**JIM** Original Article

# Increased cortical porosity in women with hip fracture

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**Abstract.** Sundh D, Nilsson AG, Nilsson M, Johansson L, Mellström D, Lorentzon M (University of Gothenburg, Sweden, Sahlgrenska University Hospital). Increased cortical porosity in women with hip fracture. *J Intern Med* 2017; **281**: 496–506.

**Background**. Hip fractures cause increased mortality and disability and consume enormous healthcare resources. Only 46% of hip fracture patients have osteoporosis at the total hip according to dualenergy X-ray absorptiometry (DXA) measurement. Cortical porosity increases with ageing and is believed to be important for bone strength.

**Objective.** To investigate whether older women with hip fracture have higher cortical porosity than controls, and if so whether this difference is independent of clinical risk factors and areal bone mineral density (aBMD).

**Methods.** From an ongoing population-based study, we identified 46 women with a prevalent X-rayverified hip fracture and 361 control subjects without any fractures. aBMD was measured with DXA. High-resolution peripheral quantitative computed tomography was used to measure bone

#### Introduction

Osteoporosis is a skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to compromised bone strength and increased risk of fracture [1, 2]. Thus, fragility fractures constitute the major clinical outcome of osteoporosis. Of all fractures, those of the hip have the largest impact on morbidity and mortality [3]. One in five patients dies within the first year of hip fracture [1], and severe negative effects on quality of life are common [4]. The hip fracture incidence rate increases exponentially with age. This age-related increase is due partly to a decrease in areal bone mineral density (aBMD) at the proximal femur (a proxy for bone strength) and an increase in the frequency of falls in women [5], in whom 70% of all hip fractures occur [6].

microstructure at the standard (ultradistal) site and at 14% (distal) of the tibial length.

**Results.** Women with a previous hip fracture had lower aBMD at the femoral neck (-11.8%) and total hip (-14.6%) as well as higher cortical porosity at the ultradistal (32.1%) and distal (29.3%) tibia compared with controls. In multivariable logistic regression analysis, with adjustment for covariates (age, height, weight, smoking, calcium intake, physical activity, walk time, oral glucocorticoids, parental hip fracture, rheumatoid arthritis, previous fall, current bisphosphonate treatment and femoral neck aBMD), cortical porosity at the ultradistal [odds ratio per standard deviation increase (95% confidence interval) 2.61 (1.77–3.85)] and distal [1.57 (1.12–2.20)] sites was associated with prevalent hip fracture.

**Conclusion.** Cortical porosity was associated with prevalent hip fracture in older women independently of femoral neck aBMD and clinical risk factors.

**Keywords:** bone mineral density, cortical porosity, hip fracture, HR-pQCT, osteoporosis, women.

Osteoporosis has been defined as aBMD of 2.5 or more standard deviations below the mean of a reference population of young women (T-score  $\leq -2.5$  SD) measured with dual-energy X-ray absorptiometry (DXA), the clinical gold standard [7]. BMD is robustly associated with clinical risk of hip fracture [8]. However, its ability to assess an individual's fracture risk has been questioned because more than half of all hip fracture patients do not have osteoporosis [9, 10]. This could be due to some extent to a limitation of the DXA technique of only measuring BMD without the ability to distinguish between trabecular and cortical bone or to evaluate bone structure, which may better reflect bone strength. With newer imaging technology, high-resolution peripheral quantitative computed tomography (HR-pQCT), bone microstructure can be measured in vivo, noninvasively, at peripheral sites such as the radius and

496 © 2017 The Authors. Journal of Internal Medicine published by John Wiley & Sons Ltd on behalf of Association for Publication of The Journal of Internal Medicine. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, tibia [11]. Earlier studies with HR-pQCT have demonstrated that alterations of trabecular and cortical bone structure are associated with prevalent fracture even after adjustment for aBMD in men [12] and women [13]. Vico et al. [14] showed impaired trabecular microstructure and changes in cortical bone geometry and density at the tibia in postmenopausal women with a prevalent hip fracture. Bone loss mainly occurs in cortical bone at older ages due to larger accessible areas for bone resorption in cortical compared to trabecular bone, resulting in increased cortical porosity and lower bone strength [15]. Increased cortical porosity of both the femur and tibia is correlated with lower shear and tensile fracture toughness [16] indicating a lower fracture resistance with increased cortical porosity. Recently, cortical porosity was reported to be important to identify individuals with an increased risk of wrist fracture without osteoporosis according to DXA (T-score  $\leq -2.5$ ) [17]. The vast majority of studies investigating cortical porosity have utilized measurements (at a fixed distance from the endplate) of the ultradistal radius or tibia, introducing large systematic errors (up to 26%) due to varying bone length of the study subjects [18]. Furthermore, the ultradistal sites predominantly consist of trabecular bone, with very small amounts of remaining cortical bone at advanced ages, and thus accurate assessment of cortical microstructure is challenging using this anatomical site [19]. Whether or not cortical porosity can distinguish between women with and without prevalent hip fracture, and if any possible difference in cortical porosity is independent of aBMD, is still unknown.

