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ORIGINAL ARTICLE

Site-specific volumetric skeletal changes in women with and without a distal forearm fracture: a case–control study with a mean 7-year follow-up

Paul Gerdhem[1,2,3] · **Axel Wihlborg**[1,4] · **Ingrid B. Bergström**[5]

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Abstract

Summary Brief rationale: To assess bone dimensions in the radius over 7 years. Main result: Cross-sectional area did not change significantly, but endosteal circumference increased, leading to decreased cortical thickness. Significance of the paper: Bone mineral density loss is associated with a decrease in cortical thickness in the forearm.

Purpose To assess site-specific volumetric bone and muscle differences in women with and without forearm fracture in a longitudinal study.

Methods One hundred four postmenopausal women with a forearm fracture and 99 age-matched controls were included and underwent peripheral quantitative computed tomography (pQCT) in the forearm at a mean age of 65 (range 44–88) years and were invited for a reassessment after mean 7 (6–11) years, at which 80 and 79 women took part, respectively. Three cases had movement artifacts on pQCT; 77 cases and 79 controls were finally analysed.

Results Twenty-two of the cases and 20 of the controls sustained a fracture during the follow-up. From baseline to follow-up, bone mineral content and bone mineral density decreased irrespective of group belonging at baseline, both at the 4% and the 66% level in the forearm. Cross-sectional area did not change significantly at the 4% and the 66% level. At the 66% level, periosteal circumference was unchanged and endosteal circumference increased, leading to decreased cortical thickness. Muscle area decreased, while muscle density was unchanged. A high cross-sectional area and low bone volumetric bone mineral density were predictive of fracture during the follow-up.

Conclusion Over a mean follow-up of 7 years, postmenopausal women lose bone mineral density, associated with a decrease in cortical thickness in the forearm.

Keywords Bone density · Distal forearm fracture · Fracture · Women

Introduction

The gold standard to diagnose osteoporosis and to predict fractures in postmenopausal women is the measurement of areal bone mineral density (aBMD) by dual-energy X-ray absorptiometry, often in combination with a fracture prediction tool, for example, the fracture risk assessment tool, FRAX. However, a large proportion of fractures occur in postmenopausal women with only a slight decrease in bone mineral density. Areal BMD alone is not able to distinguish between patients at low and high risk for fractures [1, 2].

The rate of aBMD change has in some studies been associated with incident fragility fractures [3–5], while in other studies, the opposite has been found [6–8].

To improve the identification of patients at risk for fracture, cross-sectional studies have been performed using

✉ Paul Gerdhem
paul.gerdhem@uu.se

1 Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Huddinge, Sweden

2 Department of Orthopedics and Hand Surgery, Uppsala University Hospital, Uppsala, Sweden

3 Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

4 Department of Trauma Surgery and Orthopedics, Karolinska University Hospital, Huddinge, Sweden

5 Department of Clinical Science and Education, Karolinska Institutet, Södersjukhuset, Stockholm, Sweden

three-dimensional assessments with peripheral quantitative computed tomography (pQCT) and high-resolution peripheral quantitative computed tomography (HR-pQCT) [1, 9, 10]. Prospective studies have contributed to findings of impairment in bone microarchitecture in persons with incident fractures [9, 11–13].

The association between prospective changes in bone microarchitecture and risk for fracture has been studied in a few studies [1, 14, 15]. One study concluded that the baseline values for bone mineral density and microarchitecture measured by HR-pQCT were associated with incident fractures, but not previous fractures or the changes in bone parameters over time [1]. In contrast, another study concluded the rates of change of some HR-pQCT measures of the distal forearm but not in the tibia predicted fractures [14]. A recent study found that HR-pQCT measures could improve fracture prediction for up to 2 years, beyond that of aBMD and FRAX [15].

We have in a cross-sectional study reported that the distal forearm fracture in postmenopausal women is associated with site-specific and central bone changes, with fracture patients having a larger bone area in combination with a thinner cortex and lower site-specific total BMD than controls [16]. The individuals in this study have now attended a follow-up.

