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Areal and volumetric bone mineral density and risk of multiple types of fracture in older men

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ABSTRACT

Although many studies have examined the association between low bone mineral density (BMD) and fracture risk in older men, none have simultaneously studied the relationship between multiple BMD sites and risk of different types of fractures. Using data from the Osteoporotic Fractures in Men study, we evaluated the association between areal BMD (aBMD) by dual-energy X-ray absorptiometry (DXA) and volumetric BMD (vBMD) by quantitative computed tomography (QCT) measurements, and different types of fractures during an average of 9.7 years of follow-up. Men answered questionnaires about fractures every 4 months (>97% completions). Fractures were confirmed by centralized review of radiographic reports; pathological fractures were excluded. Risk of fractures was assessed at the hip, spine, wrist, shoulder, rib/chest/sternum, ankle/foot/toe, arm, hand/finger, leg, pelvis/coccyx, skull/face and any non-spine fracture. Age and race adjusted Cox proportional-hazards modeling was used to assess the risk of fracture in 3301 older men with both aBMD (at the femoral neck (FN) and lumbar spine) and vBMD (at the trabecular spine and FN, and cortical FN) measurements, with hazard ratios (HRs) expressed per standard deviation (SD) decrease. Lower FN and spine aBMD were associated with an increased risk of fracture at the hip, spine, wrist, shoulder, rib/chest/sternum, arm, and any non-spine fracture (statistically significant HRs per SD decrease ranged from 1.24–3.57). Lower trabecular spine and FN vBMD were associated with increased risk of most fractures with statistically significant HRs ranging between 1.27 and 3.69. There was a statistically significant association between FN cortical vBMD and fracture risk at the hip (HR = 1.55) and spine sites (HR = 1.26), but no association at other fracture sites. In summary, both lower aBMD and vBMD were associated with increased fracture risk. The stronger associations observed for trabecular vBMD than cortical vBMD may reflect the greater metabolic activity of the trabecular compartment.

1. Introduction

With the increase in the average age of the world population, the number of osteoporotic fractures likely will increase [1]. Worldwide, the total disability adjusted life years (DALYs) lost attributed to fractures was about 58 million in 2008 [2].

Mortality and morbidity are two major consequences of osteoporosis, primarily due to hip fractures [3]. However, the public health impact of osteoporotic fractures is not limited to hip fractures. In Medicare enrollees, while hip fractures had the highest excess cost, many types of fractures were associated with higher health care expenditures [3,4]. Low bone mineral density (BMD) is an established risk factor for

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fractures. Indeed, low areal BMD (aBMD) has been linked to most fractures in women except for the heel, ankle, and face [5]. To our knowledge, a similar analysis has not been carried out in older men. We previously showed that low aBMD was related to all non-spine fractures and hip fractures in older men [6,7]. Furthermore, Black et al. reported that a one standard deviation (SD) decrease in trabecular and cortical FN volumetric BMD (vBMD) were associated with a 2.2 and 1.7 increased risk of hip fracture respectively [8]. However, the association between multiple measures of aBMD and vBMD and risk of different types of fractures remains unexplored.

Thus, the purpose of the current analysis was to assess the risk of multiple types of fractures in older men by aBMD and vBMD at multiple skeletal sites. A second aim was to compare fracture predictability of different BMD measurements. We hypothesized that older men with lower aBMD and vBMD will be at a higher risk for multiple types of fracture compared to older men with higher aBMD and vBMD respectively. Since the trabecular compartment is more metabolically active, we also hypothesized that older men with lower trabecular vBMD will be at higher risk for multiple types of fractures compared to older men with lower cortical vBMD.

2. Materials and methods

The Osteoporotic Fractures in Men study (MrOS) is a multicenter prospective cohort study designed to identify risk factors for osteoporosis and osteoporotic fracture. This study consists of 5994 older men recruited from six sites across the United States (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA) from March 2000 to April 2002 [9,10]. To be eligible, men needed to be age 65 years or older, be able to walk without assistance from another person, and have reported no bilateral hip replacement. Human subjects' approval was obtained at all sites with written informed consent obtained from all participants. The first 650 men and all nonwhite men enrolled at each clinical site were randomly referred for quantitative computed tomography (QCT) scans of the hip and lumbar spine as part of their baseline visit, for a total of 3786 men (63% of the MrOS cohort). Out of these participants, 134 had unusable QCT images because of insufficient number of images, interference from metal, calibration standard not visible, or unrecorded cause. From the remaining participants, 3305 had complete aBMD and vBMD measurements. We restricted analyses to 3301 after excluding 4 participants with pathological fractures. Except for a higher proportion of minorities (12.9% vs 10.5%), the characteristics of men in the vBMD subset were similar to the overall population of MrOS men.