Our aim was to investigate whether prevalent hip fracture is associated with increased cortical porosity, and if so whether this association is independent of femoral neck aBMD and clinical risk factors in older women with prevalent hip fracture.

# Materials and methods

# Study subjects

From an ongoing, prospective, population-based study, including 3030 elderly Swedish women (75–80 years), we identified 49 women with a prior X-ray-verified hip fracture. In addition, from a subpopulation consisting of the first 1093 consecutively included women with complete HR-pQCT-data, we identified 383 women without any self-reported fracture (after 50 years of age) as

controls. After exclusion of individuals with insufficient quality HR-pQCT data (as described below), 46 hip fracture cases and 361 controls without fractures remained and constituted the final study population.

# Study design

Standardized equipment was used to measure height and body weight. Two consecutive measurements of height were performed and if the two measurements differed by  $\geq 5$  mm, a third measure was obtained. An average was calculated, and if three measurements were performed, the two most similar estimates were used. To assess tibial length, the distance was measured between the medial malleolus and the medial condyle of the tibia. To evaluate physical function, all participants were asked to perform a walk test; participants were instructed to walk a distance of 10 m twice at a self-chosen pace, and the average time was calculated. Grip strength was tested with a hydraulic hand dynamometer (model SH5001; Saehan Corporation, Masan, Korea). Two attempts with each hand were made, with the elbow at a 90degree angle and the lower arm resting on a flat surface. An average value for the dominant hand was used in this study. The self-reported standardized questionnaire Physical Activity Scale for the Elderly (PASE) was used to assess physical activity. Physical activity is reported for a 7-day period before the assessment and has been evaluated in individuals aged 65 years or older [20]. The PASE score was calculated from 12 items where the amount of time spent in each activity (hours per week) or participation (yes/no) was multiplied by given weights and summarized. The Physical Component Summary (PCS) of the standardized SF-12 questionnaire was used to evaluate physical function, including pain and other factors affecting the degree of function [21].

All participants were asked to complete a standardized questionnaire regarding intake of calcium supplements, medical history, use of medications, occurrence of a fall in the last 12 months, alcohol consumption, heredity of hip fracture and smoking. Information about daily intake of calcium-containing products, such as milk, hard cheese and soft cheese, was collected with a validated questionnaire [22]. Total daily intake of calcium was estimated by adding supplement and food-derived intake. Information about ongoing treatment with bone-specific medication (i.e. bisphosphonates) was gathered by asking the participants if they had taken these drugs during the last month. Alcohol consumption was estimated by questions regarding frequency and amount of drinking [23]. To assess heredity of hip fracture, subjects were asked whether either of their parents had sustained a hip fracture. The questionnaire was also used as a first screening for fractures. Participants were asked whether they had experienced a hip fracture, and if so at what age. Fractures sustained after the age of 50 were considered and further explored in patient X-ray reports. All self-reported cases were investigated through a digital radiology database consisting of regional patient data (i.e. radiology reports and corresponding images) from all radiology examinations. All cases finally included had X-ray reports and/or X-ray images of a prevalent hip fracture. All X-ray-verified hip fractures were defined according to subtype: intracapsular femoral neck, intertrochanteric (including basocervical) and subtrochanteric fractures. Controls included in the study had not reported a prevalent fracture of any kind after the age of 50 years. All study participants provided written informed consent before study entry, and the study was approved by the ethical review board at the University of Gothenburg.

# Assessment of BMD

BMD was measured with the same Hologic Discovery A (S/N 86491) device (Waltham, MA, USA) at the femoral neck, total hip and lumbar spine. The left femoral neck and total hip were measured. In case of a previous fracture or the presence of osteosynthesis materials, the contralateral side was measured. Individuals with bilateral hip osteosynthesis materials were not eligible for the study. The coefficients of variation (CVs), assessed in 30 women aged 75–80 years, were 1.3% for the femoral neck, 0.8% for the total hip and 0.7% for the lumbar spine.