Our aim was to study differences in pQCT parameters over time and the predictive ability of pQCT parameters compared to aBMD.

Material and methods

We followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines when preparing the manuscript.

This is a case–control study with a longitudinal follow-up. The study population consists of postmenopausal women participating in the distal forearm fracture (DFF) study. Baseline data for the complete cohort has been presented in detail earlier [16].

The DFF study was conducted at the Karolinska University Hospital, Huddinge in Stockholm, Sweden. Postmenopausal women presenting with a low-energy distal forearm fracture at the orthopaedic emergency department from April 2010 to January 2015 were invited to attend the study. Of the 123 women who initially consented to participate, 7 declined to come to the research department and 12 were withdrawn from the analysis (9 had a previous fracture on the other arm and 3 had missing data), leaving 104 women in the study. Age- and gender-matched controls from the same geographic area (Huddinge, Sweden) were selected at random through the population register. Invitations were sent by mail, with one reminder, to 362 women in total. Controls were excluded in case of a history of osteoporosis-related fracture (including a distal forearm fracture), secondary osteoporosis, known bone remodelling disease, or antiresorptive, oestrogen, or oral corticosteroid treatment. In total, 99 controls with a mean age of 65 years were included (Fig. 1).

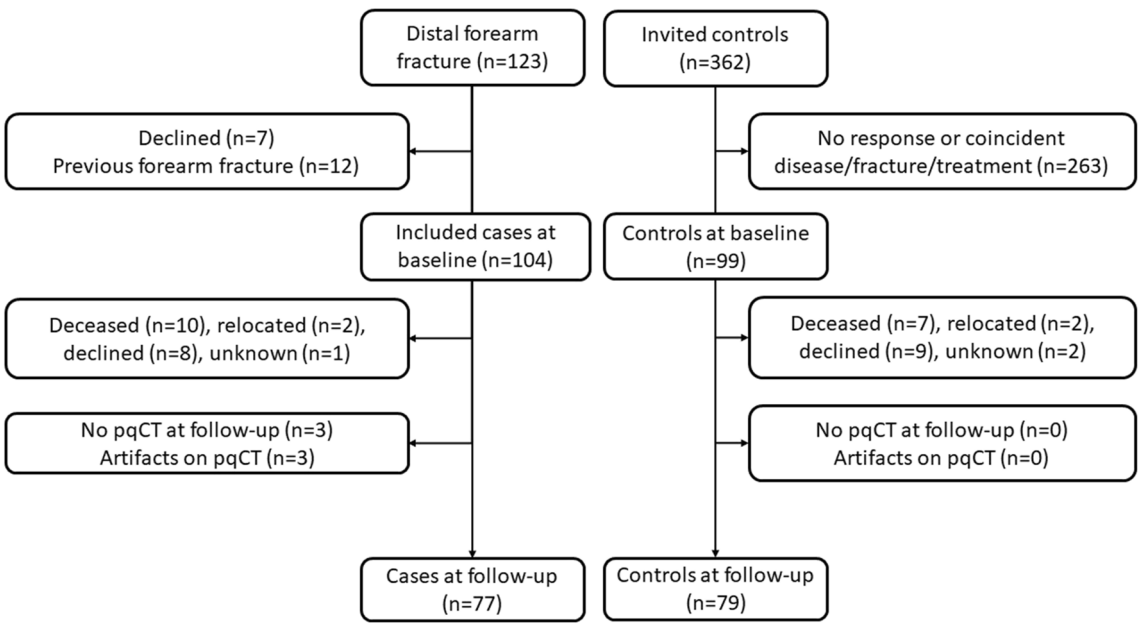

Fig. 1 Flow chart of cases and controls in the distal forearm fracture (DFF) study

Both cases and controls were after questionnaire assessment, blood sampling, and bone density measurements individually assessed by a physician (AW or IB) at baseline. Any suspicion of vertebral fracture was a reason for spine radiographs. All cases and controls were later invited to a follow-up examination.

