

Bone Mineral Density and Trabecular Bone Score in Adults With X-Linked Hypophosphatemia and Tumor-Induced Osteomalacia

Alberth Burnier

Hospital Las Higueras

Maria Paz Parodi

Pontificia Universidad Católica de Chile

Macarena Jimenez

Pontificia Universidad Católica de Chile

Luciana Pinto Valadares

Sarah Network of Rehabilitation Hospitals

Annette Madison

Pontificia Universidad Católica de Chile

Danisa Ivanovic-Zuvic

Hospital del Salvador

Maria Belen Zanchetta

Instituto de Diagnóstico e Investigaciones Metabólicas

Julieta Santagada

Instituto de Diagnóstico e Investigaciones Metabólicas

Pablo Florenzano

pflorenz@uc.cl

Pontificia Universidad Católica de Chile

Research Article

Keywords: X-linked hypophosphatemia, tumor-induced osteomalacia, DXA, trabecular bone score, FGF23, hypophosphatemia

Posted Date: October 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11194890/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: Competing interest reported. PF has received unrestricted institutional research grants from Ultragenyx Pharmaceutical and has been part of advisory boards for Ultragenyx Pharmaceutical Inc. and Kyowa Kirin. MBZ's institution receives funding from Ultragenyx Pharmaceutical Inc. for a global observational study of patients with tumor-induced osteomalacia. All other authors declare that they have no competing interests.

Abstract

Purpose

X-linked hypophosphatemia (XLH) and tumor-induced osteomalacia (TIO) are both driven by elevated fibroblast growth factor 23 (FGF23) and share overlapping clinical and biochemical features, making them difficult to distinguish. We aimed to compare bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA), trabecular bone score (TBS), and biochemical parameters between adults with XLH and TIO, and to identify DXA-based thresholds for their differential diagnosis.

Methods

Retrospective, multicenter observational study including 70 adults (46 XLH, 24 TIO) from three academic referral centers in Argentina, Brazil, and Chile. Biochemical parameters, DXA Z-scores at the lumbar spine, femoral neck, total hip, and forearm, and TBS Z-scores were compared between groups. Receiver operating characteristic (ROC) analyses with bootstrap confidence intervals assessed the discriminatory accuracy of DXA and TBS parameters.

Results

Patients with XLH presented significantly higher lumbar spine (median 1.95 vs. -2.40), femoral neck (-0.50 vs. -2.05), and total hip BMD Z-scores (0.30 vs. -2.25), as well as higher TBS Z-scores (1.80 vs. 0.00), than TIO patients (all $p < 0.001$). Forearm Z-scores did not differ significantly. ROC analyses showed excellent discrimination for lumbar spine (area under the curve [AUC] 0.914), total hip (AUC 0.914), and femoral neck Z-scores (AUC 0.893), and good discrimination for TBS (AUC 0.813). TIO patients showed more profound hypophosphatemia and markedly elevated alkaline phosphatase.

Conclusion

In adults with FGF23-mediated hypophosphatemia, lumbar spine and hip BMD Z-scores and TBS discriminate XLH from TIO with excellent accuracy. DXA-based phenotyping may support the diagnostic workup of FGF23-mediated bone diseases.

Introduction

Phosphate homeostasis is a complex process regulated mainly by fibroblast growth factor 23 (FGF23), a phosphaturic hormone that decreases renal phosphate reabsorption and suppresses the synthesis of 1,25-dihydroxyvitamin D [1]. Persistently elevated FGF23 levels results in chronic hypophosphatemia and impaired bone mineralization, manifesting as rickets in children and osteomalacia in adults. Within this

spectrum, X-linked hypophosphatemia (XLH) and tumor-induced osteomalacia (TIO) represent two of the most prevalent FGF23-mediated disorders [2].

XLH is the most common inherited form of hypophosphatemic rickets and is caused by inactivating mutations of the Phosphate Regulating Endopeptidase Homolog X-Linked (PHEX) gene leading to chronically elevated FGF23 levels [3]. In contrast, TIO is an acquired paraneoplastic syndrome caused by typically small, benign phosphaturic mesenchymal tumors that autonomously secrete FGF23 [4]. Despite differing in their underlying pathogenesis, both conditions present with overlapping clinical features, including bone pain, muscle weakness, and hypophosphatemia, that can hinder early diagnosis [5]. In TIO, insufficiency fractures are particularly prominent, and misdiagnosis is the rule rather than the exception, with rates exceeding 95% and diagnostic delays averaging nearly three years [5, 6].

Although these disorders share a common hormonal mechanism, XLH and TIO exhibit distinct skeletal manifestations. In adults with XLH, assessment of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) presents important interpretative challenges. Lumbar spine BMD may appear normal or even elevated due to enthesopathies or paraspinal calcifications, despite impaired bone quality [7]. In contrast, TIO is typically associated with severe reductions in BMD reflecting active osteomalacia and increased skeletal fragility [8]. Recent studies suggest that trabecular bone score (TBS) and microarchitectural assessments provide complementary information on bone quality that is not captured by areal BMD alone [8, 9].

