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ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/idre20

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To cite this article: Sophie Taylor, Nick Dobbin, Richard Imrich, Jean-Baptiste Arnoux & Lakshminarayan R. Ranganath (08 Jan 2025): The effects of age and sex on active and passive hip range of motion in individuals with alkaptonuria, Disability and Rehabilitation, DOI: 10.1080/09638288.2024.2447363

To link to this article: https://doi.org/10.1080/09638288.2024.2447363

Published online: 08 Jan 2025.

DISABILITY AND REHABILITATION
https://doi.org/10.1080/09638288.2024.2447363

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RESEARCH ARTICLE

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The effects of age and sex on active and passive hip range of motion in individuals with alkaptonuria

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ABSTRACT

Purpose: To report active and passive hip range of motion (ROM) data for individuals with alkaptonuria (AKU), with consideration for age, sex, and non-AKU comparative data.

Materials and Methods: Using a cross-sectional study design, 123 patients who had baseline ROM assessed in a previous international, multi-centre clinical trial were included. Data was compared between age groups, sexes, and with existing data from individuals without AKU. Data was analysed using a one-way ANOVA, paired t-test, and one-sample *t*-test, with results interpreted using partial eta squared and standardised mean differences (SMD).

Results: Differences were observed across the age groups for active and passive flexion ($F=3.815$, $p=0.006$, $\eta_p^2 = 0.115$) and active hip abduction ($F=1.941$, $p=0.108$, $\eta_p^2 = 0.062$). Differences between sexes ranged from trivial-to-large (SMD = 0.03 to 1.90), with variability evident across the age groups. Individuals with AKU were within the lower range of scores observed for healthy adults in flexion ($t=-8.545$ to -3.166, $p=0.010$ to <0.001) and abduction ($t=-20.830$ to -0.737, $p=0.478$ to <0.001).

Conclusions: Our results provide insight into the clinical value of ROM with consideration for age, sex and normative data as a determinant of disease progression and functional ability within individuals with AKU.

➤ IMPLICATION FOR REHABILITATION

- Range of movement assessment could be used in clinical practice as an early indicator of disease activity and functional ability in individuals with alkaptonuria (AKU).
- Insight into natural history of range of motion (ROM) with reference to AKU, sex, and age can inform long-term management and rehabilitation strategies in this patient population to minimise loss of ROM and function early in the life course.
- The pathophysiology underlying loss of joint range, including ochronotic changes to cartilage, tendons and ligaments, should be considered within rehabilitation strategies.

ARTICLE HISTORY
Received 31 July 2024
Revised 20 December 2024
Accepted 22 December 2024

KEYWORDS
AKU; physiotherapy; rehabilitation; lifespan; disability; ochronosis

Introduction

Alkaptonuria (AKU) is a rare, monogenic autosomal-recessive disease affecting between 1 in 250,000 to 1 million people globally [1]. It was described by Sir Archibald Garrod in the early twentieth century and is recognised for its Mendelian inheritance pattern in human disease [2]. AKU is caused by a deficiency of homogentisate dioxygenase (HGD), an enzyme involved in the metabolism of tyrosine, leading to the accumulation of homogentisic acid (HGA). HGA can either be excreted in the urine or can oxidise and polymerise in connective tissues to form a melanin-like pigment, a process known as ochronosis [3]. The progressive deposition of HGA-pigment in connective tissue leads to brittleness and degradation [4,5].

AKU is a systemic disorder, with individuals typically being asymptomatic during childhood. In the second to third decade of life, signs and symptoms of the disease appear, including musculoskeletal manifestations such as early-onset spondyloarthropathy and tendinopathy [6,7]. Early spondyloarthropathy results from articular cartilage losing its elasticity and becoming brittle. Consequently, there is often a loss of cartilage or fragmentation, forming loose bodies that can cause fibrosis or chondromatosis due to these fragments adhering to the synovial membrane [7]. Eventually, this can lead to the formation of osteophytes or subchondral cysts, resembling early osteoarthritis. The oxidation of HGA generates free radicals that may initiate both inflammatory and degenerative processes. Furthermore, ochronotic pigment deposition within the tendon is evident due to its highly stressed collagenous nature, leading to tendinopathy [7]. These result in spinal and peripheral pain associated with limited range of motion (ROM), swelling, stiffness, and premature joint failure [7].

