



The association between prevalent vertebral fractures and bone quality of the distal radius and distal tibia as measured with HR-pQCT in postmenopausal women with a recent non-vertebral fracture at the Fracture Liaison Service

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Abstract

Summary We evaluated the association between prevalent vertebral fractures and bone micro-architecture and strength measured using HR-pQCT in postmenopausal women with a recent non-vertebral fracture visiting the Fracture Liaison Service. The presence and severity of prevalent vertebral fracture reflect generalized bone deterioration.

Introduction We evaluated the association between prevalent vertebral fractures (VFs) and bone micro-architecture and strength measured using HR-pQCT in postmenopausal women visiting the Fracture Liaison Service.

Methods In this cross-sectional study in women aged 50–90 with a recent non-vertebral fracture (NVF), VFs were identified on lateral spine images by dual-energy X-ray absorptiometry. Bone micro-architecture and strength were measured at the non-dominant distal radius and distal tibia using HR-pQCT. Linear regression analyses were used to estimate the association between prevalent VFs and HR-pQCT parameters.

Results We included 338 women of whom 74 (21.9%) women had at least one prevalent VF. After adjustment for femoral neck aBMD (FN aBMD) and other parameters, women with at least one prevalent vertebral fracture had significantly lower total and trabecular vBMD and trabecular number ($\beta - 16.7, - 11.8, \text{ and } - 7.8$ in the radius and $- 21.4, - 16.6, \text{ and } - 7.2$ in the tibia, respectively), higher trabecular separation at the radius and tibia ($\beta 9.0$ and 9.3 , respectively), and lower cortical thickness and calculated ultimate failure load and compressive bone strength at the tibia ($\beta - 5.9, - 0.6, \text{ and } - 10.9$, respectively) as compared with those without prevalent VFs. Furthermore, more severe prevalent VFs were associated with even lower total and trabecular vBMD and lower ultimate failure load and compressive stiffness at the radius and tibia, and lower trabecular number and higher trabecular separation at the radius.

Conclusion This study indicates that the presence and severity of prevalent VFs reflect generalized bone deterioration in women with a recent NVF, independently of FN aBMD.

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Introduction

Vertebral fractures (VFs) are the most frequently occurring osteoporotic fractures [1–3]. Because only one-third of patients with VFs present with an acute, symptomatic episode [4], VFs are underdiagnosed [5, 6]. The Dutch guideline on osteoporosis and fracture prevention recommends vertebral fracture assessment (VFA) in all patients aged 50 years and older with a recent non-vertebral fracture (NVF) [7]. In patients with a recent NVF at the Fracture Liaison Service (FLS), prevalent VFs have been reported in 20–26% of patients [8–10] and moderate or severe prevalent VFs in 15–17% [8, 10].

Prevalent VFs have been positively associated with subsequent VFs and NVFs, independent of age and bone mineral density (BMD) [11–15]. Increased fracture risk may be caused by other factors not captured by BMD measurements, such as bone micro-architecture and bone strength. Indeed, previous cross-sectional studies have shown that, compared with subjects without a VF, patients with prevalent VFs have significantly impaired bone micro-architecture of trabecular and cortical bone in the distal radius and tibia after adjustment for BMD in the spine or hip [16–19]. Furthermore, in previous prospective studies, deterioration of HR-pQCT indices of trabecular and cortical bone and lower calculated bone strength improve prediction of fracture beyond femoral neck areal BMD or FRAX scores alone [20–24].

The abovementioned cross-sectional studies compared patients with prevalent VFs to fracture-free controls [16–19]. Additionally, Stein et al. [18] compared women with a prevalent VF with women with a NVF and reported significantly greater deterioration of bone micro-architecture at the tibia in those with VFs. Currently, there are no studies evaluating whether the presence of a prevalent VF is associated with impaired bone micro-architecture in the presence of a recent NVF. We therefore evaluated the association between prevalent VFs and bone micro-architecture and strength in the distal radius and distal tibia measured using HR-pQCT in postmenopausal women visiting the FLS after a recent NVF.

Materials and methods

Subject and study procedures

Data from the FX MoVie study, an ongoing prospective observational study, were used. The primary objective of this study is to assess bone structure parameters and bone strength by HR-pQCT and physical activity in relation to falls, fractures, and mortality in patients with a recent

clinical fracture. Included were 500 patients aged between 50 and 90 years with a recent, radiologically confirmed clinical vertebral or non-vertebral fracture, who visited the FLS of VieCuri Medical Center in The Netherlands, and who were willing and able to participate. Excluded were non-Caucasian patients; patients with a fracture due to high-energy trauma, bone metastasis, failure of prosthesis, or osteomyelitis; and patients with cognitive impairment.