Accurate differentiation between XLH and TIO is clinically critical, as management strategies differ fundamentally. Whereas XLH requires lifelong medical therapy, TIO is potentially curable through complete tumor resection. However, this distinction is not always straightforward in clinical practice. Adults with XLH may present with milder phenotypes and delayed diagnosis, particularly in the absence of a known family history and negative genetic testing. In contrast, in TIO, the causative tumor may be small, occult, or not readily identifiable on initial imaging studies. Earlier discrimination may streamline the diagnostic pathway, prioritizing tumor localization in patients most consistent with TIO and avoiding unnecessary extensive imaging in those with an XLH-like skeletal phenotype. Consequently, there is a need for additional, non-invasive diagnostic tools that may facilitate early distinction between these two entities.

From a biochemical perspective, both conditions typically present with hypophosphatemia and inappropriately low 1,25-dihydroxyvitamin D, but the magnitude of abnormalities may differ [2, 5]. Patients with TIO often exhibit more profound hypophosphatemia and higher alkaline phosphatase because of active osteomalacia [2]. FGF23 concentrations are frequently elevated in both entities, yet substantial overlap exists due to assay heterogeneity (intact vs C-terminal), timing of sampling relative to treatment, and inter-laboratory variability, which may limit the diagnostic utility of a single measurement at the individual level [10].

Despite these recognized biochemical differences, there is limited literature directly comparing densitometric patterns and trabecular bone quality between adults with XLH and TIO. While

densitometric patterns have demonstrated excellent discriminatory accuracy between TIO and XLH in pediatric populations, with a very good capacity of discrimination for lumbar spine Z-score, comparable data in adults remain scarce [11].

Therefore, the objective of this study was to describe and compare BMD and TBS in patients with XLH and TIO, and to identify DXA-based thresholds that may assist in their differential diagnosis. Additionally, differences in biochemical parameters of mineral metabolism were analyzed to further characterize the phenotypic profiles of both disorders.

Methods

Study design and population

This was a retrospective, multicenter observational study including adults with a diagnosis of X-linked hypophosphatemia (XLH) or tumor-induced osteomalacia (TIO) followed at three academic referral centers in Argentina, Brazil, and Chile. Patients evaluated between 2018 and 2025 were eligible for inclusion.

The diagnosis of XLH was confirmed by genetic testing. The diagnosis of TIO was based on characteristic clinical features, hypophosphatemia, low tubular reabsorption of phosphate (TRP), high or inappropriately normal levels of FGF-23, and the absence of a relevant family history. In cases in which tumor localization was unsuccessful, genetic testing was performed to exclude alternative diagnosis, including XLH. For tumor localization, all patients underwent a physical examination followed by 68Ga-DOTATATE PET/CT. If suspicious lesions were identified, ultrasound, CT, or MRI was performed at the corresponding anatomical sites.

Demographic, clinical, biochemical, imaging, and densitometric data were extracted from electronic health records at each participating center. For variables with repeated measurements, a single baseline value was selected per patient, obtained at diagnosis or, when unavailable, at the earliest subsequent visit, to preserve proximity to diagnosis and minimize treatment-related drift. In the XLH cohort, baseline was defined as the earliest available adult assessment. Missing data were not imputed, and the number of observations used for each analysis is reported.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committees of all participating centers. Given the retrospective design, the requirement for informed consent was waived.

Biochemical evaluation

Mineral metabolism parameters, including serum phosphate, alkaline phosphatase (ALP), parathyroid hormone (PTH), 25-hydroxyvitamin D (25-OHD), and intact fibroblast growth factor 23 (iFGF-23), were

quantified at participating academic centers using standardized automated platforms. Phosphate was assessed by UV phosphomolybdate colorimetry (Roche or Siemens), and ALP by IFCC kinetic enzymatic colorimetry (Roche or Siemens), with identical methodologies across all three centers permitting direct statistical comparison of absolute values. PTH was measured by electrochemiluminescence immunoassay (ECLIA, Roche) or two-site sandwich chemiluminescent immunoassay (CLIA, Siemens). 25-OHD was quantified by competitive ECLIA (Roche) or competitive CLIA (DiaSorin LIAISON or Siemens Atellica IM). iFGF-23 was measured by manual ELISA (Immutopics/Quidel).

Due to the use of divergent detection technologies for PTH and 25-OHD (ECLIA vs. CLIA), results for these analytes were not pooled for aggregate statistical comparison. As iFGF-23 was measured using the same ELISA platform across all participating centers, results are considered comparable and are reported alongside the other biochemical parameters.