# Assessment of bone microarchitecture

Scans of the tibia, ipsilateral to the nondominant arm (or at the contralateral side in the case of a previous fracture), were performed using HR-pQCT (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland). This three-dimensional high-resolution equipment measures volumetric BMD and bone microstructure. The images were obtained using a previously described protocol [24]. In this study, all participants underwent measurement using the standard protocol provided by the manufacturer. With this protocol, the first image was acquired at 22.5 mm from the reference line (i.e. a line placed at the articular plateau by the operator). For the more proximal section, the first image was obtained at 14% of the bone length. Together with the first slice, a total of 110 crosssectional images were obtained with an isotropic resolution of 82 µm resulting in a three-dimensional model of the bone. Each three-dimensional model (110 images) took 3 min of scan time to obtain, and the effective dose was 3 µSv. The operator investigated the first image obtained for motion artefacts and later graded all images. Image quality was assured by the manufacturer's protocol where all images are assigned a number on a five-point scale (1 = best to 5 = worst). Only data from individuals with adequate quality (1-3) at both the manufacturer's site and at 14% of tibial length were included in this analysis. According to this criterion, 24 individuals had insufficient quality in either of the two tibial sections (standard protocol or 14%). One individual was excluded due to artefacts from osteosynthesis materials. The trabecular parameters presented were obtained at the more distal section derived from the standard analysis, and the cortical parameters were obtained at both the standard section and the more proximal section (14%) [25]. Images controlled for quality were then processed according to a previously described protocol [26] resulting in separation of trabecular and cortical bone and the following parameters: trabecular bone volume fraction (BV/TV, %), derived by dividing measured trabecular BMD from the trabecular bone compartment by fully mineralized bone (1200 mg cm<sup>-3</sup>) [26]; trabecular number  $(mm^{-1})$ , defined as the inverse of the mean spacing between the ridges using a distance transformation method [27]; and trabecular thickness (mm), derived using standard histomorphometric methods from the equation: trabecular thickness = (BV/TV)/trabecular number [28]. Based on repeated measurement in six elderly women (78.0 years) after repositioning, the CVs for these trabecular parameters were as follows: BV/TV, 0.8%; trabecular number, 1.9%; and trabecular thickness, 2.6%.

# Cortical evaluation

The manufacturer's customized version of Image Processing Language (IPL v5.08b; Scanco Medical AG) was used to further process all images in accordance with a previously described method [29]. A contour was automatically placed at the periosteal surface, to delineate the bone from extra-osseal soft tissue, on all 110 cross-sectional images obtained at each measuring site. A second contour was automatically placed on the endosteal side of the cortical bone, to separate cortical from trabecular bone. To ensure that the correct bone compartment was analysed, all contours from both segmentation processes were carefully inspected and manually corrected if necessary, for example if the automated algorithms included soft tissue within the periosteal region of interest (ROI) or if trabecular bone was included within the ROI for cortical bone. After inspection of all contours (both periosteal and trabecular), cortical porosity was defined within the two contours after exclusion of artefacts such as surface roughness and transcortical foramen or erosions. To complete the process and obtain a more refined cortical compartment, the segmented cortical bone was further combined with the cortical porosity images. This more refined compartment results in parameters such as directly measured cortical thickness (mm), cortical pore volume (Ct.Po.V, mm<sup>3</sup>), cortical bone volume (Ct.BV, mm<sup>3</sup>), cortical volumetric bone mineral density (vBMD, mg cm $^{-3}$ ) and cortical area (mm $^{2}$ ). Using this segmentation process, cortical porosity could be assessed as void voxels within the cortex by the following formula [29, 30]: cortical porosity (%) = Ct.Po.V./(Ct.Po.V. + Ct.BV). Based on repeated measurement in six elderly women (78.0 years) after repositioning, the CVs at the distal tibia for these cortical parameters were as follows: cortical porosity, 0.9%; vBMD, 0.4%; thickness, 0.4%; and area, 0.6%. The CVs at the more proximal section (14% of tibial length) were as follows: cortical porosity, 4.1%; vBMD, 0.3%; thickness, 1.2%; and area, 0.7%.

#### Statistical analyses

The means for normally distributed bone parameters and covariates were compared between cases and controls with an independent samples *t*-test. For non-normally distributed continuous variables, differences in medians were compared by the Mann–Whitney U-test. Categorical variables (percentage) were compared using either chi-squared or Fisher's exact tests depending on the sample size for each variable. Non-normally distributed variables were log-transformed for all further inclusion in logistic regression models. Crude associations between bone traits and hip fractures were investigated by bivariate logistic regression models and described as odds ratios (ORs) with 95% confidence intervals (CIs) per SD decrease for all parameters except cortical porosity, which was presented as per SD increase. Associations adjusted for covariates [age, height, weight, current smoking, log daily calcium intake (supplements and dairy products), log PASE score, log walk time, oral glucocorticoid use, heredity of hip fracture, rheumatoid arthritis, previous fall in the last year and bisphosphonate treatment] were investigated using multivariable logistic regression models and reported as adjusted ORs. Furthermore, to evaluate whether cortical porosity differed between cases and controls independently of aBMD, the above models were also adjusted for femoral neck aBMD. P-values <0.05 were considered statistically significant, and all analyses were performed using spss (version 23, SPSS, Inc, Chicago, IL, USA).

