wasting disorder characterized by lifelong musculoskeletal comorbidities. Despite considerable physical disability, there are currently no disease-specific physical therapy (PT) recommendations for XLH designed to improve engagement and confidence in performing activities of daily living (ADL).

Objective: The objective of this patient-centered study was to develop an evidence-based PT program to address gaps in the management of adult XLH without imposing unintended harm.

Methods: Creation of the program was informed by a prior controlled clinical study to evaluate the physical and functional effect of XLH on adulthood, and guided by the physical presentation of participants, subjective data and patient goals acquired at intake, and by performance on multiple active range of motion (ROM) movements from the standing position. A weekly standardized interview process was used to assess progression of physical and functional abilities, gains and concerns, and to obtain timely feedback to inform future exercise modifications. Outcomes were evaluated using validated functional tools and subjective data obtained throughout the study.

Results: A remote 12-week PT program was created based on collected data. Open and closed kinetic-chain exercises were developed and implemented. Functional improvements were documented, and weekly surveys indicated improved abilities and confidence to engage in ADL. Minimal improvements were observed in active upper and lower extremity ROM, reflective of substantial bony restrictions characteristic of XLH.

Conclusion: This study represents the first disease-specific PT recommendations for XLH to mitigate the unique physical challenges of the adult disorder that can be modified to adapt to the current progression status of the adult disorder.

Key Words: X-linked hypophosphatemia, osteoarthritis, enthesopathy, functional range of motion, activities of daily living, prescription PT program

Abbreviations: 5XSTS, Five Times Sit to Stand Test; ABC, Activities-Specific Balance Confidence; ADL, activities of daily living; FGF23, fibroblast growth factor 23; HEP, home exercise program; LEFS, Lower Extremity Function Scale; OA, osteoarthritis; PT, physical therapy; ROM, range of motion; SOAP, subjective, objective, assessment and plan; TUG, Timed Up and Go Test; XLH, X-linked hypophosphatemia.

Individuals with rare diseases have the added burden of access to health care providers with expertise in care management of their condition. This includes implementation of physical therapy (PT) for patients who suffer substantial physical disability due to rare musculoskeletal disorders. A recent review of comprehensive management recommendations for X-linked hypophosphatemia (XLH) confirms that there are currently no disease-specific PT recommendations for XLH [1]. Hesitancy by physical therapists to treat patients may also be grounded by the lack of evidence-based approaches in the management of patients and unknown risk-benefits for disorders like XLH.

XLH is the most common of the phosphate-wasting disorders, arising from pathogenic variants of the *PHEX* gene that result in dysregulation of fibroblast growth factor 23 (FGF23)-mediated phosphate homeostasis and impaired 1,25-dihydroxyvitamin D production [2]. The childhood disorder presents with radiographic evidence of rickets, osteomalacia, and skeletal deformities that lead to impaired linear growth and decreased physical endurance [3]. Beyond adolescence, XLH persists as a metabolic disease with musculoskeletal comorbidities that dominate the adult clinical picture. Both the temporal pattern and scale of involvement of mineralizing enthesophytes at fibrocartilaginous insertion sites, degenerative osteoarthritis (OA), and osteophytes are magnified in the adult XLH population. In other words, they occur sooner and involve multiple sites that become radiographically evident in the early decades of life [4-6].

Generally, common subjective complaints within the adult XLH population are various in orthopedic nature but are vastly similar between patients. Consistently, they present as pain at load-bearing joints including the hips, knees, and ankles, but also at the less weight-bearing shoulder and elbow joints. Skeletal deformities arising from osteomalacia and childhood rickets contribute to an antalgic gait, and along with degenerative OA, osteophytes, and enthesophytes,

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restrict functional movements of the spine and lower extremities that are critical to ambulation. Joint disease also manifests as unsteady balance and fear of falling, along with limitations in activities of daily living (ADL) [4, 7-9].

The aim of this participant-based research study was to apply our current knowledge of the biomechanics and gait of adult patients [4], along with documented physical manifestations characteristic of adult XLH [9], with the goal of creating evidence-based recommendations for physical therapists. The program was designed to improve functional independence and engagement in ADL [4].

Materials and Methods

This study was approved by the Human Experimentation Committee/Institutional Review Board (HEC/IRB) at Quinnipiac University and informed consent obtained from the participants; the application was amended and approved for transition to a fully remote study as a consequence of COVID-19 restrictions. One male and one female adult, each with a diagnosis of XLH, were recruited to participate in this program. They had previously enrolled and completed a clinical study in our group evaluating the physical and functional effect of XLH in adults [4]. As such, comprehensive physical and functional baseline data for each individual were available, including radiographic findings detailing the extent of enthesophytes, osteophytes, and OA. Participants were provided exercise equipment and technology needed to execute the study remotely. Experimentation was overseen by a licensed physical therapist and a recognized content expert in adult XLH, who also guided medical/doctoral student coauthors.

Creation of Physical Therapy Prescription Program

Baseline demographics, diagnosis, treatment history, medication, and assistive device data were collected. Creation of the program was informed by a prior controlled clinical study to evaluate the physical and functional effect of XLH in adulthood and guided by the physical presentation of the participants (outlined in the "Physical Presentation" section) [4, 7, 9, 10]. Subjective data were acquired at intake to aid in the identification of ADL challenges and patient-centered goals. Physical performance on multiple active range of motion (ROM) movements was used to evaluate the hip, knee, ankle, shoulder, and spine from the standing position. Interventions were also informed by our prior-published key radiographical findings [4], characteristic of the chronic and progressive comorbidities of XLH [4-6].

The collective data were used to create the framework for a 12-week program of open and closed kinetic-chain exercises targeting the upper and lower body and spine and developed so it could be adapted to accommodate the existing stage of disease progression and limitations of each individual. Exercises were also modifiable to alter the exercise intensity during the program course. Owing to the considerable joint motion restriction seen in this population, only active ROM exercises were prescribed so that participants could judge their own limits.

