Cortical Bone Area Predicts Incident Fractures Independently of Areal Bone Mineral Density in Older Men

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Context: Areal bone mineral density (aBMD) measured using dual-energy X-ray absorptiometry (DXA) is used clinically to predict fracture but does not discriminate between trabecular and cortical bone assessment.

Objective: This study aimed to investigate whether information on cortical and trabecular bone predict fracture risk independently of aBMD and clinical risk factors.

Design and Participants: Cortical area, bone mass, porosity, and trabecular bone volume fraction (BVTV) were measured at the tibia using high-resolution peripheral quantitative computed tomography (HR-pQCT) in 456 men (80.2 ± 3.5 years) recruited from the general population in Gothenburg, Sweden. aBMD was measured using DXA. Incident fractures (71 men) were X-ray verified. Associations were evaluated using Cox regression.

Results: Cortical area [hazard ratio (HR) per standard deviation (SD) decrease, 2.05; 95% confidence interval (CI), 1.58 to 2.65], cortical bone mass (HR, 2.07; 95% CI, 1.58 to 2.70), and BVTV (HR, 1.62; 95% CI, 1.26 to 2.07), but not cortical porosity, were independently associated with fracture risk. These associations remained after adjustment for femoral neck aBMD and Fracture Risk Assessment risk factors (area: HR 1.96, 95% CI, 1.44 to 2.66; mass: HR 1.99, 95% CI, 1.45 to 2.74; BV/TV: HR 1.46, 95% CI, 1.09 to 1.96). After entering BV/TV and cortical area or bone mass simultaneously in the adjusted models, only the cortical parameters remained important predictors of fracture.

Conclusion: HR-pQCT measurement of cortical area and mass might add clinically useful information for the evaluation of fracture risk. (*J Clin Endocrinol Metab* 102: 516–524, 2017)

Osteoporosis is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk (1). This disease is not as well studied in men as in women, but older men are also a large contributor to the burden of fractures. Every third osteoporotic fracture occurs in men (2), and mortality after a hip fracture is higher in men than in women (3).

Areal bone mineral density (aBMD), measured with dual-energy X-ray absorptiometry (DXA), is currently the "gold standard" to diagnose osteoporosis and has been shown to strongly predict fractures (4). Nevertheless, as DXA is a 2-dimensional technique, it gives a rather crude bone measurement which does not allow discrimination between the trabecular and cortical bone compartments or assessment of cortical porosity. A large proportion of fractures in fact occur in subjects not identified by low aBMD. In contrast, 3-dimensional computed tomography (CT)-based techniques have the capacity to discriminate between these specific bone parameters. Using CT-based analyses of the tibia, we have in recent human genetic studies identified specific loci associated with cortical bone size and density, cortical porosity, and trabecular bone volume fraction, strongly suggesting that these bone parameters are separately regulated (5, 6). In the current study, we hypothesized that any of these bone parameters, measured using a CT-based technique, might add information for fracture prediction beyond DXA-derived aBMD.

Previous studies using central CT measurements at the spine or hip followed by finite element analyses have demonstrated that bone strength calculated at the evaluated fracture site predicts incident spine and hip fractures (7–10). However, central CT scans give a higher radiation dose than peripheral scans and are limited to the hospital settings. Therefore, it is of importance to determine if any bone measure from the peripheral CT scanners, giving limited radiation exposure, has the capacity to improve fracture prediction beyond aBMD.

With the introduction of high-resolution peripheral quantitative CT (HR-pQCT; resolution 82 μm), separate assessments of cortical bone mass, cortical porosity, cortical area, and trabecular bone volume fraction at peripheral bone sites has become readily available (11, 12). Previous studies have indicated that a variety of HR-pQCT-derived bone parameters are associated with previous fractures (13–16), but no study has investigated if any HR-pQCT-derived bone parameter predicts incident fractures.

Clinical risk factors such as previous fracture, heredity, smoking, and per oral glucocorticoid use predict fracture risk independently of aBMD (17–20). With the use of aBMD alone, many patients in need for intervention to prevent future fracture will be missed (13). To improve the identification of these patients, the World Health Organization introduced the Fracture Risk Assessment (FRAX) tool with which clinical risk factors could be used to estimate the probability of sustaining a fracture with or without knowing aBMD (21). Evaluation using FRAX with aBMD is nowadays included in many clinical guidelines, but still, the FRAX tool would probably be strengthened by the addition of novel aBMD-independent fracture risk markers.

The overall aim of this study was to investigate if separate information on cortical and trabecular bone mass or cortical porosity, measured using HR-pQCT, predict fracture risk independently of FRAX with aBMD.

Methods

Subjects and methods

The prospective multicenter study of osteoporotic fractures in elderly men (MrOS) consists of cohorts from the United States, Hong Kong, and Sweden (22). The Swedish cohort (23, 24) comprises 69- to 80-year-old Swedish men who were randomly selected using national population registers, and invited to participate. The 3 Swedish sites had ethical approval from each corresponding region's ethical review board for the prospective multicenter study. The ethical review board in Gothenburg, Sweden, gave approval for the follow-up study including the HR-pQCT imaging. All participants gave their written consent to participate in the complete study including DXA, HR-pQCT, and x-ray of the spine at both the baseline and follow-up study. Inclusion criteria included being able to walk without aid, sign an informed consent, and complete a questionnaire. The Swedish Gothenburg cohort consists of 1010 men, of which 600 (59.4%) attended the 5-year follow-up exam. The last 478 men attending the 5-year follow-up exam underwent HR-pQCT imaging on the distal tibia. Ultimately, 456 men had acceptable image quality of the tibia.