Imaging and bone densitometry

Areal bone mineral density (aBMD) was assessed by dual-energy X-ray absorptiometry (DXA) at the lumbar spine, femoral neck, and total hip using standardized acquisition protocols at each center. BMD was measured by DXA using GE Lunar Prodigy equipment (GE Lunar), for both cohorts. Results were expressed as Z-scores according to manufacturer reference databases, consistent with international recommendations for secondary causes of bone disease. The following skeletal sites were analyzed using Z-scores: lumbar spine (L1-L4), femoral neck, total hip, forearm, and trabecular bone score (TBS), according to the latest ISCD guidelines [12].

Additional imaging studies, including conventional radiography and advanced imaging for tumor localization in patients with TIO, were reviewed when available and recorded as part of the clinical characterization.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation or median [interquartile range], according to distribution. Normality was assessed visually and with the Shapiro-Wilk test. Between-group comparisons used Student's t test or the Mann-Whitney U test, as appropriate; categorical variables were compared using Fisher's exact test. Receiver operating characteristic (ROC) analyses were performed for DXA Z-scores (lumbar spine, femoral neck, total hip, and forearm) and TBS Z-score; areas under the curve (AUC) with 95% confidence intervals were estimated, and optimal thresholds were identified using the Youden index. Sensitivity and specificity are reported with 95% confidence intervals. Two-sided p values < 0.05 were considered statistically significant. Analyses were conducted in R (version 4.3.1).

Results

Population characterization and biochemical findings

A total of 70 adults were included, 46 with XLH and 24 with TIO. Baseline characteristics are summarized in Table 1. Patients with TIO were significantly older at the time of assessment (median 49 vs. 33 years, $p<0.001$) and at diagnosis (median 42 vs. 3 years, $p<0.001$), consistent with the congenital nature of XLH versus the acquired onset of TIO. Sex distribution was similar between groups (female: 80.4% vs. 70.8%, $p=0.383$).

Fractures or pseudofractures were present in all TIO patients (100%) compared with 39.1% of those with XLH ($p<0.001$), reflecting the more acute and severe skeletal involvement of TIO. In the subset of TIO patients with available data on treatment initiation ($n=8$), the median time from diagnosis to treatment start was 2.0 years (IQR 0.8–4.0; range 0–27 years), highlighting the substantial diagnostic delays that can occur in this condition.

From a biochemical standpoint, individuals with TIO exhibited more profound hypophosphatemia (median 1.6 vs. 2.1 mg/dL, $p<0.001$) and markedly elevated alkaline phosphatase (median 324 vs. 122 U/L, $p<0.001$) compared to the XLH group. There were no significant differences in iFGF-23 levels between the two groups. Descriptive findings for PTH and 25-hydroxyvitamin D are detailed in **Table 1**; however, due to the utilization of divergent detection technologies and assay heterogeneity across participating centers, aggregate statistical intergroup comparisons were not conducted for these specific analytes.

Table 1. Baseline demographic, clinical, and biochemical characteristics

	XLH	TIO	p value	n
	(n = 46)	(n = 24)		
Demographics				
Age (years)	33 [24–41]	49 [41–59]	<0.001	46 / 24
Age at diagnosis (years)	3 [2–8]	42 [37–50]	<0.001	42 / 24
Female sex, n (%)	37 (80.4%)	17 (70.8%)	0.383	46 / 24
Fractures				
Presence of fractures, n (%)	18 (39.1%)	24 (100%)	<0.001	46 / 24
Biochemical parameters				
Serum phosphate (mg/dL)	2.1 [1.9–2.3]	1.6 [1.4–1.8]	<0.001	46 / 24
Alkaline phosphatase (U/L)	122 [94–164]	324 [188–484]	<0.001	46 / 24
PTH (pg/mL)	73 [58–105]	73 [57–109]	—	46 / 24
25-OH Vitamin D (ng/mL)	28 [20–39]	37 [29–44]	—	46 / 24
iFGF-23 (pg/mL)‡	107 [66–133]	116 [46–179]	0.837	21 / 17

Continuous variables are expressed as median [interquartile range]. Between-group comparisons used the Mann–Whitney U test for continuous variables and Fisher’s exact test for categorical variables.

‡ iFGF-23 was available in 21/46 XLH and 17/24 TIO patients; measured by the same ELISA platform (Immutopics/Quidel) across all centers, permitting intergroup comparison.

Abbreviations: PTH, parathyroid hormone; iFGF-23, intact fibroblast growth factor 23; XLH, X-linked hypophosphatemia; TIO, tumor-induced osteomalacia; —, not compared; n, number of patients with available data (XLH/TIO).