The study protocol (registration number NL45707.072.13) was approved by an independent Medical Ethics Committee and complied with the Declaration of Helsinki. All patients gave written informed consent prior to participation.

The present cross-sectional study includes baseline data of postmenopausal women with a recent NVF. Patients who presented with a symptomatic VF were excluded. The mean time between NVF and baseline assessment was 4.2 ± 1.1 months. Baseline assessment included a detailed questionnaire for evaluation of risk factors for osteoporosis, falls, and fractures; laboratory tests to detect contributors to secondary osteoporosis and metabolic bone disease; BMD measurement and lateral imaging of the spine by dual-energy X-ray absorptiometry (DXA); and HR-pQCT scans of the distal radius and tibia. Fractures were categorized according to FRAX into major osteoporotic fractures (except clinical vertebral fractures which were excluded from this study) or all other fractures [25].

Areal bone mineral density

Areal bone mineral density (aBMD) was measured at the hip and lumbar spine by DXA using the Hologic QDR 4500 (Hologic, Bedford, MA, USA). Lumbar spine evaluation was performed according to the International Society of Clinical Densitometry (ISCD) criteria (<https://www.iscd.org/official-positions/6th-iscd-position-development-conference-adult>). Vertebrae with grade 2 or 3 deformities according to Genant [26] were excluded and lumbar spine aBMD was determined based on the remaining vertebrae. Lumbar spine evaluation was based on at least two vertebrae.

Osteoporosis was diagnosed according to the World Health Organization (WHO) criteria for BMD [27]. Patients were classified according to the lowest value of T-score in femoral neck, total hip, or lumbar spine. T-scores of ≤ -2.5 standard deviations (SD) below the reference mean were classified as osteoporosis, T-scores between -1.0 and -2.5 SD were classified as osteopenia, and T-scores ≥ -1.0 SD were classified as normal.

Vertebral fracture assessment

Prevalent vertebral fractures were identified on lateral spine images made with DXA. According to the semi-quantitative method of Genant [26], VFs were graded as mild (grade 1, height loss between 20 and 25%), moderate (grade 2, height loss between 25 and 40%), or severe (grade 3, height loss > 40%). Patients were classified according to the most severe VF as those without VFs, those with at least one mild VF, or those with at least one moderate or severe VF. Vertebral deformities related to other conditions, such as Scheuermann's disease, degenerative disease, and Schmorl's nodes, were not classified as prevalent VF.

HR-pQCT imaging

The non-dominant radius was scanned using a second-generation HR-pQCT scanner (XtremeCT II; Scanco Medical AG, Brüttisellen, Switzerland) using the standard in vivo protocol as provided by the manufacturer (effective energy of 68 kVp, tube current of 1470 μ A, and integration time of 43 ms) unless the patient had previously sustained a distal radius fracture at the non-dominant site; then, the dominant site was scanned. The distal tibia was scanned at the same site as the distal radius unless that site was previously fractured; then, the other site was scanned. The forearm and lower leg were placed into a carbon fiber cast. The region of interest was determined based on an anteroposterior scout projection of the scan site. A reference line was placed on the distal radius and distal tibia joint surface. The scan started 9.0 mm from the reference line in the proximal direction and spanned 10.2 mm in length. Images were reconstructed using an isotropic voxel size of 61 μ m, resulting in 168 consecutive slices. Each scan was graded for motion-induced image artifacts by the operator according to the manufacturer's guideline and as described by Pialat et al. [28]. In case the images were of insufficient quality, i.e., grade 4 or 5, the scan was repeated with a maximum up to two times. Only scans with quality 1 to 3 were used for analyses in this study.

Image analysis of HR-pQCT scans

All scans were evaluated using the standard patient evaluation protocol as provided by the manufacturer. We used a fully automated segmentation method, which uses two thresholds and a series of morphological dilatation and erosions to extract the endosteal and periosteal surface of the cortex [29]. This is based on the assumption that the trabecular region is enclosed by the cortical region. The periosteal contour was automatically derived and manually modified by a single operator when contours visually deviated from the periosteal boundary. The following bone parameters were measured: volumetric bone mineral density (mgHA/cm^3) was assessed for the total

region (D_{tot}) and trabecular region (D_{trab}) and cortical region (D_{cort}) separately. For the trabecular region, the micro-architectural parameters trabecular bone volume fraction (Tb.BVTV) (%), trabecular number (Tb.N) (mm^{-1}), trabecular thickness (Tb.Th) (mm), and trabecular separation (Tb.Sp) (mm) were measured. For the cortical region, cortical perimeter (Ct.Pm) (mm), cortical thickness (Ct.Th) (mm), cortical porosity (Ct.Po) (%), and cortical pore diameter (Ct.Po.Dm) (mm) were measured.

