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ORIGINAL ARTICLE

High FGF23 levels are associated with impaired trabecular bone microarchitecture in patients with osteoporosis

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Abstract

Summary This cross-sectional study examined the associations between c-terminal FGF23 levels, laboratory markers of bone metabolism and bone microarchitecture in 82 patients with osteoporosis. Higher FGF23 levels were associated with impaired trabecular but not cortical bone microarchitecture, and this was confirmed after adjusting for confounding variables such as age or BMI.

Introduction Fibroblast growth factor 23 (FGF23) is an endocrine hormone-regulating phosphate and vitamin D metabolism. While its mode of action is well understood in diseases such as hereditary forms of rickets or tumor-induced osteomalacia, the interpretation of FGF23 levels in patients with osteoporosis with regard to bone microarchitecture is less clear.

Methods C-terminal FGF23 levels and bone turnover markers were assessed in 82 patients with osteoporosis (i.e., DXA T-score ≤ -2.5 at the lumbar spine or total hip). Bone microarchitecture was measured by high-resolution peripheral quantitative computed tomography (HR-pQCT) at the distal radius and tibia. Data were analyzed in a cross-sectional design using correlation and regression models.

Results We found a significant negative logarithmic correlation between FGF23 levels and trabecular but not cortical bone microarchitecture at both skeletal sites. Furthermore, using a multiple linear regression model, we confirmed FGF23 as a predictor for reduced trabecular parameters even when adjusting for confounding factors such as age, BMI, phosphate, bone-specific alkaline phosphatase, vitamin D3, and PTH.

Conclusions Taken together, high FGF23 levels are associated with impaired trabecular bone microarchitecture in osteoporosis patients, and this association seems to occur after adjustment of confounding variables including phosphate and vitamin D. Future longitudinal studies are now needed to validate our findings and investigate FGF23 in relation to fracture risk.

Keywords Bone microarchitecture · FGF23 · HR-pQCT · Osteoporosis

Introduction

Fibroblast growth factor 23 (FGF23) is an endocrine hormone produced primarily by osteocytes that regulates phosphate and vitamin D levels. More specifically, it causes phosphaturia through downregulation of sodium-phosphate cotransporter expression (NaPi-IIa) in the proximal tubule of the kidney [1], while the production of 1,25-dihydroxyvitamin D is suppressed through inhibition of 25-hydroxyvitamin D-1α-hydroxylase and stimulation of 24-hydroxylase [2]. FGF23 was originally discovered through its mode of action in both hereditary and acquired disorders of phosphate metabolism leading to severe mineralization defects, i.e., autosomal dominant hypophosphatemic rickets (ADHR) [3] and tumor-induced osteomalacia (TIO) [4], respectively. However, FGF23 is also oversecreted in other rare genetic diseases [5], in response to high dietary phosphate intake [6] as well as in situations of impaired phosphate excretion, such as chronic kidney disease (CKD) [7].

While the connection between the severe clinical phenotype of impaired bone mineralization and phosphate wasting

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is clear in diseases such as ADRH or TIO, the role of FGF23 in relation to bone mineral density (BMD) and fracture risk is less evident in larger patient cohorts with no primary phosphate disorders. In fact, previous studies have found weak significant correlations between FGF23 and bone mineral density (BMD), which became insignificant when adjusting for confounding variables such as age or BMI [8]. Longitudinal studies on FGF23 and fracture risk showed conflicting results, where both no associations [9, 10] and positive associations [11] were found.

Regarding fracture risk assessment, DXA remains the most widely available tool to perform BMD measurements. High-resolution peripheral quantitative computed tomography (HR-pQCT) represents a three-dimensional tool that can assess volumetric bone mineral density as well as bone microarchitecture. Fracture risk correlates with the microarchitecture parameters assessed by HR-pQCT independently from BMD assessed by DXA, which highlights the additional benefit of this technique regarding fracture risk prediction [12–15]. To date, there is no available data regarding FGF23 levels in relation to microarchitecture parameters of bone. Herein, we investigated the association between C-terminal FGF23 levels and bone microarchitecture in a cohort of patients with osteoporosis according to DXA T-score (i.e., T-score ≤ -2.5).

