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# **Monitoring response to conventional treatment in children with XLH: Value of ALP and Rickets Severity Score (RSS) in a real world setting**

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## **Abbreviations:**

**ALP:** Alkaline Phosphatase

**FGF23:** Fibroblast Growth Factor 23

**RSS:** Rickets Severity Score

**PHEX:** Phosphate-regulating gene with homology to endopeptidases on X chromosome

**XLH:** X-linked Hypophosphataemia

## ABSTRACT

**Introduction:** X-linked hypophosphataemia (XLH) is conventionally managed with oral phosphate and active vitamin D analogues.

**Objectives:** To evaluate long term treatment response by assessing biochemical disease activity [serum alkaline phosphatase (ALP)], radiological rickets severity score (RSS), growth and morbidity in patients with XLH on conventional therapy and assess the correlation between serum ALP and RSS.

**Methods:** XLH patients from 3 UK tertiary centres with  $\geq 3$  radiographs one year apart were included. Data was collected retrospectively. The RSS was assessed from routine hand and knee radiographs and ALP z scores were calculated using age-specific reference data.

**Results:** Thirty-eight (male=12) patients met the inclusion criteria. The mean  $\pm$  SD knee, wrist and total RSS at baseline (median age 1.2 years) were  $2.0 \pm 1.2$ ,  $1.9 \pm 1.2$  and  $3.6 \pm 1.3$  respectively; and at the most recent clinic visit (median age 9.0 years, range 3.3-18.9) were  $1.6 \pm 1.0$ ,  $1.0 \pm 1.0$  and  $2.5 \pm 1.5$  respectively. The mean  $\pm$  SD serum ALP z scores at baseline and the most recent visit were  $4.2 \pm 2.3$  and  $4.0 \pm 3.3$ . Median height SDS at baseline and most recent visit were -1.2 and -2.1 ( $p=0.05$ ). Dental abscess, craniosynostosis, limb deformity requiring orthopaedic intervention and nephrocalcinosis were present in 31.5%, 7.9%, 31.6% and 42.1% of the cohort respectively. There was no statistically significant ( $p>0.05$ ) correlation between ALP z scores and knee ( $r=0.07$ ) or total ( $r=0.12$ ) RSS.

**Conclusions:** Conventional therapy was not effective in significantly improving biochemical and radiological features of disease. The lack of association between serum ALP and rickets severity on radiographs limits the value of ALP as the sole indicator of rickets activity.

## INTRODUCTION

Hypomineralisation resulting from low phosphate availability at the growth plate results in rickets, which is a radiological diagnosis. X-linked hypophosphataemic rickets (XLH) is the most common form of inherited rickets in children.<sup>1</sup> XLH is caused by a loss of function mutation in the *PHEX* (phosphate-regulating gene with homology to endopeptidases on X chromosome) gene which results in excessive concentrations of the hormone fibroblast growth factor 23 (FGF23).<sup>2</sup> Although the pathophysiology of XLH is complex, involving a range of molecular pathways, hypophosphatemia due to elevated FGF23 is the main disease contributor.<sup>3</sup> Excessive FGF23 results in renal phosphate wasting leading to hypophosphataemia and reduced synthesis of calcitriol (1,25 dihydroxy vitamin D) which leads to reduced gastrointestinal absorption of calcium and phosphate. Conventional treatment of XLH aims to address the above through administration of oral phosphate supplements and active vitamin D analogues such as alfacalcidol (1 $\alpha$ -Hydroxycholecalciferol) or calcitriol.<sup>4,5</sup>

One of the most important treatment goals in children with XLH is to heal rickets which is mainly assessed by normalisation of serum alkaline phosphatase (ALP) and resolution of radiological signs of rickets.<sup>6</sup> Early treatment initiation in children is reported to improve growth, radiological and biochemical outcome.<sup>7</sup> Oral phosphate is administered in multiple daily doses, given its short half-life, and dosing requires a careful balance between low doses leading to inadequate healing of rickets and high doses causing secondary hyperparathyroidism.<sup>6</sup> Similarly, alfacalcidol or calcitriol doses need adjusting to allow healing of rickets and maximise intestinal mineral absorption without causing hypercalciuria.<sup>6</sup> Despite optimum oral therapy, growth in affected children is often compromised<sup>8</sup> and significant morbidity impacts on the quality of life in both children and adults.<sup>9</sup>