Micro-finite element models were generated directly from the segmented HR-pQCT images [30, 31] by converting voxels representing bone tissue into brick elements of the same size. Young's modulus of 10 GPa and Poisson's ratio of 0.3 were assigned to every element. Compression stiffness and estimated failure load were determined by simulating a "high-friction" compression test in the axial direction [30].

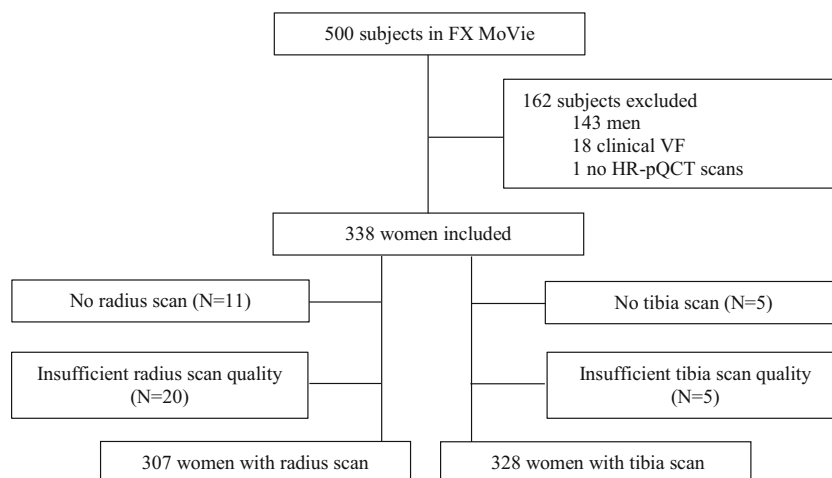
Statistical analysis

General characteristics and mean HR-pQCT parameters were compared between women with and without prevalent VFs using the independent Student's *t* test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Further, mean HR-pQCT parameters were compared between women according to prevalent VF severity (none vs. mild (grade 1) vs. moderate or severe (grades 2–3)) using one-way ANOVA with the Bonferroni correction. Descriptives are provided as mean \pm SD for continuous variables and number (%) for categorical variables. Log transformation was performed if variables showed a skewed distribution. Multiple linear regression analysis was used to estimate the association between VF and HR-pQCT parameters, yielding unstandardized beta (β) and 95% confidence interval (CI). Potential confounders were included in the analyses if they independently changed the beta coefficient for VF by at least 5%. All regression analyses were adjusted for age, height, weight, type of recent NVF (major osteoporotic fracture, i.e., hip, proximal humerus, and distal radius fractures), previous fractures at or above the age of 50 years, self-reported use of anti-osteoporosis treatment (never vs. history vs. current), and femoral neck aBMD. A *P* value $\leq .05$ was considered statistically significant for general characteristics, and a *P* value $\leq .002$ for HR-pQCT parameters. Analyses were conducted using SPSS for Mac (version 24.0, IBM SPSS Statistics, USA).

Results

In total, 338 postmenopausal women with a NVF were included in this study (Fig. 1). HR-pQCT scans were not performed in 11 women at the radius, and in 5 women at

Fig. 1 Flowchart of patient inclusion



the tibia because of bilateral fractures. Additionally, 20 radius and 5 tibia scans were excluded because of insufficient scan quality due to motion artifacts, resulting in 307 radius and 328 tibia scans that were included in the analyses.

Of the 338 women, 74 (21.9%) had at least one prevalent VF and 264 had no prevalent VF. General characteristics of women according to their prevalent VF status are shown in Table 1. Compared with women without a prevalent VF, women with at least one prevalent VF were older, had lower femoral neck (FN) and total hip (TH) aBMD, were more likely to have had a previous fracture at or above the age of 50 years, and were more likely to have ever used anti-osteoporosis treatment.