Height and weight were measured with standardized equipment and information on parameters included in the FRAX calculations [i.e., previous fracture, parental history of hip fracture, smoking, use of per oral glucocorticoids, alcohol consumption, having rheumatoid arthritis, body mass index (BMI), age, and sex] was collected by a standardized questionnaire. The prospective study period for assessing incident fractures was calculated from each study participant's study inclusion date (HR-pQCT measurements at the 5-year visit in MrOS Gothenburg study) until either an end point (i.e., fracture or death) or the end of follow-up period (1 September 2015). The average follow-up time was 5.3 ± 2.0 years. Date of death was retrieved from the regional administrative patient registry. Fracture events were obtained using a digital radiology database consisting of regional patient data (i.e., radiology reports and corresponding images) from all radiology examinations. The occurrence of fractures was cataloged by type into a main group, consisting of men with any fracture, and a subgroup including men with major osteoporotic fractures [according to the FRAX definition (25)]. All men had a spine x-ray available at study inclusion. The validation of vertebral fracture incidence included a comparison between the initial x-ray of the spine and an x-ray conducted during the study period (on clinical indication). All classified fractured vertebras were normal or had a minor deformity (<20% anterior to posterior height loss) at study inclusion, and had a moderate to severe fracture (>25% height reduction) or a radiology report stating a worsened vertebral fracture during the study period. Due to the definition of osteoporotic fracture, skull and face fractures were not included (26).

DXA measurements of aBMD

Measurements of aBMD at the femoral neck (FN-aBMD) were performed using a Hololgic QDR 4500/A-Delphi DXA (Hololgic, Waltham, MA) with a coefficient of variation less than 3.0%.

HR-pQCT measurements of cortical and trabecular bone parameters separately

Following a previously described protocol (12), a HR-pQCT device (XtremeCT; ScancoMedical AG, Brüttisellen, Switzerland) was used to measure cortical and trabecular bone parameters separately at the left distal tibia (or nonfractured leg if prior fracture). Utilizing a grading scale supported by the manufacturer, each image was ranked on a scale of 1 (*optimum quality*) to 5 (*unacceptable*). Images with a quality of 4 or 5 were discarded. All scans were analyzed with the manufacturer's standard *in vivo* analysis protocol and processed according to Laib *et al.* (27). With this automated threshold-based algorithm cortical bone was separated from trabecular bone resulting in the following parameters from both bone compartments, presented with their corresponding coefficients of variation (CVs): cortical thickness (mm, 0.3%), cortical area (mm^2, 0.4%), cortical volumetric BMD (g/cm^3, 0.1%), trabecular bone volume fraction (BV/TV; %, 0.3%), trabecular number (mm^{-1}, 1.6%), trabecular thickness (mm, 0.7%), and trabecular separation (mm, 1.4%). Additional parameters obtained were the mean cortical perimeter (mm, 0.1%; *i.e.*, the mean length of the periosteal circumference). The cortical bone mineral content (cortical bone mass) was calculated as cortical area × cortical density and is given as mg/mm cortical bone. With an extended cortical bone analysis, incorporated in a customized version of the manufacturer's Image Processing Language (IPL v5.08b Scanco Medical AG), cortical porosity was assessed according to a previously described method (28). The CV for cortical porosity measured at the tibia was 5.5%. The main bone parameters evaluated in this study included (a) a general size measurement of cortical area, (b) an overall measure of cortical bone mass (cortical bone mineral content), (c) a measure of the cortical bone quality as reflected by cortical porosity (19), and (d) an overall measure of the amount of trabecular bone given as trabecular bone volume fraction. The cortical bone mass parameter corresponds to the frequently used pQCT parameter *bone mineral content* (29).

Finite element analysis of calculated mechanical strength

Microfinite element models of the tibia were created directly from the segmented HR-pQCT images to estimate failure load in compression. This was made by a finite-element software (version V5.11/FE-V01.15), incorporated in the analysis software provided by Scanco. To estimate failure load each bone voxel tissue was converted into an equally sized brick element (30) and all bone materials were given a Young modulus of 10 GPa and a poisson ratio of 0.3 as reported by Pistoia *et al.* (31). The estimated failure load (N) was computed as earlier described (31), and the failure load is calculated based on the assumption that fracture occurs when 2% of the bone elements surpass the critical limit of 7000 microstrains. The microfinite element analyses also report bone stiffness (kN/mm). CVs for the obtained variables were 0.2% to 0.3%.

Statistical analysis

Differences in anthropometrics, covariates, and bone variables (aBMD and HR-pQCT parameters) were examined using independent samples *t* test for continuous variables between men with and without fracture. Cox proportional hazard models were used to evaluate associations between bone parameters and incident fracture. From these models, a composite variable was built, based on the beta estimates (from the Cox models) of age, BMI, and femoral neck aBMD in combination with either cortical area or cortical bone mass. The constructed composite variables were then compared with the variable only containing femoral neck aBMD, age, and BMI using receiver operating characteristic curve analysis. We further compared different models by using the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) indices to assess the improvement in risk prediction over base models containing (a) age and BMI or (b) the major osteoporotic fracture FRAX parameter with aBMD (32, 33). To identify the proportion of subjects correctly reclassified by adding either cortical area or cortical bone mass as an extra predictor, the incremental discriminative ability of cortical area or cortical bone mass compared with the base models was assessed by using category-free NRI, IDI, and relative IDI (after rounding predicted values to 4 decimal places).