DXA, trabecular bone score, and diagnostic performance

Baseline densitometric data included lumbar spine Z-scores for 46 adults with XLH and 22 with TIO, along with femoral neck (n=38/18), total hip (n=37/18), TBS (n=31/21), radius 33% (n=37/20), and ultradistal radius (radius UD) (n=25/17). Lumbar spine, femoral neck, and total hip Z-scores were significantly higher in XLH than in TIO (all $p < 0.001$), whereas forearm measurements at both the radius 33% and radius UD sites did not differ between groups ($p = 0.757$ and $p = 0.155$, respectively). The most pronounced differences were observed at the lumbar spine (XLH median 1.95 [IQR 0.62–3.30] vs. TIO -2.40 [-3.48 to -0.80]); at weight-bearing hip sites, XLH Z-scores remained near or above the reference mean (femoral neck -0.50 ; total hip 0.30), while TIO values were profoundly reduced (-2.05 and -2.25 ,

respectively). TBS was significantly lower in TIO (median 0.00 [IQR -1.10 to 0.60]) than in XLH (median 1.80 [IQR 0.60–2.65]; $p < 0.001$), confirming greater microarchitectural deterioration in this condition.

Table 2. DXA and trabecular bone score parameters

Site (Z-score)	XLH	TIO	p value
Lumbar spine (L1-L4)	1.95 [0.62, 3.30] (n=46)	-2.40 [-3.48, -0.80] (n=22)	<0.001
Femoral neck	-0.50 [-1.10, 0.20] (n=38)	-2.05 [-3.00, -1.50] (n=18)	<0.001
Total hip	0.30 [-0.70, 0.90] (n=37)	-2.25 [-2.90, -1.92] (n=18)	<0.001
Forearm (radius 33%)	-1.60 [-2.60, -1.10] (n=37)	-1.80 [-2.73, -1.27] (n=20)	0.757
Forearm (radius UD)	-0.50 [-1.70, 0.20] (n=25)	-1.20 [-2.50, 0.00] (n=17)	0.155
TBS	1.80 [0.60, 2.65] (n=31)	0.00 [-1.10, 0.60] (n=21)	<0.001

Values are median [interquartile range]. Between-group comparisons by Mann–Whitney U test. Abbreviations: TBS, trabecular bone score; TIO, tumor-induced osteomalacia; UD, ultradistal; XLH, X-linked hypophosphatemia.

Boxplots display median and interquartile range; whiskers extend to 1.5× IQR. The dashed horizontal line marks Z-score = 0. Sample sizes are shown on the x-axis for each group. p-values (Mann–Whitney U test) are shown above each pair. Abbreviations: TBS, trabecular bone score; TIO, tumor-induced osteomalacia; UD, ultradistal; XLH, X-linked hypophosphatemia.

ROC analyses demonstrated excellent discrimination between XLH and TIO for lumbar spine, femoral neck, and total hip Z-scores, and good discrimination for TBS Z-score (Table 3, Figure 2). Lumbar spine Z-score achieved an AUC of 0.914 (95% CI 0.808–0.981); a cutoff of ≥ 0.6 classified XLH with sensitivity 80.4% (95% CI 66.8–89.3) and specificity 90.9% (72.2–97.5). Total hip Z-score yielded an equivalent AUC of 0.914 (95% CI 0.824–0.980); a cutoff of ≥ -1.5 classified XLH with sensitivity 89.2% (95% CI 75.3–95.7) and specificity 88.9% (67.2–96.9). Femoral neck Z-score showed an AUC of 0.893 (95% CI 0.787–0.972), with a cutoff of ≥ -1.1 yielding sensitivity 76.3% (60.8–87.0) and specificity 94.4% (74.2–99.0). TBS Z-score provided good additional discriminatory value (AUC 0.813, 95% CI 0.681–0.920); a cutoff of ≥ 0.4 achieved sensitivity 83.9% (67.4–92.9) and specificity 71.4% (50.0–86.2). Forearm Z-score showed

poor discrimination and was not included in ROC analyses. Optimal thresholds were identified using the Youden index and are marked on **Figure 2**.

Table 3. ROC-derived diagnostic performance of DXA and TBS parameters (classification of XLH vs TIO)

Parameter	AUC (95% CI)	Cutoff (XLH if $\geq$)	Sensitivity	Specificity	n (XLH/TIO)
Lumbar spine Z	0.914 (0.808–0.981)	0.6	80.4% (66.8–89.3)	90.9% (72.2–97.5)	46/22
Femoral neck Z	0.893 (0.787–0.972)	–1.1	76.3% (60.8–87.0)	94.4% (74.2–99.0)	38/18
Total hip Z	0.914 (0.824–0.980)	–1.5	89.2% (75.3–95.7)	88.9% (67.2–96.9)	37/18
TBS Z	0.813 (0.681–0.920)	0.4	83.9% (67.4–92.9)	71.4% (50.0–86.2)	31/21

AUC, area under the curve. 95% CI for AUC estimated by bootstrap (2000 iterations). Sensitivity and specificity 95% CIs estimated by the Wilson score method. Optimal cutoffs identified by the Youden index. Positive test defined as Z-score $\geq$ cutoff for all sites (i.e., values above threshold favor XLH).