HR-pQCT parameters according to prevalent VF status

The mean unadjusted HR-pQCT parameters at the radius and tibia for women according to presence and severity of prevalent VFs are shown in Table 2. Compared with women without a prevalent VF, those with at least one prevalent VF had lower total and trabecular vBMD, trabecular number, ultimate failure load, and compression stiffness, and higher trabecular separation at both the radius and tibia, and lower cortical thickness at the tibia.

Results of linear regression analyses examining the association between prevalent VF status and HR-pQCT parameters at the radius and tibia are shown in Table 3. In the adjusted analyses, at least one prevalent VF was associated with lower total and trabecular vBMD and trabecular number (β -1.6, -11.8, and -7.8 in the radius and -21.4, -16.6, and -7.2 in the tibia, respectively), and higher trabecular separation at the radius and tibia (β 9.0 and 9.3, respectively), and lower cortical thickness, ultimate failure load, and compression stiffness at the tibia (β -5.9, -0.6 and -10.9, respectively).

HR-pQCT parameters according to prevalent VF severity

Compared with women without prevalent VFs, those with at least one moderate or severe prevalent VF had lower total and trabecular vBMD, trabecular number, ultimate failure load, and compression stiffness, and higher trabecular separation at both the radius and tibia (Table 2). Further, a similar pattern was found when patients with at least one mild prevalent VF were compared with those without prevalent VF, with the exception that ultimate failure load and compression stiffness at the radius, and trabecular number and separation at the tibia were not significantly different for these two groups (Table 2).

Adjusted regression analyses showed that total and trabecular vBMD, ultimate failure load, and compression stiffness were lower at the radius and tibia (β -26.10, -17.6, -0.3, and -4.6 in the radius and -27.6, -20.0, -0.7, and -13.2 in the tibia, respectively) and trabecular number was lower (β -10.9) and trabecular separation was higher (β 14.4) at the radius in women with moderate or severe prevalent VF as compared with those without prevalent VF (Table 3). Further, in women with at least one mild prevalent VF, total and trabecular vBMD and calculated ultimate failure load and compressive bone strength were lower at the tibia (β -16.4, -13.1, -0.5, and -9.1, respectively) than in those without prevalent VF.

In addition, there was a significant trend analysis for lower total and trabecular vBMD, trabecular number, ultimate failure load, and compression stiffness, and higher trabecular separation at the radius and tibia, and lower cortical thickness at the tibia with increasing prevalent VF severity (Table 3).

Discussion

In this study, in postmenopausal women attending the FLS with a recent NVF, the presence of at least one prevalent VF was independently associated with lower total and

Table 1 General characteristics of patients with a recent NVF at the FLS according to the presence of prevalent vertebral fracture

| | Women (<i>n</i> = 338) | | <i>P</i> value |
|--|-------------------------|---------------------------------|----------------|
| | No VF (<i>n</i> = 264) | ≥ 1 VF Gr. ≥ 1 (<i>n</i> = 74) | |
| Age (years) | 62.9 ± 7.8 | 67.7 ± 8.4 | .000* |
| Height (cm) | 1.6 ± 0.1 | 1.6 ± 0.1 | .295 |
| Weight (kg) | 74.6 ± 14.3 | 72.7 ± 12.1 | .296 |
| BMI (kg/m ²) | 27.6 ± 5.0 | 27.1 ± 4.0 | .474 |
| FRAX major osteoporotic fractures | 82 (31.1) | 30 (40.5) | .126 |
| LS aBMD (g/cm ²) | 0.93 ± 0.14 | 0.91 ± 0.17 | .388 |
| FN aBMD (g/cm ²) | 0.70 ± 0.11 | 0.67 ± 0.10 | .032* |
| TH aBMD (g/cm ²) | 0.85 ± 0.13 | 0.81 ± 0.12 | .028* |
| Normal BMD | 72 (27.3) | 13 (17.6) | .113 |
| Osteopenia | 135 (51.1) | 38 (51.4) | |
| Osteoporosis | 57 (21.6) | 23 (31.1) | |
| Previous fracture after age 50 years | 48 (18.2) | 36 (48.6) | .000* |
| Parent fractured hip | 17 (6.4) | 4 (5.4) | .999 |
| Current smoking | 36 (13.6) | 9 (12.2) | .741 |
| Glucocorticoids | 12 (4.5) | 3 (4.1) | .999 |
| Rheumatoid arthritis | 10 (3.8) | 4 (5.4) | .516 |
| Secondary osteoporosis | 70 (26.5) | 21 (28.4) | .749 |
| Alcohol ≥ 3 units/day | 4 (1.5) | 1 (1.4) | .999 |
| History or current use of anti-osteoporosis drugs | 21 (8.0) | 19 (26.0) | .000* |
| Self-reported use of anti-osteoporosis medication, <i>n</i> (%) | 18 (6.9) | 18 (24.7) | .000* |
| Type, <i>n</i> (%) [#] | | | |
| Alendronic acid | 11 (61.1) | 9 (50.0) | .887 |
| Risedronic acid | 5 (27.8) | 6 (33.3) | |
| Zoledronic acid | 0 (0.0) | 1 (5.6) | |
| Unknown | 2 (11.1) | 2 (11.1) | |
| Duration (year), mean ± SD [#] | 4.5 ± 2.7 | 5.2 ± 4.1 | .577 |
| Current, <i>n</i> (%) [#] | 3 (16.7) | 10 (55.6) | .015* |
| History, <i>n</i> (%) [#] | 15 (83.3) | 8 (44.4) | |
| Time since cessation of treatment (year), mean ± SD [#] | 2.6 ± 2.6 | 1.1 ± 2.3 | .109 |
| Falls past year | 79 (30.0) | 21 (28.8) | .834 |