Methods

Patients

Four hundred sixty-two patients from our outpatient clinic were assessed by dual-energy X-ray absorptiometry (DXA, Lunar iDXA, GE Healthcare; Madison, WI, USA) at the lumbar spine and hip, and the indication for DXA bone densitometry was determined according to fracture risk assessment based on the German guidelines for osteoporosis (including clinical risk factors for fractures such as age, previous fractures and history of steroids). From this collective, 105 patients had been diagnosed with osteoporosis according to the WHO criteria (DXA T-score ≤ -2.5 at the lumbar spine or total hip) and underwent laboratory testing including c-terminal FGF23 measurements and HR-pQCT analysis in a routine setting for extended diagnostics and individual treatment decision. The clinical and laboratory evaluation resulted in exclusion of 21 patients with a glomerular filtration rate (GFR) < 60 ml/min and two patients with TIO confirmed by DOTA-TATE PET/CT as described previously [16]. The remaining 82 patients were evaluated in a cross-sectional design. An overview of the study collective can be found in Table 1. An additional flowchart on the inclusion/exclusion is included as Supplementary Fig. 1. This study was performed in accordance with the Declaration of Helsinki and the rules of the local ethics committee (HmbKHG §12).

Laboratory assessments and HR-pQCT

Laboratory analyses included phosphate, GFR (based on serum creatinine and calculated using the CKD-EPI equation [17]), 25-hydroxyvitamin D, parathyroid hormone (PTH), bone-specific alkaline phosphatase (BAP), and deoxypyridinoline (DPD)/creatinine in the urine. C-terminal FGF23 was measured by ELISA. For bone microarchitecture analysis, high-resolution peripheral quantitative computed tomography (HR-pQCT; XtremeCT, Scanco Medical, Switzerland) was performed at the distal radius and tibia in a standardized procedure using the in vivo protocol [15]. Namely, we assessed bone volume per tissue volume (BV/TV), trabecular number (Tb.N, 1/mm), and thickness (Tb.Th, mm) as well as cortical thickness (Ct.Th, mm) and cortical BMD (Ct.BMD, mgHA/cm^3) according to the JBMR guidelines for nomenclature [18].

Statistical analysis

SPSS 25 software (version 25.0, IBM, Armonk, New York, USA) was used for statistical analyses. The quantitative characteristics are presented as mean ± SD. We calculated Pearson's correlation coefficient r to test pairwise linear associations between variables. Given its right-skewed distribution, FGF23 was log-transformed. We additionally applied multiple linear regression models for the collected bone microarchitecture parameters as dependent variables and FGF23, bone microarchitecture, age, BMI, inorganic phosphate, bone-specific alkaline phosphatase, vitamin D3, and PTH as independent variables. p values below 0.05 were considered statistically significant.

Table 1 Study group characteristics ($n = 82$)

	Mean (±SD)	Min	Max
Male/Female	16/66		
Age (years)	64.0 (± 12.7)	23.9	85
BMI (kg/m^2)	23.7 (± 4.2)	18.1	32.5
FGF23 (kRU/L)	98 (± 133)	33	1105
DXA			
T-score (lumbar spine)	− 2.7 (± 1.2)	− 5.9	1.5
BMD (lumbar spine, g/cm^2)	0.826 (± 0.143)	0.46	1.38
T-score (total hip)	− 2.6 (± 0.8)	− 5.4	− 0.3
BMD (total hip, g/cm^2)	0.681 (± 0.091)	0.35	0.93

Results

Study population

The included patients had a mean age of 64 years (women = 66; men = 16). Of the FGF23 measurements, 16 (19.5%) were above the specified reference range for FGF23 (10–110 kRU/l). The basic characteristics of the study group are presented in Table 1. All patients had a T-score ≤ −2.5 at the lumbar spine or hip. The mean spinal and femoral T-score lies within the range of osteoporosis (spinal BMD 0.826 g/cm^2, T-score = − 2.7; femoral BMD 0.681 g/cm^2, T-score = − 2.6) (Table 1).