2.1. Areal bone mineral density (aBMD) measurement

Femoral neck (FN) aBMD (g/cm^2) and lumbar spine (LS) (L1–L4) aBMD (g/cm^2) were measured using dual-energy X-ray absorptiometry (DXA) with the Hologic QDR 4500 (Bedford, MA). Details of the measurement and densitometry procedures have been published elsewhere [6,11]. Standardized procedures for positioning the participants and analyzing the scans were followed for all scans. All DXA operators were centrally certified based on an evaluation of their scanning and analysis techniques. Cross-calibration studies performed before the baseline MrOS visit found no linear differences across the scanners, and the maximum percentage difference in mean total LS aBMD between scanners was 1.4%. To assess longitudinal performance of the scanners, an anthropometric spine phantom was scanned daily and a hip phantom weekly at each clinical center. The right hip was scanned unless there was a fracture, implant, hardware, or other problem, in which case the left hip was scanned. The T-scores at the femoral neck, total hip, and lumbar spine were calculated using the National Health and Nutrition Examination Survey III reference database [12,13] . Young Caucasian women were used as the reference population as recommended by the International Society for Clinical Densitometry (ISCD) [14].

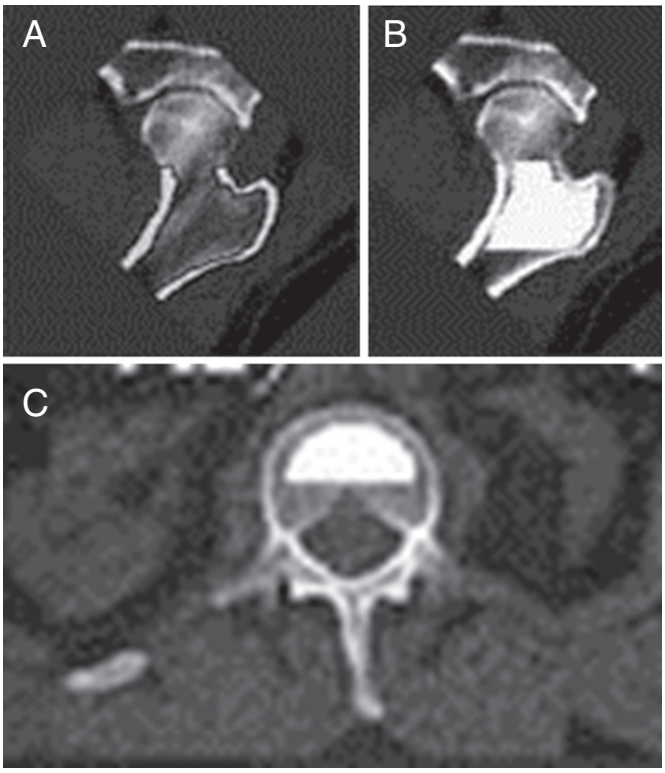

Fig. 1. QCT vertebral and hip regions of interest [17]. A) cortical and B) trabecular femoral neck regions of interest. C) Vertebral trabecular region of interest.

2.2. Volumetric BMD measurement

Volumetric BMD (g/cm^3) of the LS and hip regions was measured using QCT [15,16]. As previously described, images were acquired using a GE Prospeed (Birmingham), GE Hispeed Advantage (Minneapolis), Philips MX-8000 (Palo Alto), Siemans Somatom +4 (Pittsburgh), Philips CT-Twin (Portland), Toshiba Acquilion (Portland) site, or Picker PQ-5000 (San Diego). All QCT scans were transferred to the University of California at San Francisco for processing and central review. Image processing was performed using published methods [15,17]. Each participant's scan included a calibration standard of three hydroxyapatite concentrations (150, 75, and 0 mg/cm^3; Image Analysis). Images were converted from the native scanner Hounsfield Units (HU) to equivalent concentration (g/cm^3) of calcium hydroxyapatite contained in the calibrations standard.

