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Original Article

Digital X-ray Radiogrammetry Predicts Hip, Wrist and Vertebral Fracture Risk in Elderly Women: A Prospective Analysis from the Study of Osteoporotic Fractures

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Abstract. Digital X-ray radiogrammetry (DXR) is a technique that uses automated image analysis of standard hand radiographs to estimate bone mineral density (DXR-BMD). Previous studies have shown that DXR-BMD measurements have high precision, are strongly correlated with forearm BMD and are lower in individuals with prevalent fractures. To determine whether DXR-BMD measurements predict wrist, hip and vertebral fracture risk we conducted a case–cohort study within a prospective study of 9704 community-dwelling elderly women (the Study of Osteoporotic Fractures). We compared DXR-BMD, and BMD of the radius (proximal and distal), calcaneus, femoral neck and posteroanterior lumbar spine in women who subsequently suffered a wrist (n = 192), hip (n = 195), or vertebral fracture (n = 193) with randomly selected controls from the same cohort (n = 392–398). DXR-BMD was estimated from hand radiographs acquired at the baseline visit. The radiographs were digitized and the Pronosco X-posure System was used to compute DXR-BMD from the second through fourth metacarpals. Wrist fractures were confirmed by radiographic reports and hip fractures were confirmed by radiographs. Vertebral fractures were defined using morphometric analysis of lateral spine radiographs acquired at baseline and an average of 3.7 years later. Age-adjusted odds ratio (OR, vertebral fracture) or relative hazard (RH, wrist and hip fracture) for a 1 SD decrease in BMD were computed. All BMD measurements were similar for prediction of wrist (RH = 1.5–2.1) and vertebral fracture (OR = 1.8–2.5). Femoral neck BMD best predicted hip fracture (RH = 3.0), while the relative hazards for all other BMD measurements were similar (RH = 1.5–1.9). These prospective data indicate that DXR-BMD performs as well as other peripheral BMD measurements for prediction of wrist, hip and vertebral fractures. Therefore, DXR-BMD may be useful for prediction of fracture risk in clinical settings where hip BMD is not available.

Keywords: BMD; Digital X-ray radiogrammetry; DXR; Fracture risk; Hip fracture; Osteoporosis; Vertebral fracture; Wrist fracture

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Introduction

Several interventions, pharmacologic and otherwise, have been shown to reduce osteoporotic fracture risk among women [1–3]. Due to issues related to the cost–benefit profile, these interventions are usually offered only to those individuals at highest risk of fracture [4,5]. It is therefore of paramount importance to identify those individuals at greatest risk for fracture. Despite this obvious need, facilities for diagnosis of osteoporosis are inadequate in many countries [5]. The relatively low rate of diagnostic evaluation may be

attributed to the lack of widespread availability of testing devices, costs of performing the testing, and limited awareness of testing options among patients and physicians. Thus, to increase the proportion of at-risk women who are tested and ultimately treated for osteoporosis, a combined approach is needed to expand the use of existing techniques and introduce new, widely available diagnostic techniques.

Measurement of cortical bone width and geometry from radiographs, or radiogrammetry, was among the first methods used to assess skeletal status quantitatively [6]. The most commonly assessed skeletal sites include the metacarpals, radius and ulna. The use of radiogrammetry for osteoporosis assessment decreased with the introduction of single- and dual-photon absorptiometry techniques in the 1970s, and single- and dual-energy X-ray absorptiometry in the 1980s [7]. However, in the past several years there has been increased interest in radiogrammetry due to the improvement in digital imaging and the development of automated and semi-automated image analysis algorithms [8,9]. Radiogrammetry has potential to be useful for diagnosis of osteoporosis, as previous studies have shown that age- and menopause-related decreases in radiogrammetry measurements are similar to the observed decrements in bone mineral density (BMD) [9–12]. In addition, radiogrammetry measurements of the metacarpals and radius are associated with prevalent wrist and vertebral fractures [9,13–16]. One major advantage to radiogrammetry measurements is that they can be performed on standard radiographs of the hand and forearm, thereby giving the procedure the potential to be widely available. However, similar to other peripheral bone densitometry techniques, one potential disadvantage of radiogrammetry is that the measurements are not performed at the actual sites of fracture (i.e., the wrist, hip and spine).