Correlation analysis of FGF23 with biochemical parameters and bone microarchitecture

In the initial part of the analyses, we tested for potential correlations between FGF23 and other biochemical parameters of mineral and turnover status as well as GFR. Correlation analyses between FGF23 and phosphate (r = − 0.0161; $p = 0.148$), 25-OH-D3 (r = 0.205; $p = 0.065$), PTH (r = 0.496; $p = 0.076$), BAP (r = 0.205; $p = 0.065$), and DPD (r = 0.050; $p = 0.666$) showed no significant correlation (Fig. 1a–e). A significant negative correlation between GFR and FGF23 levels was found (r = − 0.220; $p = 0.047$) although having excluded all patients with a GFR < 60 ml/min (Fig. 1f).

Subsequently, correlation analyses of FGF23 and bone microarchitecture were performed. These results highlighted a significant negative correlation between FGF23 and BV/TV (tibia: r = − 0.362, $p = 0.001$; radius: r = − 0.287, $p = 0.009$) as well as trabecular number (tibia: r = − 0.281, $p = 0.012$; radius: r = − 0.281, $p = 0.012$) at the distal radius and tibia (Fig. 2). Relative to the mean, a difference of 1 SD FGF23 was associated with a 13.7% difference of BV/TV at the tibia and a 11.1% difference of BV/TV at the radius as well as a 6.8% difference of trabecular number at the tibia and a 7.5% difference of trabecular number at the radius. The other assessed microstructural parameters trabecular thickness (tibia: r = − 0.213, $p = 0.055$; radius: r = − 0.201, $p = 0.061$), cortical thickness (tibia: r = − 0.112, $p = 0.318$; radius: r = − 0.167, $p = 0.134$) and cortical BMD (tibia: r = − 0.173, $p = 0.123$; radius: r = − 0.163, $p = 0.147$) pointed to no significant correlation with FGF23 in this analysis (Fig. 2). The respective differences in bone microarchitecture could be visualized in exemplary patients with low and high FGF23 levels (Fig. 3). We also tested the potential associations between FGF23 levels and DXA BMD (i.e., lowest BMD and DXA T-score at hip and spine) and found no significant correlations (spine BMD $p = 0.221$, T-score $p = 0.365$; hip BMD $p = 0.285$, T-score $p = 0.249$) (Supplementary Fig. 2). When evaluating both sexes separately, a significant correlation for FGF23 and trabecular thickness was found in women at both skeletal sites, while the correlation with trabecular number only remained significant at the distal tibia. Although not on a significant level (besides the correlation between FGF23 and trabecular thickness at the distal tibia), similar trends were found in men (Supplementary Fig. 3).

Associations in the multiple linear regression model

To further evaluate the association between FGF23 and microarchitecture parameters with respect to known interfering factors, we performed a multivariate regression model with adjustment for age, BMI, phosphate, PTH, 25-OH-D3, BAP. The association between FGF23 and BV/TV (tibia: β = − 0.040, $p = 0.001$ radius: β = − 0.045, $p = 0.001$) and trabecular number (tibia: $\beta = -0.343$, $p = 0.030$ radius: $\beta = -0.442$, $p = 0.025$) still remained significant negative in the tibia and the radius. Additionally, the trabecular thickness (tibia: $\beta = -0.017$, $p = 0.010$ radius: $\beta = -0.012$, $p = 0.002$) showed a significant association with FGF23 after adjustment at both skeletal sites. After standardization of the β coefficient, the ranking of the influence of FGF23 on the different microarchitecture parameters becomes visible. This way, the highest influence of FGF23 on bone microarchitecture was found for BV/TV (tibia: β = − 0.388; radius: β = − 0.414) followed by trabecular thickness (tibia: β = − 0.328; radius: β = − 0.383) and trabecular number (tibia: β = − 0.253; radius: β = − 0.277) (Table 2).

Discussion

High FGF23 levels are associated with phosphate wasting resulting in poor bone mineralization, yet the effects of FGF23 on bone microarchitecture in osteoporosis patients had not been demonstrated to date. We here demonstrated that FGF23 levels correlate significantly with trabecular bone microarchitecture, while no significant correlation could be observed between FGF23 and cortical bone parameters such as cortical thickness and cortical BMD. At the same time, FGF23 did not correlate with BMD or T-score and the lumbar spine or hip. The absent association between FGF23 and DXA values was previously also demonstrated in premenopausal women [19] as well as in elderly men [8]. The associations between FGF23 and trabecular bone microarchitecture remained significant after applying a multiple linear regression model with adjustment for confounding factors such as age, BMI, phosphate, 25-OH D3, PTH, and BAP. Since we found similar effects in both of the two peripheral examined locations (i.e., distal radius and tibia), a systemic influence of FGF23 on bone microarchitecture can be expected.