Rickets severity score is a quantitative method based on the degree of metaphyseal fraying, concavity, and the proportion of the growth plate affected in the wrist and knee.<sup>10</sup> Total RSS or Thacher score assigns a score of 0 (no rickets) to 10 (severe rickets) based on metaphyseal changes at the wrist (scored from 0-4) and knee (scored from 0-6) joints.<sup>10</sup> RSS has been validated in nutritional rickets where it is reported to correlate well with the degree of ALP activity.<sup>10</sup> More recently, in a clinical trial setting, a slightly modified RSS has been shown to reliably predict biochemical, clinical and functional impairments in children with XLH receiving burosumab therapy, a fully human anti-FGF23 monoclonal antibody.<sup>11</sup> Descriptive grading systems have been used to report rickets severity in single centre cross-sectional studies of children with XLH on conventional therapy.<sup>7,12</sup> However, to the best of our knowledge, no studies have reported longitudinal radiological disease activity, in children on conventional therapy, using a validated RSS. We report results from disease activity monitoring during conventional therapy using a validated RSS and serum ALP levels in a longitudinal multi-centre retrospective study.

## **AIMS AND OBJECTIVES**

### **Aims**

Evaluate long term disease activity and morbidity due to complications in children with XLH on conventional therapy

### **Objectives**

#### ***Primary***

- 1) To report long term disease activity assessed by a validated RSS on wrist and knee radiographs and serum ALP levels

#### ***Secondary***

- 2) To assess the correlation between serum ALP levels and RSS
- 3) To assess the agreement between RSS on wrist and knee radiographs
- 4) To report the proportion of individuals with disease or treatment related complications of XLH i.e. dental abscess, craniosynostosis, limb deformities and nephrocalcinosis.

## **SUBJECTS AND METHODS**

In this multi-centre study, data was collected retrospectively on children and adolescents with a confirmed diagnosis of XLH. Longitudinal biochemical data representing disease activity was gathered and radiographs scored for rickets severity using a validated scoring system.<sup>10,11</sup>

### **Subjects:**

All patients receiving treatment for XLH at the time of the study (August – December 2017) at 3 UK tertiary centres were screened: 1) Birmingham Women's and Children's Hospital, Birmingham, 2) Nottingham Children's Hospital, Nottingham and 3) Royal Manchester Children's Hospital, Manchester.

### ***Inclusion criteria:***

1. Confirmed genetic diagnosis of XLH, with documented *PHEX* mutation, in the subject or a family member with X-linked dominant inheritance.
2. Patients with  $\geq 3$  radiographs of knee and/or wrist at least 1 year apart.

### ***Exclusion criteria:***

1. Patients with insufficient data on diagnosis or follow up
2. Patient with  $<3$  years follow up

### **Clinical and laboratory data:**

Data collected at routine clinical visits was gathered retrospectively from clinical notes and electronic health records. The following details were gathered: age at presentation, family history of XLH, treatment received (in dose per kg body weight), presence of dental abscesses, craniosynostosis, limb deformities requiring orthopaedic intervention and nephrocalcinosis. Data on serum ALP (and lab specific reference range) was gathered at diagnosis, most recent visit and around the time of radiographs.

Due to the variations in assays used for ALP measurements at different centres, ALP z scores were calculated (as below) using age- and sex-specific mean/standard deviation (SD) CALIPER reference data<sup>13</sup>.

**Step 1:**  $ALP\_logmean = [Ln(upper) + Ln(lower)]/2$ , where upper=upper limit of CALIPER published range for age group, lower=lower limit of range

**Step 2:**  $ALP\_logSD = [Ln(upper) - Ln(lower)]/4$

**Step 3:**  $ALP\_z\_score = [Ln(ALP) - ALP\_logmean] / ALP\_logSD$

"Ln" denotes the natural log (i.e. Log base e), SD= standard deviation

*Laboratory methods:* Serum ALP activities were determined using a dye-based assay, which measures the enzyme activity by monitoring the rate of hydrolysis of p-nitrophenylphosphate to p-nitrophenol at 410/480 nm in the presence of magnesium on the 182 Olympus AU640 analyser at centre 1. Similar dye-based assays were used and measurements performed on the Beckman AU5800 analyser at centre 2 and Roche Cobas 8000 c702 analyser at centre 3.