Volumetric properties

Volumetric properties of the forearm were assessed by peripheral quantitative computed tomography (pQCT) with a Stratec XTC-2000 (Stratec Medizintechnik, Pforzheim, Germany). Version 6.2 of the manufacturer software was used. The coefficient of variation (CV) was 0.27% when calculated from 31 consecutive measurements with the forearm phantom after repositioning. Measurements were performed at the distal (4%) and shaft (66%) sites of the radial bone with voxel size 0.5 mm, 2.3-mm slice thickness, and 20 mm/s scanning speed. Contourmode 1 was used with a density threshold of 180 mg/cm^3 at the distal (4%) site and 280 mg/cm^3 at the shaft (66%) site to separate the outer edge of bone from soft tissue. Trabecular bone was distinguished by 45% of the area at the distal site (Peel mode 1). Cortical bone was distinguished by cortical mode 1 with an inner threshold of 711 mg/cm^3 at the shaft site. Muscle tissue was separated by contour mode 3 with a threshold of 40 mg/cm^3 at the shaft site. Trabecular bone properties were assessed at the 4% site by trabecular BMD, total bone mineral content (BMC), and total BMD. Cortical bone properties were assessed at the 66% site by total BMD, cortical BMD, and total BMC. Bone geometric properties were assessed by cross-sectional area (CSA) at the 4% site as well as cortical thickness, periosteal and endosteal circumference, and CSA at the 66% site. Cortical variables were retrieved at the shaft site due to pQCT-associated measurement uncertainty of cortical variables at the distal site. Cortical bone properties at the shaft site were presumed to reflect cortical bone properties throughout the bone. Muscle properties were assessed as muscle area and density. pQCT were performed at the non-fractured forearm with a matching number of left and right arm measurements in the controls.

All measurements throughout the whole study period, both at baseline and at the follow-up, were made by the same research nurse, certified for pQCT measurements with the device. Large area differences (> 40 mm^2) at the 4% level between baseline and the follow-up were rechecked for scan measurement positioning before analysis. Three cases were excluded at follow-up due to movement artifacts. No controls were excluded. After exclusions, 77 cases and 78 controls remained for the analysis of the long-term follow-up.

Areal Bone mineral density measurements

Areal Bone mineral density (aBMD) measurements were performed at baseline for both cases and controls. aBMD was measured at the hip and lumbar spine (L1-L2) with a GE Lunar iDXA (GE Medical systems, Chalfont St. Giles, UK) [17]. The coefficient of variation (CV) was 1.5% for the spine phantom provided by the manufacturer.

Blood samples

Blood samples were drawn at baseline and stored at − 80 °C and were analysed at the same time in the same laboratory [16]. Parathyroid hormone was analysed as intact PTH on Modular analytics E170 (Roche diagnostics Ldt) using electrochemiluminescence immunoassay (ECLIA) with intra- and inter-assay CV ranging between 1.1–2.0% and 2.8–3.4%, respectively. 25-Hydroxy vitamin D3 (25OHD) was analysed on API 4000 LC–MS/MS (Sciex), assay CV ranging between 4.0 and 6.0%. Calcium was analysed on Cobas c502 (Roche diagnostics Ldt) by NM-BAPTA method, assay CV ranging between 0.6 and 0.5%. Serum calcium was corrected for serum albumin by the formula: calcium + 0.01 * (39-albumin).

Incident fractures

All types of clinical fractures between baseline and follow-up were recorded. Fracture data were based on self-report, and were confirmed in radiological reports based on each individual's personal identification number. Fractures were treated in accordance with clinical routine.

Ethics

The study was approved by the Regional Ethical board in Stockholm (2009/913–31 and 2017/2131–2). Informed consent was obtained from all participants included in the study.