While this is the first study demonstrating these associations in a cohort of osteoporosis, it was previously shown that patients with X-linked hypophosphatemia (a hereditary disease characterized by excessive FGF23 production) have

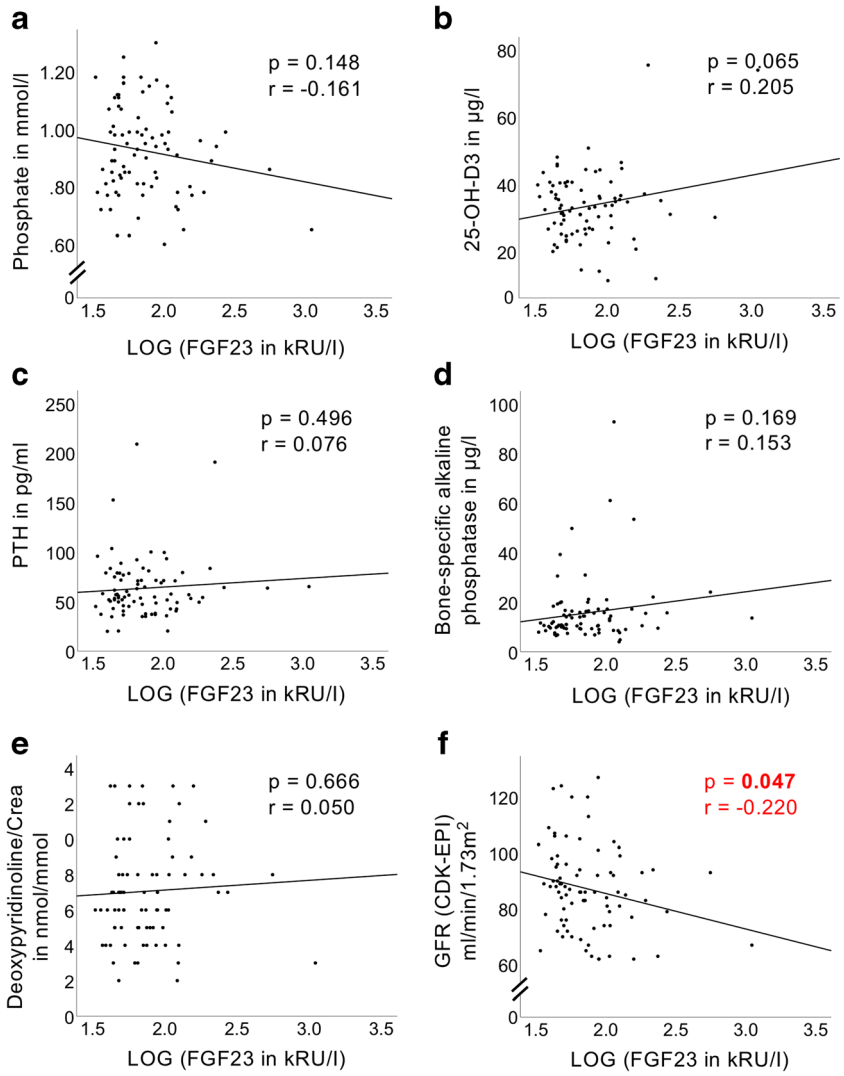

Fig. 1 Correlation analyses between FGF23 and laboratory parameters. **a** Serum phosphate as well as **b** 25-OH-D3 showed no significant correlation with FGF23. In addition, FGF23 did not correlate with other laboratory markers such as **c** PTH, **d** BAP, and **e** DPD. **f** A significant negative correlation was found between FGF23 and GFR even in patients with GFR > 60 ml/min

reduced microarchitectural parameters compared to healthy controls [20]. In fact, these patients similarly demonstrated trabecular deficits but absent changes of cortical thickness and BMD at the distal tibia [20].