### **Radiographs and rickets severity score:**

Radiographs are generally performed at 2-3 yearly intervals<sup>4</sup> based on clinical indication at the treating clinician's discretion. Routinely performed radiographs were anonymised and electronically transferred to a single centre where they were scored for RSS by a consultant in metabolic bone disease (RP) and radiologist (RS). The clinicians did the scoring together and were blinded to patient details including timing of radiographs. The wrist was scored from 0-4 and knee from 0-6, with a higher number representing greater severity. Both knee (0-6) and

wrist (0-4) radiographs were scored where available and the scores added to obtain a total RSS or Thacher score (0-10). A slightly modified version<sup>11</sup> of the original scoring system<sup>10</sup> was used which is detailed in **Table 1**. The modified score allows for 0.5 point increments at the wrist rather than only 1.0 point increments. And for the knee, the method assigns a multiplier factor to the score at the femur and tibia: 0.5 if one condyle or plateau is affected, and 1.0 if both condyles or plateaus are affected.<sup>11</sup> Radiographs reported to have fused growth plates were excluded.

WRIST grade definitions for radius and ulna				TOTAL SCORE = Radius Grade + Ulna Grade		
0      Normal growth plate without changes of rickets						
0.5      Lucency of the metaphyseal margin without fraying or irregularity						
1      Widened growth plate, irregularity of the metaphyseal margin without concave cupping						
1.5      Partial metaphyseal concavity or incomplete fraying of metaphyseal margin						
2      Metaphyseal concavity with fraying of margins						
Grade radius	0	0.5	1	1.5	2	
Grade ulna	0	0.5	1	1.5	2	
					<b>Total</b>	
Knee grade definitions for femur and tibia				TOTAL SCORE = Femur grade x multiplier + Tibia grade x multiplier		
0      Normal growth plate without changes of rickets						
1      Partial lucency, smooth margin of metaphysis visible						
2      Partial lucency, smooth margin of metaphysis <b>NOT</b> visible						
3      Complete lucency, epiphysis appears widely separated from distal metaphysis						
Grade femur	0	1	2	3	<b>Femur Multiplier</b> One or less condyle or plateau affected = 0.5 Two condyles or plateaus affected = 1	
Grade tibia	0	1	2	3	<b>Tibia Multiplier</b> One or less condyle or plateau affected= 0.5 Two condyles or plateaus affected = 1	
				<b>Total</b>		

**Table 1:** Rickets severity grading scores used to assess the severity of rickets at wrist and knee joints<sup>11</sup>



**Statistical analysis:**

Descriptive statistics are presented as median (range) or mean (standard deviation (SD)) for continuous variables, and frequencies with percentages for categorical variables. Wilcoxon Signed Ranks test was used to compare knee and wrist RSS. Kappa statistics was used to assess the agreement between knee and wrist RSS. Mann-Whitney U test was used to compare baseline and most recent parameters (knee RSS, ALP z scores and height SDS) and to compare the frequency of complications in males and females. Spearman's correlation was used to determine the relation of serum ALP z scores to knee RSS, wrist RSS and total RSS. All statistical analyses were performed using the statistical software SAS V 9.4.

**Ethics:**

This is an observational study and since this project was undertaken as a routine service/therapy evaluation in the three UK centres, it did not require ethical approval.

## **RESULTS**

**General characteristics**

A total of thirty-eight (male=12) patients with a median age of 9.0 years (range 3.3-18.9) at the most recent clinic visit met the inclusion criteria. The median age at diagnosis/ baseline visit was 2.0 years (range 0.2-7.4). The mean follow-up duration was 8.4 ( $\pm$  5.2) years, with nearly 37% (n = 14) having > 10 years of follow up. Nearly half of the cohort (47.3%, n=18) were diagnosed in the first year of life. A family history of XLH was present in 71% (n=27) and the rest had genetic confirmation (29%, n=11).