QCT measurement of the LS was obtained using an anatomical region 5 mm above the L1 superior endplate to 5 mm below the L2 inferior endplate. LS images were acquired using a setting of 120 kVp, 150 mA, 1-mm slice thickness, and 512 × 512 matrix in spiral reconstruction mode. To derive trabecular vBMD, previously described analytical techniques were employed to orient the vertebrae so that the vertebral cross-sections were obtained in a plane parallel to the two endplates and to segment the vertebral body from the scans. Vertebral trabecular vBMD was determined in a region containing most of the trabecular bone in the vertebral body. This QCT protocol has been described previously [18].

To measure vBMD at the femoral neck, a QCT scan of the pelvic region (from the femoral head to 3.5 cm below the lesser trochanter) was acquired at settings of 80 kVp, 280 mA, 3-mm slice thickness, and 512 × 512 matrix in spiral reconstruction mode [16].

Regions of interest (ROI) in the left proximal femur were identified in QCT images reformatted along the neutral axis of the FN. The periosteal boundary of the femur was determined with a threshold-based region growing algorithm. Using this boundary, the cross-sectional area in each slice along the neutral axis of the FN between the proximal FN and

the lateral edge of the trochanter was calculated, and the minimum and maximum areas were determined. The FN ROI was defined as the portions of the neck extending from the slice with minimum cross-sectional area (medial boundary) to a point 25% of the distance toward the maximal cross-sectional area. Integral volume of the ROI was computed as the total volume within the periosteal boundary. A trabecular volume of the ROI was obtained by applying an erosion process to the integral volume to retain the same shape in a region fully contained within the medullary space. This morphological operation was applied to process the bony shapes and remove the pixels on object boundaries. The cortical volume was then defined by applying a threshold of 0.35 g/cm^3 to all voxels between the periosteal boundary and the outer boundary of the trabecular volume. Volumetric BMD for trabecular and cortical compartments was computed over all voxels in the respective volumes (Fig.1).

2.3. Clinical fractures ascertainment

Questionnaires were mailed to participants every 4 months to identify fractures, with >97% complete ascertainment. If a fracture was reported, the participants were contacted to obtain a copy of the radiographic report. All clinical fractures were confirmed by central review of radiographic report during an average of 9.7 years (0–13.7) from study enrollment until February 2014. Clinical spine fractures were confirmed by radiologist review of clinical images (X-ray, MRI, etc.). To account for preexisting fractures, we compared these images with lateral spine radiographs collected at the baseline visit. Fractures due to any level of trauma (minimal, moderate, and severe) were included since they have been previously associated with low aBMD [19]. Multiple fracture sites were studied including hip, spine, wrist, shoulder, pelvis/coccyx, rib/chest/sternum, skull/face, hand/finger, ankle/foot/toe, arm, and leg.

2.4. Statistical methods

The analytical cohort consisted of 3301 older men with both complete aBMD and vBMD measurements. Age and race adjusted Cox proportional hazards modeling with 95% confidence intervals (CI) was used to calculate hazard ratios (HR) per one SD decrease in aBMD and vBMD. Since obesity could have specific microstructural effects on the bones, sensitivity analyses adjusting for BMI were conducted. A logistic regression was used to study receiver operating characteristic (ROC) curves of different aBMD and vBMD measurements for the major osteoporotic fractures which consist of the hip, spine, shoulder, and wrist. The ability of BMD measurements to predict fracture risk was assessed by the area under the curve (AUC) or C statistics. Statistical comparison was conducted between different AUC curves to determine which one most strongly predicts fracture risk. Statistical analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC).

3. Results

The average age of the men at baseline was 73.5 years with 2.4% and 36% of them being osteoporotic and osteopenic respectively (Table 1). Over a mean of 9.7 years, 580 men experienced 748 fractures, 305 (39% hip; 33% spine; 15% wrist; 13% shoulder) of which were major osteoporotic fractures. On average, men were overweight and primarily white race.

