Physical function and physical activity in adults with X-linked hypophosphatemia

G. Orlando[1] · J. Bubbear[2] · S. Clarke[3] · R. Keen[2] · M. Roy[3] · A. Anilkumar[3] · M. Schini[4] · J. S. Walsh[4] · M. K. Javaid[5] · A. Ireland

Abstract

Summary We described physical function and activity in UK adults with X-linked hypophosphatemia (XLH). Our data indicate that low physical activity and impaired mobility are common in adults with XLH. Deficits in lower limbs muscle power and functional capacity contribute to the loss of physical function in adults with XLH.

Introduction There is a dearth of literature on physical function and physical activity in adults with X-linked hypophos-phatemia (XLH). We described muscle strength and power, functional capacity, mobility and physical activity level and explored the relationships among these variables in adults with XLH.

Methods Participants were recruited as part of a UK-based prospective cohort study, the RUDY Study. They underwent a clinical visit and physical examination, including assessment of handgrip strength, jump power (mechanography), six-minute walk test (6MWT) and short physical performance battery (SPPB), and completed the International Physical Activity Questionnaire (IPAQ). Performance data were analysed using parametric and non-parametric tests, whereas correlations were assessed by univariate analysis.

Results Twenty-six adults with XLH (50% males) with a mean age of 44 ± 16.1 years were recruited. Jump power and 6MWT distances ($p < 0.0001$) were 54.4% and 38.6% lower respectively in individuals with XLH compared with normative values. These deficits were not associated with age or sex. Handgrip strength values were similar to expected values. Deficits in muscle power were more pronounced than those reported at 6MWT ($p < 0.0001$). Univariate analysis revealed only a cor-relation between total physical activity and muscle power ($r = 0.545$, $p = 0.019$).

Conclusions Adults with XLH have a marked deficit in lower limb muscle power and a reduced functional capacity, with a high incidence of impaired mobility and inactivity. In addition to metabolic effects of XLH, low physical activity may contribute to deficits in lower limb power. Further studies are required to develop novel treatment approaches to improve physical function and mobility.

Keywords Musculoskeletal function · Physical activity and disability · X-linked hypophosphatemia

Introduction

X-linked hypophosphatemia (XLH) is an hereditary skeletal disorder occurring in approximately 1 in 20,000 births [1]. This condition is the most common form of heritable hypophosphatemic rickets worldwide, and as an X-linked-dominant genetic disorder is twice as common in females than males [2]. Whilst skeletal deformities and fractures are recognised as key clinical consequences of this disorder in adults, XLH is also associated with reduced physical function and mobility, which contribute to impaired quality of life [3]. The magnitudes of these functional deficits appear comparable with those documented for other rare bone diseases, including osteogenesis imperfecta [4, 5].

XLH is caused by a mutation in the PHEX gene, leading to an excessive circulating level of fibroblast growth factor 23 (FGF-23). Consequently, patients display renal phosphate wasting and impaired renal production of 1,25-dihydroxyvitamin D (1,25-(OH)2-D)[1]. The main skeletal manifestations include rickets, growth retardation and deformities that develop during childhood, and osteomalacia-related fractures or pseudo-fractures, degenerative osteoarthritis, enthesopathy, dental anomalies and hearing loss during adulthood [6].

These manifestations are accompanied by debilitating symptomatology, which can be particularly severe in adults [3]. Symptoms may include bone and joint pain as well as stiffness and fatigue, which contribute not only to impaired physical function but also predispose to psychological distress [3, 7]. Moreover, adults with XLH often have marked limitations in joint mobility and present with lower neuromuscular performance and muscle volume at the calf muscles [8, 9]. Recent evidence also reports complex biomechanical alterations of the lower limb, leading to an impaired gait pattern (i.e. waddling gait) associated with unsteadiness. Adults with XLH are thus also predisposed to a high risk of falling [9].