### Results

The cohort consisted of 46 women with hip fractures, including both intracapsular and intertrochanteric fractures (Table 1). Women with hip fractures were older, had a higher daily intake of calcium, lower PASE and PCS scores and walked more slowly than the 361 control subjects without fractures (Table 1). The proportion treated with bisphosphonates was higher in the fracture group (Table 1). The hip fracture cases reported a higher prevalence of falls in the last 12 months (Table 1). In addition, a higher proportion of the hip fracture cases reported the occurrence of hip fracture in either of their parents (Table 1).

#### BMD and prevalent hip fracture

Fracture cases had lower aBMD at the femoral neck (-11.8%) and total hip (-14.6%) than controls, whereas no difference was seen for lumbar spine aBMD (Table 2).

#### Bone microstructure and prevalent hip fracture

Representative images for women with and without prevalent hip fracture are presented in Fig. 1. Women with hip fracture had higher cortical porosity (32.1%) and lower cortical vBMD (-8.4%), cortical thickness (-9.6%), trabecular bone volume fraction (-15.7%), trabecular number (-10.1%) and trabecular thickness (-5.6%) than controls without fractures (Table 2). For cortical parameters assessed at the more proximal section, women with hip fracture had higher cortical porosity (29.3%) and lower cortical area (-11.8%), cortical vBMD

Controls $(n = 301)$ Cases $(n = 46)$ P	
	Type of hip fracture
- 76.1 (35) -	Intracapsular hip fracture, % (n)
- 23.9 (11) -	Intertrochanteric hip fracture, $\%$ ( <i>n</i> )
- 5.4 (2.5–9.8) -	Duration since hip fracture, years
77.6 $\pm$ 1.57 78.4 $\pm$ 1.49 <b>0.0</b>	Age, years
$162.3 \pm 5.62$ $162.5 \pm 7.30$ $0.83$	Height, cm
$68.4 \pm 12.2 \qquad \qquad 67.0 \pm 14.4 \qquad \qquad 0.44$	Weight, kg
$13.2 \pm 5.37^{\rm e}$ $13.6 \pm 6.83^{\rm g}$ $0.63$	Grip strength, kg
603 (426–824) <sup>b</sup> 887 (550–1211) < <b>0.0</b>	Calcium intake, mg day <sup>-1</sup>
102 (71.5–141) <sup>b</sup> 80.9 (49.9–117) <b>0.0</b>	Physical activity, PASE score
bre 49.9 (38.5–55.4) 40.1 $(33.2-48.9)^{\rm f}$ <b>&lt;0.0</b>	Physical Component Summary (SF12) score
$1.03 (0.34-3.75)^{a}$ 0.34 (0.34-3.75) 0.2	Alcohol consumption, units per week
$4.66 (4.17-5.16)^{c}$ 5.32 $(4.22-6.88)^{f}$ <b>0.0</b>	Walk time, s
14.0 (50) <sup>d</sup> 26.1 (12) <b>0.0</b>	Heredity of hip fracture, $\%$ ( <i>n</i> )
24.4 (88) 43.5 (20) <b>0.0</b>	Fall during the last 12 months, % (n)
7.2 (26) 10.9 (5) 0.38	Current smoking, % ( <i>n</i> )
3.0 (11) 21.7 (10) <b>&lt;0.0</b>	Current use of bisphosphonates, % (n)
1.9 (7) 2.2 (1) 1.00	Current use of oral glucocorticoids, % (n)
3.3 (12) 6.5 (3) 0.23	Rheumatoid arthritis, % (n)
6.9 (25) 10.9 (5) 0.30	Stroke, % ( <i>n</i> )
5.6 (20) <sup>b</sup> 10.9 (5) 0.19	Angina pectoris, % ( <i>n</i> )
6 ( <i>n</i> ) 6.9 (25) 10.9 (5) 0.30	Chronic obstructive pulmonary disease, % (n)
$ 5.4 (2.5-9.8)$ $ 77.6 \pm 1.57$ $78.4 \pm 1.49$ $0.0$ $162.3 \pm 5.62$ $162.5 \pm 7.30$ $0.8$ $68.4 \pm 12.2$ $67.0 \pm 14.4$ $0.4$ $13.2 \pm 5.37^{e}$ $13.6 \pm 6.83^{g}$ $0.6$ $603 (426-824)^{b}$ $887 (550-1211)$ $<0.0$ $102 (71.5-141)^{b}$ $80.9 (49.9-117)$ $0.0$ $0102 (71.5-141)^{b}$ $80.9 (49.9-117)$ $0.0$ $0.103 (0.34-3.75)^{a}$ $0.34 (0.34-3.75)$ $0.2$ $4.66 (4.17-5.16)^{c}$ $5.32 (4.22-6.88)^{f}$ $0.0$ $14.0 (50)^{d}$ $26.1 (12)$ $0.0$ $24.4 (88)$ $43.5 (20)$ $0.0$ $7.2 (26)$ $10.9 (5)$ $0.3$ $3.0 (11)$ $21.7 (10)$ $<0.0$ $1.9 (7)$ $2.2 (1)$ $1.0$ $3.3 (12)$ $6.5 (3)$ $0.2$ $6.9 (25)$ $10.9 (5)$ $0.3$ $5.6 (20)^{b}$ $10.9 (5)$ $0.3$ $6(n)$ $6.9 (25)$ $10.9 (5)$ $0.3$	Duration since hip fracture, years Age, years Height, cm Weight, kg Grip strength, kg Calcium intake, mg day <sup>-1</sup> Physical activity, PASE score Physical Component Summary (SF12) score Alcohol consumption, units per week Walk time, s Heredity of hip fracture, % ( <i>n</i> ) Fall during the last 12 months, % ( <i>n</i> ) Current smoking, % ( <i>n</i> ) Current use of bisphosphonates, % ( <i>n</i> ) Current use of oral glucocorticoids, % ( <i>n</i> ) Rheumatoid arthritis, % ( <i>n</i> ) Stroke, % ( <i>n</i> ) Angina pectoris, % ( <i>n</i> ) Chronic obstructive pulmonary disease, % ( <i>n</i> )