A previous study in patients with chronic kidney disease (CKD) reported stronger correlations between bone formation markers and trabecular vBMD than for bone formation markers and cortical vBMD [21]. Similarly, patients with early kidney disease had deficits of trabecular but not cortical microarchitecture [22]. Since increased FGF23 is likely involved in specific trabecular bone loss patterns in CKD, trabecular but not cortical deficits might also occur in patients with high FGF23 levels but normal kidney function as evidenced in this study. Although renal insufficiency (defined as GFR < 60 ml/min) was one of the exclusion criteria in our study, we did find a significant correlation between FGF23 and GFR, which also points to the potential value of FGF23 as an early marker of renal dysfunction.

We did not find any associations between FGF23 and most laboratory values as well as markers of bone turnover and mineralization. Although FGF23 is especially known to influence vitamin D and phosphate homeostasis, there were no significant associations between FGF23 and 25-hydroxyvitamin D or phosphate. This could be due to the physiological control loop between these parameters under normal conditions, where FGF23 is secreted, e.g., by moderate hyperphosphatemia leading to phosphate excretion and subsequent lowering of phosphate levels. Supporting this theory, it was shown that FGF23 levels increase in response to dietary phosphate loading leading to phosphaturia but unchanged serum phosphate levels [23]. The observation that the associations between FGF23 and bone microarchitecture are still detectable after adjustment for confounding factors such as phosphate and vitamin D may also be explained by the complexity of the FGF23 physiology. For example, fgf23-deficient mice (characterized by hyperphosphatemia) have an even more severe osteomalacia than hyp-mice (the mouse