At present, there is a dearth of information about the impact of XLH on neuromuscular performance in adults, with only one study exploring lower body muscle power [8]. Thus, questions remain as to whether neuromuscular deficits are confined to the lower limbs or are present in other regions. In addition, how other aspects of physical function such as functional capacity, mobility and physical activity level are affected and the interrelationships between these variables remain unexplored. Furthermore, whilst there is no clinical evidence of any differences in the impact of XLH physical function by sex or age, this has not previously been confirmed quantitatively.

Therefore, the purpose of this study was to assess physical activity level and multiple components of physical function, namely upper and lower body strength, functional capacity and mobility as well as explore the relationship between these variables in adults with XLH in the UK. We hypothesised that adults with XLH would present with lower functional capacity, impaired mobility, lower levels of physical activity and poorer muscle strength and power in the upper and lower body when compared with age- and sex-matched reference values. We also hypothesised that these deficits would be independent of sex and age and strongly correlated with physical activity levels.

Methods

Participants

Twenty-six adults with XLH were identified across four UK hospitals and recruited as part of the Rare and Undiagnosed Diseases Study (RUDY). Patients were all individuals scheduled to subsequently receive burosumab treatment as part of an Early Access Programme supported by the drug manufacturer Kyowa Kirin. As previously described, RUDY is an ongoing UK-based prospective cohort study whose aim is to improve the understanding of different hereditary musculoskeletal diseases [10]. The inclusion criteria were a diagnosis of XLH and age ranging from 18 to 70 years. XLH was confirmed by the presence of the PHEX mutation in the patient or a serum intact FGF-23 level of more than 30 picograms per millilitre. The study was conducted according to the principles of the Declaration of Helsinki, and all participants gave written informed consent.

Experimental procedures

The participants underwent one daily experimental session, including a clinical visit and a physical examination. Demographic, clinical and anthropometrical data were collected during the clinical visit, whereas physical performance was assessed during the physical examination. In particular, the upper and lower body function were assessed by a handgrip dynamometer and force platform, respectively. Functional capacity was evaluated by the six-minute walk test (6MWT); mobility, by the short physical performance battery (SPPB) test; and physical activity (PA) level, by the International Physical Activity Questionnaire (IPAQ).

Anthropometric and clinical characteristics

The participants' medical records were reviewed and the following data were recorded: age at diagnosis, last value of serum Pi, musculoskeletal manifestations, surgeries and current XLH treatment. Body mass and height were measured using a Leonardo force plate (Novotec Medical, Pforzheim,

Germany) and stadiometer, respectively. Body mass index (BMI) was then calculated.

Neuromuscular performance

Upper body strength was evaluated by means of a handgrip dynamometer (Jamar Hydraulic Hand Dynamometer, Sammons Preston Rolyan, Bolingbrook, IL, USA). The participants were asked to stand up and hold the dynamometer with the arm flexed at 90 degrees, the forearm in the mid-prone position and the wrist in the neutral position. A gap of 5 cm was maintained between the arm and trunk during the test. Participants were encouraged to squeeze as hard as possible and maintain the contraction for 3 s. The width of the handle was set for each participant according to their hand size (i.e. the middle phalanx on the inner handle). Three maximal contractions were performed, each separated by 30 s of rest. The highest strength value was considered in the analysis and compared with age-, sex- and height-matched UK reference values [11].

Neuromuscular performance of the lower limbs was evaluated through the Leonardo platform during a single two-leg jump. The device was connected to a laptop, and force measurements were sampled at a frequency of 800 Hz. The participants were instructed to start in a standing position, with feet placed apart by one shoulder width and hands placed above their hips. Then, they were asked to rapidly drop into the countermovement position (i.e. knee joint flexion to about 90 degrees) and jump as high as possible. Support for balance was provided to participants presenting with marked balance problems. Three jumps were performed, with 60 s of rest between each jump. Peak power (watts), peak mass-adjusted power (watts per kg) and the Esslinger Fitness Index (EFI) (i.e. jump power adjusted by age, sex and body mass and compared to reference data [12]) were recorded, and the highest value was used for the statistical analysis.