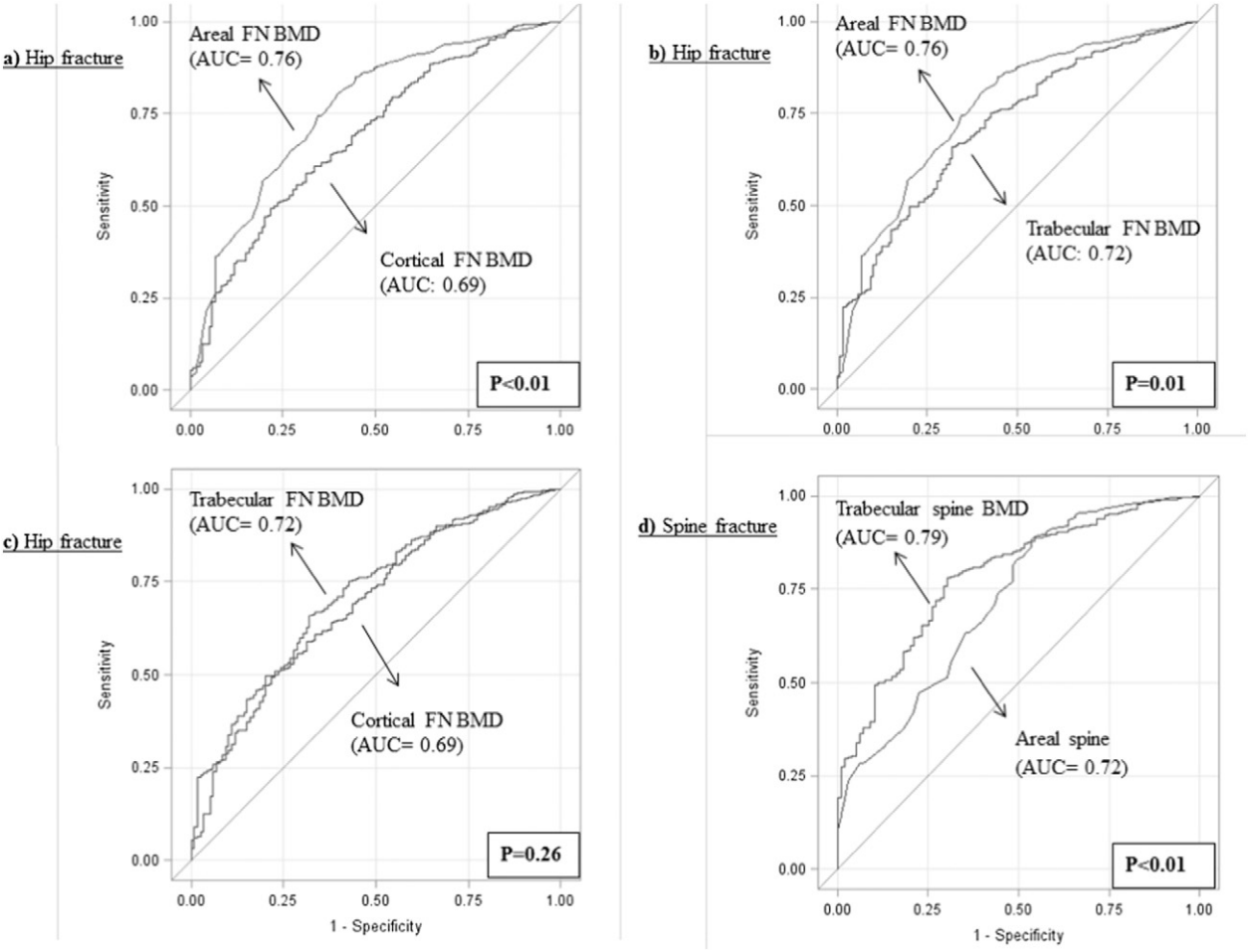

Fig. 2. Receiver operating characteristic (ROC) curves comparisons of hip and spine fractures.

Table 1
Baseline characteristics.