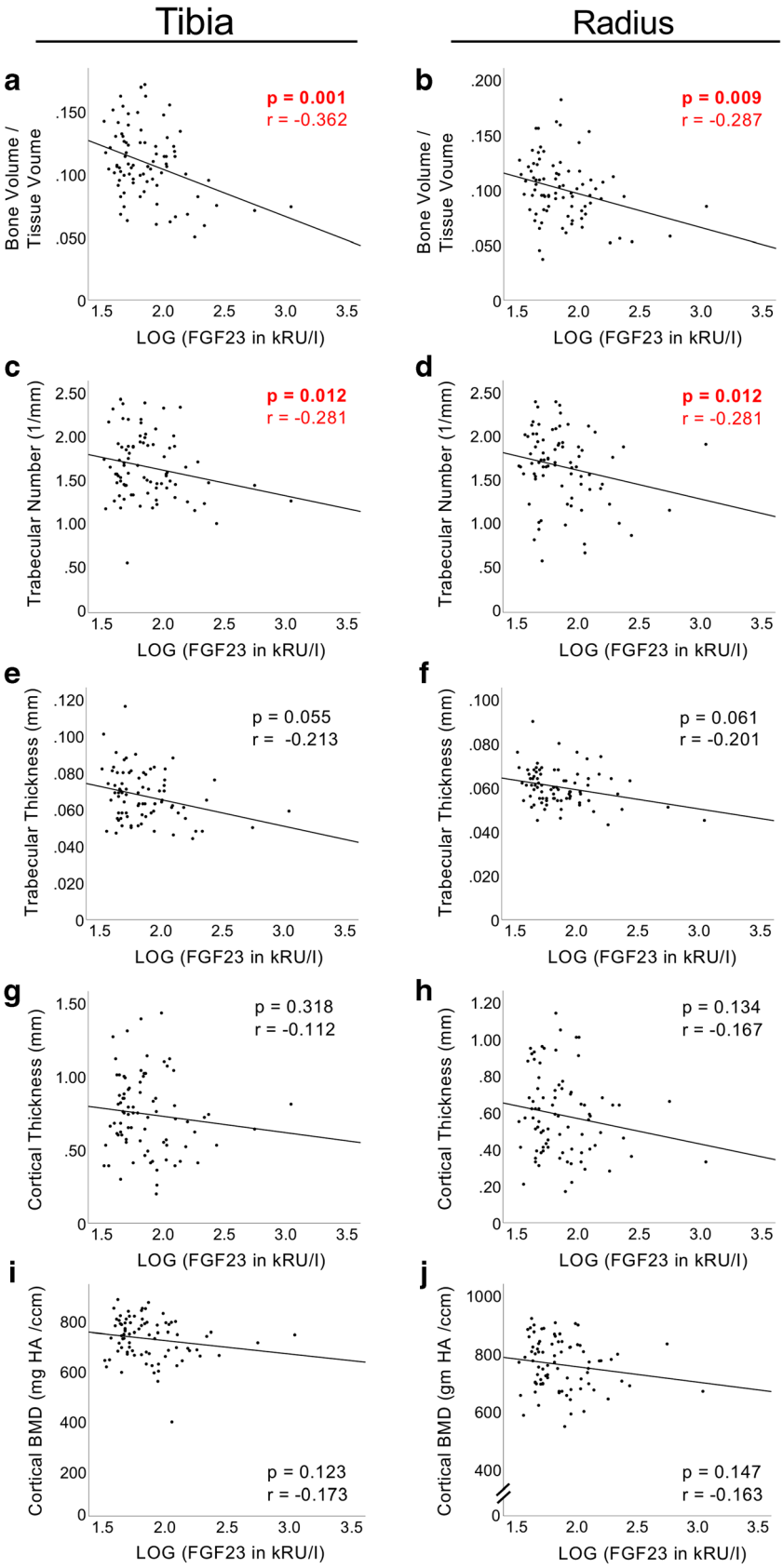

Fig. 2 Associations between FGF23 and microarchitecture parameters assessed by HR-pQCT. **a**, **b** Higher FGF23 was significantly associated with lower BV/TV in the distal tibia and radius (logarithmic correlation). **c, d** Trabecular number correlated negatively with FGF23 levels. **e**, **f** For trabecular thickness, no significant correlation was detected with FGF23 at both skeletal sites. **g**, **h** Cortical thickness and **i**, **j** cortical BMD displayed no significant correlation with FGF23 at the distal tibia or radius. FGF23 was log-transformed due to its right-skewed distribution

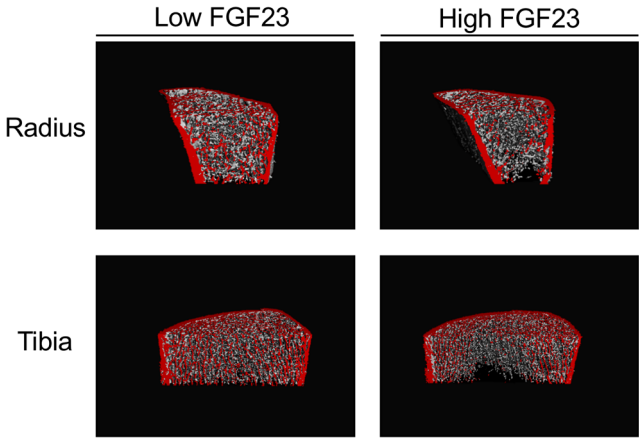

Fig. 3 3D visualization of HR-pQCT microarchitecture from exemplary patients with low vs. high FGF23 levels. HR-pQCT images display the difference in trabecular structure when comparing the images of a patient with low FGF23 (87 kRU/l) to a patient with high FGF23 (558 kRU/l)

model of XLH characterized by FGF23 overproduction and hypophosphatemia). This observation leads to the assumption of a direct effect of FGF23 on biomineralization and consequently also on bone microarchitecture.

Given our findings on the negative effect of FGF23 on bone microarchitecture, it is reasonable to speculate that FGF23 also influences fracture risk. Indeed, while FGF23 was previously proposed as a novel predictor of fracture risk in elderly men [11], a predictive value of FGF23 regarding fracture risk could not be confirmed in other longitudinal studies [9, 10]. However, these studies focused on older patients with BMD values that were not predefined to be in the range of osteoporosis. As we were exclusively focusing on patients with osteoporosis, this may explain the diverging findings.

Burosumab, a fully human monoclonal FGF23 antibody was recently approved for the treatment of XLH [24]. Given the negative influence of FGF23 on bone microarchitecture, and beyond that its well-known phosphaturic effects in acquired diseases such as TIO leading to poor bone mineralization, it will be of future interest if these patients (both TIO and patients with low bone mass and unexplained high FGF23 levels but no tumor detection) could benefit from a similar or modified FGF23 antibody treatment.