Functional capacity, mobility and physical activity

Functional capacity was assessed by a 6MWT on a marked 10-m flat walkway. Standardised instructions and encouragement were given to the participants according to the American Thoracic Society guidelines [13]. Walk distance was recorded in metres and compared with reference values calculated by the equation in Beekman et al. (2014). This equation has been validated in a UK population over a 10-m course and accounts for age and BMI [14].

The SPPB test is a tool used to measure physical performance and mobility in three different areas: gait (speed test), neuromuscular performance (chair stand test) and balance (side-by-side stand, semi tandem stand and tandem stand). For each test, a 5-level summary scale (0–4) is assigned, with a score of 0 indicating "unable to perform", whereas values ranging from 1 to 4 represent the hierarchical performance of the participants according to specific cut-points. A total score ranging from 0 to 12 was then calculated by adding the scores of all functional areas. Higher scores indicate better mobility.

PA was evaluated using the long version of the IPAQ. This tool measures the duration of moderate- and vigorous-intensity leisure, work, active commuting and yard/household PA conducted in the past week. According to the IPAQ guidelines [15], total PA is expressed as energy expenditure in metabolic equivalent–min/weeks, and participants were categorised into the following three categories of PA: (1) low active, (2) moderate active and (3) high active. PA data of 3 participants (2 males and 1 female) were excluded because they were considered outliers.

Statistical analysis

Data were expressed as the mean ± standard deviation for parametric variables, median and interquartile range for non-parametric data and percentages for categorical variables. All parameters were tested for normal distribution by the Kolmogorov–Smirnov test and visual inspection. Sex differences were assessed using the ANOVA for parametric variables or the corresponding Mann–Whitney test for non-parametric variables. If any significance was found, comparisons were further tested with Bonferroni adjustment.

Comparison between performance data with normative data and sex differences were assessed using *t* tests or Wilcoxon Signed-Rank tests. Fisher's exact tests were performed to assess sex differences in the skeletal manifestations and XLH treatment. Univariate correlation analyses between functional deficits and age and total PA were performed using Pearson or Spearman's rho test. Statistical significance was accepted if the P value was < 0.05. When considering Bonferroni corrections for sex comparisons in basic and clinical characteristics (11 variables), sex differences in physical function (7 variables) and comparisons with normative data (3 variables), these represented critical P values of 0.0042, 0.007 and 0.0167, respectively. Data analyses were performed using the Statistical Package for Social Sciences 20.0 for Windows (SPSS; Chicago, IL, USA).

Results

The participants' characteristics are shown in Table 1. Our cohort included 26 adults with XLH, 13 males and 13 females, with a mean age of 44 ± 16.1 years old. The height and body mass were 154 ± 8.7 cm and 68.9 ± 17.3 kg, respectively, and the serum Pi concentration was 0.62 ± 0.22 nmmol/L.

Table 1 Characteristics of the study population

Variables	All	Male	Female	*P* values
Number of participants	26	13	13	-
Age (years)	44 ± 16.1	39.6 ± 12.7	48.5 ± 18.4	0.163
Height (cm)	154 ± 8.7	159.6 ± 6	148.4 ± 7.4	< 0.0001
Body mass (kg)	68.9 ± 17.3	69 ± 12	68.9 ± 21.9	0.991
BMI (kg/m^2)	27 (24; 33)	26 (23.5; 29.5)	29 (25; 33)	0.223
Serum Pi (nmol/L)	0.62 ± 0.22	0.54 ± 0.23	0.70 ± 0.19	0.079
Skeletal manifestations (24 participants) *n* (%)				
Genu varum	14 (56%)	8 (32%)	6 (24%)	0.680
Genu valgus	8 (32%)	3 (12%)	5 (20%)	0.667
OA hip	11 (44%)	6 (24%)	5 (20%)	0.695
OA knee	7 (28%)	2 (8%)	5 (20%)	0.378
Surgical treatments (26 participants) *n* (%)				
Hip replacement	6 (23.1%)	3 (11.5%)	3 (11.5%)	1.000
Knee replacement	4 (15.3%)	1 (3.8%)	3 (11.5%)	0.593
Other procedures	12 (46.2%)	7 (26.9%)	5 (19.2%)	0.695