Each curve represents the ROC analysis for a single DXA or TBS parameter. Filled circles mark the optimal operating point identified by the Youden index. The dashed diagonal represents chance discrimination. AUC values and 95% bootstrap confidence intervals are shown in the legend.

Abbreviations: AUC, area under the curve; TBS, trabecular bone score.

Discussion

In this multicenter, retrospective study of 46 adults with XLH and 24 with TIO, distinct densitometric and microarchitectural profiles were identified despite their shared FGF23-mediated mechanism. Lumbar spine Z-scores were markedly elevated in XLH, reflecting enthesopathy and periosteal apposition rather than preserved bone quality, whereas hip Z-scores and TBS were profoundly reduced in TIO, yielding excellent to good diagnostic discrimination across all axial skeletal sites (AUC 0.813–0.914). Importantly, this study extends previous observations by providing practical ROC-derived DXA thresholds that may assist clinicians in the early phenotypic differentiation of XLH and TIO. Forearm Z-scores did not differ between groups, suggesting comparable peripheral cortical involvement regardless of etiology.

The value of densitometric assessment in FGF23-mediated hypophosphatemia has been increasingly recognized, yet systematic comparisons between XLH and TIO in adults remain scarce. Beck-Nielsen et al. attributed elevated spine Z-scores in hypophosphatemic rickets to structural alterations rather than preserved bone quality [7]. Similarly, in a large comparison of XLH and TIO, DeCorte et al. reported higher spine Z-scores in XLH and profoundly reduced hip Z-scores in TIO, a pattern fully consistent with the

present findings [2]. The present study extends these observations to a multicenter adult cohort, incorporating site-specific Z-scores and TBS to provide a more comprehensive densitometric framework for early discrimination between these entities.

Reflecting the acquired onset of the condition, individuals with TIO were significantly older at diagnosis and presented with a clinical picture consistent with acute, active osteomalacia: more profound hypophosphatemia, markedly elevated alkaline phosphatase, a substantially higher incidence of skeletal fractures, and the presence of significant diagnostic delays. Nevertheless, considerable overlap was observed across several biochemical parameters, including iFGF-23 levels, which must be interpreted cautiously given the limited number of available measurements and the potential influence of the timing of sampling relative to therapy. Taken together, these clinical and biochemical features underscore the need for complementary, non-invasive tools to facilitate early discrimination, of which the densitometric profile, particularly hip Z-scores and TBS, emerges as a particularly informative candidate.

Hip measurements offered the most robust clinical discrimination. Total hip and femoral neck Z-scores were profoundly reduced in TIO relative to XLH, and ROC-derived thresholds — total hip $Z \geq -1.5$ (AUC 0.914) and femoral neck $Z \geq -1.1$ (AUC 0.893), both favoring XLH, achieved high sensitivity and specificity. Beyond demonstrating diagnostic discrimination, these thresholds provide practical imaging markers that may support the initial evaluation of adults with FGF23-mediated hypophosphatemia before definitive genetic testing or tumor localization. These results reflect the expected phenotype: rapid-onset osteomalacia in TIO drives pronounced bone loss at weight-bearing sites, whereas XLH displays a lifelong adaptive skeletal response. In contrast, forearm Z-scores did not differ significantly between groups, suggesting that peripheral cortical involvement is comparable across etiologies and less useful for differential diagnosis.

Lumbar spine Z-scores were markedly elevated in XLH, reflecting the well-recognized confounding effects of enthesopathy and paraspinal calcifications on areal BMD in adults with long-standing disease [2,7]. Despite this structural confounding, lumbar spine Z-score demonstrated excellent discriminatory performance on ROC analysis (AUC 0.914) and should therefore not be dismissed, rather, it must be interpreted in conjunction with hip measurements and TBS, never in isolation, to avoid misclassification. In clinical practice, a markedly elevated lumbar spine Z-score in the context of hypophosphatemia should raise strong suspicion for XLH, while a severely negative value combined with a high fracture burden should prompt consideration of TIO.

TBS further complemented areal DXA by capturing microarchitectural deterioration not reflected in areal BMD alone. TBS Z-scores were significantly lower in TIO and demonstrated good diagnostic performance (AUC 0.813), consistent with published data using both HR-pQCT [8] and TBS [9]. A similar discriminative pattern has been described in pediatric populations: Jiajue et al. reported that lumbar spine Z-score, together with age at onset and FGF23, each achieved an AUC of 1.0 for distinguishing TIO from XLH in children and adolescents [11], further supporting the biological plausibility of these densitometric findings across age groups. Integrating hip DXA with TBS and core biochemistry may

therefore streamline the diagnostic pathway, particularly in adults with atypical presentations or incomplete prior records. Rather than replacing biochemical or genetic evaluation, the ROC-derived DXA thresholds proposed in this study provide a practical framework for early phenotypic classification, potentially helping clinicians prioritize tumor localization in patients most consistent with TIO while recognizing an XLH-compatible skeletal phenotype before extensive imaging investigations.