Statistical analysis

Normally distributed continuous data is shown as mean (standard deviation; SD) or mean (95% confidence interval; CI), and non-normally distributed continuous data is shown as median (interquartile range; IQR). Normality was checked for by visual inspection of histograms. Categorical data is shown as number (%).

Cases and controls were additionally grouped into those that sustained a fracture during the follow-up and those that did not and into those that had received treatment for osteoporosis during the follow-up and those that did not. The individuals were additionally grouped into those receiving an active pharmacological treatment for osteoporosis:

bisphosphonate, denosumab, teriparatide, or hormone replacement therapy/oestrogen, during the complete, or part, of the follow-up.

Fracture risk was calculated for cases and controls together, with logistic regression, adjusted for group (case or control) and follow-up time. In the analyses for any fracture, additional adjustment for body mass index or age at baseline was performed. To allow comparisons of risk between different variables, these were standardized to a mean of 0, with a standard deviation of 1.

In case of missing data, cases were excluded analysis by analysis. IBM SPSS Statistics version 28 was used for statistical analysis.

Sample size

The study was originally powered to detect a 10% difference in volumetric density between cases and controls at baseline (corresponding to 20 mg/cm^3 total BMD difference) with a standard deviation of 22.5% (corresponding to 45 mg/cm^3) with alfa 0.05 and 80% power. Sample size was calculated to be 81 cases and 81 controls. Data from 104 cases and 99 controls were included at baseline. For the follow-up assessments, no additional power calculation was made.

Results

Descriptive baseline data is shown in Table 1. The follow-up was mean 7 (range 6–11) years. Twenty-two of the cases and 20 of the controls had sustained a clinical fracture during the follow-up, and fractures in the vertebras and upper extremities were the most common sites.

Baseline and follow-up pQCT data are shown in Table 2. In summary, from baseline to follow-up, bone mineral content and bone mineral density decreased, both at the 4% and the 66% level. Cross-sectional area did not change significantly at the 4% and the 66% level. At the 66% level, periosteal circumference was unchanged and endosteal circumference increased, leading to decreased cortical thickness (Tables 2 and 3, Supplementary Fig. 1). Muscle area decreased, while muscle density was unchanged (Tables 2 and 3). Changes occurred in both cases and controls and were of similar magnitude (Table 3).

Table 1 Descriptive data for the cohorts at baseline and at follow-up. Data shown as mean (SD), median (IQR), or number for cases and controls that participated in the follow-up. If data is missing, this is indicated

Variable	Baseline		Follow-up	
	Cases ($n=77$)	Controls ($n=79$)	Cases ($n=77$)	Controls ($n=79$)
Age (years)	64 (8)	63 (8)	72 (8)	70 (8)
Body height (m)	1.64 (0.06)	1.64 (0.06)	1.64 (0.06)	1.64 (0.06)
Body weight (kg)	69 (12)	70 (13)	69 (12)	70 (13)
Body mass index (kg/m^2)	25.7 (4.4)	26.0 (5.1)	25.7 (4.4)	26.0 (5.0)
Alcohol (units/day)	0.4 (0.1,0.8)	0.4 (0.1,0.8)	0.3 (0.1,0.8)	0.4 (0.1,0.7)
Serum calcium (mmol/L) (corrected for albumin)	2.4 (2.3,2.4)	2.4 (2.3,2.4)		
Parathyroid hormone (pmol/L)	4.4 (3.7,5.0)	4.5 (3.6,5.6)		
25OHD (nmol/L)	59 (48,76)	58 (48,75)		
Areal BMD femoral neck (g/cm^2)	0.82 (0.10)	0.88 (0.13)		
T-score femoral neck	−1.5 (0.7)	−1.1 (0.9)		
Areal BMD lumbar spine L1-L2 (g/cm^2)	0.94 (0.11)	1.0 (0.17)		
T-score lumbar spine	−1.8 (0.9)	−1.2 (1.4)		
Smoking (n)	7	5	2	2
History of at least one fall the previous year	50 (out of 72)	27 (out of 77)	26 (out of 72)	28 (out of 77)
History of at least two falls the previous year	24 (out of 72)	14 (out of 77)	17 (out of 72)	11 (out of 77)
History of osteoporosis-related fracture	8 (out of 74)	0 (out of 77)		
Vertebral fracture at inclusion, radiographically verified	16	5		
Any incident fracture (between baseline and follow-up)			22	20
Number of incident fractures (between baseline and follow-up)			25	23
-of which any incident vertebral fracture at follow-up			12	8
-of which any incident upper extremity fracture at follow-up			5	7
Osteoporosis treatment* (any active pharmacological treatment)	4	0	24	20