Clinical assessment of spondyloarthropathy includes measuring ROM at the ankle, knee, hip, spine, shoulder, wrist, and hand, which

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can be reduced due to both age-related wear and tear as well as AKU spondyloarthropathy and tendinopathy [8–10]. Specifically, the hip joint is one of the largest weight-bearing joints in the body with a wide ROM and joint mobility. Hip ROM is known to be influenced by age and sex in populations without AKU [11]; however, the extent to which AKU affects ROM is largely unknown. A decline in normal ROM with advancing age is particularly important, given the association between restricted ROM and functional disability in older individuals [12], though restrictions may also occur in younger age groups considering the pathogenesis of AKU. To the authors' knowledge, there is no current published research exploring ROM of the hip in individuals with AKU with consideration for age and sex. However, such insights could prove valuable in clinical practice to target specific interventions to maintain ROM with age in a sex-specific manner, to tailor advice given to individuals with AKU, and to help inform future clinical guidelines.

In setting the context for this manuscript, a four-year randomised controlled trial was conducted [13], during which baseline musculoskeletal data, including hip ROM, were collected alongside other key outcome measures. For this study, the hip ROM data were used to meet the following objectives:

- To present a normative data set of active and passive hip ROM for individuals with AKU
- To identify if active and passive hip ROM changes across the lifespan in individuals with AKU.
- To identify if there are differences in active and passive hip ROM between males and females with AKU.
- To compare hip ROM in individuals with AKU with normative hip ROM from individuals without AKU

It was hypothesised that: (1) ROM would exhibit a similar age-related trend to that observed in individuals without AKU; (2) only trivial-to-small differences in ROM would be observed between sexes; and (3) individuals with AKU would have reduced hip ROM compared to those without AKU.

Materials and methods

Study design

This study used a cross-sectional research design with data from an existing study, SONIA 2 [13], which was a four-year, multicentre, open-label, evaluator-blind, randomised, no-treatment controlled, parallel-group design. ROM was a secondary outcome of the SONIA 2 study and one of many assessments undertaken with participants on entry to the study. The study followed an annual visit design over four years, completed at three clinical sites: Royal Liverpool University Hospital, Liverpool, UK; Hospital Necker-Enfants Malades, Paris, France; and National Institute of Rheumatic Diseases, Piestany, Slovakia. Further details on the SONIA 2 study can be found in the previous publication [13]. The associated ethics approval numbers for each site were: 13/NW/0567, 04196/0029/001/001, and 2013-08-08. The STORBE guidelines were considered in the production of this work.

Participants

Eligible participants of European and Jordanian origin were enrolled in the study [13]. A sample of 138 participants was assessed for eligibility, of whom 123 participants (77 males and 46 females, aged 26–67 years) completed all baseline measurements, including hip ROM, and had not previously had a hip replacement. Participants reflected those involved in the larger clinical trial [13]. Those included were diagnosed with AKU and who presented with any clinical manifestation of AKU (e.g. clinical ochronosis or chronic joint pain), were aged ≥25 years, and were able to visit the hospital for the initial assessment. Exclusion criteria included: being treated with nitisinone within 3 month of the initial assessment of ROM, participation in another clinical trial within the previous three months, known allergy to nitisinone, non-contraceptive use in females, currently being pregnant or lactating, current malignancy, uncontrolled hypertension or cardiovascular disease, history of substance abuse, evidence of non-compliance with, and understanding of, the study, and a range of blood parameters falling outside of normal limit (see Ref. [13] for more detail). In addition to the exclusion criteria of the main trial, we also excluded those that had a hip replacement given the known impact this has on range of motion. No power calculation was conducted *a-priori* as the data was provided from an existing study [13]. All participants provided written informed consent prior to enrolling in the study.