Characteristics	Values	Range
Age (years)	73.5(5.9)	65–100
BMI (kg/m^2)	27.3 (3.8)	17.2–50.7
Race, n(%)		
White	2878 (87.7)	
African American	170 (5.2)	
Asian	121 (3.7)	
Hispanic	91 (2.8)	
Other	41(1.2)	
Previous fracture, n(%)	1791 (54.3)	
Areal BMD (g/cm^2)		
Total spine	1.07 (0.19)	0.51–2.10
Total spine T-score	0.18(1.72)	−4.87–9.56
Total hip	0.96 (0.14)	0.53–1.45
Total hip T-score	0.13(1.14)	−3.40–4.16
Femoral neck	0.78 (0.13)	0.35–1.49
Femoral neck T-score	−0.61 (1.06)	−4.25–5.27
Volumetric BMD (g/cm^3)		
Femoral neck		
Cortical bone	0.53 (0.06)	0.33–0.93
Trabecular bone	0.07 (0.04)	−0.06–0.29
Total femur		
Cortical bone	0.52 (0.05)	0.35–0.81
Trabecular bone	0.10(0.04)	−0.01–0.25
Total spine		
Trabecular bone	0.11 (0.04)	0.01–0.35

3.1. BMD and fracture risk

Lower LS and FN aBMD were associated with a statistically significantly higher risk of fracture at the hip, spine, wrist, shoulder, rib/chest/sternum, and arm (Table 2). The HRs ranged from 1.31 (rib/chest/sternum) to 2.74(hip) per one SD decrease in FN aBMD, and between 1.24 (rib/chest/sternum) and 3.56 (spine) per one SD decrease in total spine aBMD. The associations with ankle/foot/toe (spine), hand/finger (FN), pelvis/coccyx (spine) were borderline significant. There was no relationship between aBMD, and leg and skull/face fractures.

For all non-spine fractures, one SD decrease in LS aBMD and FN aBMD was associated with a 31% and 53%, respectively, increase in fracture risk.

Trabecular vBMD of both the LS and FN were also related to many fractures (Table 2). In particular, one SD decrease in trabecular vBMD of the LS was associated with almost a 3.7-fold increase in clinical spine fractures. Lower trabecular vBMD at both the spine and hip was also associated with a higher risk of hip, wrist, shoulder, rib/chest/sternum, ankle/foot/toe, arm and leg fractures. The association between trabecular vBMD at the LS and FN and any non-spine fractures was similar in magnitude to the association between aBMD and any non-spine fracture.

In contrast, FN cortical vBMD was statistically significantly associated with hip (HR = 1.55) and clinical spine (HR = 1.26) fractures, but there was no association between cortical vBMD and fractures at other fracture locations. There was a modest relationship between FN cortical vBMD and any non-spine fracture, HR = 1.13 (1.04, 1.24).

There was evidence of site specificity where a strong relationship was found for LS aBMD and spine fractures (HR = 3.57) and between FN aBMD and hip fractures (HR = 2.74). Site specificity was present as well between LS vBMD and spine fracture (HR = 3.69). The effect size was the highest for spine fracture and lower for other fracture types. On the other hand, the specificity between FN vBMD and hip fracture was not as robust. The hazard ratios of the hip (HR = 1.74), clinical spine (HR = 1.74), wrist (HR = 1.74), and shoulder (HR = 1.46) were similar per a one SD decrease in trabecular FN vBMD (Table 2). Sensitivity analyses adjusting additionally for BMI resulted in similar hazard ratios (not shown here).

The results of the AUC comparisons are shown in Table 3. FN aBMD (AUC = 0.76) had a higher predictability of hip fractures compared to cortical FN vBMD (AUC = 0.69). Furthermore, FN aBMD had a better predictability of hip fractures compared to trabecular FN vBMD (AUC = 0.72). Nonetheless, there was no difference in AUCs between trabecular and cortical FN vBMD for hip fractures. Trabecular vBMD of LS had better predictability of spine fractures (AUC = 0.79) compared to spine aBMD (AUC = 0.72) (Fig. 2).

4. Discussion

The risk of most types of fractures is higher with lower areal and volumetric BMD. Stronger associations were seen with trabecular vBMD compared to cortical vBMD. Furthermore, there was high specificity between BMD site and fracture type, especially for aBMD. Several fracture types were for the most part unrelated to low BMD, including fractures that occurred at the hand or finger; pelvis or coccyx; skull or face. Results showed that FN aBMD is a better predictor of hip fractures compared to trabecular and cortical FN aBMD. However, trabecular vBMD of LS had better predictability of spine fractures compared to spine aBMD.

