

Development of an X-ray–Based Bone Oxalosis Grading Scale to Assess Oxalate Accumulation in Patients with Primary Hyperoxaluria Type 1

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INTRODUCTION

- Primary hyperoxaluria type 1 (PH1) is a rare genetic disease in which hepatic oxalate overproduction can lead to kidney stones, nephrocalcinosis, kidney failure, and systemic oxalosis, a condition in which calcium oxalate is deposited in various tissues, including bone^{1,2}
- Radiological signs of bone oxalosis include dense and radiolucent metaphyseal bands, coarse trabeculation, vertebral “bone within a bone” appearance, and bulbous growth of rib ends^{3,4}
- Previously, no scale existed to grade the severity of bone oxalosis using x-rays

METHODS

- An x-ray grading scale to evaluate systemic oxalosis in specific bones was developed based on expert opinion
- Areas evaluated included the bilateral hands and wrists, hips (proximal femur), knees (distal femur, tibia, and fibula), and humeri (proximal only) as well as the spine and ribs
- Scores on individual items ranged from 0 to 4, except for spine and ribs, which ranged from 0 to 2 (higher values represent more advanced oxalosis)
- Fracture assessment was not included in the scale
- Eighty-five x-ray images from 5 pediatric patients with PH1 who had developed bone oxalosis were collected from charts at Shaare Zedek Medical Center (Jerusalem, Israel) and de-identified
- Two blinded, independent raters evaluated each x-ray image twice and assigned a numerical score to each applicable item on the scale
- Inter-rater and intra-rater reliability analyses were conducted using the weighted Cohen’s kappa statistic⁵ (Table 1)⁶; total weighted kappa estimates were generated by pooling all observed ratings for each evaluated area

Table 1. Reliability Interpretation⁶ of Kappa Statistic

Kappa	Strength of Agreement
<0.00	Poor
≥0.00–0.20	Slight
>0.20–0.40	Fair
>0.40–0.60	Moderate
>0.60–0.80	Substantial
>0.80–1.00	Almost perfect

RESULTS

- Total overall inter-rater and intra-rater kappa estimates demonstrated almost perfect agreement (Table 2)
- Overall inter-rater kappa estimates demonstrated the following:
 - Almost perfect agreement (kappa estimates of >0.80–1.0) was observed for the left hand/wrist, left hip, left knee (femur), and left humerus
 - An example of scoring results for the left hand/wrist is shown in Table 3. An example x-ray is shown in the Figure
 - Substantial agreement (kappa estimates of >0.60–0.80) was observed for the right hip, right knee (tibia), right humerus, spine, and ribs
 - Moderate agreement (kappa estimates of >0.40–0.60) was observed for the right knee (femur) and right knee (fibula)
 - The overall inter-rater kappa estimate for the left knee (fibula) demonstrated poor agreement (–0.08 [95% CI: –0.27 to 0.10])
 - Overall inter-rater kappa estimates for the right hand/wrist and left knee (tibia) were considered unreliable due to lack of variability in the data, and the standard errors were not estimable
- Overall intra-rater kappa estimates demonstrated the following:
 - Almost perfect agreement (kappa estimates of >0.80–1.00) was observed for the spine
 - Substantial agreement (kappa estimates of >0.60–0.80) was observed for the right knee (femur) and right knee (fibula)
- Most other overall intra-rater kappa estimates could not be calculated due to lack of variability in the estimates for one or both raters. In these instances, intra-rater kappa estimates for the first and second raters demonstrated moderate to almost perfect agreement (>0.40–1.00; left hand/wrist, right hip, left hip, left knee [femur], right knee [tibia], left knee [tibia], right humerus, left humerus, and ribs). For the left knee (fibula), intra-rater kappa estimates for the first and second raters were –0.14 (–0.34 to 0.05) and 1.00, respectively, and for the right hand/wrist, they were 1.00 and 0.00

Table 2. Total Overall Kappa Estimates^a

	Weighted Kappa (95% CI)/N ^b
Inter-rater	
Overall	0.83 (0.79–0.87)/479
First rating	0.82 (0.77–0.87)/242
Second rating	0.84 (0.79–0.89)/237
Intra-rater	
Overall	0.95 (0.93–0.97)/482
First rater	0.82 (0.77–0.87)/237
Second rater	0.97 (0.95–0.99)/245