Results

Of the 456 men enrolled, 71 (15.6%) sustained 1 or more incident fractures (any fracture group) during the in average 5.3-year follow-up period, and 50 men suffered a major osteoporotic fracture (Table 1). Men with any incident fracture had reduced FN-aBMD (–8.9%), cortical bone mass (–20.0%), cortical area (–17.1%), and trabecular bone volume fraction (–8.6%), whereas cortical porosity was unchanged compared with men with no fracture (Table 2).

Cortical area and bone mass measured using computed tomography predict fracture risk

We first evaluated if any of the main separate CT parameters, cortical bone mass, cortical area, cortical porosity, or trabecular bone volume fraction, predicted fracture risk. In Cox proportional hazard models adjusted for age and BMI, cortical bone mass was a robust [hazard ratio (HR) per standard deviation (SD) decrease, 2.07; 95% confidence interval (CI), 1.58 to 2.70] as well as cortical area (HR per SD decrease, 2.05; 95% CI, 1.58 to 2.65) and trabecular bone volume fraction a moderate (HR per SD decrease, 1.61; 95% CI, 1.26 to 2.07) predictor of any fracture risk (Table 3). Similar associations were seen when major osteoporotic fractures were evaluated separately (Table 3). When cortical area or cortical bone mass were included together with trabecular bone volume fraction in the same age and BMI-adjusted Cox model, cortical area and bone mass (HR 1.87; 95% CI, 1.41 to 2.48, and 1.88; 95% CI, 1.40 to

Table 1. Number of Each Type of Incident Fracture

	Any Fracture	Major Osteoporotic
Vertebral	22	22
Hip	14	16
Humerus	7	6
Wrist and forearm	6	5
Femur (avulsion fracture)	1	1
Rib	9	—
Pelvis	2	—
Patella	1	—
Hand and fingers	3	—
Shoulder and clavicle	3	—
Ankle	2	—
Foot and toes	1	—

Number of fractures used in the Cox proportional hazard models is presented for each individual according to location of the fracture and fracture category.

Em dash indicates no incident fracture for the corresponding fracture type.

2.51, respectively), but not trabecular bone volume fraction, was independently associated with any fracture risk. The proposed cortical bone quality measure cortical porosity did not significantly predict fracture risk (Table 3).

Calculated mechanical strength parameters stiffness and failure load both moderately predicted fracture risk (Table 3). However, after additional adjustment for cortical area (stiffness: HR 1.34; 95% CI, 0.99 to 1.79, and failure load: 1.35; 95% CI, 1.01 to 1.81) only failure load remained a significant predictor of any fracture. In contrast, adjusting for cortical bone mass, both strength measures remained significant (HR 1.36; 95% CI, 1.02 to 1.81 and 1.37; 95% CI, 1.03 to 1.83, respectively).

We next determined if cortical area, cortical bone mass or the other HR-pQCT derived predictors (in Table 3) predicted fractures independently of the "gold standard" clinically used DXA-derived bone parameter FN-aBMD.

Cortical area and cortical bone mass predict fracture risk independently of aBMD

Importantly, the association of cortical area and cortical bone mass with any fracture risk remained essentially unaffected after further adjustment for FN-aBMD (area: HR 1.91; 95% CI, 1.39 to 2.63) and (mass: HR 1.94; 95% CI, 1.39 to 2.71; Table 4). Cortical area (HR 1.96; 95% CI, 1.44 to 2.66) and cortical bone mass (HR 1.99; 95% CI, 1.45 to 2.74) were robust independent predictors of any fracture risk in models adjusted for FRAX with femoral neck aBMD (Table 4). Similar aBMD- and FRAX- independent associations for cortical area and cortical bone mass were observed when major osteoporotic fracture risk was evaluated (Table 4). Adding any of these bone traits to FN-aBMD and covariates resulted in a higher area under the curve (Fig. 1). Cortical density, trabecular BV/TV, and the bone strength measures (stiffness and failure load) all predicted any fracture and MOF moderately and independently of