Both low aBMD and vBMD were associated with an increased risk of different types of fractures. In a large cohort of older women with similar inclusion criteria to our study, Stone et al. showed that one SD decrease in aBMD was associated with a higher risk of almost all types of fractures. After adjusting for the same confounders, the statistically significant hazard ratios of the different types of fractures ranged between 1.20 and 2.06 for LS aBMD and between 1.21 and 2.50 for FN aBMD.

Table 2
Areal and volumetric BMD and risk of various types of fractures (FX): age and race adjusted hazard ratios (HR) and 95% confidence intervals (CI) HR per one SD decrease in BMD. The values highlighted in bold are statistically significant ($P < 0.05$).

		Areal BMD		Volumetric BMD		
	N of FX	Total spine	Femoral neck	Trabecular spine	Cortical FN	Trabecular FN
Hip	119	**1.29 (1.07, 1.56)**	**2.74 (2.19, 3.42)**	**1.80 (1.43, 2.26)**	**1.55 (1.28, 1.87)**	**1.74 (1.41, 2.13)**
Clinical spine	99	**3.57 (2.78, 4.58)**	**1.95 (1.54, 2.47)**	**3.69 (2.78, 4.90)**	**1.26 (1.02, 1.55)**	**1.74 (1.39, 2.18)**
Wrist	46	**1.43 (1.04, 1.97)**	**1.82 (1.30, 2.55)**	**1.46 (1.04, 2.05)**	1.28 (0.95, 1.72)	**1.74 (1.25, 2.43)**
Shoulder	41	**1.63 (1.17, 2.28)**	**1.88 (1.31, 2.70)**	**1.73 (1.18, 2.54)**	1.14 (0.83, 1.56)	**1.46 (1.05, 2.04)**
Rib/chest/sternum	141	**1.24 (1.04, 1.48)**	**1.31 (1.09, 1.57)**	**1.27 (1.05, 1.54)**	1.05 (0.88, 1.24)	**1.26 (1.06, 1.51)**
Ankle/foot/toe	91	1.21 (0.97, 1.51)	1.18 (0.94, 1.47)	**1.35 (1.06, 1.73)**	0.99 (0.80, 1.22)	**1.26 (1.01, 1.58)**
Arm	55	**1.68 (1.25, 2.27)**	**1.55 (1.14, 2.09)**	**1.75 (1.26, 2.44)**	1.09 (0.83, 1.43)	**1.35 (1.01, 1.81)**
Hand/finger	52	1.20 (0.89, 1.60)	1.30 (0.97, 1.76)	0.94 (0.71, 1.24)	1.08 (0.82, 1.43)	1.28 (0.95, 1.73)
Leg	43	1.22 (0.88, 1.68)	1.32 (0.94, 1.84)	**1.56 (1.08, 2.25)**	1.06 (0.78, 1.44)	**1.54 (1.10, 2.16)**
Pelvis/coccyx	34	1.38 (0.96, 1.99)	1.11 (0.78, 1.59)	1.45 (0.97, 2.17)	0.86 (0.62, 1.20)	1.29 (0.90, 1.85)
Skull/face	27	1.17 (0.78, 1.75)	1.09 (0.73, 1.63)	0.91 (0.61, 1.34)	1.08 (0.73, 1.59)	1.06 (0.71, 1.57)
Any non-spine fracture	524	**1.31 (1.19, 1.43)**	**1.53 (1.38, 1.68)**	**1.39 (1.26, 1.54)**	**1.13 (1.04, 1.24)**	**1.34 (1.22, 1.47)**

Table 3
Age and race adjusted area under the curve (AUC) comparisons for all types of fractures.