Procedures

Baseline measurements of active and passive hip ROM, including flexion, abduction, and lateral rotation, were undertaken using a Universal Goniometer before participants were allocated to a treatment arm in the SONIA 2 trial. Measurements were taken on both the right and left sides of the body. A single measure for each movement, using a standardised positioning protocol was completed by clinicians in the clinical trial centres. Clinicians were either specialist physiotherapists or rheumatologists, with extensive experience in goniometry. The same investigator in each centre completed all ROM assessments before participants had been allocated to a trial arm (the baseline assessment). A standardised data collection worksheet and checklist for ROM were developed at the UK site. Video and written material with pictorial instructions were also developed and shared with the French and Slovakian sites to ensure consistency across sites. It was not possible to determine the inter-rater reliability due to the multi-site approach; however, it is generally accepted that for experienced clinicians, the reliability (ICC) ranges from 0.55 to 0.95 [14].

Statistical analysis

All data were checked for compatibility with the assumptions of normality using the Shapiro-Wilk test. To assess the differences in hip ROM across age groups, a one-way analysis of variance was used, with a follow-up Bonferroni-adjusted post-hoc test applied when a main effect was found. A partial eta squared (η_p^2) was also derived for the main effect to provide a measure of magnitude, interpreted as: small (0.01), moderate (0.06), and large (0.14). To support the interpretation of change across ages, a simple linear regression was used to provide an estimate of the change per year. Comparisons between active and passive ROM within each age group were also undertaken using a paired sample *t*-test, and differences between sexes within each age category were compared using an independent sample *t*-test. Both comparisons of the means were accompanied by a standardised mean difference (active vs. passive = Cohen's d; sexes and vs. normative = Hedges' g) and interpreted as: trivial (<0.20), small (0.21–0.60), moderate (0.61 to 1.20), large (1.21 to 2.00), and very large (>2.00). Finally, to determine if passive ROM within each age-group and for each action was different from normative data, the results from Macedo and Magee [15] were used for ages 18–59 years, and those from Roach and

Miles [16] for the 60–74 years age-group. In the study by Macedo and Magee [15], the participants included 90 healthy Caucasian women aged between 18 and 59 years. Roach and Miles included 1,683 participants for hip ROM, described as white men, white women, black men, and black women. We highlight here that our categorisation of age groups (e.g. 18–29 despite only having participant aged 26–29) were chosen to facilitate the use of comparative data for populations without AKU. The mean, standard deviation, range, and confidence intervals were extracted or calculated. A one-sample *t*-test was used to compare the data in this study against the mean values from the two studies. A standardised mean difference was also determined using the same qualitative descriptors above. All data analysis was completed using SPSS for Macintosh (Version 29, IBM SPSS Statistics, Armonk, NY). The p-value was interpreted on a scale of compatibility with the absolute value presented to allow readers to interpret their own level of compatibility within their clinical context.

Results

Characteristics

A total of 123 participants were included in the final analysis, comprising 77 males (mean age = 46.4 ± 10.5 years, range = 26–66 years) and 46 females (mean age = 47.7 ± 9.4 years, range = 27–67 years). The mean body mass for the entire group was 74.4 ± 15.1 kg. The sample included participants who were assessed at one of three centres: Royal Liverpool University Hospital, England; Hospital Necker-Enfants Malades, France; and the National Institute of Rheumatic Diseases, Slovakia. A total of 8 participants (6.5%) used a walking aid, while almost half of the participants ($n = 61$, 49.5%) reported pain in one or both of their hips.

Differences in hip ROM between age groups

A moderate effect of age was observed for active hip flexion ($F = 3.815$, $p = 0.006$, $\eta_p^2 = 0.115$) and active hip abduction ($F = 1.941$, $p = 0.108$, $\eta_p^2 = 0.062$). For active hip flexion, the largest mean difference was observed between the age groups 18–29 and 30–39 versus 50–59 years (11.0° [$p = 0.132$] and 10.6° [$p = 0.009$], respectively). A small effect of age was observed for passive hip flexion ($F = 1.660$, $p = 0.164$, $\eta_p^2 = 0.053$), hip abduction ($F = 1.422$, $p = 0.231$, $\eta_p^2 = 0.046$), and external rotation ($F = 0.988$, $p = 0.417$, $\eta_p^2 = 0.033$). A small effect of age was also observed for active external rotation ($F = 0.699$, $p = 0.594$, $\eta_p^2 = 0.046$) (Figure 1). Results from the linear regression indicated that, per year, active and passive flexion are reduced by 0.4° ($p < 0.001$) and 0.3° ($p = 0.015$), respectively; active and passive abduction are reduced by 0.2° ($p = 0.005$) and 0.2° ($p = 0.007$), respectively; and active and passive hip rotation are reduced by 0.1° ($p = 0.178$) and 0.2° ($p = 0.085$), respectively.