*Bisphosphonates were used by 18 out of 24 cases and 19 out of 20 controls during part of, or the whole, follow-up period

Table 2 Mean (SD) for pqCT variables for all 156 individuals at baseline and at follow-up; mean 7 (range 6–11) years from baseline. The difference between follow-up and baseline is shown as a mean (95% CI). Negative values for the difference represent a decrease since baseline. Numbers in italics indicate that a significant change from the baseline measurement has occurred

Variable	Baseline	Follow-up	Difference (95% CI) (follow-up–baseline)	Difference in % (95% CI) (follow-up–baseline)
Cross-sectional area 4% level (mm^2)	322 (51)	324 (60)	2 (−4 to 8)	0.6% (−1.2 to 2.5%)
Total bone mineral content 4% (mg/mm)	0.91 (0.16)	0.86 (0.18)	*−0.05 (−0.06 to −0.03)*	*−5.5% (−6.6 to −3.3%)*
Total bone mineral density 4% (mg/cm^3)	288 (61)	271 (59)	*−16 (−21 to −12)*	*−5.9% (−7.3 to −4.2%)*
Trabecular area 4% (mm^2)	145 (23)	147 (32)	2 (−2 to 6)	1.4% (−1.4 to 4.1%)
Trabecular density 4% (mg/cm^3)	149 (41)	148 (44)	0 (−4 to 3)	−0.7% (−2.7 to 2.0%)
Cross-sectional area 66% level (mm^2)	131 (23)	130 (20)	0 (−1 to 1)	−0.8% (−0.8 to 0.8%)
Total bone mineral content 66% (mg/mm)	0.86 (0.16)	0.81 (0.16)	*−0.05 (−0.06 to −0.03)*	*−5.8% (−7.0 to −3.5%)*
Total bone mineral density 66% (mg/cm^3)	667 (112)	627 (114)	*−40 (−48 to −31)*	*−6.0% (−7.2 to −4.6%)*
Cortical density 66% (mg/cm^3)	1112 (43)	1093 (46)	*−18 (−23 to −14)*	*−1.7% (−2.1 to −1.3%)*
Cortical thickness 66% (mm)	1.89 (0.40)	1.75 (0.42)	*−0.14 (−0.18 to −0.10)*	*−7.4% (−9.5 to −5.3%)*
Periosteal circumference 66% (mm)	40.4 (3.1)	40.4 (3.1)	0.0 (−0.2 to 0.2)	0.0% (−0.5 to 0.5%)
Endosteal circumference 66% (mm)	28.5 (4.4)	29.4 (4.1)	*0.9 (0.6 to 1.2)*	*3.2% (2.1 to 4.2%)*
Muscle area (mm^2)	2628 (430)	2525 (437)	*−103 (−162 to −44)*	*−3.9% (−6.2 to −1.7%)*
Muscle density (mg/cm^3)	73.6 (6.2)	72.4 (6.3)	−1.2 (−2.5 to 0.1)	−1.6% (−3.4 to 0.1%)

Table 3 Data (mean and 95% confidence interval) for change of pqCT variables during the follow-up for cases (forearm fracture at baseline) and controls (no forearm fracture at baseline). Negative values for the difference represent a decrease since baseline. Numbers in italics indicate that a significant change from the baseline measurement has occurred