This study has limitations inherent to its retrospective design, including missing data, particularly for iFGF-23 (available in 21/46 XLH and 17/24 TIO patients), and referral bias. PTH and 25-hydroxyvitamin D were measured using different assay platforms across centers and are therefore reported descriptively, without formal between-group statistical comparison. Although serum phosphate, ALP, and iFGF-23 were measured using the same analytical methodology across all centers, the assays were performed on instruments from different manufacturers, each with their own proprietary calibration and reference ranges; these inter-manufacturer differences should be taken into account when interpreting absolute values and applying the reported thresholds to other clinical settings. Because the proposed thresholds were derived from this cohort, prospective validation in independent cohorts with harmonized biochemical measurement protocols will be required before routine clinical implementation.

In conclusion, axial Z-scores and TBS offer a distinctive phenotypic profile in adults with FGF23-mediated hypophosphatemia, providing critical diagnostic information beyond standard biochemical assays for distinguishing XLH from TIO. Total hip and femoral neck Z-scores above the identified thresholds (≥ -1.5 and ≥ -1.1 , respectively) serve as robust indicators favoring XLH with high sensitivity and specificity, whereas profound hypophosphatemia, markedly elevated alkaline phosphatase, and severely negative axial Z-scores should raise suspicion for TIO. Lumbar spine Z-score demonstrated excellent discriminatory performance; however, because it is frequently elevated in XLH due to enthesopathies and paraspinal calcifications, it should be integrated with hip measurements and TBS rather than interpreted as a stand-alone parameter. Integrating this densitometric profile with core biochemistry may help guide the diagnostic algorithm at an early stage, prioritizing tumor localization in patients most consistent with TIO and avoiding extensive unnecessary imaging in those with an XLH-compatible skeletal phenotype. Prospective studies with larger cohorts and standardized biochemical protocols are needed to validate the proposed thresholds and incorporate this densitometric profile into routine clinical management.

Declarations

Funding

This study was partially funded by an unrestricted institutional research grant from Ultragenyx Pharmaceutical Inc.

Competing Interests

PF has received unrestricted institutional research grants from Ultragenyx Pharmaceutical and has been part of advisory boards for Ultragenyx Pharmaceutical Inc. and Kyowa Kirin. MBZ's institution receives funding from Ultragenyx Pharmaceutical Inc. for a global observational study of patients with tumor-induced osteomalacia. All other authors declare that they have no competing interests.

Ethics Approval

All procedures were performed in accordance with the ethical standards of the institutional research committees and with the 1964 Declaration of Helsinki and its later amendments. The study was approved by the ethics committees of each participating center: the Scientific Ethics Committee of the Pontificia Universidad Católica de Chile, Santiago, Chile; the Research Ethics Committee of the SARAH Network of Rehabilitation Hospitals, Brasília, Brazil; and the Research Ethics Committee CEI-INAPSI, Buenos Aires, Argentina.

Consent to Participate

Given the retrospective design, the requirement for informed consent was waived by the ethics committees of all participating centers.

Data Availability

The datasets generated and analyzed during the current study are not publicly available due to patient privacy restrictions but are available from the corresponding author on reasonable request, subject to approval by the participating ethics committees.

Author Contributions

Conceptualization: AB, PF; Methodology: AB, MPP, MJ, PF; Data collection: AB, MPP, MJ, LPV, ALM, DIZ, MBZ, JS; Data curation and validation: AB; Formal analysis: AB, MPP; Writing – original draft: AB and MPP (lead), MJ (supporting); Writing – review and editing: PF, DIZ, ALM, MBZ, JS, LPV; Supervision: PF. All authors read and approved the final manuscript. PF is the guarantor of this work.

References

1. Álvarez-Rivas N, Lugo-Rodríguez G, Maneiro JR, Iñiguez-Ubiaga C, Melero-Gonzalez RB, Iglesias-Cabo T, Carmona L et al (2024) Tumor-induced osteomalacia: a systematic literature review. *Bone Rep* 21:101772. <https://doi.org/10.1016/j.bonr.2024.101772>
2. DeCorte J, Randazzo E, Black M, Hendrickson C, Dahir K (2022) Rare diseases that impersonate one another: X-linked hypophosphatemia and tumor-induced osteomalacia, a retrospective analysis of discriminating features. *JBMR Plus* 6:e10580. <https://doi.org/10.1002/jbm4.10580>
3. Beck-Nielsen SS, Mughal Z, Haffner D, Nilsson O, Levtchenko E, Ariceta G, de Lucas Collantes C et al (2019) FGF23 and its role in X-linked hypophosphatemia-related morbidity. *Orphanet J Rare Dis* 14:58. <https://doi.org/10.1186/s13023-019-1014-8>