Table 1 Cohort characteristics for hip fracture cases and controls

Cohort characteristics were analysed using an independent samples *t*-test for the normally distributed continuous variables and presented as mean  $\pm$  standard deviation. Non-normally distributed continuous variables were analysed using the Mann–Whitney U-test and, as well as duration since hip fracture, are presented as median and interquartile range. Dichotomous variables with large samples were analysed using the chi-squared test, and variables with small sample sizes were analysed using Fisher's exact test (\*). Grip strength was measured in the dominant hand. Significant results were defined as *P*-values <0.05 and are presented in bold.

<sup>a</sup>n = 360, <sup>b</sup>n = 359, <sup>c</sup>n = 358, <sup>d</sup>n = 356, <sup>e</sup>n = 355, <sup>f</sup>n = 45, <sup>g</sup>n = 44. PASE, Physical Activity Scale for the Elderly.

(-2.2%) and cortical thickness (-15.2%) (Table 2). Amongst the 46 women with hip fractures, HR-pQCT measurements were obtained at the same side as the hip fracture for 20 and at the contralateral side for 26. Comparing these two groups revealed no significant differences in cortical porosity at either the ultradistal (ipsilateral side 13.7%  $\pm$  5.7% vs. contralateral side 14.2%  $\pm$  4.1%; *P*=0.71) or distal (5.8%  $\pm$  2.5% vs. 6.2%  $\pm$  2.2%; *P*=0.56) tibial sites.

#### Associations between aBMD and prevalent hip fracture

In bivariate logistic regression analysis, lower aBMD at both the femoral neck and total hip but not at the lumbar spine was associated with prevalent hip fracture (Table 3). These associations were still apparent after adjustment for covariates (Table 3).

#### Associations between microstructure and prevalent hip fracture

In bivariate logistic regression analysis, cortical porosity, vBMD and thickness, and trabecular bone volume fraction, number and thickness were all associated with prevalent hip fracture (Table 3). For parameters obtained at the more proximal site (14% of tibial length), cortical porosity, area, vBMD and thickness were all associated with prevalent hip fracture (Table 3).