Variables are presented as mean ± standard deviation or number (percentage). *P* value < 0.05 is considered significant (*)

[#] In patients who have ever used anti-osteoporosis medication

VF, vertebral fracture; BMI, body mass index; LS, lumbar spine; FN, femoral neck, TH, total hip; aBMD, areal bone mineral density

trabecular vBMD, lower trabecular number, and higher trabecular separation at the radius and tibia and with lower cortical thickness, ultimate failure load, and compressive stiffness at the tibia. Furthermore, moderate or severe prevalent VFs were associated with even lower total and trabecular vBMD and lower ultimate failure load and compressive stiffness at the radius and tibia, and lower trabecular number and higher trabecular separation at the radius.

To the best of our knowledge, there are no studies evaluating the association between prevalent VFs and bone micro-architecture and bone strength in patients with a recent NVF. Previous cross-sectional studies have shown that, compared with fracture-free controls, patients with VFs have significantly

impaired bone micro-architecture of trabecular and cortical bone in the distal radius and tibia after adjustment for BMD in the spine or hip [16–19]. Furthermore, Stein et al. [18] reported a significantly greater deterioration of bone micro-architecture in the tibia, but not the radius in women with a VF compared with those with a NVF. However, in the study by Stein et al. [18], only 12 out of 30 women with a VF had a history of a NVF, whereas in our study, all patients had a recent NVF.

In line with our findings, two previous studies reported more bone micro-architectural deterioration with increasing severity of prevalent VFs in women [16, 17], whereas one study found no association between severity of prevalent VFs and HR-pQCT parameters [18]. In contrast to our study,

Table 2 HR-pQCT parameters at the distal tibia and radius according to presence and severity of prevalent VFs in women with a recent NVF at the FLS