Equipment and Treatment Schedule

Exercise equipment included common household items, 5 pairs of dumbbells (1-5 lb [0.4-2.2 kg]), resistance bands, Airex foam balance pads, and yoga balls, purchased and shipped to participants' homes.

A flowchart of the 12-week treatment schedule is shown in Figure 1. Participants were evaluated weekly by a standardized interview process to assess subjective progression regarding physical and functional abilities, gains and concerns, and to obtain timely feedback to inform future modifications. During the first 8 weeks of programming, the prescribed course of exercise was completed twice weekly under the direction and supervision of members of the research team. Participants were also provided detailed verbal and visual feedback instruction on the safe and proper technique of all exercises. They were instructed to complete and document their home exercise program (HEP) independently a third time during the same week during the first 8 weeks. Subjective, objective, assessment and plan (SOAP) notes were created for each of the 2 weekly directed prescription sessions to document individual exercises and equipment used, to track patient status, to track changes and progress related to exercises, and to formulate upcoming goals for subsequent sessions. At regular weekly intervals, informed by SOAP notes, HEPs were intensified by the addition of exercise equipment or increasing repetitions, sets, or duration of activities. In the final 4 weeks, participants completed prescribed exercise regimens 3 times weekly in the absence of directed instruction and without further exercise modification.

Functional progression was assessed using validated tools to evaluate lower-extremity function, mobility, and fall risk and compared to baseline, 4 weeks (evaluation period 1), 8 weeks (evaluation period 2), and 12 weeks (evaluation period 3). Functional measures included the Berg Balance Scale, the Timed Up and Go Test (TUG), and the Five Times Sit to Stand Test (5XSTS). The Berg Balance Scale assessed balance, with a score of 56 indicating full functional balance [11]. TUG times, with a score greater than 14 seconds, is associated with an increased fall risk and poorer mobility [12, 13]. Finally, the timed 5XSST was used as an assessment of lower limb strength, balance, and ability to perform ADL

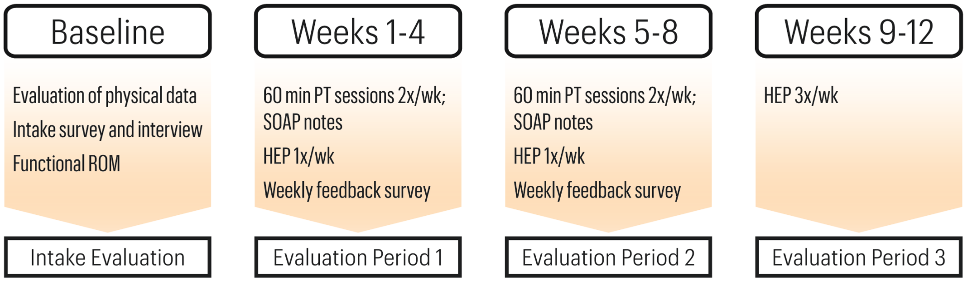

Figure 1. Flowchart diagram of study design.

Table 1. Demographics

Data	Participant A	Participant B
Age, y	65	54
Sex, assigned at birth	Female	Male
Age at diagnosis, y	3	7
PHEX mutation	Spontaneous	Inherited
Height	4 feet 9 inches/145 cm	5 feet 1 inch/155 cm
Varus or valgus knee deformity	Yes	Yes
In-toeing (internal tibial torsion)	Yes	No
Corrective surgery	No	Yes
Joint replacement surgery	No	No
Assistive device use	Cane, dressing stick, modified walk-in shower, and long-handled grabber to retrieve items	Occasional cane; shower bar, long-handled grabber to retrieve items, sock device
Treatment history, childhood	Prescription-strength vitamin D_2, calcium supplements	Prescription-strength vitamin D_2, oral phosphate supplements
Treatment history, adult	Intermittent calcitriol with and without oral phosphate salts for 3 y; burosumab phase 3, July 2016/current therapy	Calcitriol/oral phosphate salts; burosumab phase 3, July 2016/current therapy
Current pain medication	Naproxen, 1000 mg as needed	Tramadol, 50 mg as needed

Table 2. Intake survey

Question
1. Tell us what a typical day looks like for you.
2. Do you use a device to assist you with walking?
3. Do you have any adaptive equipment in your home?
4. What are some tasks you have difficulty with every day?
5. What movements are easier to complete?
6. What is something you want to be able to do in your everyday life with more ease?
7. What are your physical therapy goals?
8. How difficult is it to get in/out of bed?
9. What prevents you from walking longer distances
10. How difficult is it to get in and out of the shower?
11. How difficult is it to put on shoes/socks?
12. Do you have difficultly climbing the stairs?

[14-16]. Questionnaires, including the Lower Extremity Function Scale (LEFS) to assess lower limb function and the Activities-Specific Balance Confidence (ABC) Scale to assess balance confidence, were also administered, along with a weekly survey [17].

Results

Demographics

Two individuals enrolled in the study: participant A, a 65-year-old woman, and participant B, a 54-year-old man (Table 1), and were asked to complete an intake survey (Table 2). Both had a clinical diagnosis of XLH based on molecular identification of a *PHEX* gene pathogenic variant. Both participants had no known underlying disorders beyond XLH that precluded them from participating in the exercise prescription.