The limitations of our study include the cross-sectional study design and the small sample size resulting in absent significant correlations in some of the parameters when evaluating both sexes individually (especially men). As we focused on patients with osteoporosis only and excluded patients with renal impairment, the resulting pre-selected group may have biased the data leading to potential underestimation of the detected associations. However, the aim of this study was to test whether higher FGF23 are associated with impaired bone microarchitecture independent of renal status (i.e., FGF23 production non-related to kidney disease). Although this analysis was only achievable in a small patient cohort, this is the first study that includes FGF23 measurements in association with microarchitectural parameters assessed by HR-pQCT. We demonstrated a weak significant association between FGF23 and trabecular bone microarchitecture at both skeletal sites that remained significant after adjustment for other factors with a known influence on bone microarchitecture and FGF23.

Although bone loss often affects both trabecular and cortical compartments of bone, we did not find significant associations with cortical bone parameters. Indeed, there are certain diseases beyond XLH or CKD (e.g., psoriatic arthritis) that have been associated with trabecular rather than cortical bone loss [25]. Nonetheless, we cannot exclude segmentation inaccuracies as a cause for the absent correlations between FGF23 and cortical parameters. Moreover, it is likely that high FGF23 levels lead to poorly mineralized bone (i.e., osteoid) and intracortical remodeling (i.e., cortical porosity). As cortical porosity could not be determined in our study and both of these processes are initially not covered by the HR-pQCT

Table 2 Multiple linear regression models with microarchitecture parameters at the distal radius and tibia as dependent variables and FGF23 as independent variable adjusting for age, BMI, phosphate, PTH, 25-OH-D3 and BAP. *β* regression coefficient, *CI* confidence interval. Italics indicates significant associations (p<0.05).

	p Value	Regression coefficient β (95% CI)	Standardized β coefficient
Radius			
Bone volume/tissue volume	*0.001*	− 0.045 (− 0.070 to − 0.020)	− 0.414
Trabecular number (1/mm)	*0.025*	− 0.442 (− 0.826 to − 0.057)	− 0.277
Trabecular thickness (mm)	*0.002*	− 0.012 (− 0.020 to − 0.004)	− 0.383
Cortical thickness (mm)	0.416	− 0.076 (− 0.819–0.416)	− 0.092
Cortical BMD (mg HA/ccm)	0.671	− 14.56 (− 82.65–53.52)	− 0.045
Tibia			
Bone volume/tissue volume	*0.001*	− 0.040 (− 0.067 to − 0.017)	− 0.388
Trabecular number (1/mm)	*0.030*	− 0.343 (− 0.652 to − 0.033)	− 0.253
Trabecular thickness (mm)	*0.010*	− 0.017 (− 0.029 to − 0.004)	− 0.328
Cortical thickness (mm)	0.754	− 0.034 (− 0.250–0.182)	− 0.035
Cortical BMD (mg HA/ccm)	0.818	− 6.745 (− 64.39–51.45)	− 0.022

standard parameters such as cortical thickness, potential cortical bone loss with high FGF23 levels may have been underestimated.

Taken together, we have shown that higher FGF23 levels are associated with lower trabecular bone microarchitecture in osteoporosis patients. The value of FGF23 as a routine laboratory marker in osteoporosis patients and relation to, e.g., fracture risk remain unknown. Whether increased FGF23 levels also lead to future (trabecular) bone loss has to be confirmed in longitudinal studies. Further mechanistic data beyond the known phosphate-mediated effects are now needed to understand the role of FGF23 in biomineralization and the pathogenesis of osteoporosis.

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Authors' roles Study design: MA and T Rolvien.
Study conduct: T Rupp, SB, EV, RO, FB, MA, and T Rolvien.
Data analysis: T Rupp, SB, EV, RO, FB, MA, and T Rolvien.
Drafting manuscript: T Rupp and T Rolvien.
Revising manuscript: T Rupp, SB, EV, RO, FB, MA, and T Rolvien. T Rupp and T Rolvien take responsibility for the integrity of the data analysis.

Compliance with ethical standards

This study was performed in accordance with the Declaration of Helsinki and the rules of the local ethics committee (HmbKHG §12).

Conflicts of interest None.

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