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Controls ( $n = 361$ )	Cases $(n = 46)$	Р
$0.68\pm0.10$	$0.60\pm0.10$	<0.001
$0.82\pm0.11$	$0.70\pm0.10$	<0.001
$0.96\pm0.17$	$0.92\pm0.15$	0.17
$12.7\pm3.0$	$10.7\pm2.6$	<0.001
$1.79\pm0.35$	$1.61\pm0.34$	0.001
$0.071\pm0.01$	$0.067\pm0.01$	0.03
$86.5\pm19.1$	$81.5\pm19.7$	0.09
$753\pm60.8$	$690\pm74.9$	<0.001
$0.94\pm0.22$	$0.85\pm0.20$	0.005
$10.6\pm2.8$	$14.0\pm4.8$	<0.001
$136 \pm 24.5$	$120\pm22.9$	<0.001
$941 \pm 44.5$	$920\pm44.6$	0.003
$1.97\pm0.41$	$1.67\pm0.37$	<0.001
$4.67 \pm 2.2$	$6.04\pm2.3$	<0.001
	Controls $(n = 361)$ 0.68 ± 0.10         0.82 ± 0.11         0.96 ± 0.17         12.7 ± 3.0         1.79 ± 0.35         0.071 ± 0.01         86.5 ± 19.1         753 ± 60.8         0.94 ± 0.22         10.6 ± 2.8         136 ± 24.5         941 ± 44.5         1.97 ± 0.41         4.67 ± 2.2	Controls $(n = 361)$ Cases $(n = 46)$ $0.68 \pm 0.10$ $0.60 \pm 0.10$ $0.82 \pm 0.11$ $0.70 \pm 0.10$ $0.96 \pm 0.17$ $0.92 \pm 0.15$ $12.7 \pm 3.0$ $10.7 \pm 2.6$ $1.79 \pm 0.35$ $1.61 \pm 0.34$ $0.071 \pm 0.01$ $0.067 \pm 0.01$ $86.5 \pm 19.1$ $81.5 \pm 19.7$ $753 \pm 60.8$ $690 \pm 74.9$ $0.94 \pm 0.22$ $0.85 \pm 0.20$ $10.6 \pm 2.8$ $14.0 \pm 4.8$ $136 \pm 24.5$ $120 \pm 22.9$ $941 \pm 44.5$ $920 \pm 44.6$ $1.97 \pm 0.41$ $1.67 \pm 0.37$ $4.67 \pm 2.2$ $6.04 \pm 2.3$

Table 2 DXA- and HR-pQCT-derived bone variables in hip fracture cases and controls

Bone variables obtained from DXA and HR-pQCT are presented as mean  $\pm$  standard deviation. Differences were analysed using an independent samples *t*-test. Ultradistal, manufacturer's standard site; distal, 14% of tibial bone length. Significant results were defined as *P*-values <0.05 and are presented in bold.

HR-pQCT, high-resolution peripheral quantitative computed tomography; DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density.

In a multivariable regression analysis, associations were investigated between HR-pQCT bone variables and hip fracture after adjustment for covariates. In this model, associations were still apparent for cortical porosity (at both measuring sites), whereas only cortical area and cortical thickness remained significant at the 14% site. At the ultradistal site, cortical vBMD, trabecular bone volume fraction and trabecular number remained significantly associated with hip fracture (Table 3).

# Multivariable logistic regression: bone microstructure and femoral neck aBMD

After adjusting for femoral neck aBMD (in addition to the covariates described above), cortical porosity (OR 2.61, 95% CI: 1.77–3.85; P < 0.001) and cortical vBMD (OR 2.08, 95% CI: 1.36–3.18; P < 0.001) at the ultradistal site were still associated with prevalent hip fracture, as was cortical porosity (OR 1.57, 95% CI: 1.12–2.20; P = 0.01) at the 14% site. By contrast, none of the other cortical or trabecular measurements, at either bone site, was associated with prevalent hip fracture independently of femoral neck aBMD (Table 4). When cortical porosity and femoral neck BMD were simultaneously entered into the adjusted model, both were associated with hip fracture at the ultradistal (cortical porosity: OR 2.61, 95% CI: 1.77–3.85; P < 0.001 and femoral neck BMD: OR 2.57, 95% CI: 1.47–4.48; P < 0.001) and distal sites (cortical porosity: OR 1.57, 95% CI: 1.12–2.20; P = 0.01 and femoral neck BMD: OR 2.56, 95% CI: 1.50–4.38; P = 0.001).

#### Discussion

This is the first study to demonstrate that women with prevalent hip fracture have higher cortical porosity than control subjects without fractures. Using an additional, more proximal measuring site, relative to the bone length, we obtained a more robust characterization of cortical bone in our cohort. With the use of multivariable logistic regression models, we found that cortical porosity measured at both these sites was associated with hip fracture independently of femoral neck aBMD and clinical risk factors in older women.

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Because of an increase in the total number of hip fractures, due to an increase in the size of the elderly population [31], it is of great importance for society to improve the identification of individuals at high risk of hip fracture to minimize both suffering and costs. Today, the method used to identify these individuals (i.e. DXA) is not sufficiently accurate and more than half of these patients do not have osteoporosis based on DXAderived BMD [9, 10]. As a result of methodological limitations, DXA measures two-dimensional aBMD and has limited ability to capture the structural components of the bone, previously shown to be of great importance for bone strength [16]. Vico et al. [14] showed an altered bone microstructure in the trabecular bone compartment and reduced cortical area, thickness and volumetric BMD, including after adjustment, in postmenopausal women with a prevalent hip fracture compared to controls. However, they did not investigate any differences in cortical porosity between the groups. In the present study, we were able to show a remarkably higher cortical porosity in women with prevalent hip fracture compared to controls. Furthermore,