Both individuals had participated in the treatment arm of an adult clinical trial for an FGF23-blocking antibody, burosumab, from 2016 and continued therapy to date after US Food and Drug Administration approval. Assistive devices for participant A included a cane, dressing stick, a modified walk-in shower, and a long-handled grabber to retrieve items. She reported needing assistance for some activities but otherwise was able to complete household chores, limited by variable fatigue and pain. Getting into and out of a car and using stairs were identified as particular challenges, navigating a single step at a time with both feet, and descending stairs backward while rail-holding. Participant A also reported being able to better engage in activities using her hands like typing, knitting, and sewing. Participant B reported using a shower bar, long-handled grabber to retrieve items, and a device to put on socks. He had previously used a cane but at the time of intake reported using it only for longer excursions or if unfamiliar with the terrain. He also reported difficulty with stairs, navigating a single step at a time with both feet, and being limited by fatigue and pain when engaging in ADL. Similarly, participant B reported being able to engage in ADL in moderation. Both reported difficulties getting in or out of bed and had created multiple self-modifications to adapt to ADL. Both participants also expressed a considerable fear of falling and inability to confidently navigate some activities for fear of falling population [10]. Both had prior sought physical therapy care and reported that therapists were not familiar with XLH, nor had direct access to additional clinical information on best practices for treatment. Both individuals also reported that previous PT progress was, in part, evaluated on goniometric gains in joint angles (contraindicated in this population). Participant A subjectively stated the experience was exceptionally negative and painful and did not follow up with additional PT. Participant B reported receiving PT annually during childhood and intermittently in adulthood, with exercises that targeted physical limitations. He was also fitted with an orthotic shoe insert as an adult to correct leg length discrepancy. In addition, the intake survey revealed that both individuals shared similar goals with the desire to improve deficits in strength and balance, to increase available ROM when performing tasks, and to increase confidence when engaging in ADL.

Prior to transitioning to a fully remote model, active and passive goniometric joint angles were solely obtained from participant B (Table 3). Functional restrictions were visually assessed by PT remotely in both participants at intake (Table 4) and, informed by key radiographical findings of the 2 test individuals summarized in our prior publication [4], were determined to be characteristic of the chronic and progressive comorbidities of XLH [4-6]. The assessments included in Table 4 were performed only at each evaluation period and were not exercises included in the PT program.

Physical Presentation

In general, the physical presentations were similar but more progressed in participant A, who was 10 years older than participant B. At intake, both individuals presented with limited active ROM of the spine with lumbar hypolordosis, thoracic kyphosis, and significant restriction of cervical spine extension, a consequence of near-total fusion at all spinal levels due to enthesophytes. Both displayed cervical flexion that was more pronounced in participant A, likely due to nuchal ligament calcification.

The upper body presentation of participants A and B were also consistent with the functional assessment of shoulder ROM and with documented radiological findings of the individuals [4]. Bilateral enthesophytes of the acromioclavicular joint and bilateral osteophytes of the glenohumeral joint likely contributed to the observed limited active flexion of the shoulder. Restriction is also affected by calcification of the triceps brachii insertion at the humeral head. While shoulder restriction and radiological findings were similar between the individuals, participant B generally presented with a wider range of active movement by approximately 20 to 25° in bilateral shoulder flexion, and right shoulder abduction. Relative to the right shoulder, participant B had a wider ROM of approximately 40° in left shoulder abduction relative to participant A. In addition, shoulder flexion and abduction were limited by pain at the end ROM for both participants A and B.

Substantial restriction of lower body joints was also observed in both individuals, again with severity relatively greater in participant A. No objective measures of hip extension could be made from standing positions. However, active hip extension (noted on gait) and flexion (noted on gait and functional assessment; see Table 4) were likely limited by lesser and greater trochanter insertion calcification. Enthesophyte formation of the insertion of the iliopsoas at the lesser trochanter in both individuals also likely contributed to a deficit in hip extension past the neutral angle [4]. Together these limitations also contributed to observational gait abnormalities including flexed posture and waddling gait, as previously reported by gait kinematics [4].

Knee flexion limitations were noted in the participants because of varus deformities, along with degenerative joint disease and patellar insertion enthesophytes [4]. Knee flexion

Table 3. Goniometric range of motion angles, participant B

Hip, deg	Position	Active, deg	Passive, deg
Hip flexion right, left	Supine	80; 100	108; 115
Hip extension right, left	Prone	15 lag;18 lag	10 lag; 16 lag
Hip abduction right, left	Supine	5; 4	8; 2
Hip adduction right, left	Supine	10; 5	15; 12
Hip internal rotation right, left	Seated	5; 0	6; 0
Hip external rotation right, left	Seated	20; 23	25; 30
Knee, deg		**Active**, deg	**Passive**, deg
Knee flexion right; left	Supine	138; 135	148; 145
Knee extension right; left	Supine	10 lag; 25 lag	5 lag; 18 lag
Ankle, deg		**Active**, deg	**Passive**, deg
Ankle dorsiflexion right, left	Supine	5; 2	5; 4
Ankle plantarflexion right, left	Supine	55; 45	58; 60
Ankle inversion right, left	Supine	40; 36	55; 45
Ankle eversion right, left	Supine	20; 20	25; 22
Shoulder, deg		**Active**, deg	**Passive**, deg
Shoulder flexion right, left	Standing	135; 150	150; 175
Shoulder abduction right, left	Supine	120; 125	145; 158
Shoulder internal rotation right, left	Supine	35; 65	40; 70
Shoulder external rotation right, left	Supine	110; 100	125; 105
Spine, deg		**Active**, deg	**Passive**, deg
Cervical spine flexion	Supine	20	25
Cervical spine extension	Supine	22	28
Cervical spine rotation right, left	Supine	55; 60	65; 65
Cervical spine lateral flexion right, left	Supine	15; 15	18; 20
Lumbar flexion	Standing	85	N/A
Lumbar extension	Standing	5	N/A
Thoracic rotation right, left	Sitting	45; 55	N/A

Abbreviations: deg, degree; N/A, not available.