All children were treated with oral phosphate and active vitamin D analogues commencing at diagnosis/ baseline visit following biochemical confirmation. Phosphate supplements were

started at a dose of 20mg/kg/day and titrated up to a maximum dose of 80 mg/kg/day based on tolerability and disease activity as per the treating clinician's discretion. Phosphate was usually administered in 3-6 divided doses through the day. Alfacalcidol, which is the vitamin D analogue of choice in the UK, was prescribed in a dose range of 30-50 ng/kg/day. At the most recent visit the median daily dose of phosphate and alfacalcidol were 52.6 mg/kg and 48.3 ng/kg respectively. At diagnosis, four children received high dose cholecalciferol (3000-6000 IU) for concomitant vitamin D deficiency and a further two were documented to be on long term maintenance supplements (400 – 600 IU daily).

### **Rickets severity score**

Knee radiographs were performed in 44.7% (17/38) of the cohort at baseline, of whom 35.3% (6/17) had both wrist and knee radiographs. The mean  $\pm$  SD knee, wrist and total RSS at baseline were  $2.0 \pm 1.2$ ,  $1.9 \pm 1.2$  and  $3.6 \pm 1.3$  respectively. At the most recent clinic visit, knee radiographs were available in 73.7% (28/38) of whom 25% (7/28) also had a wrist radiograph. The mean  $\pm$  SD knee, wrist and total RSS at the most recent clinic visit were  $1.6 \pm 1.0$ ,  $1.0 \pm 1.0$  and  $2.5 \pm 1.5$  respectively. There was no difference between knee RSS at baseline visit and most recent visit ( $p=0.2$ ). Longitudinal data on mean RSS values for all visits are listed in **Table 2** and represented in a line graph in **Figure 1**.

### **Serum ALP levels**

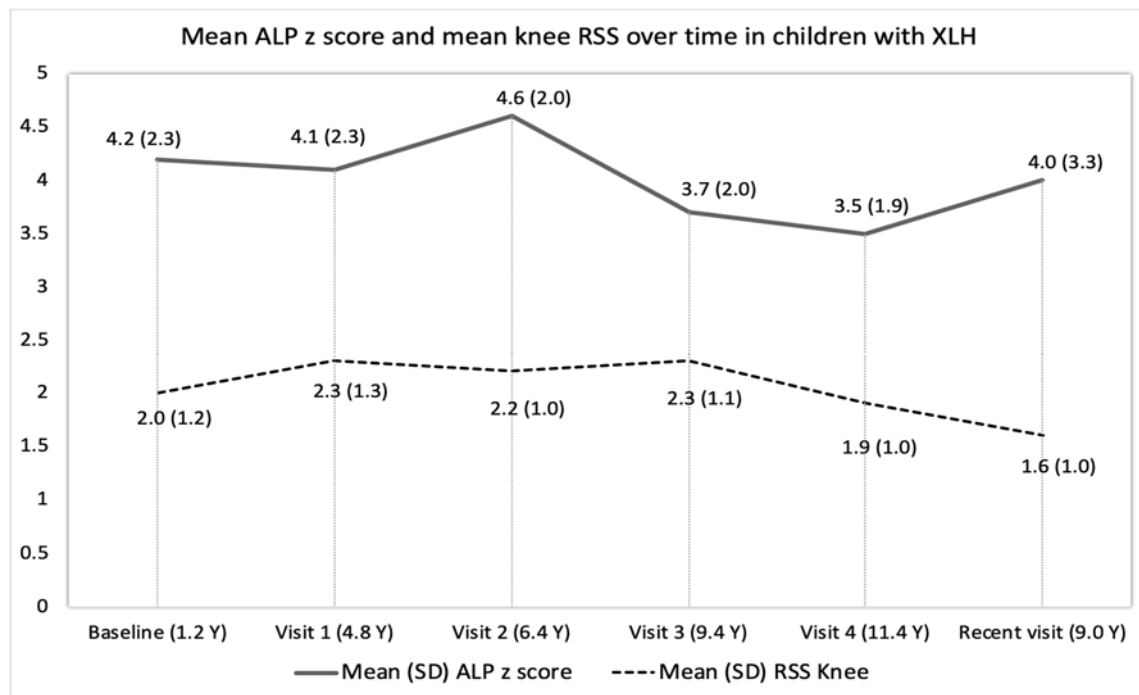
Serum ALP level was measured in the majority of patients at both baseline (92%, 35/38) and the most recent visit (100%, 38/38). The mean  $\pm$  SD serum ALP z scores at baseline and the most recent visit were  $4.2 \pm 2.3$  and  $4.0 \pm 3.3$  respectively. There was no significant difference

between baseline and most recent ALP z scores ( $p=0.4$ ). The longitudinal data on mean serum