Data expressed as mean ± standard deviation or median and interquartile range or number of cases and percentages as appropriate. Critical value for Bonferroni-corrected comparisons was $P < 0.0042$

Abbreviations: *OA* osteoarthritis; *Pi* phosphate

A majority of XLH cases were diagnosed in childhood, with the exception of one participant, who was diagnosed during adulthood. The males were taller than the females (159.6 ± 6 vs 148.4 ± 7.4 cm, $p < 0.0001$), whereas no differences were found in age (39.6 ± 12.7 vs 48.5 ± 18.4 years, $p = 0.163$), body mass (69 ± 12 vs 68.9 ± 21.9 kg, $p = 0.991$) and BMI (26 (23.5; 29.5) vs 29 (25; 33) kg/m^2, $p = 0.223$). Low PA levels were noted in 72.7% of participants, with moderate PA levels in 27.3%, and none was classified as highly active.

Deformities, such as genu varum and valgus (Table 1), were documented in 56% (50% bilateral, 6% unilateral) and 32% (8.3% bilateral, 23.7% unilateral) of the adults with XLH. Osteoarthritis at the hip and knee was diagnosed in 44% (40% bilateral, 4% unilateral) and 28% (20% bilateral, 8% unilateral) of the participants, respectively. Among the XLH adults, 23% (7.7% bilateral, 15.4% unilateral) had undergone a hip replacement, and 15.3% (3.8% bilateral, 11.5% unilateral) a knee replacement. Approximately half (46.1%) of the participants had also undergone surgical corrections to the lower limbs. Currently, 15 participants (57.7%) were receiving conventional therapy with oral phosphate in combination with active vitamin D, 6 (23%) were without treatment, 3 (11.6%) took oral phosphate alone and 2 (7.7%) were treated with active vitamin D. There was no difference in the sexes across skeletal manifestations and pharmacological and surgical treatments. Data about deformity and osteoarthritis were missing for two participants.

During the physical examination, 5 participants (3 males and 2 females) used an assistive device for ambulation (i.e. crutches), 1 participant was unable to walk due to severe pain symptoms and 4 participants (2 males and 2 females) did not perform the jump due to reasons pertaining to recent surgery, pain (hip, knee or back) and fear of skeletal complications. As seen in Table 2, the males had a higher handgrip strength (36.4 ± 11 vs 24.9 ± 5.8 kg, $p = 0.003$) compared with the females. No difference was reported between the males and females in the 6MWT (373.2 ± 121.7 vs 296.8 ± 63.8 m, $p = 0.056$), SPPB scores (11 (8; 12) vs 10 (5.5; 11.5), $p = 0.287$), peak power (1502 ± 858 vs 1187 ± 628.5 W, $p = 0.346$), relative muscle power (20.2 (12.3; 25.8) vs 19 (8.6; 23.2) W kg^{-1}, $p = 0.654$), EFI (40.9 ± 18.8 vs 47.9 ± 16.4%, $p = 0.375$) and the total amount of PA (1681 ± 1472 vs 1558 ± 1686 MET-min/week, $p = 0.857$). Ten out of twenty-six participants (38.6%) had an SPPB score of 8 or lower indicating impaired mobility.

Compared with specific reference data (Table 3), the participants with XLH expressed 55.4% lower relative muscle power (EFI, $p < 0.0001$) but achieved a similar handgrip strength ($p = 0.317$). They were found to have covered a shorter 6MWT distance (by 38.6%, $p < 0.0001$) compared with age- and sex-specific reference values (Fig. 1). Comparable deficits (Fig. 1) were found in the males and females with XLH for muscle power (59.1 ± 18.8 vs 52.1 ± 16.4%, $p = 0.375$) and 6MWT (37.5 ± 22.1 vs 39.8%, $p = 0.733$). These impairments were not associated with age (all $P > 0.1$). Muscle power deficits were significantly higher than those reported during the 6MWT (55.4 ± 17.5 vs 38.6 ± 16.3%, $p = < 0.0001$). There was no difference in handgrip strength values between the males and females with XLH and normative values ($p = 0.195$). The results from the univariate analysis showed that total PA was correlated significantly