Table 4. Remote functional range of motion assessment

Hip	Assessment
Hip flexion right, left	Asked to go into deepest squat
Knee	**Assessment**
Knee flexion right, left	Asked to go into deepest squat
Ankle	**Assessment**
Ankle dorsiflexion right, left	Asked to go into deepest squat
Shoulder	**Assessment**
Shoulder flexion right, left	Reach overhead in sagittal plane to highest height
Shoulder abduction right, left	Reach overhead in coronal plane to highest height
Shoulder internal rotation right, left	Reach behind lower back and reach up back to furthest point
Shoulder external rotation right, left	Reach behind head down neck to furthest point
Spine	**Assessment**
Lumbar flexion	Bend forward at waist reaching toward ground, recorded distance from fingertip to floor
Lumbar extension	Hands on hips bend backward
Thoracic rotation right; left	Seated arms crossed in front of body, recorded amount of rotation of midpoint body

at intake for both were well under the 90 to 120° of functional ROM, although participant A had a deficit of approximately 40° in right knee flexion and 20° in left knee flexion, compared to participant B. Participant A subjectively reported chronic instability of the right knee, despite bilateral knee similarities [4]. Knee extension angles could not be evaluated remotely; however, in-person goniometric measurements of participant B revealed a lack of full knee extension (see Table 3).

The resulting program, created to address patient goals while accommodating physical findings, is summarized in Table 5, including modifications where noted. Accompanying PT exercise demonstrations for providers are available in an online repository [18].

Both participants successfully completed the 12-week program and had minimal difficulty in performing the exercises and maneuvers, which were progressively modified contingent on their respective ability level and physical capability. Critically, owing to the restrictive physical barriers for joint motion, significant gains in passive ROM were not an explicit goal of this study as this may impose unintentional and irreversible harm to the patient, especially in patients with spinal calcifications and stenosis [6].

Physical Therapy Exercises

Lower-body exercises

A number of resistance and nonresistance open- and closed-chain exercises were used to target the hip, knee, ankle, and spine, employing modifications where noted (see Table 5). Lower-extremity stretches were conducted in the supine, seated, and standing positions. Strength exercises included seated and standing toe and heel raises, mini-squats, along with sit-to-stand activities. Balance promotion activities included lateral standing movements, various walking/marching activities along with Romberg, tandem, and single-leg balance activities. Participant A variably performed lower limb exercises such as lunge and mini-squats due to right knee pain.

Upper-body/spine exercises

Shoulder/scapular functional mobility and stability were targeted using open- and closed-chain exercises (see Table 5). This included standing scapular stabilization exercises, standing anterior stretch mobilizations, glenoid humeral, and rotator cuff–stabilizing exercises. Pain arising from the olecranon process enthesophytes was targeted with weighted bicep curls and tricep extensions. These exercises also functioned as an adjunct to improve reach, bracing ability, and ability to lift loads.

Balance exercises

To improve balance and confidence and to diminish fear of falling, exercises consisting of activities targeting the lower extremity, hip stability, and proprioception were employed. These included standing with legs together with eyes open and closed, single-leg stance, and tandem and modified tandem stance exercises, with and without an Airex pad (see Table 5).

Outcomes

Weekly assessments of the participants' program occurred weekly during weeks 1 to 8, and at the final twelfth week, and revealed excellent adherence to the program and to goals (Supplementary Table S1) [19]. Guided by SOAP notes and weekly subjective feedback, participants were encouraged and able to increase the complexity and exercise intensity at regular intervals. Participant A did not complete incremental increases in lower-extremity exercises that targeted the right knee. No injuries were reported or observed; however, symptoms such as soreness are common in PT as the exercises progress and become more challenging.

Weekly subjective progress was obtained during weeks 1 to 8, and at the final twelfth week, and revealed improvements in both individuals (Table 6). Participant B had greater gains than participant A across all domains measured. It was also noted that both participants had variable energy and pain levels during different evaluation days that affected weekly assessments. Perceived energy levels by participant A correlated with burosumab treatment.

Weekly longitudinal interview data revealed subjective improvement in confidence level, agility, functional ability, and lessened pain (see Table 6). Both participants routinely reported improved confidence when engaged in activities that had previously caused fear and hesitation. For instance,

Table 5. Physical therapy program

Exercise	Itemized exercise	Description	Purpose; sets; repetitions	Modification
Balance progression	Romberg	Stand facing forward with feet together (eyes open/ closed)	To assist in improving balance; hold each position for 20 s; wk 1-12	Use an Airex (Airex, Sins, Switzerland) pad to increase difficulty, hold each position for a longer duration of time
	Modified tandem stance	Stand with one foot forward and one foot back		
	Tandem stance	Stand facing forward with one foot directly in front of other		
	Single-leg stance	Stand on one leg		
Step-ups	Forward step-ups	Stand facing step, alternate using left and right leg to climb step	To strengthen hip and leg muscles, and assist in stair-climbing; 1 set of 10 repetitions per leg; wk 3-12	Increase height of step, or carry handheld weights
	Lateral step-ups	Stand with step to left or right, use left or right leg to climb step		
Heel raises	N/A	Stand with feet together, go on tip-toes, and slowly relax	To strengthen lower leg and ankle muscles, improve balance, and increase height of reach; 2 sets of 10 repetitions; wk 1-12	May use chair for assistance, single-leg heel raises, may carry handheld weights
Lateral walks	N/A	Keep hands near chest, bend knees slightly, and side-step walk with slow and controlled movements	To improve lateral hip stability for balance and walking and change-of-direction movement patterns; 3 times across room and back; wk 2-12	Hold resistance band tied to stationary object, walking away from object increases resistance band tension
Scapular retractions	N/A	Stand or sit as tall as possible, place elbows by side, and pinch shoulder blades together to feel muscles of back working	To improve rounded, forward shoulder posture by increasing strength of shoulder musculature; 1 set of 10 repetitions; wk 4-12	A resistance band may be tied to a stationary object, hold ends of resistance band and perform exercise as described
Mini squats	Assisted mini-squats	While holding on to stationary object for support (eg, backrest of chair), squat so knees are partially bent, slowly stand back up, ensuring back is completely straight	To improve hip and knee motion and strength, and assist with standing from a seated position; 1 set of 10 repetitions; wk 1-12	Use a yoga ball between back and sturdy wall, squat to comfortable depth and slowly stand up again
	Sit-to-stand	Stand up from seated position without using hands		
Ball roll-outs	Ball roll-outs	Sit at edge of chair with yoga ball in front, bend forward, and use hands to roll ball forward and backward in a controlled motion; may also roll ball to the left or right	To improve hip and trunk motion, assist with forward momentum to help with standing up from a seated position; while reaching out, lift bottom off chair at end of motion; 1 set of 10 repetitions; wk 1-12	While reaching out, lift bottom off chair at end of motion
	Modified ball roll-outs	Sit at edge of chair in front of low table, bend forward and slide hands forward, left, or right along surface of table and back		
Modified golfer's pickup	N/A	Place object on elevated surface (eg, stool), face object, and keep left hand on a stable surface for support, swing left leg back so toes are touching floor and reach down to grab object; repeat on right side	To improve ability to pick objects from floor and improve balance and stability; 1 set of 10 repetitions per leg; wk 7-12	Lift leg off floor completely, place object on floor or lower surface, change object size and weight as tolerated