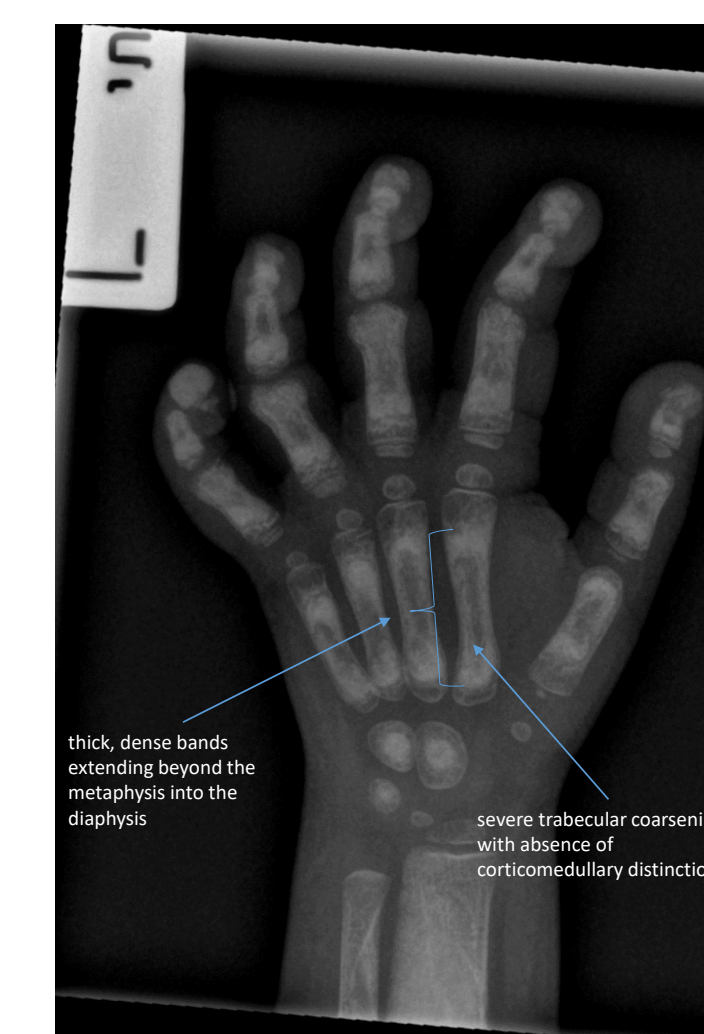
CI, confidence interval.
^aTotal kappa estimates were generated by pooling all observed ratings across all questions.
^bNumber of paired observations.

Table 3. Scoring for the Left Hand/Wrist^{a,b}

	Weighted Kappa (95% CI)/N ^c
Inter-rater	
Overall	0.83 (0.72–0.93)/54
First rating	0.76 (0.58–0.94)/27
Second rating	0.86 (0.73–0.99)/27
Intra-rater	
Overall	N/A (N/A)/54
First rater	0.76 (0.58–0.94)/27
Second rater	1.00 (N/A)/27

CI, confidence interval; N/A, not adequate.
^aTwenty-seven images contained the targeted bone. Overall intra-rater kappa estimate and asymptotic CI could not be calculated.
^bRight hand/wrist was assessed separately using the same criteria.
^cNumber of paired observations.

Figure. Left Hand/Wrist X-ray. Bone Oxalosis Grading Scale Score: 4



CONCLUSIONS

- We developed a novel x-ray–based bone oxalosis grading scale for patients with PH1
- Total overall weighted kappa estimates for inter-rater and intra-rater reliability demonstrated almost perfect strength of agreement
- Most individual items demonstrated reliable kappa estimates (in some cases, sample sizes were limited)
- The right and left knee (fibula) were removed from the scale due to poor reliability

ACKNOWLEDGEMENTS

We thank Travis Hillen and Andrew Kompel for serving as the raters. Medical writing and editorial assistance was provided by Peloton Advantage, LLC, an OPEN Health company, in accordance with Good Publication Practice (GPP 2022) guidelines and funded by Alnylam Pharmaceuticals.

FUNDING

Alnylam Pharmaceuticals

DISCLOSURES

J Baker: Consulting fees from Alnylam Pharmaceuticals.
J Bacchetta: Consulting fees from Alnylam Pharmaceuticals, Dicerna and Biocodex.
LC: Former employee of Alnylam Pharmaceuticals; currently employed with Alexion Pharmaceuticals.
JMG & RW: Employees of Alnylam Pharmaceuticals and hold shares in Alnylam Pharmaceuticals.
YF: Consultancy fees from Alnylam Pharmaceuticals and membership in the safety review committee.
RC-K: Consulting fees from Alnylam Pharmaceuticals and Medpace.

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