Table 2. Extended Baseline Characteristics

	All Subjects (N = 456)	No Fracture (n = 385)	Any Fracture (n = 71)
Age (years)	80.2 ± 3.5	80.2 ± 3.5	79.8 ± 3.4
BMI (kg/m^2)	25.9 ± 3.2	25.9 ± 3.2	25.7 ± 3.3
FN-aBMD (g/cm^2)[a]	0.78 ± 0.13	0.79 ± 0.13	0.72 ± 0.13**
FRAX score with FN-aBMD (%)[a]	9.6 ± 5.4	9.2 ± 4.6	12.6 ± 8.3***
HR-pQCT			
Cortical bone parameters	(n = 456)	(n = 385)	(n = 71)
Cortical bone mass (mg/mm)	95.2 ± 34.0	98.3 ± 33.2	78.6 ± 33.5***
Cortical area (mm^2)	120 ± 35	123 ± 34	102 ± 35***
Cortical thickness (mm)	0.99 ± 0.31	1.02 ± 0.30	0.84 ± 0.32***
Cortical perimeter (mm)	122 ± 9	122 ± 9	123 ± 9
Cortical density (mg/cm^3)	779 ± 75	784 ± 74	750 ± 76***
Cortical porosity (%)	11.8 ± 4.1	11.7 ± 4.1	12.2 ± 4.0
Trabecular bone parameters	(n = 456)	(n = 385)	(n = 71)
Trabecular bone mass (BV/TV %)	14.9 ± 2.8	15.1 ± 2.8	13.8 ± 2.7***
Trabecular number (mm^{-1})	1.97 ± 0.30	1.98 ± 0.30	1.91 ± 0.33
Trabecular thickness (μm)	76.0 ± 11.6	76.6 ± 11.4	72.8 ± 12.0*
Trabecular separation (mm)	0.44 ± 0.08	0.44 ± 0.08	0.47 ± 0.09*
FEA calculated mechanical strength	(n = 450)	(n = 380)	(n = 70)
Stiffness (kN/mm)	240 ± 46	244 ± 45	219 ± 43***
Failure load (kN)	12.2 ± 2.2	12.3 ± 2.2	11.2 ± 2.0***

Variables are presented as mean ± SD, and statistical differences were investigated with an independent samples t test. FRAX score is shown as a 10-year fracture probability given for major osteoporotic fracture with FN-aBMD. *P < 0.05; **P < 0.01; ***P < 0.001.

Abbreviation: FEA, finite element analyses.

[a]n = 405, as FN-BMD was not available in all subjects.

Table 3.   Association Between Multiple HR-pQCT Variables and Incident Fractures

	Any Fracture (n = 456/71)	MOF Fracture (n = 456/50)
DXA		
FN-aBMD (g/cm^2)[a]	**1.88 (1.34–2.62)**	**2.79 (1.83–4.25)**
HR-pQCT		
Cortical bone parameters		
Cortical bone mass (mg/mm)	**2.07 (1.58–2.70)**	**2.46 (1.78–3.40)**
Cortical area (mm^2)	**2.05 (1.58–2.65)**	**2.34 (1.73–3.16)**
Cortical thickness (mm)	**1.96 (1.51–2.54)**	**2.26 (1.65–3.08)**
Cortical perimeter (mm)	0.84 (0.66–1.07)	0.78 (0.58–1.04)
Cortical density (mg/cm^3)	**1.71 (1.38–2.12)**	**1.83 (1.45–2.32)**
Cortical porosity (%)	1.15 (0.92–1.45)	1.22 (0.94–1.59)
Trabecular bone parameters		
Trabecular bone mass (BV/TV; %)	**1.61 (1.26–2.07)**	**1.90 (1.41–2.57)**
Trabecular number (mm^{-1})	1.23 (0.95–1.60)	1.27 (0.93–1.74)
Trabecular thickness (μm)	**1.51 (1.18–1.94)**	**1.84 (1.36–2.47)**
Trabecular separation (mm)	**1.28 (1.03–1.61)**	**1.35 (1.04–1.75)**
FEA calculated mechanical strength	(n = 450/70)	(n = 450/49)
Stiffness (kN/mm)	**1.66 (1.37–2.01)**	**1.84 (1.49–2.27)**
Failure load (kN)	**1.68 (1.38–2.04)**	**1.86 (1.50–2.31)**

Values are presented as HRs with 95% CIs per SD decrease (cortical bone mass, cortical area, cortical thickness, cortical perimeter, cortical density, trabecular bone mass, trabecular number, trabecular thickness, stiffness, and failure load) or SD increase (cortical porosity and trabecular separation). Cox proportional hazard models were used to investigate the associations, and significant results are presented in bold. The models were adjusted for age and BMI.

Abbreviation: FEA, finite element analyses.

[a]n = 405, as FN-BMD was not available in all subjects.

FN-aBMD and FRAX score. These analyses reveal that cortical area and cortical bone mass were the strongest predictors of fracture risk independently of aBMD and FRAX with aBMD.

Cortical bone mass improves fracture reclassification

Finally, we evaluated if cortical area or cortical bone mass improved fracture reclassification as evaluated by NRI and IDI. Addition of cortical area or cortical bone mass both to a base model of age and BMI and to a base model of FRAX with aBMD resulted in significant improvements of NRI (Table 5). The improved combined NRIs were the result of both a correct upward reclassification of those with a fracture and a correct downward reclassification of those without a fracture (Table 5). The probability change for any fracture as determined by IDI was also significantly improved by adding cortical area or cortical bone mass to a base model of FRAX with aBMD

Table 4.   Bone and Strength Parameters Predict Fractures Independently of DXA aBMD