Table 5. Continued

Exercise	Itemized exercise	Description	Purpose; sets; repetitions	Modification
Hamstring stretch	Seated hamstring stretch	Stay seated, place leg on stool directly in front, lean forward until stretch is felt in back of upper leg	To stretch muscles of back of upper leg to improve hip motion, length of step while walking, and ability to pick up objects from floor; hold stretch for 10 s for 1 set of 10 repetitions per leg; wk 1-12	
	Seated hamstring stretch with strap	Stay seated, place stretching strap around ball of foot, hold ends of strap with either hand, and pull back until stretch is felt in back of upper leg		
	Supine hamstring stretch	Laying down, place stretching strap around ball of foot and lift leg towards ceiling until stretch is felt in back of upper leg		
	Walking hamstring stretch	Stand and step forward with toes pointed upward, bend hip and reach down until stretch is felt in back of upper leg; step forward with other leg and repeat		
Doorway stretch	Medium arm position	Standing in doorway, place hands and elbows on either side of frame, place one leg in front and step forward until stretch is felt in chest muscles	To stretch front of chest to improve rounded, forward posture; perform 3 times, holding stretch for 30 seconds; wk 6-12	
	Low arm position	Standing in doorway, place hands on either side of frame at hip level, place one leg in front and lean forward until stretch is felt in chest muscles		
Hamstring strengthening	Standing hamstring curls	Standing in front of stable support object (eg, chair), bend knee and lift heel backward while keeping knees in line with each other	To strengthen back of upper leg to assist in uphill propulsion, climbing stairs, and performance of sit-to-stands; 1 set of 10 repetitions/each leg; wk 1-12	
	Seated hamstring curls	Sit at edge of chair, place towel under heel of one foot and slide towel forward and backward across ground		
Shoulder stretch and strengthening	Wall washes	Slide towel up and down wall (eg, washing motion) to point of discomfort, making sure not to push past point of discomfort; pause at end of motion for 1 set of 10 repetitions	To improve shoulder motion and strength to improve overhead functional activities; 1 set of 10 repetitions; wk 3-12	Use small ball instead of towel
	Scarecrows	Start with arms at side and thumbs pointed forward, bring arms forward and upward as far as tolerable for 1 set of 10 repetitions		If too difficult, place elbows out to side with palms facing back, rotate arms so palms face forward (with elbows stationary), and reach overhead with palms facing forward; slowly bring arms down in reverse pattern; may add handheld weights to increase difficulty

Abbreviation: N/A, not available.

participant B, who was initially wary of performing heavy lifting, was able to lift and transfer heavy items toward the end of the program. Participant A reported feeling more comfortable with walking around rough terrain and both were more comfortable in their ability to balance and maneuver on uneven ground. Interviews also revealed that both individuals felt better changing direction while walking, and were able to reach lower to the ground with decreased pain. Participant B

Table 6. Participants' weekly progress report

Wk 1. Have you noticed any changes you perceive as being a result of the PT program?	Participant A	Participant B
a. Strength	No change	No change
b. Balance	Tandem stance, can hold position for one minute rather than 30 s (R leg forward/L leg forward). Still feels instability in R knee	Balance seems better, was able to catch himself after tripping over a rock while carrying buckets of mulch
c. ROM	No change from prior week	Notices hamstrings are not as tense during exercises
d. Energy	Noted that energy levels fluctuate (improve) with burosumab therapy	Energy levels low in morning, increase with activity
e. Change in frequency of taking pain meds	No change from prior week	No change from prior week
Wk 2. Have you noticed any changes you perceive as being a result of the PT program?	**Participant A**	**Participant B**
a. Strength	No change from prior week	Worked sawmill for first time, easier to do than expected
b. Balance	May be better, feels more stable on her feet; fear of falling still present, no change from prior week in usage of cane	Fear of falling is slightly less, increased confidence in performing PT exercises
c. ROM	No change from prior week	Morning stiffness, ROM improves with activity
d. Energy	Low	Lack of energy in morning, improves with activity
e. Change in frequency of taking pain meds	No change from prior week	No change from prior week
Wk 3. Have you noticed any changes you perceive as being a result of the PT program?	**Participant A**	**Participant B**
a. Strength	No change from prior week	Increased stamina, trying new physical activities (eg, lifting bags, helping parents)
b. Balance	No change from prior week	No change from prior week
c. ROM	Notices that stride lengths are longer	Notices easier to reach to ground without shoes
d. Energy	Low	No change from prior week
e. Change in frequency of taking pain meds	No change from prior week	No change from prior week
Wk 4. Have you noticed any changes you perceive as being a result of the PT program?	**Participant A**	**Participant B**
a. Strength	It was easier carrying cat carrier + cat (~ 20 lb [9 kg]) to car	No change from prior week
b. Balance	Noticed improvement while doing yardwork. She can catch her balance better during activity. Fear of falling is still present (somewhat ingrained at this point)	More at ease when walking on rough or uneven surfaces
c. ROM	Joints tend to "creak and crack" during exercises, but now "creaks and cracks" less during normal activities; notices less joint pain	Continued minor subjective improvements
d. Energy	Low	Some increased energy in afternoon
e. Change in frequency of taking pain meds	No change from prior week	No change from prior week
Wk 5. Have you noticed any changes you perceive as being a result of the PT program?	**Participant A**	**Participant B**
a. Strength	No change from prior week	Minor improvements
b. Balance	Easier to use Airex pad	Continued improvement
c. ROM	Able to reach lower to ground	No change from prior week
d. Energy	Better, reported receiving burosumab therapy	Less fatigue, able to sustain physical activity
e. Change in frequency of taking pain meds	No change from prior week	No change from prior week