| | Presence of prevalent VFs | | | Severity of prevalent VFs | | <i>P</i> value for trend |
|--------------------------------|---------------------------|---------------------------------|-------------------------------|---------------------------------|------|--------------------------|
| | No VF (<i>n</i> = 240) | ≥ 1 VF Gr. ≥ 1 (<i>n</i> = 67) | ≥ 1 VF Gr. 1 (<i>n</i> = 35) | ≥ 1 VF Gr. 2–3 (<i>n</i> = 32) | | |
| Radius (<i>n</i> = 307) | | | | | | |
| vBMD | | | | | | |
| Dtot (mgHA/cm ³) | 270 ± 62 | 233 ± 55* | 236 ± 56* | 230 ± 55* | .000 | |
| Dtrab (mgHA/cm ³) | 121 ± 39 | 96 ± 37* | 101 ± 33* | 91 ± 41* | .000 | |
| Dcort (mgHA/cm ³) | 892 ± 62 | 872 ± 69 | 870 ± 64 | 875 ± 75 | .068 | |
| Micro-architecture | | | | | | |
| Tb.N (mm ⁻¹) | 1.20 ± 0.26 | 1.02 ± 0.31* | 1.06 ± 0.28* | 0.97 ± 0.34* | .000 | |
| Tb.Th (mm) | 0.22 ± 0.02 | 0.23 ± 0.02 | 0.23 ± 0.02 | 0.23 ± 0.02 | .362 | |
| Tb.Sp (mm) | 0.86 ± 0.27 | 1.15 ± 0.68* | 1.04 ± 0.46* | 1.28 ± 0.86* | .000 | |
| Ct.Po (%) | 0.86 ± 0.56 | 0.88 ± 0.49 | 0.86 ± 0.43 | 0.90 ± 0.56 | .899 | |
| Ct.Th (mm) | 0.92 ± 0.18 | 0.85 ± 0.15 | 0.85 ± 0.15 | 0.84 ± 0.15 | .012 | |
| Ct.Po.Dm (mm) | 0.19 ± 0.03 | 0.20 ± 0.03 | 0.20 ± 0.04 | 0.20 ± 0.03 | .359 | |
| Biomechanical | | | | | | |
| F.Ult (kN) | 2.81 ± 0.72 | 2.49 ± 0.55* | 2.58 ± 0.51 | 2.40 ± 0.59* | .002 | |
| Scomp (kN/mm) | 52 ± 13 | 47 ± 10* | 49 ± 9 | 45 ± 10* | .002 | |
| Tibia (<i>n</i> = 328) | | | | | | |
| vBMD | | | | | | |
| Dtot (mgHA/cm ³) | 243 ± 54 | 209 ± 46* | 211 ± 42* | 207 ± 52* | .000 | |
| Dtrab (mgHA/cm ³) | 140 ± 38 | 119 ± 34* | 121 ± 31* | 117 ± 37* | .000 | |
| Dcort (mgHA/cm ³) | 837 ± 73 | 813 ± 72 | 820 ± 66 | 806 ± 77 | .035 | |
| Micro-architecture | | | | | | |
| Tb.N (mm ⁻¹) | 1.19 ± 0.23 | 1.08 ± 0.29* | 1.10 ± 0.28 | 1.06 ± 0.30* | .004 | |
| Tb.Th (mm) | 0.25 ± 0.02 | 0.25 ± 0.02 | 0.25 ± 0.02 | 0.25 ± 0.02 | .405 | |
| Tb.Sp (mm) | 0.87 ± 0.33 | 1.02 ± 0.45* | 0.99 ± 0.44 | 1.05 ± 0.46* | .004 | |
| Ct.Po (%) | 3.22 ± 1.32 | 3.22 ± 1.37 | 3.04 ± 1.12 | 3.41 ± 1.59 | .505 | |
| Ct.Th (mm) | 1.21 ± 0.25 | 1.10 ± 0.21* | 1.10 ± 0.19* | 1.11 ± 0.22 | .005 | |
| Ct.Po.Dm (mm) | 0.23 ± 0.03 | 0.23 ± 0.04 | 0.23 ± 0.03 | 0.24 ± 0.04 | .426 | |
| Biomechanical | | | | | | |
| F.Ult (kN) | 8.00 ± 1.62 | 7.14 ± 1.49* | 7.27 ± 1.35* | 7.00 ± 1.63* | .000 | |
| Scomp (kN/mm) | 147 ± 32 | 131 ± 28* | 133 ± 26* | 128 ± 31* | .000 | |

Variables are presented as mean ± SD. *P* value < 0.05 is considered significant

**P* < 0.05 compared with patients without a prevalent VF (with Bonferroni correction for multiple testing)

VF, vertebral fracture; vBMD, volumetric bone mineral density; Dtot, total density; Dtrab, trabecular density; Dcort, cortical density; Tb.N, trabecular number; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation; Ct.Th, cortical thickness; Ct.Po, cortical porosity; Ct.Po.Dm, cortical pore diameter; F.Ult, ultimate failure load; Scomp, compression stiffness

all three studies compared women with prevalent VFs with fracture-free controls.

The short time since the NVF is important, because patients with a fracture have an increased risk of subsequent fractures, which is highest immediately after the fracture. This imminent subsequent fracture risk emphasizes the need for immediate and accurate secondary fracture prevention. The fact that the presence of a vertebral fracture in postmenopausal women with a NVF at the FLS is associated with impaired bone quality compared with not having a VF may indicate that patients with a prevalent VF are even at higher subsequent fracture risk.