	Base Model	Any Fracture [N = 456 (n = 71)]	MOF Fracture [N = 456 (n = 50)]
Cortical bone mass (mg/mm)	Age, BMI, FN-aBMD	1.94 (1.39–2.71)	2.16 (1.46–3.19)
	FRAX with FN-aBMD	1.99 (1.45–2.74)	2.43 (1.68–3.53)
Cortical area (mm^2)	Age, BMI, FN-aBMD	1.91 (1.39–2.63)	2.00 (1.39–2.87)
	FRAX with FN-aBMD	1.96 (1.44–2.66)	2.27 (1.61–3.20
Cortical density (mg/mm^3)	Age, BMI, FN-aBMD	1.65 (1.28–2.13)	1.61 (1.23–2.12)
	FRAX with FN-aBMD	1.74 (1.36–2.21)	1.81 (1.39–2.34)
Trabecular bone mass (BV/TV; %)	Age, BMI, FN-aBMD	1.39 (1.01–1.90)	1.39 (1.01–1.90)
	FRAX with FN-aBMD	1.46 (1.09–1.96)	1.46 (1.09–1.96)
Stiffness (kN/mm)	Age, BMI, FN-aBMD	1.49 (1.15–1.93)	1.49 (1.15–1.93)
	FRAX with FN-aBMD	1.52 (1.20–1.93)	1.52 (1.20–1.93)
Failure load (kN)	Age, BMI, FN-aBMD	1.50 (1.14–1.96)	1.50 (1.14–1.96)
	FRAX with FN-aBMD	1.53 (1.19–1.95)	1.53 (1.19–1.95)

Values are presented as HRs with 95% CIs per SD decrease. Number of subjects with fractures are given within parenthesis. Cox proportional hazard models were used to investigate the associations. In models adjusted for FN-aBMD as measured by DXA, 405 subjects are included (55 any fracture; 41 MOF fractures).

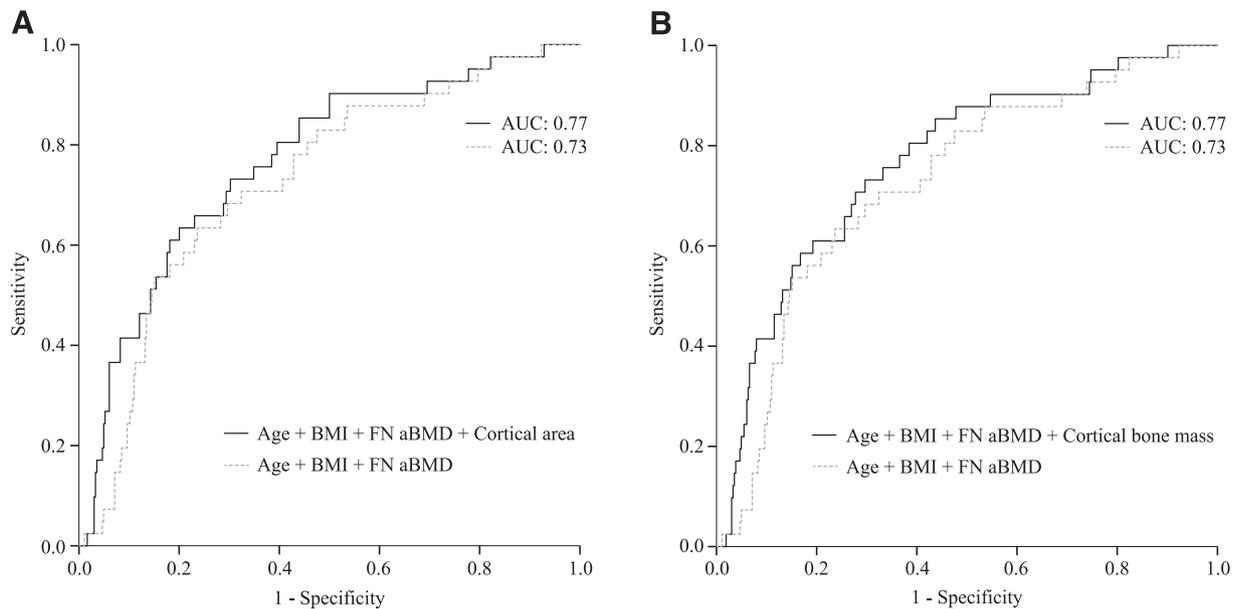Abbreviation: MOF, major osteoporotic fracture.

Figure 1. Receiver operating characteristic curves for a composite variable constructed from age, BMI, femoral neck bone mineral density, and (A) cortical area or (B) cortical bone mass compared with femoral neck bone mineral density combined with age and BMI. AUC, area under the curve.

(Table 5). These reclassification improvements were also reflected by the relative IDI (Table 5). Similar significant improvements of NRI and IDI were observed for major osteoporotic fractures when either cortical area or cortical bone mass was added to a base model of FRAX with aBMD (Table 5). Thus, the reclassification parameters NRI and IDI were significantly improved when either cortical area or cortical bone mass was added to FRAX models with aBMD.

Discussion

Although aBMD, measured using 2-dimensional DXA, is a robust and clinically useful predictor of fracture

risk, it cannot determine the cortical and trabecular bone compartments separately or analyze the cortical porosity, requiring 3-dimensional HR-pQCT analyses. This study is the first prospective study evaluating the associations between these parameters, as assessed by HR-pQCT, and fracture risk. We, herein, demonstrate that cortical area and cortical bone mass were independently of aBMD associated with fracture risk and that fracture reclassification was significantly improved when either of these bone parameters were added to FRAX models with aBMD.