4. Folpe AL (2019) Phosphaturic mesenchymal tumors: a review and update. *Semin Diagn Pathol* 36:260–268. <https://doi.org/10.1053/j.semdp.2019.07.002>
5. Brandi ML, Clunie GPR, Houillier P, Jan de Beur SM, Minisola S, Oheim R, Seefried L (2021) Challenges in the management of tumor-induced osteomalacia (TIO). *Bone* 152:116064. <https://doi.org/10.1016/j.bone.2021.116064>
6. Feng J, Jiang Y, Wang O, Li M, Xing X, Huo L, Li F et al (2017) The diagnostic dilemma of tumor induced osteomalacia: a retrospective analysis of 144 cases. *Endocr J* 64:675–683. <https://doi.org/10.1507/endocrj.EJ16-0587>
7. Beck-Nielsen SS, Brusgaard K, Rasmussen LM, Brixen K, Brock-Jacobsen B, Poulsen MR, Vestergaard P et al (2010) Phenotype presentation of hypophosphatemic rickets in adults. *Calcif Tissue Int* 87:108–119. <https://doi.org/10.1007/s00223-010-9373-0>
8. Zanchetta MB, Jerkovich F, Nuñez S, Mocarbel Y, Pignatta A, Elías N, Díaz AG et al (2021) Impaired bone microarchitecture and strength in patients with tumor-induced osteomalacia. *J Bone Min Res* 36:1502–1509. <https://doi.org/10.1002/jbmr.4325>
9. Ni X, Feng Y, Guan W, Chi Y, Li X, Gong Y, Zhao N et al (2022) Bone impairment in a large cohort of Chinese patients with tumor-induced osteomalacia assessed by HR-pQCT and TBS. *J Bone Min Res* 37:454–464. <https://doi.org/10.1002/jbmr.4476>
10. Heijboer AC, Cavalier E (2023) The measurement and interpretation of fibroblast growth factor 23 (FGF23) concentrations. *Calcif Tissue Int* 112:258–270. <https://doi.org/10.1007/s00223-022-00987-9>
11. Jiajue R, Ni X, Jin C, Huo L, Wu H, Liu Y, Jin J et al (2021) Early discrimination between tumor-induced rickets/osteomalacia and X-linked hypophosphatemia in Chinese children and adolescents: a retrospective case-control study. *J Bone Min Res* 36:1739–1748. <https://doi.org/10.1002/jbmr.4331>
12. Krueger D, Tanner SB, Szalat A, Malabanan A, Prout T, Lau A, Rosen HN et al (2024) DXA reporting updates: 2023 official positions of the International Society for Clinical Densitometry. *J Clin Densitom* 27:101437. <https://doi.org/10.1016/j.jocd.2023.101437>