Interestingly, we found no difference in LS aBMD between women with at least one prevalent VF in addition to a NVF and those without VF, whereas previous studies reported lower LS aBMD in (asymptomatic and/or symptomatic) VF patients than in fracture-free controls. Similarly to our results, Stein et al. [18] reported that there was no difference in LS aBMD when vertebral subjects were compared with NVF subjects. One explanation could be that in NVF patients, the presence of prevalent VFs is not associated with lower LS aBMD. Another explanation could be the impact of degenerative changes in the lumbar

Table 3 Associations between the presence, severity, and number of prevalent vertebral fractures and HR-pQCT parameters in women with a recent NVF at the FLS

| | | Presence of prevalent VFs | | Severity of prevalent VFs | | <i>P</i> value for trend |
|-------------------------------|-------|---------------------------|-------------------------|------------------------------|--------------------------------|--------------------------|
| | | No VF | VF (β (95% CI)) | Gr. 1 VF (β (95% CI)) | Gr. 2–3 VF (β (95% CI)) | |
| Radius | No VF | | | | | |
| vBMD | | | | | | |
| Dtot (mgHA/cm ³) | Ref. | | –16.66 (–31.93, –1.39)* | –10.05 (–28.65, 8.56) | –26.10 (–47.65, –4.56)* | .015* |
| Dtrab (mgHA/cm ³) | Ref. | | –11.75 (–21.91, –1.58)* | –7.66 (–20.06, 4.73) | –17.57 (–31.92, –3.22)* | .012* |
| Dcort (mgHA/cm ³) | Ref. | | –9.88 (–26.38, 6.62) | –7.58 (–27.74, 12.58) | –13.16 (–36.50, 10.18) | .216 |
| Micro-architecture | | | | | | |
| Tb.N (1/mm) | Ref. | | –7.83 (–15.19, –0.46)* | –5.50 (–14.49, 3.49) | –11.15 (–21.56, –0.75)* | .024* |
| Tb.Th (mm) | Ref. | | 0.20 (–0.27, 0.67) | 0.16 (–0.41, 0.74) | 0.25 (–0.42, 0.91) | .400 |
| Tb.Sp (mm) | Ref. | | 8.98 (0.68, 17.29)* | 5.21 (–4.91, 15.33) | 14.37 (2.66, 26.08)* | .014* |
| Ct.Po (%) | Ref. | | 3.26 (–16.09, 22.61) | 0.07 (–23.57, 23.70) | 7.82 (–19.55, 35.19) | .628 |
| Ct.Th (mm) | Ref. | | –3.10 (–7.70, 1.51) | –1.62 (–7.24, 4.00) | –5.21 (–11.71, 1.30) | .117 |
| Ct.Po.Dm (mm) | Ref. | | 3.41 (–1.59, 8.41) | 2.24 (–3.86, 8.34) | 5.08 (–1.99, 12.14) | .136 |
| Biomechanical | | | | | | |
| F.Ult (kN) | Ref. | | –0.15 (–0.32, 0.02) | –0.08 (–0.28, 0.13) | –0.26 (–0.49, –0.02)* | .038* |
| Scomp (kN/mm) | Ref. | | –2.47 (–5.49, 0.55) | –1.02 (–4.69, 2.66) | –4.55 (–8.80, –0.29)* | .045* |
| Tibia | No VF | | | | | |
| vBMD | | | | | | |
| Dtot (mgHA/cm ³) | Ref. | | –21.35 (–33.04, –9.66)* | –16.83 (–31.23, –2.42)* | –27.58 (–44.02, –11.13)* | .000* |
| Dtrab (mgHA/cm ³) | Ref. | | –16.55 (–25.22, –7.66)* | –13.88 (–24.70, –3.05)* | –19.96 (–32.32, –7.61)* | .000* |
| Dcort (mgHA/cm ³) | Ref. | | –1.65 (–19.28, 15.97) | 3.7 (–18.26, 25.20) | –8.69 (–33.50, 16.12) | .637 |
| Micro-architecture | | | | | | |
| Tb.N (1/mm) | Ref. | | –7.18 (–13.69, –0.67)* | –6.81 (–14.85, 1.22) | –7.68 (–16.85, 1.49) | .040* |
| Tb.Th (mm) | Ref. | | –0.28 (–0.84, 0.27) | –0.40 (–1.09, 0.28) | –0.12 (–0.90, 0.66) | .479 |
| Tb.Sp (mm) | Ref. | | 9.31 (1.92, 16.70)* | 8.74 (–0.38, 17.86) | 10.09 (–0.32, 20.50) | .018* |
| Ct.Po (%) | Ref. | | –8.90 (–21.20, 3.39) | –8.10 (–23.28, 7.07) | –10.00 (–27.32, 7.33) | .167 |
| Ct.Th (mm) | Ref. | | –5.90 (–11.69, –0.11)* | –4.49 (–11.63, 2.65) | –7.83 (–15.99, 0.32) | .036* |
| Ct.Po.Dm (mm) | Ref. | | 0.95 (–2.71, 4.62) | 0.20 (–4.32, 4.72) | 1.99 (–3.17, 7.15) | .492 |
| Biomechanical | | | | | | |
| F.Ult (kN) | Ref. | | –0.55 (–0.90, –0.21)* | –0.47 (–0.89, –0.04)* | –0.67 (–1.15, –0.18)* | .002* |
| Scomp (kN/mm) | Ref. | | –10.88 (–17.56, –4.21)* | –9.20 (–17.43, –0.97)* | –13.20 (–22.59, –3.80)* | .001* |