ALP z score for each visit are detailed in **Table 2** and illustrated in a line graph in **Figure 1**.

	Age in years Median (range)	ALP z score Mean $\pm$ SD (n)	Knee RSS Mean $\pm$ SD (n)	Wrist RSS Mean $\pm$ SD (n)	Total RSS Mean $\pm$ SD (n)
Diagnosis/ baseline visit	1.2 (0.2-7.4)	4.2 $\pm$ 2.3 (35)	2.0 $\pm$ 1.2 (17)	1.9 $\pm$ 1.2 (7)	3.6 $\pm$ 1.3 (6)
Visit 1	4.8 (0.7-11.9)	4.1 $\pm$ 2.3 (32)	2.3 $\pm$ 1.3 (34)	0.6 $\pm$ 0.8 (9)	3.0 $\pm$ 1.1 (9)
Visit 2	6.4 (1.8-13.4)	4.6 $\pm$ 2.0 (26)	2.2 $\pm$ 1.0 (28)	0.5 $\pm$ 0.9 (7)	3.0 $\pm$ 1.7 (6)
Visit 3	9.4 (2.6-14.4)	3.7 $\pm$ 2.0 (18)	2.3 $\pm$ 1.1 (17)	0.0 $\pm$ 0.0 (4)	2.0 $\pm$ 0.9 (3)
Visit 4	11.4 (4.6-14.1)	3.5 $\pm$ 1.9 (9)	1.9 $\pm$ 1.0 (10)	0 (1)	1.5 (1)
Recent visit	9.0 (3.3-18.9)	4.0 $\pm$ 3.3 (38)	1.6 $\pm$ 1.0 (28)	1.0 $\pm$ 1.0 (11)	2.5 $\pm$ 1.5 (7)

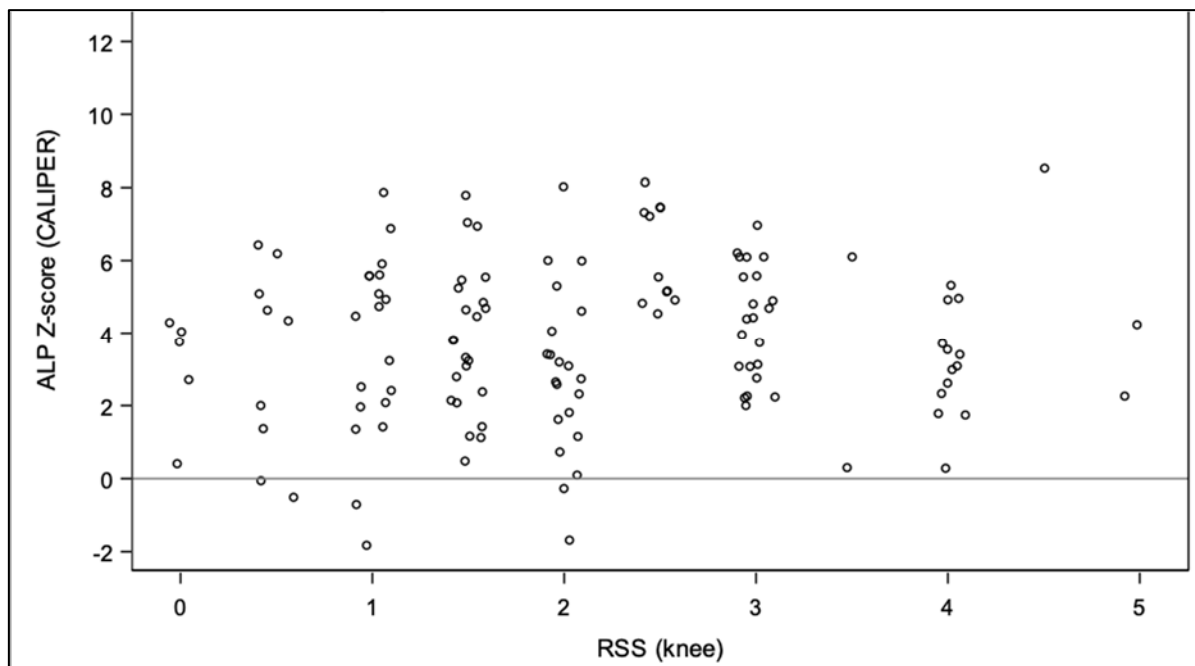
**Table 2:** Longitudinal data on the median age at each visit and mean ALP z scores and rickets severity scores (RSS) for knee, wrist and total.