Several CT-based techniques exist for 3-dimensional analyses of the human skeleton including central CT (hip or spine), standard-resolution pQCT (resolution $\cong 500 \, \mu m$),

Table 5. Reclassification for Fracture Using Cortical Area or Cortical Bone Mass

Base Model	Reclassification NRI (95% CI)			Probability Change IDI (95% CI)			
	Combined	Event	Nonevent	Combined	Event	Nonevent	Relative IDI
Any fracture							
Age and BMI + cortical area	**0.60** (0.35–0.86)	**0.35**	**0.25**	**0.06** (0.03–0.08)	**0.05**	**0.01**	14.69
FRAX with FN-aBMD + cortical area	**0.54** (0.25–0.82)	**0.27**	**0.26**	**0.03** (0.01–0.05)	**0.02**	0.00	0.57
Age and BMI + cortical bone mass	**0.61** (0.36–0.87)	**0.41**	**0.21**	**0.06** (0.03–0.08)	**0.05**	**0.01**	14.22
FRAX with FN-aBMD + cortical bone mass	**0.61** (0.33–0.89)	**0.38**	**0.23**	**0.03** (0.01–0.04)	**0.02**	0.00	0.54
MOF fracture							
Age and BMI + cortical area	**0.73** (0.44–1.02)	**0.44**	**0.29**	**0.06** (0.04–0.09)	**0.05**	0.01	5.42
FRAX with FN-aBMD + cortical area	**0.76** (0.43–1.08)	**0.41**	**0.34**	**0.03** (0.01–0.06)	**0.03**	0.00	0.46
Age and BMI + cortical bone mass	**0.73** (0.44–1.03)	**0.48**	**0.25**	**0.06** (0.04–0.09)	**0.06**	0.01	5.50
FRAX with FN-aBMD + cortical bone mass	**0.71** (0.38–1.03)	**0.41**	**0.29**	**0.03** (0.01–0.06)	**0.03**	0.00	0.45

Bold indicates significant improvement in reclassification.

Abbreviation: MOF, major osteoporotic fracture.

and high-resolution pQCT (resolution 40 to 82 μm). Previous studies using central CT measurements revealed that bone strength measures from finite element analyses at the evaluated fracture site predict fracture risk (7–10). However, central CT scans give a higher radiation dose than peripheral scans and are limited to the hospital settings.

One previous study with limited statistical power, including 39 men with incident fractures during an average follow-up of 2.9 years, evaluated the association between bone parameters measured by a standard resolution pQCT and nonvertebral fracture risk (34). The authors used non-hypothesis-driven principal component analyses of as many as 58 different pQCT parameters in search of a bone parameter to be selected for subsequent studies of fracture discrimination. These broad analyses indicated that bone strength measurements of the radius might add information beyond aBMD for fracture prediction but the significance threshold was not adjusted for the multiple testing of as many as 58 parameters (34).

In the current study, we used HR-pQCT, providing a detailed separation of the trabecular and cortical bone compartments and also a measure of cortical bone porosity. So far, this fairly new technique has only been used to investigate the association with prevalent fractures, revealing significant associations for a variety of HR-pQCT derived parameters (13–16). To avoid multiple testing, the present prospective study was hypothesis driven. Based on our previous human genetic findings that separate loci were identified as determinants of cortical bone size and density (mass), trabecular bone volume fraction, and cortical porosity (5, 6), we hypothesized that any of these principally distinct bone measures might add information beyond aBMD for fracture prediction. When evaluating 456 men, of whom 71 sustained an incident fracture during the average follow-up of 5.3 years, we, herein, clearly demonstrated that tibial cortical bone area and bone mass were both aBMD-independent predictors of fracture risk. Importantly, addition of these bone traits to FRAX models with aBMD revealed that reclassification was significantly improved as a result of both a correct upward reclassification of those with a fracture and a correct downward reclassification of those without a fracture.

This observed association between cortical bone mass and incident fracture in the current study risk can be expected as cortical bone comprises more than 80% of the skeleton and is proposed to be the major contributor to overall fracture risk (35). It is also obvious that the 2-dimensional technique DXA cannot give a true specific estimate of cortical bone mass, whereas this bone parameter can be accurately and specifically determined by the 3-dimensional technique HR-pQCT. We believe this is the reason why cortical bone mass, measured by HR-pQCT, adds information beyond aBMD, measured by DXA, for fracture prediction. Although HR-pQCT measurements may not be used in clinical practice due to high costs related to the procedure, we propose that simpler and less expensive single slice pQCT could be used in the clinic to measure cortical area and cortical bone mass.

The lack of significant association between cortical porosity, a measure of cortical bone quality, and incident fractures in the current study is in contrast to some previous cross-sectional studies suggesting that cortical porosity is associated with fractures (13, 14, 36). This discrepancy might be due to a lack of statistical power in our study, insufficient algorithms, or scan resolution for the accurate determination of cortical porosity and/or the fact that cortical porosity may only have a modest impact on fracture risk. Additional well-powered prospective studies are required to determine if cortical porosity also might add information beyond aBMD and cortical bone mass for fracture prediction.

The current study has limitations. Peripheral CT scans do not analyze the actual bone site of the most important osteoporosis fractures, and, therefore, the site-specific bone parameters from peripheral CT scans might be less informative. In addition, all fractures included in the current study have been used regardless of trauma severity. The quality of the HR-pQCT images obtained at the tibia was low for 18 men and therefore these men could not be included in the present analyses. Our cohort included only men, all of whom were older than 75 years and most of whom were white. Additional studies are therefore required to confirm these results for other cohorts of men and women.

The study also has strengths. MrOS Sweden is a well-characterized, population-based cohort of older men. It is the first prospective study investigating the association between HR-pQCT–derived bone parameters and fracture risk. In addition, all fractures that were included in the study were x-ray verified. The study participants were carefully characterized at baseline, including measures of FN-aBMD by DXA and distal tibia HR-pQCT scans. The availability of both 2-dimensional and high resolution 3-dimensional measures of bone parameters enabled a unique comparison of the association of aBMD and HR-pQCT-derived parameters with incident fractures.