Variable	Cases ($n=77$)	Controls ($n=79$)
Cross-sectional area 4% level (mm^2)	*8 (1 to 13)*	−3 (−13 to 6)
Total bone mineral content 4% (mg/mm)	*−0.03 (−0.05 to −0.01)*	*−0.06 (−0.09 to −0.04)*
Total bone mineral density 4% (mg/cm^3)	*−15 (−23 to −8)*	*−17 (−23 to −12)*
Trabecular area 4% (mm^2)	*3 (1 to 6)*	1 (−6 to 8)
Trabecular density 4% (mg/cm^3)	0 (−5 to 4)	0 (−6 to 6)
Cross-sectional area 66% level (mm^2)	−2 (−3 to 0)	1 (−1 to 3)
Total bone mineral content 66% (mg/mm)	*−0.06 (−0.08 to −0.04)*	*−0.04 (−0.06 to −0.01)*
Total bone mineral density 66% (mg/cm^3)	*−43 (−55 to −32)*	*−36 (−50 to −23)*
Cortical density 66% (mg/cm^3)	*−20 (−27 to −14)*	*−0.16 (−21 to −11)*
Cortical thickness 66% (mm)	*−0.16 (−0.21 to −0.11)*	*−0.13 (−0.19 to −0.06)*
Periosteal circumference 66% (mm)	−0.2 (−0.4 to 0.0)	0.2 (−0.1 to 0.5)
Endosteal circumference 66% (mm)	*0.8 (0.4 to 1.2)*	*1.0 (0.6 to 1.4)*
Muscle area (mm^2)	*−97 (−130 to −64)*	−108 (−222 to 5)
Muscle density (mg/cm^3)	−1.2 (−1.5 to 0.8)	−1.2 (−3.8 to 1.5)

When comparing individuals with and without incident fractures, similar changes between baseline and follow-up were observed in both groups (Table 4).

A high cross-sectional area and low volumetric bone mineral density in the radius at the 4% level were predictive of fracture during the follow-up (Table 5). Areal BMD in the lumbar spine was predictive of any fracture and vertebral fractures and aBMD in the femoral neck was predictive of any fracture (Table 5). Additional adjustment of BMI or age at baseline in the logistic regressions did not substantially change the odds ratios and their confidence intervals (data not shown).

Although no statistically significant differences were observed, pharmacological treatment for osteoporosis tended to be associated with lower loss of total bone mineral content and total bone mineral density at the 4% level (Supplementary Table 1).

Discussion

In summary, in this mean 7-year follow-up of a case–control study, cortical thickness in the forearm decreased as a result of endosteal resorption resulting in decreased bone mineral density. A high forearm cross-sectional area and a low bone volumetric bone mineral density were predictive of fracture.

A well-known fact is that baseline aBMD predicts fractures [1], and in our study, aBMD in the femoral neck as

Table 4 Data (mean and 95% confidence interval) for the 156 individuals comparing individuals who sustained a fracture ($n=42$) and individuals who did not sustain a fracture ($n=114$) during the follow-up; mean 7 (range 6–11) years. Negative values for the difference represent a decrease since baseline. Numbers in italics indicate that a significant change from the baseline measurement has occurred