**Figure 1:** Graphical representation of mean serum alkaline phosphatase z scores (ALP z scores) and knee rickets severity scores (RSS) over time in children with XLH on conventional therapy. The median age at each visit (in years) is represented in parenthesis on the x-axis.

### Correlation between ALP z scores and RSS

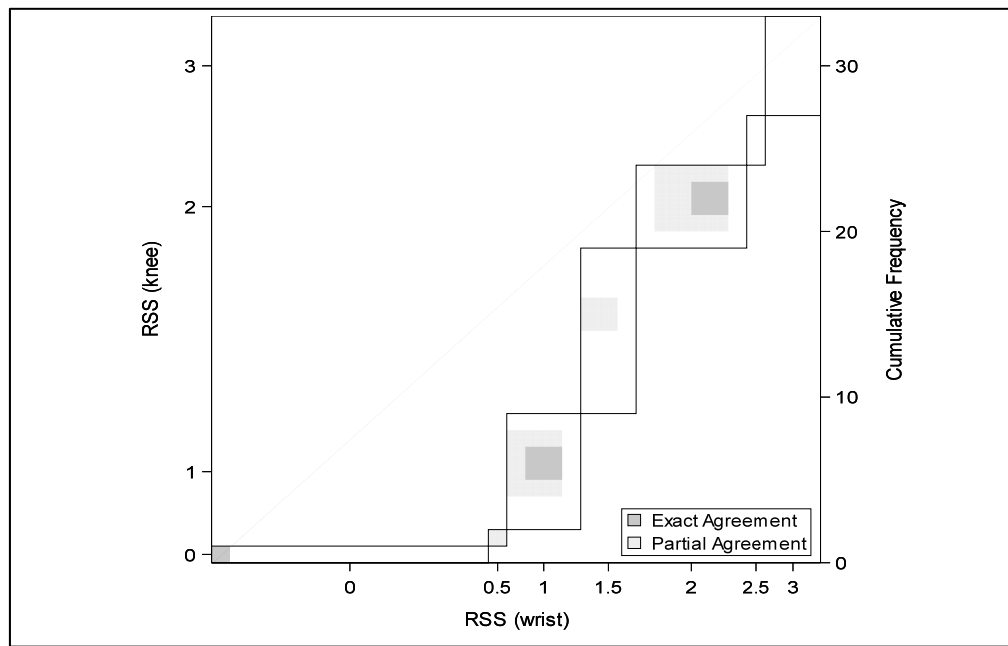
For all data points correlation between ALP z scores and knee RSS (n=127), wrist RSS (n=39) and total RSS (n=32) were determined. There was no statistically significant ( $p>0.05$ ) correlation between ALP z scores and Knee RSS ( $r=0.07$ ) **Figure 2**, wrist RSS ( $r=-0.01$ ) and total RSS ( $r=0.12$ ). The correlation at baseline and most recent visit were analysed separately, which were not statistically significant ( $p>0.05$ ).



**Figure 2:** For all data points (n=129), there was no correlation between ALP z scores and knee RSS ( $r=0.07$ ,  $p>.05$ ).

### Agreement between wrist and knee RSS

The wrist RSS was significantly lower than the knee RSS ( $p<0.001$ ) in the whole cohort (n=32). Only four patients had a wrist RSS  $>$  knee RSS at diagnosis, of whom three were aged under 9 months and one was 3.3 years and non-ambulatory due to co-existent developmental delay. There was no agreement between the wrist and knee RSS ( $k= 0.005$ ), **Figure 3**.