In conclusion, cortical area and cortical bone mass predict fracture risk independently of aBMD in older men. We propose that HR-pQCT measurement of either cortical area or the composite trait of cortical bone mass might add clinically useful information to improve the identification of individuals at high risk for fracture.

References

1. Consensus development conference. Consensus development conference: prophylaxis and treatment of osteoporosis. *Am J Med.* 1991;**90**(1):107–110.
2. Nguyen TV, Center JR, Eisman JA. Osteoporosis in elderly men and women: effects of dietary calcium, physical activity, and body mass index. *J Bone Miner Res.* 2000;**15**:322–331.
3. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet.* 1999;**353**(9156): 878–882.
4. Kelsey JL, Browner WS, Seeley DG, Nevitt MC, Cummings SR; The Study of Osteoporotic Fractures Research Group. Risk factors for fractures of the distal forearm and proximal humerus. *Am J Epidemiol.* 1992;**135**(5):477–489.
5. Paternoster L, Lorentzon M, Lehtimäki T, Eriksson J, Kähönen M, Raitakari O, Laaksonen M, Sievänen H, Viikari J, Lyytikäinen LP, Mellström D, Karlsson M, Ljunggren O, Grundberg E, Kemp JP, Sayers A, Nethander M, Evans DM, Vandenput L, Tobias JH, Ohlsson C. Genetic determinants of trabecular and cortical volumetric bone mineral densities and bone microstructure. *PLoS Genet.* 2013;**9**(2):e1003247.
6. Zheng HF, Tobias JH, Duncan E, Evans DM, Eriksson J, Paternoster L, Yerges-Armstrong LM, Lehtimäki T, Bergström U, Kähönen M, Leo PJ, Raitakari O, Laaksonen M, Nicholson GC, Viikari J, Ladouceur M, Lyytikäinen LP, Medina-Gomez C, Rivadeneira F, Prince RL, Sievanen H, Leslie WD, Mellström D, Eisman JA, Movérare-Skrtic S, Goltzman D, Hanley DA, Jones G, St Pourcain B, Xiao Y, Timpson NJ, Smith GD, Reid IR, Ring SM, Sambrook PN, Karlsson M, Dennison EM, Kemp JP, Danoy P, Sayers A, Wilson SG, Nethander M, McCloskey E, Vandenput L, Eastell R, Liu J, Spector T, Mitchell BD, Streeten EA, Brommage R, Pettersson-Kymmer U, Brown MA, Ohlsson C, Richards JB, Lorentzon M. WNT16 influences bone mineral density, cortical bone thickness, bone strength, and osteoporotic fracture risk. *PLoS Genet.* 2012;**8**(7):e1002745.
7. Keyak JH, Sigurdsson S, Karlsdottir G, Oskarsdottir D, Sigmarsdottir A, Zhao S, Kornak J, Harris TB, Sigurdsson G, Jonsson BY, Siggeirsdottir K, Eiriksdottir G, Gudnason V, Lang TF. Male-female differences in the association between incident hip fracture and proximal femoral strength: a finite element analysis study. *Bone.* 2011;**48**(6):1239–1245.
8. Kopperdahl DL, Aspelund T, Hoffmann PF, Sigurdsson S, Siggeirsdottir K, Harris TB, Gudnason V, Keaveny TM. Assessment of incident spine and hip fractures in women and men using finite element analysis of CT scans. *J Bone Miner Res.* 2014;**29**: 570–580.
9. Orwoll ES, Marshall LM, Nielson CM, Cummings SR, Lapidus J, Cauley JA, Ensrud K, Lane N, Hoffman PR, Kopperdahl DL, Keaveny TM; Osteoporotic Fractures in Men Study Group. Finite element analysis of the proximal femur and hip fracture risk in older men. *J Bone Miner Res.* 2009;**24**:475–483.
10. Wang X, Sanyal A, Cawthon PM, Palermo L, Jekir M, Christensen J, Ensrud KE, Cummings SR, Orwoll E, Black DM. Osteoporotic Fractures in Men Research Group, Keaveny TM. Prediction of new clinical vertebral fractures in elderly men using finite element analysis of CT scans. *J Bone Miner Res.* 2012;**27**:808–816.
11. Boutroy S, Bouxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab.* 2005;**90**(12):6508–6515.
12. MacNeil JA, Boyd SK. Improved reproducibility of high-resolution peripheral quantitative computed tomography for measurement of bone quality. *Med Eng Phys.* 2008;**30**(6):792–799.
13. Bala Y, Zebaze R, Ghasem-Zadeh A, Atkinson EJ, Iuliano S, Peterson JM, Amin S, Bjornerem A, Melton LJ, 3rd, Johansson H, Kanis JA, Khosla S, Seeman E. Cortical porosity identifies women with osteopenia at increased risk for forearm fractures. *J Bone Miner Res.* 2014;**29**:1356–1362.
14. Sundh D, Mellstrom D, Nilsson M, Karlsson M, Ohlsson C, Lorentzon M. Increased cortical porosity in older men with fracture. *J Bone Miner Res.* 2015;**30**:1692–1700.
15. Stein EM, Liu XS, Nickolas TL, Cohen A, McMahon DJ, Zhou B, Zhang C, Kamanda-Kosseh M, Cosman F, Nieves J, Guo XE, Shane E. Microarchitectural abnormalities are more severe in postmenopausal women with vertebral compared to nonvertebral fractures. *J Clin Endocrinol Metab.* 2012;**97**(10):E1918–E1926.
16. Szulc P, Boutroy S, Vilayphiou N, Chaitou A, Delmas PD, Chapurlat R. Cross-sectional analysis of the association between fragility fractures and bone microarchitecture in older men: the STRAMBO study. *J Bone Miner Res.* 2011;**26**:1358–1367.
17. Kanis JA, Johnell O, Oden A, Johansson H, De Laet C, Eisman JA, Fujiwara S, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman A, Tenenhouse A. Smoking and fracture risk: a meta-analysis. *Osteoporos Int.* 2005;**16**:155–162.
18. Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Eisman JA, McCloskey EV, Mellstrom D, Melton LJ III, Pols HA, Reeve J, Silman AJ, Tenenhouse A. A family history of fracture and fracture risk: a meta-analysis. *Bone.* 2004;**35**(5):1029–1037.
19. Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton IL, Tenenhouse A, Reeve J, Silman AJ, Pols HA, Eisman JA, McCloskey EV, Mellstrom D. A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res.* 2004;**19**:893–899.
20. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, Eisman J, Fujiwara S, Garnero P, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman A, Tenenhouse A. A meta-analysis of previous fracture and subsequent fracture risk. *Bone.* 2004;**35**(2):375–382.
21. Kanis JA, McCloskey EV, Johansson H, Oden A, Strom O, Borgstrom F. Development and use of FRAX in osteoporosis. *Osteoporos Int.* 2010;**21**(Suppl 2):S407–S413.
22. Orwoll E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, Lewis C, Cawthon PM, Marcus R, Marshall LM, McGowan J, Phipps K, Sherman S, Stefanick ML, Stone K. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study: a large observational study of the determinants of fracture in older men. *Contemp Clin Trials.* 2005;**26**(5):569–585.
23. Mellstrom D, Johnell O, Ljunggren O, Eriksson AL, Lorentzon M, Mallmin H, Holmberg A, Redlund-Johnell I, Orwoll E, Ohlsson C. Free testosterone is an independent predictor of BMD and prevalent fractures in elderly men: MrOS Sweden. *J Bone Miner Res.* 2006; **21**:529–535.
24. Mellström D, Vandenput L, Mallmin H, Holmberg AH, Lorentzon M, Oden A, Johansson H, Orwoll ES, Labrie F, Karlsson MK, Ljunggren O, Ohlsson C. Older men with low serum estradiol and high serum SHBG have an increased risk of fractures. J Bone Miner Res. 2008;**23**:1552–1560.
25. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int.* 2008;**19**(4):385–397.