Variable	Individuals without fracture ($n=114$) Change fu-base	Individuals with fracture ($n=42$) Change fu-base
Cross-sectional area 4% level (mm^2)	0 (−7 to 7)	6 (−4 to 16)
Total bone mineral content 4% (mg/mm)	*−0.06 (−0.08* to *−0.05)*	*−0.06 (−0.08* to *-0.04)*
Total bone mineral density 4% (mg/cm^3)	*−20 (−25* to *−15)*	−20 (−18 to 4)
Trabecular area 4% (mm^2)	2 (−3 to 7)	3 (−2 to 7)
Trabecular density 4% (mg/cm^3)	−3 (−6 to 0)	6 (−5 to 18)
Cross-sectional area 66% level (mm^2)	0 (−2 to 2)	0 (−2 to 1)
Total bone mineral content 66% (mg/mm)	*−0.05 (−0.07* to *−0.03)*	*−0.05 (−0.08* to *-0.02)*
Total bone mineral density 66% (mg/cm^3)	*−39 (−49* to *−30)*	*−42 (−62* to *−23)*
Cortical density 66% (mg/cm^3)	*−18 (−22* to *−13)*	*−20 (−30* to *−11)*
Cortical thickness 66% (mm)	*−0.14 (−0.19* to *−0.10)*	*−0.14 (−0.22* to *−0.06)*
Periosteal circumference 66% (mm)	0.0 (−0.2 to 0.3)	−0.1 (−0.3 to 0.1)
Endosteal circumference 66% (mm)	*0.9 (0.6* to *1.2)*	*0.8 (0.2* to *1.4)*
Muscle area (mm^2)	*−100 (−180* to *−21)*	*−109 (−156* to *−63)*
Muscle density (mg/cm^3)	−1.1 (−2.9 to 0.1)	−1.5 (−2.1 to −0.1)

Table 5 Odds ratio (95% confidence interval) for baseline variables and the risk of incident fracture (any fracture, vertebral fracture, upper arm fracture) for both cases and controls. All baseline variables are standardized (mean 0, standard deviation 1) to allow comparisons. Numbers larger than 1 indicate an increased fracture risk per standard deviation increase of the independent variable. Numbers lower than 1 indicate a decreased fracture risk per standard deviation decrease of the independent variable. Numbers in italics indicate that the 95% confidence interval does not cross 1. All analyses are adjusted for group (case or control) and follow-up time

Variable	Any fracture ($n=42$)	Vertebral fracture ($n=20$)	Upper arm fracture ($n=12$)
Cross-sectional area 4% level	*1.58 (1.06–2.37)*	1.59 (0.97–2.62)	1.46 (0.80–2.66)
Total bone mineral content 4%	0.93 (0.63–1.39)	0.88 (0.51–1.52)	0.59 (0.30–1.19)
Total bone mineral density 4%	*0.54 (0.33–0.89)*	*0.49 (0.25–0.97)*	*0.33 (0.14–0.81)*
Trabecular area 4%	*1.59 (1.06–2.37)*	1.59 (0.97–2.62)	1.46 (0.80–2.66)
Trabecular density 4%	0.63 (0.39–1.01)	0.65 (0.34–1.23)	*0.36 (0.15–0.84)*
Cross-sectional area 66% level	1.01 (0.68–1.50)	0.86 (0.50–1.50)	0.69 (0.33–1.45)
Total bone mineral content (cortical) 66%	0.94 (0.64–1.37)	0.97 (0.66–1.42)	0.87 (0.46–1.63)
Total bone mineral density 66%	0.97 (0.65–1.44)	1.10 (0.64–1.86)	1.25 (0.63–2.49)
Cortical density (66%)	0.89 (0.58–1.38)	1.03 (0.58–1.84)	1.37 (0.64–2.94)
Cortical thickness 66%	0.99 (0.67–1.47)	1.08 (0.63–1.82)	1.11 (0.57–2.15)
Periosteal circumference 66%	1.02 (0.69–1.49)	0.88 (0.52–1.50)	0.72 (0.36–1.43)
Endosteal circumference 66%	1.02 (0.68–1.53)	0.87 (0.49–1.52)	0.70 (0.33–1.50)
Muscle area	1.10 (0.77–1.57)	1.09 (0.68–1.75)	0.93 (0.58–1.50)
Muscle density	1.81 (0.61–5.37)	1.42 (0.37–5.46)	1.63 (0.27–9.89)
Areal BMD femoral neck	*0.50 (0.32–0.77)*	0.59 (0.34–1.03)	*0.62 (0.32–1.19)*
Areal BMD L1-L2	*0.61 (0.40–0.93)*	*0.47 (0.26–0.86)*	*0.84 (0.46–1.57)*

well as in L1-L2 predicted fractures and the aBMD L1-L2 predicted vertebral fractures. Total volume bone mineral density measured with pQCT at the distal radius could predict any fracture, vertebral fractures, and upper extremity fractures in this population which neither femoral neck DXA nor lumbar spine DXA were able to do as single measurements. That pQCT to some extent performed better than the DXA measurements could possibly be attributed to the more exact measurement of bone density.