Table 2 Physical function and mobility in adults with XLH

Variables	All	Male	Female	*P* values
Total PA (MET-min/week)	1,620 ± 1,546	1,681 ± 1,472	1,558 ± 1,686	0.857
Handgrip strength (kg)	30.7 ± 10.4	36.4 ± 11	24.9 ± 5.8	0.003
Peak power (W)	1,337 ± 744.8	1,502 ± 858	1,187 ± 628.5	0.346
Peak adjusted power (W kg^{-1})	19.6 (12.2; 22.9)	20.2 (12.3; 25.8)	19 (8.6; 23.2)	0.654
EFI (%)	44.5 ± 17.5	40.9 ± 18.8	47.9 ± 16.4	0.375
6MWT (m)	335 ± 102	373.2 ± 121.7	296.8 ± 63.8	0.056
SPPB interquartile (score: 0 to 12)	10.5 (7.7; 12)	11 (8; 12)	10 (5.5; 11.5)	0.287

Data expressed as mean ± standard deviation or median and interquartile range as appropriate. Critical value for Bonferroni-corrected comparisons was $P < 0.007$

Abbreviations: *EFI* Esslinger Fitness Index; *6MWT* six-minute walk test; *PA* physical activity; *SPPB* short physical performance battery

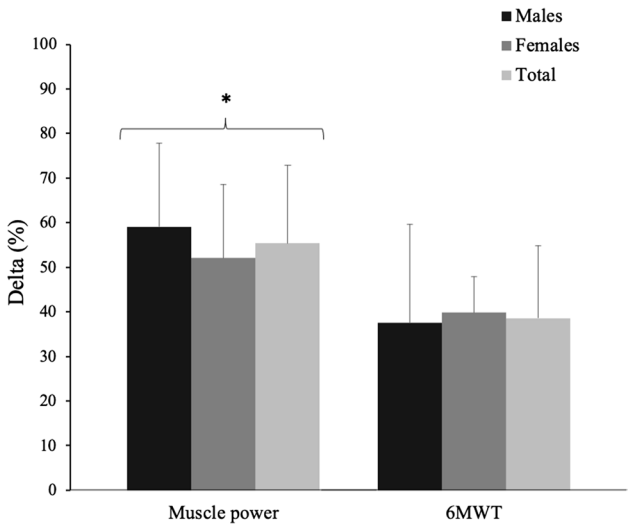

Fig. 1 Performance deficits in males and females with XLH, relative to age- and sex-matched normative data. *Significantly higher than 6MWT ($p < 0.001$)

with EFI ($r = 0.545$, $p = 0.019$), whereas no associations were found with the other performance data.

Discussion

We assessed multiple components of physical function in males and females with XLH. We observed large deficits in lower limb power assessed by jumping mechanography and a reduced functional capacity assessed by 6MWT. Approximatively 40% of participants had impaired mobility as assessed by SPPB and nearly three quarters reported a low level of daily PA. In contrast, handgrip strength was similar to that observed in age- and sex-matched individuals. The degree of impairment in physical function relative to normative values was independent of sex and age. Muscle power particularly deteriorates in XLH, and this defect is positively related to physical activity.