26. Warriner AH, Patkar NM, Curtis JR, Delzell E, Gary L, Kilgore M, Saag K. Which fractures are most attributable to osteoporosis? *J Clin Epidemiol*. 2011;**64**(1):46–53.

27. Laib A, Hauselmann HJ, Ruegsegger P. In vivo high resolution 3D-QCT of the human forearm. *Technol Health Care*. 1998;**6**:329–337.

28. Burghardt AJ, Buie HR, Laib A, Majumdar S, Boyd SK. Reproducibility of direct quantitative measures of cortical bone microarchitecture of the distal radius and tibia by HR-pQCT. *Bone*. 2010;**47**(3):519–528.

29. Lorentzon M, Swanson C, Eriksson AL, Mellstrom D, Ohlsson C. Polymorphisms in the aromatase gene predict areal BMD as a result of affected cortical bone size: the GOOD study. *J Bone Miner Res*. 2006;**21**:332–339.

30. van Rietbergen B, Weinans H, Huiskes R, Odgaard A. A new method to determine trabecular bone elastic properties and loading using micromechanical finite-element models. *J Biomech*. 1995;**28**(1):69–81.

31. Pistoia W, van Rietbergen B, Lochmüller EM, Lill CA, Eckstein F, Rüegsegger P. Estimation of distal radius failure load with micro-finite element analysis models based on three-dimensional peripheral quantitative computed tomography images. *Bone*. 2002;**30**(6):842–848.

32. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;**27**:157–172; discussion 207–112.

33. Pencina MJ, D'Agostino RB, Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011;**30**(1):11–21.

34. Sheu Y, Zmuda JM, Boudreau RM, Petit MA, Ensrud KE, Bauer DC, Gordon CL, Orwoll ES, Cauley JA. Osteoporotic Fractures in Men (MrOS) Research Group. Bone strength measured by peripheral quantitative computed tomography and the risk of non-vertebral fractures: the osteoporotic fractures in men (MrOS) study. *J Bone Miner Res*. 2011;**26**:63–71.

35. Khosla S, Melton LJ, 3rd, Riggs BL. The unitary model for estrogen deficiency and the pathogenesis of osteoporosis: is a revision needed? *J Bone Miner* Res. 2011;**26**:441–451.

36. Bala Y, Bui QM, Wang XF, Iuliano S, Wang Q, Ghasem-Zadeh A, Rozental TD, Bouxsein ML, Zebaze RM, Seeman E. Trabecular and cortical microstructure and fragility of the distal radius in women. *J Bone Miner Res*. 2015;**30**:621–629.