Table 6. Continued

Wk 6. Have you noticed any changes you perceive as being a result of the PT program?	**Participant A**	**Participant B**
a. Strength	No change from prior week	More confidence in performance of physical tasks, increased strength
b. Balance	Able to catch balance when walking on uneven surfaces, still cautious of falling	Improved ability to change direction while walking
c. ROM	Feels ROM is increased due to decreased pain, states that bony changes are now limiting ROM	Turning, twisting trunk and reaching is better, continued difficulty with bending over
d. Energy	Good	No change from prior week (continued morning stiffness)
e. Change in frequency of taking pain meds	No change from prior week	No change from prior week
Wk 7. Have you noticed any changes you perceive as being a result of the PT program?	**Participant A**	**Participant B**
a. Strength	No change from prior week	More confidence in lifting heavier objects
b. Balance	No change from prior week	Able to balance with feet farther apart
c. ROM	No change from prior week	More flexibility in performance of tasks (ie, helping cousin do construction work outdoors)
d. Energy	Low	More stamina
e. Change in frequency of taking pain meds	No change from prior week	No change from prior week
Wk 8. Have you noticed any changes you perceive as being a result of the PT program?	**Participant A**	**Participant B**
a. Strength	No change from prior week	Able to carry heavier loads, increased confidence
b. Balance	Able to catch her balance while weed whacking; states that she would not have been able to do this prior to starting PT program	Improved overall
c. ROM	No change from prior week	Overall improved, shoulder not as sore after activity, leg muscles feel more limber, increased mobility
d. Energy	Improved, reported burosumab treatment	Performance of exercises in morning help with morning stiffness, help get him going for the day
e. Change in frequency of taking pain meds	No change from prior week	Reduced intake of tramadol (2 pills/wk) for past few weeks
Wk 12. Have you noticed any changes you perceive as being a result of the PT program	**Participant A**	**Participant B**
a. Strength	Able to use heavier weights during PT exercises	Improved
b. Balance	No change from prior week	No major changes from wk 8, walking on uneven ground is easier, confidence when walking on a dock in the dark
c. ROM	No change from prior week	Able to pick up items on floor better
d. Energy	Low	Continued morning stiffness
e. Change in frequency of taking pain meds	No change from prior week	No change from prior week
Do you find it easier or harder to complete any tasks that were normally difficult to complete (eg, picking up something off floor, reaching to grab objects overhead, etc)?	**Participant A**	**Participant B**
Wk 1	No change	No change
Wk 2	No change from prior week	No change from prior week
Wk 3	Reaching up to grab is easier, can reach further	Can get on tip-toes easier to reach items overhead, easier to take socks off

Table 6. Continued

Do you find it easier or harder to complete any tasks that were normally difficult to complete (eg, picking up something off floor, reaching to grab objects overhead, etc)?	Participant A	Participant B
Wk 4	No change from prior week	Picking up objects from floor is somewhat easier
Wk 5	Can reach lower, can touch cat's litterbox, able to get into car better	Able to reach ground without shoes
Wk 6	Moving and reaching hurts less 8/10 before, now 6-7/10	Various tasks feel easier to complete (eg, cleaning closet, going up and down a stool)
Wk 7	No change from prior week	No change from prior week
Wk 8	Reaching down better w/ less pain. Biggest change overall is balance and stability; feels comfortable performing exercises independently	Reaching overhead is easier, reaching floor is hard; biggest overall change is confidence and ability to walk with more stability and agility
Wk 12	No change from prior week	Able to reach up and grab a box from a shelf with good balance

Abbreviations: L, left; PT, physical therapy; R, right; ROM, range of motion.

reported reduced as-needed intake of pain medication from an average of 3 times a week to once or twice a week toward the conclusion of the study.

Functional assessments

Progressive improvement in functional assessments from baseline values were demonstrated in both participants in balance, balance confidence, fall risk, and mobility measured at the 4-, 8-, and 12-week study period (Fig. 2; evaluation periods 1, 2, and 3, respectively). Data are reported as participant A and B. TUG test times decreased by 2.8 and 4.32 seconds, respectively. Reductions were similarly observed in the 5XSTS by 8.4 and 2.4 seconds, respectively. Of note, participant A used the arm rest at each time point from a seated position because of an inability to stand without support. Berg scores improved by 6 and 9 points and LEFS scores improved for both individuals, by 8 and 12 points, respectively. Participant A had a decline in the LEFS score second evaluation period 2 due to a self-reported flair of chronic right knee pain. Both participants also gained a 17- and 19.5-percentage point increase in respective ABC scores. Because these functional assessments are objective and validated tools, the measured results are clinically significant.

Discussion

Effective and impactful treatment of a lifelong musculoskeletal disorder requires a multidisciplinary and interprofessional health care team to address both treatment and management, including PT [1, 10]. A translational study was developed using a multipronged approach to assess the potential benefit and efficacy of a PT program that specifically addresses the progressive physical and functional limitations common to the affected adult XLH population. While this included remote evaluation of functional ROM, goniometric joint angles can be measured in person at intake to evaluate current patient status. Nonetheless, a standard assessment, that is, visual assessment by a physical therapist, confirmed that joint restriction patterns were consistent with adult XLH presentation [4, 8-10]. Because the primary comorbid features in adults are progressive and irreversible, outcome goals did not, and should not, include gains in full ROM not limited by pain. Rather, the goals of this study targeting the trunk and upper and lower body included lessening pain-provoking motions, which can result in gains in ROM by increasing proximal strength gains and improved mobility of the surrounding joint tissue within the functional range and with greater neuromuscular control.