Previous studies have reported that the total volume bone mineral density predicts fracture risk [1, 11, 18]. Concerning the microarchitecture, most studies conclude that the cortical and trabecular components are of most importance for the prediction of fracture [9, 11, 15]. In our study, these conclusions cannot be confirmed. However, not found in other pQCT studies as far as we know, a high cross-sectional area in the forearm was predictive of fracture. It is known that bone expansion compensates for pathogenic events such as a

reduction in bone quality [19, 20]. In our earlier publication, we presented that the postmenopausal women with fractures had a larger bone area, indicating a previous bone expansion due to a reduction in bone quality [16]. It is likely that this expansion occurs early in the menopausal period [19].

The cases had inferior bone parameters at baseline [16]. However, the incident fractures in our study seemed to be independent of earlier fractures, and of the changes in pQCT parameters observed over the 7-year period, confirming the results of the Calgary follow-up study of postmenopausal women where previous fractures or the changes in bone parameters over time did not predict incident fractures [1].

Changes in volumetric bone density with increasing age have been described earlier in a cross-sectional study and in prospective studies spanning up to 3 years [21–23]. Common findings are loss of trabeculae, increased cortical porosity, and declining cortical thickness with age. Decreased cortical thickness and cortical density with age in our study confirm the previous findings.

During the study period, incident fractures occurred in 42 of the 156 postmenopausal women. Although the cases sustained a few more fractures during the follow-up, the difference to the controls was very small. The cases tended to have more vertebral fractures and upper extremity fractures than the controls, but the current sample size is not enough to be able to draw any firm conclusions about possible differences.

In a clinical perspective, it is of importance to select women with a high risk for future fractures, especially vertebral fractures, for treatment. In women with distal radius fracture, with generally fair BMD measurements and relatively low age, the FRAX tool often indicates a low 10-year risk of fracture [12, 24]. A pQCT measurement seems to at least capture fracture risk on par with or even better than a central DXA measurement, and it is possible that the addition of volumetric bone density measurements can further improve fracture risk assessments [15].

A pQCT measurement also provides site-specific muscle parameters, but these do not differ significantly between cases and controls [16] and do not hold a fracture-predictive ability.

The study has some advantages. The follow-up rate was high. More than 80% of women alive took part in the follow-up, which stretched over several years. The same pQCT technician and the same equipment were available for all measurements. Both cases and controls were from the same catchment area. Fracture identification could be considered complete and possible through self-assessment with cross-checking of radiology reports based on unique personal identification numbers.

The study also has some limitations. The case–control study design limits the analysis of risk estimates. There were slight differences in follow-up time between cases and controls, but adjustment for group belonging and follow-up was done statistically. No obvious differences were seen over time in the two groups. The sample could be considered small, which limits the precision of risk estimates. No DXA was performed at the follow-up so inferences for central skeletal DXA changes cannot be made. The cases are likely to be representative for women seeking care for distal forearm fractures, but we note that it was difficult to recruit controls at baseline. Therefore, external validity may be questioned.

In summary, in postmenopausal women, bone mineral content and bone mineral density decreased in the forearm because of increased endosteal resorption, while cross-sectional area was mainly unchanged. A high cross-sectional area and low bone volumetric bone mineral density were predictive of fracture, and the highest risks were site specific. During the mean 7-year follow-up in this study, bone volumetric and density changes could not be specifically coupled to previous fractures, or pharmacological treatment for osteoporosis.

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Data Availability Deidentified data can be supplied by the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

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