A comparison between active and passive hip ROM through each of the movements indicated higher ROM across all age groups in flexion ($t = -4.477$ to -10.800, all $p < 0.001$, $d = -0.934$ to -1.708), abduction ($t = -2.343$ to -7.617, $p < 0.001$ to 0.024, $d = -0.747$ to -1.27), and external rotation ($t = -4.941$ to -11.973, all $p < 0.001$, $d = -1.130$ to -1.996) (Figure 1).

Differences in hip ROM between sexes

Across the 18–29 to 50–59 age ranges, between-sex differences were largely trivial-to-small ($t = 0.047$ to 1.540, $p = 0.135$ to 0.967, $g = -0.03$ to 0.50) (Table 1).

Moderate between-sex differences were observed for both active ($t = -2.677$, $p = 0.007$, $g = -0.96$) and passive ($t = -2.682$, $p = 0.007$, $g = -1.04$) abduction in the 30–39-year age group. A moderate between-sex difference was also observed for passive

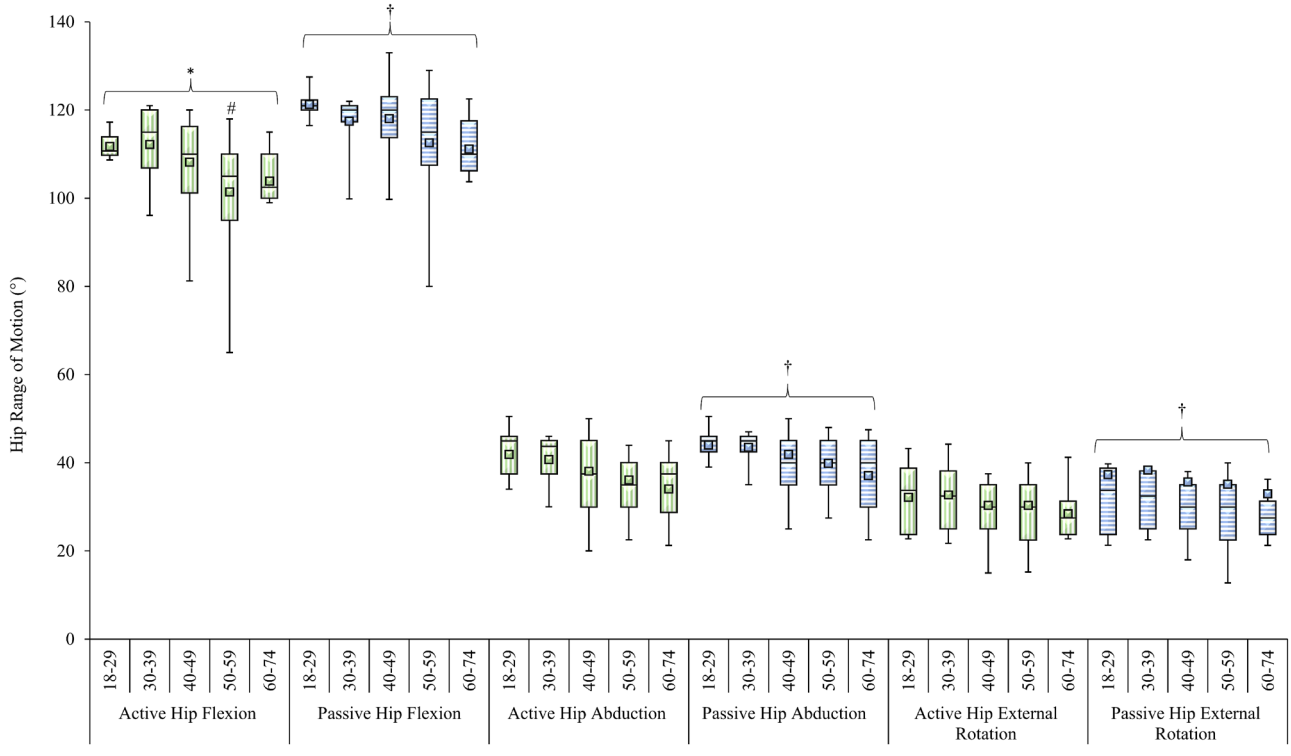

Figure 1. Box and whiskers plot for active (green, vertical lines) and passive (blue, horizontal lines) hip range of motion across age groups (years). *Note:* Middle solid line = median. Square = mean value for aiding with interpretation. *Main effect of age; #different to 30–39 years; †difference observed when compared to active ROM.

flexion, active external rotation, and passive external rotation in the 60–74-year age group ($t = 1.073$, $p = 0.303$, $g = 1.05$; $t = 1.029$, $p = 0.323$, $g = 1.00$; $t = 1.188$, $p = 0.256$, $g = 1.16$, respectively).

A large between-sex difference was observed for passive flexion in the 18–29 group ($t = -1.005$, $p = 0.496$, g = −1.20), and active flexion, active abduction, and passive abduction in the 60–74-year group ($t = -1.545$, $p = 0.146$, $g = 1.51$; $t = 2.043$, $p = 0.062$, $g = 1.90$; $t = 1.929$, $p = 0.076$, $g = 1.88$, respectively).