		Areal BMD		Volumetric BMD			
	N of FX	Total spine	Femoral neck	Trabecular spine	Cortical FN	Trabecular FN	*p*-value
Hip	119	0.67	0.76	0.71	0.69	0.72	a,b,c,d,e,f,g
Clinical spine	99	0.72	0.70	0.79	0.63	0.69	b,c,e,f,h,i,j
Wrist	46	0.51	0.58	0.59	0.57	0.64	d
Shoulder	41	0.74	0.75	0.75	0.72	0.74	
Rib/chest/sternum	141	0.62	0.59	0.61	0.59	0.60	
Ankle/foot/toe	91	0.59	0.58	0.60	0.59	0.62	
Arm	55	0.64	0.60	0.66	0.60	0.62	
Hand/finger	52	0.57	0.58	0.57	0.58	0.59	
Leg	43	0.58	0.61	0.64	0.59	0.65	
Pelvis/coccyx	34	0.69	0.66	0.68	0.66	0.67	
Skull/face	27	0.59	0.62	0.59	0.58	0.59	f
Any non-spine fracture*	524	0.60	0.61	0.62	0.59	0.62	b,d,f,h,j

Significant with $p < 0.05$:
[a] Total spine vs femoral neck.
[b] Total spine vs trabecular spine.
[c] Total spine vs cortical FN.
[d] Total spine vs trabecular FN.
[e] Femoral neck vs trabecular spine.
[f] Femoral neck vs cortical FN.
[g] Femoral neck vs trabecular FN.
[h] Trabecular spine vs cortical FN.
[i] Trabecular spine vs trabecular FN.
[j] Cortical FN vs trabecular FN.

With the exception of spine fractures, which have an apparently stronger association in men (HR = 3.57 in men, HR = 2.06 in women for one SD decrease in LS aBMD) results were roughly the same across gender [5].

Areal BMD is a strong independent risk factor for fractures in men [20]. Our results are consistent with previous MrOS reports which found strong associations between hip aBMD and nonvertebral fractures (especially hip) in older men [7] [21]. The current analysis extends these findings to most fracture types.

On the other hand, the relationship between trabecular and cortical vBMD with fracture risk is less well understood. We showed that trabecular vBMD of LS and FN were both associated with many types of fractures. In contrast, cortical vBMD was related to hip and spine fractures only. Although hip fractures are attributed to both cortical and trabecular bone loss, very few studies have examined the association between vBMD and hip fractures [8,22]. Our results for hip fracture are consistent with an earlier MrOS report with shorter follow-up.

The stronger associations observed for trabecular vBMD compared to cortical vBMD may be explained by the greater metabolic activity of the trabecular compartment. Trabecular and cortical compartments have different metabolic activities with the former being more active contributing to greater rates of bone loss [22]. With age, trabeculae become thinner, the number of trabeculae decreases, and trabecular spacing increases. The cortical compartment also undergoes age-related changes such as increase in porosity, but we were unable to capture cortical porosity with our measurements [23]. Although both compartments demonstrate microarchitecture changes, the different effect sizes may be explained by the trabecular and cortical bone-specific proportions. For instance, the vertebral body consists of largely trabecular bone with a thin layer of cortical bone [22]. The majority of the vertebral body strength is maintained by trabecular bone. Therefore, this may explain why trabecular vBMD was more highly associated with spine fractures compared to cortical vBMD. The reason why some of the volumetric trabecular BMD were negative is because CT density numbers – known as Hounsfield Units (HU) - are scaled to materials of known density, with the density of water set to 0. Tissues (or materials) that are less dense than water have negative HU and those that are denser have positive HU. The negative BMD value results because the voxels in the volume of interest are representing primarily fatty marrow tissues that have negative HU. This occurs when bone loss at the endosteal surface is extensive. Thus, participants with negative BMD values appear to have sustained considerable bone loss.

Cortical FN vBMD was associated with only hip and spine fractures perhaps because cortical bone at least at the hip plays a key role at this site relative to the other fracture locations. Yoshikawa et al. demonstrated that the loss of bone occurs more on the superior aspect of the FN [24]. At the FN, the superior region of the cortical bone is thinner compared to its inferior region. With age, thinning of the superior region occurs, and compromises the capacity of the femur to absorb energy independently of bone mass assessed by DXA. The thinning of this region with age may reflect a lower mechanical load. Since most hip fractures result from a fall, the impact on the hip reverses the stress pattern leading to increase in compressive stress on the superior neck which is mainly cortical bone [25]. This may explain why low cortical FN was associated with an increased risk of hip fractures. Although loss of cortical bone occurs at other sites as well, the biomechanics of fractures as well as the proportion of cortical bone in individual bones may explain why we did not detect statistically significant associations with other fracture sites. Risk of spine fractures was also higher with lower cortical FN vBMD. Although the trabecular bone is known to constitute the majority of the vertebra, the cortical thickness influences vertebral strength mostly when the trabecular bone volume gets low [26–28]. Since our cohort consists of elderly men with low trabecular spine vBMD (0.11 g/cm^3), it is likely that the cortical bone influenced the vertebral strength and hence, spine fracture risk.