To our knowledge, this is the first study to examine grip strength and functional capacity in individuals with XLH. Our findings support earlier work [8], in which adults and children with XLH had ~ 30% lower jump power than controls. These deficits were more pronounced in the current study (55.4%), which may be related to greater severity of the cases in our cohort. This is supported by findings of greater impairments in power in individuals with more

Table 3 Physical performance in adults with XLH and normative values. Peak relative power data are from a German cohort [12]; handgrip and 6MWT [14] are from UK adults

Variables	XLH	Norm	*P* values	Male	Norm	*P* values	Female	Norm	*P* values
Peak relative power (W.kg^{-1})	19.3 ± 8.6	44 ± 11.1	< 0.0001	21.5 ± 10.1	53 ± 6.5	< 0.0001	17.4 ± 6.8	35.8 ± 7.5	< 0.0001
Handgrip strength (kg)	30.7 ± 10.4	33.7 ± 10.8	0.317	36.4 ± 11	42.2 ± 7.2	0.130	24.9 ± 5.8	25.2 ± 6.1	0.505
6MWT (m)	335 ± 102.9	548.8 ± 99.3	< 0.0001	373.2 ± 121.7	602.7 ± 174	0.001	296.8 ± 63.8	495 ± 93	< 0.0001

Critical value for Bonferroni-corrected comparisons was $P < 0.0167$

Abbreviations: *6MWT* six-minute walk test

pronounced symptoms in the previous study. However, the previous study included limited clinical details about the severity of the condition; therefore, we are unable to investigate this possibility further. This is also the first study to assess whether deficits in physical function differ between sexes or with age; no evidence was found for an association in either case. Our study of 26 adults (13 each sex) is similar in size to the only previous study of muscle function in XLH, in which 34 adults and children (9 males) participated [8]. The previous study focused largely on younger individuals (mean age 23.8 ± 13.3 years, 1 participant > 50 years) whereas our study included adults across a broader age range (44 ± 16.1 years).

Impaired physical function is an important consequence of XLH, with > 80% UK adults with XLH reporting problems with mobility compared to 26% in the general population [4]. In addition, in qualitative patient interviews, impaired physical functioning was the most prominent and most commonly reported impact of XLH [16]. Despite this, examination of the effects of existing and new treatments on physical function in XLH has been limited, and we suggest that this should be considered in future studies. Whilst physical function deficits identified in this study were independent of sex and age, evidence of a similar age-related decline in physical function to individuals without XLH suggests that sarcopenia and functional impacts may become evident much earlier in this population and hence intervention in childhood or early adulthood could/might help promote mobility across the lifespan.

The aetiology of effects of XLH on physical function remains unclear but is probably multi-factorial. Whilst impaired phosphate metabolism is likely the underlying cause of these impairments, this relationship has not been well explored. In a previous study, the authors found no association between phosphorus levels (in addition to PTH levels and treatment status) and muscle function. Such lack of association might be attributed to high intra-day variation in phosphorus levels [8]. Whilst muscle imaging was not performed in this study, previous reports suggest that deficits in muscle function result from impaired muscle quality (i.e. low/reduced force per unit of muscle area) rather than quantity (which appeared similar relative to body size) [8]. The causes of this impairment have not been explored in humans, although animal studies have identified changes in mitochondrial structure [17] and transmembrane potential [18]. Musculoskeletal pain and stiffness commonly reported in XLH are also likely contribute to impaired performance, whilst skeletal abnormalities are clearly associated with altered gait [9]. In particular, deformities, pseudofractures, osteoarthritis and enthesopathies are common in XLH causing pain and limiting mobility [19]. That these problems are more common in the lower than upper limbs likely contributes to observed differences in function between the two regions. Related to this, groups with impaired lower limb strength such as elderly individuals or those with osteoarthritis use the upper limbs in tasks such as rising from a chair [20] or stair negotiation [21]. The additional workload on the upper limbs may also explain the lack of a pronounced deficit in handgrip performance.

Physical activity is associated with a number of components of physical function, and low physical activity may contribute to physical function deficits in this population. Whilst physical activity was positively associated with jump power, associations were not observed with other components of physical function. This may be related to the use of questionnaires to assess physical activity in this study. Associations between physical activity and physical function are specific to the type/intensity of activity performed and component of function assessed. Future studies examining physical activity in more detail via, e.g., accelerometry may help identify more specific associations, and identify specific interventional targets, e.g. increase in vigorous physical activity.