A comparison between AKU and non-AKU groups

Differences between those with and without AKU per age group is presented in Figure 2.

Table 1. Mean and standard deviation for hip ROM for each age group per sex.

	Active flexion (°)	Passive flexion (°)	Active abduction (°)	Passive abduction (°)	Active external rotation (°)	Passive external rotation (°)
			18–29 years			
Men ($n = 6$)	112 ± 4	120 ± 3	42 ± 6	43 ± 4	32 ± 8	38 ± 8
Women ($n = 2$)	113 ± 4^{T}	125 ± 7^{L}	43 ± 25^{T}	46 ± 20^{S}	33 ± 17^{T}	37 ± 12^{T}
			30–39 years			
Men ($n = 15$)	112 ± 9	117 ± 6	39 ± 7	42 ± 5	32 ± 7	37 ± 7
Women ($n = 9$)	113 ± 11^{T}	118 ± 12^{T}	44 ± 3^{M}	47 ± 4^{M}	35 ± 9^{S}	41 ± 10^{S}
			40–49 years			
Men ($n = 25$)	109 ± 10	118 ± 11	38 ± 11	42 ± 9	31 ± 9	36 ± 9
Women ($n = 14$)	107 ± 16^{T}	117 ± 18^{T}	38 ± 12^{S}	42 ± 9^{T}	30 ± 8^{S}	35 ± 7^{S}
			50–59 years			
Men ($n = 21$)	101 ± 17	111 ± 17	36 ± 9	39 ± 6	29 ± 8	33 ± 8
Women ($n = 20$)	101 ± 10^{T}	111 ± 13^{S}	36 ± 6^{T}	39 ± 6^{S}	32 ± 16^{S}	33 ± 16^{S}
			60–74 years			
Men ($n = 10$)	105 ± 9	112 ± 7	36 ± 8	39 ± 7	26 ± 9	34 ± 6
Women ($n = 1$)	90 ± 0^{L}	103 ± 0^{M}	15 ± 0^{L}	20 ± 0^{L}	24 ± 0^{M}	25 ± 0^{M}

Note: ^{T} = trivial, ^{S} = small, ^{M} = moderate, ^{L} = large standardised mean difference compared to men.

A small to very large difference in hip flexion ROM was observed when compared to individuals without AKU (Figure 2). Flexion was lower across all ages: 18–29 ($t = -8.545$, $p < 0.001$, $g = 2.57$), 30–39 ($t = -7.384$, $p < 0.001$, $g = 1.49$), 40–49 ($t = -5.436$, $p < 0.001$, $g = 0.85$), 50–59 ($t = -4.767$, $p < 0.001$, $g = 0.73$), and 60–74 ($t = -3.166$, $p = 0.010$, $g = 0.88$). Compatibility with the hypothesis was high in all cases.