Figures

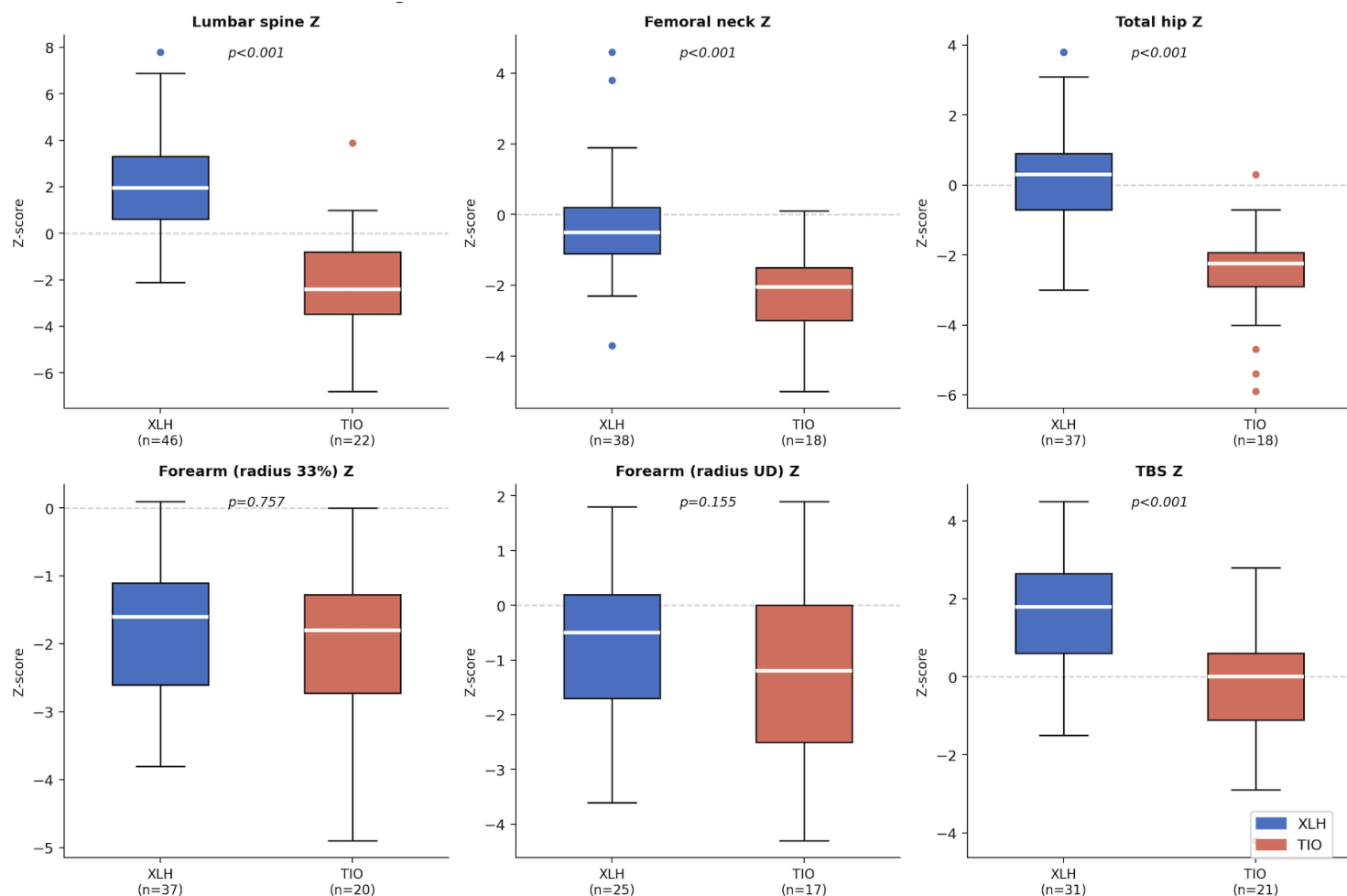


Figure 1

DXA and TBS Z-scores in adults with XLH vs TIO

Boxplots display median and interquartile range; whiskers extend to 1.5× IQR. The dashed horizontal line marks Z-score = 0. Sample sizes are shown on the x-axis for each group. p-values (Mann–Whitney U test) are shown above each pair. Abbreviations: TBS, trabecular bone score; TIO, tumor-induced osteomalacia; UD, ultradistal; XLH, X-linked hypophosphatemia.

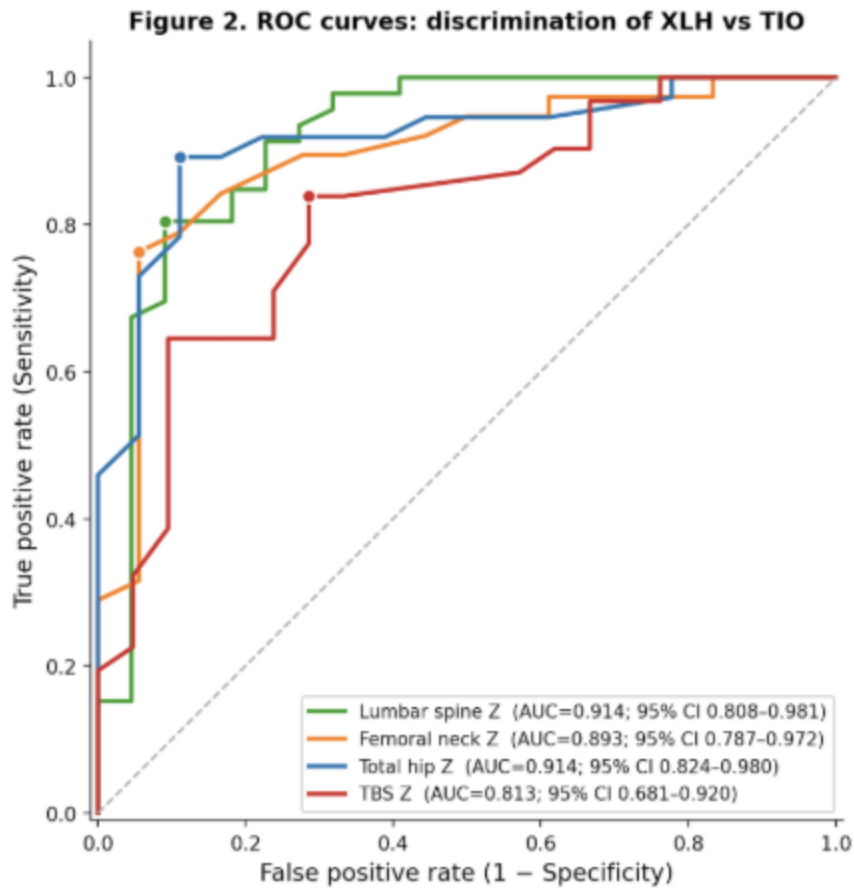


Figure 2

ROC curves: discrimination of XLH vs TIO

Each curve represents the ROC analysis for a single DXA or TBS parameter. Filled circles mark the optimal operating point identified by the Youden index. The dashed diagonal represents chance discrimination. AUC values and 95% bootstrap confidence intervals are shown in the legend.

Abbreviations: AUC, area under the curve; TBS, trabecular bone score.