Upper-extremity restriction is typical of advanced XLH due to the bony changes described and translate into a number of functional limitations involving movement of the shoulder joint in all planes, including reaching overhead, toward the ground, and personal hygiene and grooming activities [20]. Limitations are also exacerbated by involvement of the elbow and hand joints [4]. Both participants exhibited OA at these joints, and although participant A also had involvement of the trapeziometacarpal joint and prominent digit enthesophytes, she reported being more able to perform ADL related to the isolated hand.

Addressing balance and fear of falling were important features of the program. In addition to the physical features contributing to balance, kyphosis secondary to spinal enthesopathy also contributed to the slouching posture of both individuals. Functionally, the vertebral enthesopathy mimics an ankylosing spondylitis, characterized by pain, stiffness, and a forward shift from the center of gravity with a resultant sense of imbalance [21]. Performance of single-leg stand, tandem stance, and other exercises with and without an Airex pad were used to improve balance. Exercises targeting balance resulted in improvements in both participants, reflected in Berg Balance and ABC Scale scores. Both individuals also noted improvement in their ability to perform exercises targeting the shoulder/scapular-humeral region as the program progressed, although trapeziometacarpal A had

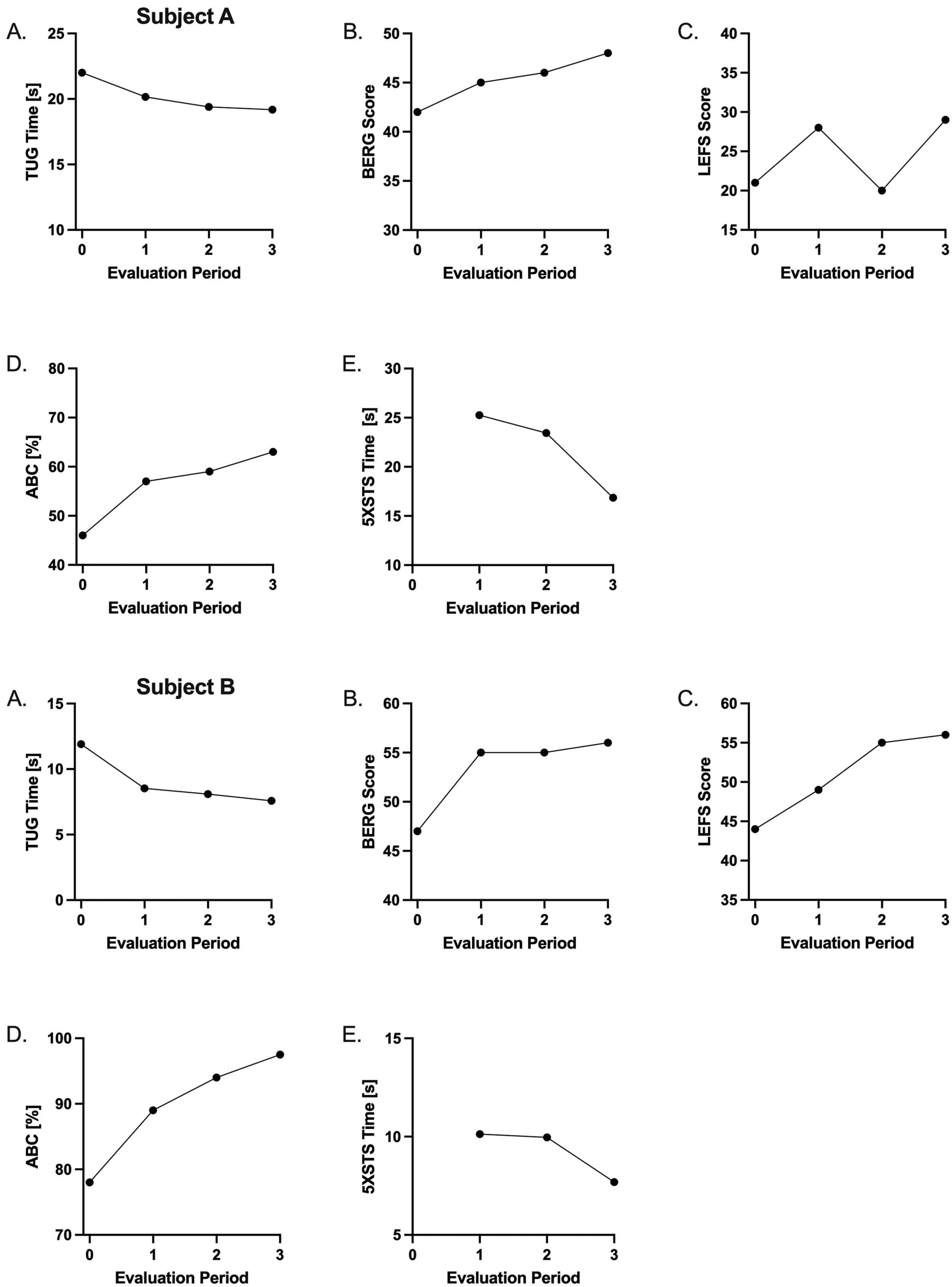

Figure 2. Functional assessments taken during intake period and evaluation periods 1, 2, and 3 for participant A top panels, and participant B, bottom panels, respectively. Results illustrate overall trends for A, Timed Up and Go Test (TUG); B, Berg; C, Lower Extremity Function Scales (LEFS); D, Activities-Specific Balance Confidence (ABC); and E, Five Times Sit to Stand Test (5XSTS) assessments. Baseline 5XSTS values at intake were not obtained.

some difficulty performing standing doorway stretches and Ys and Ts exercises because of greater shoulder restriction. Exercises targeting the shoulders to improve alignment of the head with the vertical body axis served to improve center of gravity and sense of balance. Another important function of the major upper-extremity joints is their role in breaking falls.