A small to very large difference was also observed for passive hip adduction with lower scores in the AKU group at: 18–29 ($t = -6.110$, $p < 0.001$, $g = 1.84$), 30–39 ($t = -16.161$, $p < 0.001$, $g = 3.25$), 40–49 ($t = -14.017$, $p < 0.001$, $g = 2.20$), 50–59 ($t = -20.830$, $p < 0.001$, $g = 3.19$), and 60–74 ($t = -0.737$, $p = 0.478$, $g = 2.05$). For the most part, compatibility was deemed high to acceptable within the context of this study.

Differences in passive lateral rotation were mostly small in magnitude and generally supported the notion of being in the higher range of normative: 18–29 ($t = 0.157$, $p = 0.879$, $g = 0.05$), 30–39 ($t = 1.264$, $p = 0.219$, $g = 0.26$), 40–49 ($t = 1.940$, $p = 0.060$, $g = 0.31$), 50–59 ($t = 1.707$, $p = 0.096$, $g = 0.27$), and 60–74 ($t = 2.017$, $p = 0.071$, $g = 0.56$). Compatibility with the hypothesis was mixed in the case of lateral rotation.

Discussion

This study aimed to understand hip ROM in individuals with AKU during active and passive movement across the lifespan and between sexes. We also sought to compare hip ROM in individuals with AKU to those without AKU to better understand the function of individuals with AKU and guide management and treatment strategies. Overall, our findings suggest that differences in active and passive ROM exist, as expected, with a reduction in hip flexion over the course of the lifespan. Minimal difference was observed across the lifespan for abduction and external rotation, which remained relatively stable. Trivial to large between-sex differences