Handgrip strength is the most common method of assessing muscle function clinically, but it is only moderately associated with lower limb function relevant to important clinical outcomes such as mobility, falls and fractures [22]. In this population, handgrip strength did not reflect deficits in other components of physical function which may limit its clinical utility. Whilst the 6MWT and countermovement jump detected large deficits, in a minority of participants, they were not applicable due to pain or other concerns. Therefore, future studies of physical function in this population should consider both applicability and sensitivity of the assessment techniques used.

There are limitations to this study; as participants were recruited from those due to receive burosumab for XLH symptoms, therefore, they likely represent a higher level of impairment than the broader clinical population. Comparisons with existing data were made from multiple publications; therefore, we were unable to directly assess deficits of physical function within the same reference individuals. Recruitment of specific age- and sex-matched controls may have represented a more robust study design and should be considered in similar studies in future. We applied a conservative Bonferroni correction, which increases the risk of type II error. However, in no case was a P value between 0.05 and the critical value hence our main findings was unaffected by our choice of analysis. Previous reported incidence of skeletal manifestations such as hip and knee osteoarthritis and genu valgum vary substantially but values in our cohort appear to be within typical range [9, 19]. Therefore, we are confident that the observed deficits in physical function are broadly typical of individuals with XLH receiving clinical care and are not unduly affected by reduced mobility associated with a high degree of deformity and/or osteoarthritis.

XLH is associated with substantial deficits in multiple clinically relevant components of physical function, independent of sex or age. These deficits were not evident in handgrip strength, which is the most common clinical tool for assessment of muscle function. These impairments likely contribute significantly to impaired mobility and increased fall and fracture risk reported in this population. Future studies should examine the mechanisms underlying this dysfunction, whilst treatment studies should also consider these endpoints in addition to skeletal assessments.

Funding This work was supported by a research grant from Kyowa Kirin.

Data availability The authors do not have permission to share the data.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of interest GO and AI were supported by research funding from Kyowa Kirin. MS receives honorarium from Kyowa Kirin and grant funding from Roche Diagnostics.