Both participants reported feeling more confident in settings conducive to falls. Because of the significant fear of falling [10], strengthening and improving shoulder and elbow function may contribute to increased confidence in performing ADL and decreased hesitation in completing activities that involve maintaining balance. In addition, hearing loss and tinnitus may be present in the XLH population and should be considered when assessing balance [1, 6, 9]. Together, a program that combines other fall-prevention initiatives including STEADI and FPIPTP algorithms, optimizes interprofessional solutions to fall risk assessment and prevention within the XLH population [22, 23].

Lower-extremity and trunk radiological findings were similar between the participants. Owing to these progressive changes, individuals with XLH often score low on lower-extremity functional measures, and also bear the burden of fracture history, which substantially contributes to the prototypical waddling gait of XLH [4, 7, 9]. In addition, spinal syndesmophytes, enthesophytes, and fusion of vertebral bodies result in decreased cervical and lumbar ROM and causes a forward-leaning displacement of posture from the center of gravity, contributing to imbalance [21], increased fear of falling, and decreased confidence [10].

Both participants were unable to reach the ground at the start of this study. This was due to combined fear of falling and physical manifestations of the disease. This includes an altered center of gravity and impaired hip and knee flexion, and ankle dorsiflexion secondary to significant enthesopathy of the calcaneal tendon. The practical consequence of these findings result in requirement of the use of adaptive equipment including grabbers, shoe horns, and other specialized devices to perform activities like putting on shoes, picking up items from the floor, and lower-limb care (eg, bathing and cutting toenails). Although targeting these functional limitations by PT would produce little significant effect on ROM values for lower extremities because of the pathological manifestations of the disease, both participants provided subjective feedback that they were able to better perform tasks associated with reaching toward the ground. It is possible that the participants gained greater functional control over movement and were able to learn proper squat form to maximize reach.

Kinematic gait analysis was not amenable to this remote model. However, improved ambulatory function could be seen and deduced from the improved TUG scores and movement patterns observed as well as improved subjective description of better balance and walking control. Importantly, consultation with occupational therapy as part of the interprofessional health care team is an important consideration to assess the built environment and use of adaptive equipment [10].

This study also represents the first of its kind, showing that telehealth PT provides multiple benefits to patients including ease of access in keeping and attending appointments and allowing HEPs for those with limited access to a PT facility [24]. Patient satisfaction in those receiving telehealth PT has also been shown to be comparable to satisfaction in those receiving in-person PT [25]. It is likely that telehealth PT will remain as a mode of delivery. However, telehealth PT is not without its limitations. Although participants were able to perform exercises with proper form and receive real-time feedback and input regarding correction of form, goniometric measurement of joint angles could not be accurately assessed remotely throughout the study. Safety in this population with a remote HEP must also be regarded. It was necessary to proceed cautiously during the program because of the increased likelihood of injury due to improper exercise technique or falls. To decrease risk of the latter, participants kept a stationary object within reach. Next, exercises were modified depending on each participant's pain level and physical ability. This was also likely the cause of mild deviations noted in the weekly HEPs.

Limitations

Limitations of this study, not related to the remote nature of this study, were that the adult study participants may not be representative of all patients. As with many rare disorders, there is a phenotypic spectrum within the population. In this proof-of-principle study, the sample size of 2 adults may not completely represent this spectrum. While biomechanical characteristics of this population are remarkably homogeneous, both participants who were enrolled in this study display a common phenotype, based on prior studies [4, 7, 9]. Regardless, the progressive nature of the musculoskeletal comorbidities of the disorder in adults infers that the program would require modification in more mild cases or as the disease progresses. In this study, both participants had significant radiographic similarities, but different levels of progression and function. Regardless, we were able to demonstrate gains across this spectrum. Continued data collection to assess maintenance of these gains will inform future studies.

Owing to the remote nature of this PT study, many of the data were subjective in nature, including information gathered during weekly interviews. As a consequence, study results may be influenced by participant bias. We have attempted to minimize the effect of this by including several validated functional assessments that are widely accepted as objective measures by all major US insurance carriers, including Medicare. We believe that the validity of these subjective reports is supported by the accordant trends seen in these objective studies.

Finally, the effect of newer therapies like the FGF23-neutralizing monoclonal antibody burosumab has been demonstrated in the adult population with significant improvement in biochemical values, fracture-healing, and reported improvements in pain, stiffness, and physical function [26-28]. However, the efficacy of this therapy on the progressive comorbidities outlined in this study from childhood have not yet been determined in humans. Based on the cellular and molecular findings conducted in murine studies, the development of these disorders is unique to phosphate-wasting, occurs early in life, and is progressive [5, 29, 30]. As the drug is fully approved for patients aged 1 year or older and has been shown to be effective in treating rickets, osteomalacia, and skeletal deformities [26-28, 31-33], the real possibility exists that the sequalae of events that lead to the progressive physical disabilities of adult XLH will be reduced. In the interim, there is a real need to make available interventions to improve the quality of life for these individuals. Moreover, burosumab is a costly therapy that is not currently universally available to all adults with XLH—which underlies the need for an intervention, like PT, that may be made widely available and provides a follow-up independent HEP. This program provides patients an opportunity to improve their proprioception, balance, strength, and confidence while engaging in physical activities. Increased use of telehealth under the guidance of a trained professional may assist in helping treatment reach those who may lack access.

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Disclosures

The authors have nothing to disclose.

Data Availability

Some data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request. Accompanying PT exercise demonstrations for providers and supplemental figure are cited and available in an online repository.

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