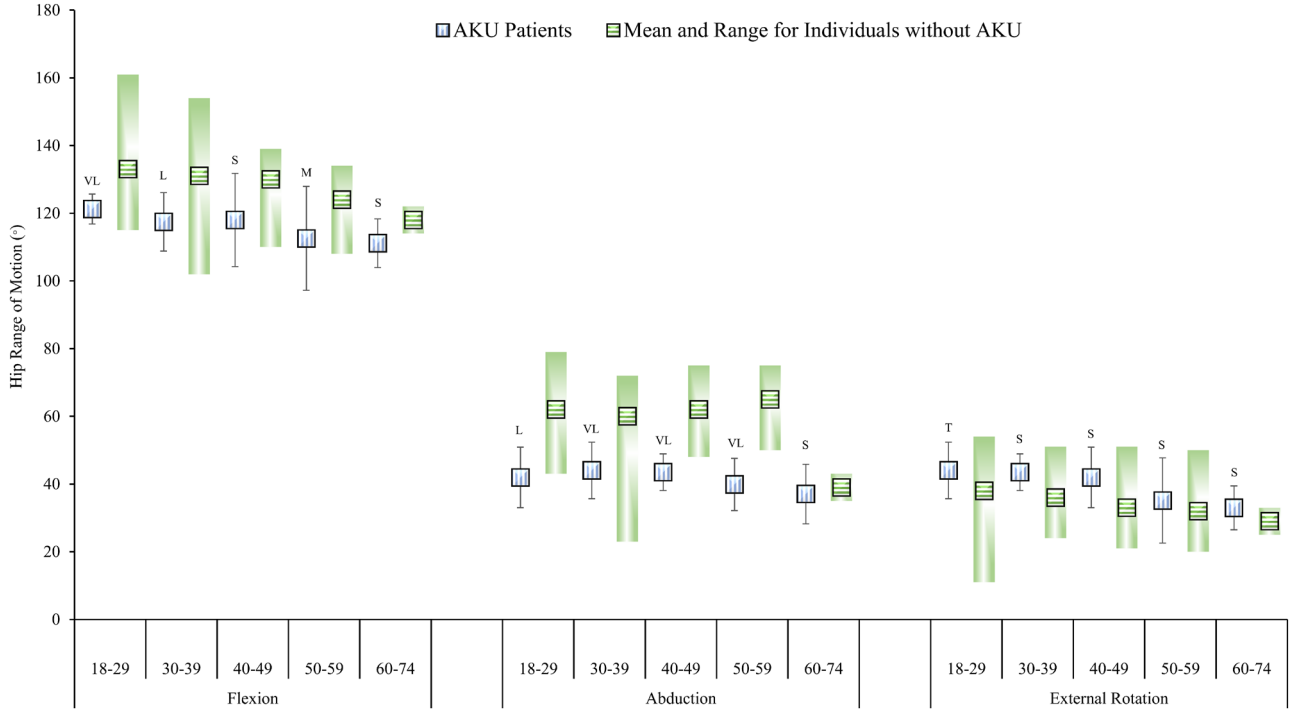

Figure 2. Differences in AKU patients' passive ROM (blue, vertical lines) and normative data expressed as mean (green, horizontal lines) and range (shaded area) using the work of Macedo and Magee (2009) and Roach and Miles (1991). *Note:* T = trivial, S = small, M = moderate, L = large and VL = very large standardised mean difference compared to individuals without AKU.

were observed with some variability in the magnitude of difference across the age categories. Finally, when comparing our data to individuals without AKU, passive ROM for flexion and abduction generally fell within the lower range of "normal".

Previous research has noted that hip ROM decreases over the lifespan in non-AKU populations [15,16], which is likely explained by reduced overall physical activity, joint degradation, loss of cartilage, connective tissue changes [17], and other comorbidities associated with age, such as strength loss, obesity, and medical or psychosocial issues [18]. We speculate that tendons become swollen and hardened due to ochronotic pigment build-up, which may subsequently limit movement within the tendon sheath. In AKU populations specifically, the pattern of our data suggests a decline in hip ROM, with a difference of 8 to 10 degrees observed between the youngest and oldest age groups for hip flexion (active and passive). There appeared to be minimal difference in hip flexion between the two older age groups. This may reflect the pooling of data from both men and women, with men with AKU experience smaller losses in hip flexion ROM (~7 to 8 degrees) compared to women (~22 to 23 degrees), and with women being underrepresented in the oldest age group. While we acknowledge that hip ROM remains at a level considered functional for most everyday activities, the observed changes may be exacerbated by ochronotic arthropathy, with ochronotic pigment causing narrowing of the joint space due to calcification and fragmentation of the tendons and cartilage [19]. In this study, we observed a greater reduction in passive and active hip flexion and external rotation compared to that observed in healthy individuals [15]. The magnitude of difference between the youngest and oldest grouping in flexion and abduction was similar to that of Macedo and Magee [15] in healthy individuals (~9 degrees). For external rotation, similar observations were reported to those in individuals without AKU, where smaller changes are observed. These findings may be explained by the accumulation of homogentisic acid, leading to ochronosis and degradation of the hip joint, as well as changes in the surrounding musculature, tendons, and ligaments [7]. It is possible that the impact of AKU is more evident during actions (e.g. flexion) that involve global mobilising muscles compared to smaller, more refined and local movements (e.g. rotation).

When comparing active and passive ROM in individuals with AKU, we observe a similar pattern to that in those without AKU, with greater passive ROM compared to active ROM. However, we recognise the smaller than expected difference in active and passive ROM in abduction, where a mean difference of approximately 3° was observed. This finding may indicate that reduced ROM in abduction is due to joint restriction. These findings provide useful clinical insights when assessing individuals with AKU across multiple ROMs. The data also provides sex-specific normative data for both active and passive ROM across three ranges that can be used to understand if/when patient values deviate from the population norm. Notably, our results show a moderate to large between-sex difference in active and passive flexion for individuals over the age of 60 years, which was not observed in populations without AKU [16]. The exact reasons for this distinct difference remain largely unknown with reference to AKU. This may be associated with reduced bone mineralisation and a greater risk of osteopenia or osteoporosis [7], alongside other factors associated with older women, such as reduced muscle strength [20,21], lower physical activity levels [21], and hormonal changes, such as reductions in oestradiol during menopause, which may exacerbate the redox properties of homogentisic acid. Overall, this normative data provides insight into both active and passive ROM for men and women and may support further understanding of the clinical presentation of AKU and overall management approaches.