**Figure 3:** There is lack of agreement in the severity of rickets, as assessed by Rickets Severity Score (RSS), between the wrist and knee ( $k = 0.005$ ).

### Growth and Morbidity

The median height SDS at the most recent visit was lower than the height SDS at baseline (-2.1 vs -1.2 respectively,  $p=0.05$ ). The total and gender-based prevalence of complications identified are listed in **Table 3**. Dental abscesses were present in 31.5% (12/38) of the cohort, of whom 50% (6/12) had recurrent abscesses ( $\geq 3$ ) documented. Craniosynostosis was present in 7.9% of the cohort, all of whom were male. Lower limb bone deformities were present in 52.6% (20/38) of whom 60% (12/20) underwent orthopaedic interventions; more males ( $n=7$ ) underwent interventions when compared to females ( $n=5$ ). The most frequently recorded bony abnormalities were varus deformity (bowing) of the lower limb long bones (femur and tibia) followed by tibial torsion leading to intoeing gait. The most commonly performed corrective procedures were 8 plate insertion and epiphysiodesis followed by tibial osteotomy. Grade 3 nephrocalcinosis with chronic kidney disease stage 3 was only recorded in one patient, the rest

had grade 2 or grade 1 nephrocalcinosis. Onset of nephrocalcinosis ranged from 2-10 years from start of treatment. The timing of progression from grade 1 to 3 was variable and ranged from 3-12 years of treatment. Secondary hyperparathyroidism (defined as serum intact parathyroid hormone levels > upper limit of normal, normal range 10-55 pg/ml without hypercalcaemia) was present in 47.5% (n=18/38). None of the patients were noted to have tertiary hyperparathyroidism (elevated parathyroid hormone and hypercalcaemia). Chiari malformation was documented in four individuals (10.5%). Three patients complained of recurrent headaches of whom 1 had a Chiari malformation. Significant issues with non-adherence to treatment was documented in 3 patients.

<i>Study numbers</i>	<b>Total %(n)</b> 38	<b>Male %(n)</b> 12	<b>Female %(n)</b> 26	<b>Significance value (p)</b>
Dental abscess	31.5% (12)	58.3% (7)	19.2% (5)	0.01
Craniosynostosis	7.9% (3)	25% (3)	0	0.00
Orthopaedic interventions for bony deformities	21.0% (8)	8.3% (1)	26.9% (7)	0.29
Bony deformities without orthopaedic intervention	31.6% (12)	58.4% (7)	19.2% (5)	0.01
Nephrocalcinosis	42.1% (16)	41.6% (5)	42.3% (11)	0.56
Hyperparathyroidism	47.5% (18)	66.7% (8)	38.5% (10)	0.16

**Table 3:** Proportion of patients experiencing disease or treatment related morbidity

## DISCUSSION

This study has demonstrated that in children with XLH, there was ongoing evidence of radiological and biochemical disease activity on conventional therapy. There was a poor correlation between serum ALP z scores and rickets activity, as assessed by rickets severity scores (RSS) on radiographs, which indicates ALP's limited value as the sole indicator of disease activity on conventional therapy. Rickets severity was significantly lower on wrist than knee radiographs, except in children who were not weight bearing. Disease related morbidity such as dental abscess and craniosynostosis were more prevalent in males than females whereas treatment related morbidity such as nephrocalcinosis and secondary hyperparathyroidism were equally prevalent in both genders. Despite surgical correction, there was a reduction in height SDS at follow up, demonstrating poor growth.