All analyses are adjusted for age, weight, height, type of recent non-vertebral fracture type (major osteoporotic fracture vs. other fractures), previous fractures at or above the age of 50 years, anti-osteoporosis medication (never vs. history vs. current), and femoral neck areal BMD

No prevalent VF is used as the reference group. *Significant

VF, vertebral fracture; Ref., reference; vBMD, volumetric bone mineral density; Dtot, total density; Dtrab, trabecular density; Dcort, cortical density; Tb.N, trabecular number; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation; Ct.Th, cortical thickness; Ct.Po, cortical porosity; Ct.Po.Dm, cortical pore diameter; F.Ult, ultimate failure load; Scomp, compression stiffness

spine on the LS aBMD. This should be confirmed and evaluated in future research.

This study has important implications. In women with a recent NVF, the presence of morphometric VF can be used as a marker for generalized bone micro-architecture deterioration, independent of areal BMD and prior fracture. Our results extend previous observations towards women with a NVF, in whom the presence of at least one prevalent VF was associated with impaired trabecular micro-architecture in the radius and tibia, and cortical micro-architecture and bone strength in the tibia.

This study has several limitations. First, this is a cross-sectional study. Hence, the interpretation of our findings in the context of subsequent fracture risk in FLS patients cannot be addressed. In previous prospective studies, deterioration of HR-pQCT indices of trabecular and cortical bone and lower bone strength improved prediction of fracture beyond femoral neck areal BMD or FRAX scores alone [20–24]. Future studies are needed to determine the relevance of prevalent VF in addition to a NVF, in terms of subsequent VF and NVF risk. Second, prevalent VFs were identified on lateral spine images

by DXA instead of X-ray. The reproducibility of vertebral fracture assessment by DXA is limited, especially for mild (i.e., grade 1) VFs. The inter-rater reliability of absorptiometry was better when only grade 2 or 3 deformities were considered fractured (kappa (95% CI) 0.640 (0.621–0.659)), as compared with when grade 1 deformities were also considered fractures (kappa (95% CI) 0.560 (0.541–0.580)) [32]. Additionally, sensitivity was reported to be 62.5% and specificity was 93.1% for grade 2–3 vertebral deformities, and 51.8% and 88.7%, respectively, when grade 1 vertebral deformities were also considered fractured [32]. This implies that patients could have been incorrectly classified as mild (i.e., grade 1) VF cases [33]. However, a false-positive VF classification would probably only reduce the HR-pQCT differences between patients with at least one (mild) VF and patients without VFs. Fourth, the reference line for the HR-pQCT scans was placed at a fixed reference point, which resulted in scanning the same region in all patients. However, bone morphology at that region differs between individual patients, where a higher amount of cortical bone will be present in patients with relatively short extremities [34, 35]. A recent study suggests scanning at a percentage distance of the total length of the bone [36]. Since this information was not available, as an alternative, we have adjusted all the analyses for height. Finally, our results cannot be generalized to the total fracture population, since probably only the most fit and mobile patients were willing and able to visit the FLS and participate in our study, with a healthy complier bias as a consequence.

In conclusion, in this cross-sectional study in postmenopausal women with a recent NVF, the presence and severity of prevalent VF were associated with impaired bone micro-architecture and strength in the radius and tibia. Therefore, in postmenopausal women with a recent NVF, evaluation of morphometric VF can be used as a marker of generalized micro-architecture deterioration, independent of BMD. Future studies are needed to confirm our results and to determine the relevance of prevalent VF in addition to a NVF, in terms of subsequent VF and NVF risk.

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Compliance with ethical standards

The study protocol (registration number NL45707.072.13) was approved by an independent Medical Ethics Committee and complied with the Declaration of Helsinki. All patients gave written informed consent prior to participation.

Conflicts of interest Drs. Vranken has nothing to disclose.

Dr. Wyers has nothing to disclose.

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