Compared to individuals without AKU, our data revealed that passive ROM generally fell within the lower range for flexion and abduction. This suggests that changes in hip ROM appear to occur earlier in those with AKU than the natural changes in ROM within flexion and abduction, potentially due to cartilage, tendon, and ligament disease. For the older age group, we found similar mean values, though it is important to note that the comparative data used was from a different population compared to those used for the younger age groups. Furthermore, we found that individuals with AKU may be susceptible to loss of ROM at the hip in flexion and abduction from the second decade of life. Such findings are not observed in external rotation, potentially due to the available range of movement being much less than in flexion and abduction. These results indicate that the pathophysiology of AKU causes changes within the hip joint and tendons that limit ROM in flexion and abduction. Clinical indicators of AKU, such as pigmentation of the ear and eye, commonly present in the third decade of life and are often used as indicators of AKU in the absence of changes in urine colour [22]. Based on the findings of this study, our results suggest that hip ROM might also be sensitive to changes caused by AKU from an earlier age, though we acknowledge that further research is needed to assess measures that meet the Bradford Hill guidelines to draw out more meaningful inferences towards causality. While the youngest individual involved in the study was 26 years old, recent work suggests that loss of ROM impacting gait function due to ochronosis might be seen earlier (SOFIA study; [23]). As such, hip ROM in flexion and abduction could be an important part of patient evaluation given its ease of use, minimal cost, and non-invasiveness.

Despite being the largest study in the inborn error of metabolism field, comprising 123 patients with an ultra-rare condition, this study is not without its limitations. Firstly, we recognise the descriptive nature of this study and acknowledge that the use of a cross-sectional study design limits its impact. Therefore, further research is needed before establishing any causality. However, we aimed to describe the ROM within an understudied and rare population across three different countries, and believe the findings can be effectively used by clinicians working with this group. Secondly, the data used in this study were secondary from a randomised clinical trial led by one of the authors. As such, all patients included in the study were diagnosed with AKU, meaning that comparisons to non-AKU populations involved accessing existing data from two published studies rather than our own control group. We also highlight that the sample size was relatively small when considering some sub-groupings (e.g. 64–75 women, $n = 1$). We also note that use of medication such as non-steroidal inflammatory drugs or other analgesics was unknown and may have impacted ROM. Further, the data in this study were limited to the hip, and there is scope to consider ROM in other joints. The reliability of the measurement approach, including intra- or inter-rater reliability of goniometry, was not established for this study. A standardised approach was adopted across each centre, and video recordings of each measurement technique were produced, supported by written and pictorial guidance. Measurements were undertaken by the same experienced clinicians at each site for the duration of the study.

This study is the first to show differences in active and passive ROM across three different movements for men and women, across the lifespan, and with reference to individuals without AKU. Our results provide important insights into the clinical value of ROM as an early indicator of disease progression and the functional ability of individuals with AKU. ROM of the hip can reveal

differences between those with and without AKU, which is more evident in older adults and female patients in particular. Our results can guide future studies and clinical practice, focusing on the long-term management and rehabilitation strategies for patients with AKU, considering the ochronotic changes to cartilage, tendons, and ligaments.

Acknowledgments

We would like to thank the participants who completed the SONIA 2 study. We also extend our thanks to Nadia Loftus who assisted with the data collection and early stages of this project.

Ethics statement

Ethical approval for the original study was granted by: EC Liverpool (NRES Committee North-West – Liverpool Central) Reference number: 13/NW/0567, EC Piešťany (NURCH Ethica Committee, National Institute of Rheumatic Diseases, Ivana Krasku 4,92101 Piešťany, Slovak Republic) Reference number: 04196/0029/001/001, and EC Paris (EC Ile De France II, hospital Necker 149 Rue de Sevres 75 743 Paris Cedex 15, Porte N2, 1er etage, France). Reference number: 2013-08-08.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The data used in this study was collected under funding from the European Commission Seventh Framework Programme (DevelopAKUre; project number 304985). No funding was received for the writing of this manuscript.

Data availability statement

Data can be provided upon reasonable request directed to Professor Lakshminarayan R Ranganath.

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