The risk of hip fracture was higher with low FN aBMD compared to the trabecular and cortical vBMD. Indeed, FN aBMD was a better predictor of hip fractures compared to trabecular and cortical FN vBMD. This finding could be explained by the fact that, unlike vBMD, FN aBMD is not compartment specific and is an integrative measurement that comprises both trabecular and cortical bone. Areal BMD is known to highly correlate with and account for 60–70% of the bone strength [29,30]. In agreement with our findings, a previous study showed that the QCT parameters' prediction of hip fracture was not improved compared to aBMD [8]. On the other hand, our findings showed that trabecular spine vBMD was a better predictor of spine fractures compared to areal spine BMD. Using MrOS data, Wang et al. conducted a case-cohort analysis to show that vBMD improved vertebral fracture risk assessment compared to aBMD [31]. Here, although areal spine BMD comprises both compartments, the fact that the trabecular proportion of

the vertebrae is much greater than the cortical proportion may explain the higher predictability of the trabecular vBMD at the LS. Furthermore, the artifacts seen on DXA scans may explain the lower predictability of areal spine BMD.

There are several strengths to our study. MrOS is a multicenter prospective study examining potential risk factors for fractures in a large population of older men. We were able to examine the association of both aBMD and vBMD including both the trabecular and cortical compartments and fractures risk in the same group of men.

There are advantages associated with the use of QCT scans. It provides a compartment specific, three dimensional assessment of bone that is not size dependent. Furthermore, QCT gives a better assessment of treatment monitoring compared to DXA. On the other hand, QCT has several disadvantages such as its high cost, radiation exposure, not having cutoff points for osteoporosis diagnosis, and not being readily clinically accessible [32]. Due to the low spatial resolution of the CT, measuring cortical BMD is not possible at the spine. In addition, the central QCT has a weaker spatial resolution (in the order of millimeters) compared to the high resolution peripheral QCT (in the order of micrometers).

However, there are also several limitations. Most importantly, the men were primarily Caucasians and our results may not be generalizable to men of other race/ethnic groups. In addition, the number of specific fractures varied by site limiting our power to detect an association for fracture locations that were uncommon. Another limitation was that we did not include information about the participants' comorbidities and their respective treatments. To assess predictability of fractures, we used the widely used method of area under the curve. However, there are other methods based on the integrated sensitivity and specificity, and on reclassification tables that may provide additional information compared to AUC [33].

5. Conclusions

Low aBMD and trabecular vBMD were associated with an increased risk of most fractures. There was no evidence that trabecular vBMD was superior to aBMD in predicting hip fractures, which was not the case for spine fractures. With the exception of spine fractures, QCT does not appear to add additional information to fracture risk assessment once aBMD from DXA is known. Future studies might be needed to understand further the advantage of QCT over DXA in predicting spine fractures. In addition, screening for osteoporosis using DXA may help in preventing multiple types of fractures.

Disclosures

Eric S. Orwoll consults for and has received research support from Amgen, Lilly, and Merck and serves on the advisory board of Wright Medical Tech. Kristine E. Ensrud serves as a consultant on a Data Monitoring Committee for Merck Sharpe & Dohme. Peggy M. Cawthon has received research support from GSK, Lilly, IMS Health, and Merck and serves as a consultant for Lilly. Other authors do not have conflicts of interests or disclosures to make.

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Didier Chalhoub (email: dic14@pitt.edu) conducted the data analysis. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

All authors 1) made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) participated in drafting the manuscript or revising it critically for important intellectual content; 3) approved the final version of the submitted manuscript, and 4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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