References

1. Carpenter TO, Imel EA, Holm IA, Jan De Beur SM, Insogna KL (2011) A clinician's guide to X-linked hypophosphatemia. J Bone Miner Res 26:1381–8. https://doi.org/10.1002/jbmr.340
2. Pettifor JM (2008) What's new in hypophosphataemic rickets? Eur J Pediatr 167:493–499. https://doi.org/10.1007/s00431-007-0662-1
3. Seefried L, Smyth M, Keen R, Harvengt P (2021) Burden of disease associated with X-linked hypophosphataemia in adults: a systematic literature review. Osteoporos Int 32:7–22. https://doi.org/10.1007/s00198-020-05548-0
4. Forestier-Zhang L, Watts L, Turner A, Teare H, Kaye J, Barrett J et al (2016) Health-related quality of life and a cost-utility simulation of adults in the UK with osteogenesis imperfecta, X-linked hypophosphatemia and fibrous dysplasia. Orphanet J Rare Dis 11:1–9. https://doi.org/10.1186/s13023-016-0538-4
5. Orlando G, Pinedo-Villanueva R, Reeves ND, Javaid MK, Ireland A (2021) Physical function in UK adults with osteogenesis imperfecta: a cross-sectional analysis of the RUDY study. Osteoporos Int 32:157–164. https://doi.org/10.1007/s00198-020-05537-3
6. Linglart A, Biosse-Duplan M, Briot K, Chaussain C, Esterle L, Guillaume-Czitrom S et al (2014) Therapeutic management of hypophosphatemic rickets from infancy to adulthood. Endocr Connect 3:R13-30. https://doi.org/10.1530/ec-13-0103
7. Lo SH, Lachmann R, Williams A, Piglowska N, Lloyd AJ (2020) Exploring the burden of X-linked hypophosphatemia: a European multi-country qualitative study. Qual Life Res 29:1883–1893. https://doi.org/10.1007/s11136-020-02465-x
8. Veilleux LN, Cheung M, Ben Amor M, Rauch F (2012) Abnormalities in muscle density and muscle function in hypophosphatemic rickets. J Clin Endocrinol Metab 97:1492–8. https://doi.org/10.1210/jc.2012-1336
9. Steele A, Gonzalez R, Garbalosa JC, Steigbigel K, Grgurich T, Parisi EJ et al (2020) Osteoarthritis, osteophytes, and enthesophytes affect biomechanical function in adults with X-linked hypophosphatemia. J Clin Endocrinol Metab 105:e1798–e1814. https://doi.org/10.1210/clinem/dgaa064
10. Javaid MK, Forestier-Zhang L, Watts L, Turner A, Ponte C, Teare H et al (2016) The RUDY study platform - a novel approach to patient driven research in rare musculoskeletal diseases. Orphanet J Rare Dis 11:1–9. https://doi.org/10.1186/s13023-016-0528-6
11. Spruit MA, Sillen MJH, Groenen MTJ, Wouters EFM, Franssen FME (2013) New normative values for handgrip strength: results from the UK Biobank. J Am Med Dir Assoc 14:775.e5-775.e11. https://doi.org/10.1016/j.jamda.2013.06.013
12. Runge M, Rittweger J, Russo CR, Schiessl H, Felsenberg D (2004) Is muscle power output a key factor in the age-related decline in physical performance? A comparison of muscle cross section, chair-rising test and jumping power. Clin Physiol Funct Imaging 24:335–340. https://doi.org/10.1111/j.1475-097X.2004.00567.x
13. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories (2002) ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 166:111–117. https://doi.org/10.1164/ajrccm.166.1.at1102
14. Beekman E, Mesters I, Gosselink R, Klaassen MPM, Hendriks EJM, Van Schayck OCP et al (2014) The first reference equations for the 6-minute walk distance over a 10 m course. Thorax 69:867–868. https://doi.org/10.1136/thoraxjnl-2014-205228
15. Ipaq (2005) Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ) – short and long forms. Ipaq 1–15
16. Theodore-Oklota C, Bonner N, Spencer H, Arbuckle R, Chen C-Y, Skrinar A (2018) Qualitative Research to explore the patient experience of X-linked hypophosphatemia and evaluate the suitability of the BPI-SF and WOMAC® as clinical trial end points. Value Health 21:973–983. https://doi.org/10.1016/j.jval.2018.01.013
17. Finol H, De Venanzi F, Pereyra B, Alfonso C, Sánchez J (2001) Effects of phosphorus deficiency on the ultrastructure of the rat fast twitch skeletal muscle. Interciencia 26:62–66
18. Fuller TJ, Carter NW, Barcenas C, Knochel JP (1976) Reversible changes of the muscle cell in experimental phosphorus deficiency. J Clin Invest 57:1019–1024. https://doi.org/10.1172/JCI108343
19. Hardy DC, Murphy WA, Siegel BA, Reid IR, Whyte MP (1989) X-linked hypophosphatemia in adults: prevalence of skeletal radiographic and scintigraphic features. Radiology 171:403–414. https://doi.org/10.1148/radiology.171.2.2539609
20. Smith SHL, Reilly P, Bull AMJ (2020) A musculoskeletal modelling approach to explain sit-to-stand difficulties in older people due to changes in muscle recruitment and movement strategies. J Biomech 98:109451. https://doi.org/10.1016/j.jbiomech.2019.109451
21. Reeves ND, Spanjaard M, Mohagheghi AA, Baltzopoulos V, Maganaris CN (2008) Influence of light handrail use on the biomechanics of stair negotiation in old age. Gait Posture 28:327–336. https://doi.org/10.1016/j.gaitpost.2008.01.014
22. Yeung SSY, Reijnierse EM, Trappenburg MC, Hogrel JY, McPhee JS, Piasecki M et al (2018) Handgrip strength cannot be assumed a proxy for overall muscle strength. J Am Med Dir Assoc 19:703–709. https://doi.org/10.1016/j.jamda.2018.04.019