Fig. 1 Representative highresolution peripheral quantitative computed tomography (HR-pQCT) images for hip fracture cases and controls. Impaired cortical microstructure was apparent in women with hip fracture at both the standard (a) and the more proximal sites (b) compared to controls without hip fracture at the standard (c) and more proximal sites (d).

with more detailed cortical evaluation in our study we were able to compare the actual measured cortical thickness instead of using an annular approach as in the previously used method [32]. In the study by Vico *et al.*, the selected hip fracture patients were considerably older than the control subjects (77.5  $\pm$  11.5 vs. 67.3  $\pm$  8.7 years) and were recruited from the orthopaedic and rheumatology departments of a single hospital. In the present study, we compared the bone phenotype between hip fracture cases and controls from a large population-based study. Cases and controls were of the same sex and highly similar in body composition and age. Furthermore, we showed that only cortical bone parameters were of clinical usefulness as only cortical vBMD and porosity were associated with prevalent hip fracture after adjustment for femoral neck aBMD and clinical risk factors. Of the cortical parameters, only porosity was consistently, at both measuring sites, associated with hip fracture prevalence. These results suggest that cortical porosity is an important factor for bone strength and possibly for hip fracture risk.

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	Crude		Adjusted	
	odds ratio (95% CI)	Р	odds ratio (95% CI)	Р
DXA				
Femoral neck, g $\rm cm^{-2}$	2.52 (1.69–3.75)	<0.001	2.66 (1.58-4.48)	<0.001
Total hip, g $\rm cm^{-2}$	3.24 (2.17-4.84)	<0.001	3.53 (2.07-6.02)	<0.001
Lumbar spine, g ${ m cm}^{-2}$	1.26 (0.91–1.75)	0.17	1.27 (0.85–1.88)	0.24
HR-pQCT ultradistal				
Trabecular bone volume fraction, $\%$	2.05 (1.46-2.88)	<0.001	1.68 (1.12–2.52)	0.01
Trabecular number, $\mathrm{mm}^{-1}$	1.66 (1.21–2.27)	0.002	1.73 (1.13–2.65)	0.01
Trabecular thickness, mm	1.47 (1.04–2.07)	0.03	1.10 (0.76–1.61)	0.61
Cortical area, mm <sup>2</sup>	1.32 (0.96-1.81)	0.09	1.07 (0.74–1.55)	0.71
Cortical volumetric BMD, mg $\rm cm^{-3}$	2.68 (1.90-3.77)	<0.001	2.39 (1.61–3.57)	<0.001
Cortical thickness, mm	1.61 (1.15–2.26)	0.01	1.29 (0.87-1.90)	0.20
Cortical porosity, %	2.54 (1.86-3.46)	<0.001	2.63 (1.82-3.80)	<0.001
HR-pQCT distal (14% site)				
Cortical area, mm <sup>2</sup>	1.82 (1.34–2.47)	<0.001	1.55 (1.07–2.25)	0.02
Cortical volumetric BMD, mg $\rm cm^{-3}$	1.59 (1.17-2.16)	0.003	1.32 (0.93-1.87)	0.13
Cortical thickness, mm	2.07 (1.50-2.87)	<0.001	1.69 (1.15–2.48)	0.01
Cortical porosity, %	1.72 (1.30–2.28)	<0.001	1.65 (1.20–2.28)	0.002

Table 3 Crude and adjusted logistic regressions for DXA- and HR-pQCT-derived bone variables association with hip fracture

Associations between bone variables obtained with DXA and HR-pQCT and hip fracture were investigated with logistic regression models. Results are presented as odds ratios with 95% confidence interval (CI) per standard deviation decrease for all parameters except cortical porosity, which is presented as per standard deviation increase. Results are presented for both crude (unadjusted) and adjusted models [adjusted for age, height, weight, current smoking, log daily calcium intake (supplements and dairy products), log PASE score, log walk time, oral glucocorticoid use, heredity of hip fracture, rheumatoid arthritis, previous fall in the last year and bisphosphonate treatment] n = 390 for the adjusted model; all participants were included in the crude model (n = 407). Significant results were defined as *P*-values <0.05 and are presented in bold. Ultradistal, manufacturer's standard site; distal, 14% of tibial bone length. HR-pQCT, high-resolution peripheral quantitative computed tomography; DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density.