We observed a high mean RSS at diagnosis and at subsequent follow up visits, which indicates the limitations of conventional therapy in complete healing of rickets. Previous imaging studies in patients with XLH have reported similar findings. A single centre prospective observational study evaluating the utility of knee MRI scans in assessing rickets severity reported active disease indicated by epiphyseal widening in 100% of the individuals studied (n=27).<sup>12</sup> Similarly, a cross-sectional study (total n=34 of whom 7/34 children on phosphate and calcitriol treatment) assessing volumetric bone mineral density (vBMD) using forearm peripheral quantitative computed tomography (pQCT) reported low mean (SD) cortical vBMD [-1.3 (-1.9 to -0.6)] at the radial diaphysis indicating a mineralization defect not entirely corrected by current treatment approaches.<sup>14</sup>

The mean serum ALP levels remained high at >+2 SDS throughout the study period indicating suboptimal control. Contrary to the report by Thacher et al,<sup>11</sup> we did not find a correlation between serum ALP and rickets severity on radiographs either at baseline or at follow up visits.

Thacher et al report findings from a clinical trial setting where most children achieved normalisation of ALP and healing of rickets, while we report real world data where there was evidence of ongoing disease activity. The lack of correlation observed in our cohort may potentially be due to variations in assay methodologies. Nonetheless, radiology is the gold standard for diagnosis of rickets and serum ALP should only be used as a surrogate marker at interim visits. Moreover, changes of rickets on radiographs, healing or worsening, is likely to lag behind changes in serum ALP.<sup>15</sup>

For the whole cohort RSS at wrist was significantly lower than that at the knee. Only a handful of non-ambulatory or non-weight bearing patients had more severe rickets in the wrist compared to knee. This finding is logical due to the effect of loading on the undermineralised growth plates. For the same reason, leg length has been recognised to be more affected than arm span in individuals with XLH.<sup>16</sup> Knee radiographs are therefore more useful for surveillance compared to wrist radiographs in ambulatory patients. Both knee and wrist radiographs may be useful in young infants but did not confer any added value in older children.

There is significant morbidity in children with XLH despite treatment. We observed a higher prevalence of disease related morbidity in males compared to females. Although there have been suggestions that hemizygous males respond less well to treatment than heterozygous females in this X-linked dominant condition,<sup>17,8</sup> there is no conclusive evidence to support the same.<sup>18</sup> Similarly, a higher prevalence of craniosynostosis in males has been reported in the literature<sup>19,20</sup> which we observed. Craniosynostosis was only noted in males in our cohort. Nephrocalcinosis on the other hand was equally prevalent in both genders and progression was very gradual.



Excess FGF23 is implicated in the majority of the morbidities associated with XLH.<sup>3</sup> Therefore, newer therapeutic agents such as burosumab which target the underlying pathology are expected to reduce these complications and improve quality of life. Burosumab has been shown to be effective in improving radiological and biochemical disease activity in a trial setting<sup>21,22</sup> and has been approved for clinical use in children.<sup>23</sup> Its effect on long term disease activity and morbidity in the real world setting is yet to be evaluated.

As with most real-world studies, our study had certain limitations. Radiographs were performed based on the clinician's discretion and therefore the frequency varied between centres and individual patients. There may be some variations in treatment approaches between various clinicians. Nonetheless, the data provided represent real-world experience of treating patients with XLH. The limitation posed by different laboratories using different ALP assays was overcome by converting these to standard z scores using age, gender and centre specific ALP reference range.

In conclusion, our study highlights that conventional therapy in this UK cohort was not effective in improving long term radiological and biochemical disease activity. Serum ALP should not be used as the sole indicator of disease activity. For accurate assessment of disease activity, we recommend knee radiographs at regular intervals, 1-2 yearly. Wrist or combined wrist and knee radiographs did not provide any additional benefit, except in non-ambulatory children.

**Conflict of interest:**

**SU:** Received research grant from Kyowa Kirin. **NJS:** Received consultancy fees from Kyowa Kirin. **MZM:** Received honorarium for lectures and advisory boards from Kyowa Kirin. **TR:** No potential conflicts of interest. **WH and RP:** Received grant for research trials, honorarium and travel grant from Ultragenyx and Kyowa Kirin. **RS: No conflict of interest.**

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**Contributorship:** **SU:** Conceptualisation, data curation, investigations, methodology, statistical analysis, original draft writing and final review. **NS:** Conceptualisation, Investigation, methodology and review and editing of manuscript. **MZM and TR:** review and editing of manuscript. **WH and RS:** Investigations, methodology, review and editing of manuscript. **RP:** Conceptualisation, data curation, investigations, methodology, review and editing of manuscript.

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