Most previous case-controls studies examined patients with wrist fracture and showed impaired trabecular and cortical bone structure in fracture cases [11, 33]. One previous study showed major differences in HR-pQCT-derived trabecular parameters, such as separation and connectivity, and cortical vBMD and thickness. However there was no difference in cortical porosity [34]. Only a few studies have shown that cortical porosity is associated with prevalent fracture. We recently reported that older men with any prevalent fracture had higher cortical porosity at the tibia than control subjects without fractures [12]. Additionally, Bala et al. [17] reported that cortical porosity analysed using the STRAX method was able to discriminate between osteopenic women with and without a wrist fracture. These results indicate that measuring cortical bone microstructure might improve the prediction of fracture risk, but large prospective

studies investigating incident fractures are needed to confirm this hypothesis. In a recent, large, population-based, multicentre study, it was shown that bone microstructure at both the radius and tibia was altered in women with major osteoporotic fractures independently of total hip T-score. The authors of this multicentre study also showed that amongst the fracture cases, more than half were within the normal to osteopenic range of aBMD [35]. The study was well powered to investigate many fracture types (e.g. major osteoporotic fracture), but was limited by a low number of hip fractures (n = 20) and cortical porosity was not analysed.

Amongst our cases, we observed more frequent prior falls, lower physical activity and signs of reduced physical function, which is in agreement with earlier findings in elderly women [5]. The women with hip fracture in this study displayed  
 Table 4
 Multivariable logistic regression models for HRpQCT-derived bone variables association with hip fracture independently of covariates and femoral neck aBMD

	Odds ratio	_
	(95% CI)	Р
HR-pQCT ultradistal		
Trabecular bone volume	1.27 (0.80–2.03)	0.31
fraction, %		
Trabecular number,	1.43 (0.91-2.23)	0.12
$\mathrm{mm}^{-1}$		
Trabecular thickness,	0.86 (0.56-1.30)	0.46
mm		
Cortical area, mm <sup>2</sup>	0.83 (0.55–1.25)	0.37
Cortical volumetric BMD,	2.08 (1.36–3.18)	<0.001
${ m mg~cm^{-3}}$		
Cortical thickness, mm	0.99 (0.65–1.53)	0.98
Cortical porosity, %	2.61 (1.77–3.85)	<0.001
HR-pQCT distal (14% site)		
Cortical area, mm <sup>2</sup>	1.21 (0.80–1.83)	0.38
Cortical volumetric BMD,	1.06 (0.72–1.56)	0.76
${ m mg~cm^{-3}}$		
Cortical thickness, mm	1.32 (0.87–2.02)	0.20
Cortical porosity, %	1.57 (1.12–2.20)	0.01

Associations between bone variables obtained with HRpOCT and hip fracture were investigated with multivariable logistic regressions. Results are presented as odds ratios with 95% confidence interval (CI) per standard deviation decrease for all parameters except cortical porosity, which is presented as per standard deviation increase. Results are presented for fully adjusted models [adjusted for age, height, weight, current smoking, log daily calcium intake (supplements and dairy products), log PASE score, log walk time, oral glucocorticoid use, heredity of hip fracture, rheumatoid arthritis, previous fall in the last year and bisphosphonate treatment] with additional adjustment for femoral neck aBMD. Significant results were defined as P-values <0.05 and are presented in bold; n = 390. Ultradistal, manufacturer's standard site; distal, 14% of tibial bone length.

HR-pQCT, high-resolution peripheral quantitative computed tomography; aBMD, areal bone mineral density.

signs of frailty, which could be due to the hip fracture itself, but the association between cortical porosity and hip fracture was independent of physical activity, physical function and history of falls. Nevertheless, declining physical function and frailty, causing increased risk of falling, are probably important contributors to hip fracture risk, in addition to reduced bone strength.

This study has several limitations. We did not examine the medical records of the control subjects who denied having a fracture, to ensure that indeed no fracture had occurred. This could have led to inclusion of false negatives within the control group. However, in a previous study, self-reporting of hip fractures had a sensitivity of 100% (i.e. no false negatives were reported) [36]. An underlying reason for such excellent recollection is probably the severe consequences of surgery and a long hospital stay. The crosssectional design of our study does not allow conclusions of causality, only association. This study also has several strengths. Because previous studies have shown a false-positive rate of 4.8-11% for hip fractures, it is possible that all cases were not actually cases in previously investigated cohorts [36, 37] whereas we were able to verify the presence of fractures in an X-ray registry. In addition, using our novel site, 14% relative to the bone length, to investigate cortical bone, we believe that we were able to obtain a more robust evaluation of cortical bone and that errors introduced by varying bone lengths were minimized [18].

In conclusion, we have demonstrated that cortical porosity is associated with prevalent hip fracture, independently of femoral neck aBMD and clinical risk factors. Future studies are needed to investigate whether assessment of cortical porosity can improve the prediction of hip fracture.

#### **Conflict of interest statement**

All authors state that they have no conflicts of interests. The manuscript has been handled by an external editor, Professor Sam Schulman, Mac Master University, Hamilton, Ontario, Canada.

#### **Funding sources**

This study was supported by the Swedish Research Council, the Lundberg Foundation, the ALF/LUA grant from Sahlgrenska University Hospital and King Gustaf V's and Queen Victoria's Freemason Foundation.

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