Digital X-ray radiogrammetry (DXR) is a technique that uses automated image analysis of standard hand or forearm radiographs to estimate bone mineral density of the forearm (DXR-BMD). Previous studies have shown that DXR-BMD measurements have high precision, are strongly correlated with forearm BMD assessed by dual-energy X-ray absorptiometry, and are lower in individuals with prevalent fractures [8,17–20]. However, the ability of DXR to predict fracture risk in a prospective study has not been investigated.

Therefore, the primary objectives of this study were to determine whether DXR-BMD measurements predict wrist, hip and vertebral fracture risk, and to compare their ability to predict fracture risk with that of other peripheral BMD measurements. In addition, we compared DXR-BMD with hip and spine BMD with regard to their abilities to predict fracture risk. To accomplish these objectives, we conducted a case-cohort study within the Study of Osteoporotic Fractures (SOF), a prospective study of 9704 community-dwelling elderly women.

Materials and Methods

Subjects and Clinical Assessments

From 1986 to 1988, 9704 Caucasian women aged 65 years or older were recruited from population-based listings for participation in the SOF [21]. Subjects were recruited from four regions of the United States, including Baltimore County, Maryland; Minneapolis, Minnesota; Portland, Oregon; and the Monongahela Valley near Pittsburgh, Pennsylvania. Black women were excluded (due to their low risk of hip fracture), as were women with a history of bilateral hip replacement and women who were unable to walk without assistance. At the baseline visit, lateral radiographs of the thoracic and lumbar spine and anteroposterior radiographs of the nondominant distal forearm and hand were acquired. The study was approved by the institutional review boards at each study center and all participants gave informed written consent.

Assessment of Fractures

Participants were contacted every 4 months by postcard or telephone to ascertain whether they had sustained a fracture. Self-reported wrist fractures were confirmed by radiograph reports. Self-reported hip fractures were confirmed by a review of the radiographs obtained at the time of hospitalization following the fracture [22]. Vertebral fractures were identified by quantitative morphometric evaluation of baseline and follow-up lateral spine radiographs acquired on average 3.7 years later. A new fracture was considered to have occurred if there was a decrease of 20% and at least 4 mm in any one of the vertebral heights [23,24].

Selection of Case and Cohort Samples

Using the case–cohort approach [25,26], we randomly selected 200 of the 224 women in the cohort of 9704 who suffered a hip fracture during the first 5 years of follow-up after the baseline evaluation, of whom 188 had a valid hand radiograph for evaluation. Similarly, we randomly selected 200 of the 342 women who suffered a wrist fracture during the first 5 years of follow-up (of whom 178 had an evaluable hand radiograph), and 200 of the 389 women who suffered a new vertebral fracture during an average of 3.7 years of follow-up (of whom 174 had an evaluable hand radiograph).

The wrist fractures and hip fractures occurred on average 2.4 years (range 0.02–4.98 years) and 2.8 years (range 0.05–4.98 years), respectively, after the baseline visit. The vertebral fractures were identified using morphometric analysis of lateral spine radiographs obtained an average of 3.7 years (range 1.6–4.9 years) after the baseline visit.

In addition, we randomly selected 411 women from the original cohort to serve as nonfractured controls for the hip and wrist fracture cohort. This sample of the original cohort was increased to 555 women in order to identify sufficient participants with spine radiographs at the baseline and follow-up visits. Among this sample of the cohort, 7 women had suffered an incident hip fracture, 17 had suffered a wrist fracture and 19 had suffered a vertebral fracture. These individuals were counted as case patients in the analysis of hip, wrist and vertebral fractures.

Bone Densitometry Assessments

At baseline, bone mineral content (BMC) and density (BMD) of the distal forearm and calcaneus were assessed by single-photon absorptiometry (OsteoAnalyzer, Siemens-Osteon, Wahiana, HI). All densitometry measurements were performed on the right side, except in subjects who had suffered a fracture, stroke or severe injury involving that limb. In these cases, bone density measurements were performed on the contralateral limb. At the second visit (approximately 2 years after the baseline visit) BMD and BMC of the lumbar spine and proximal femur were assessed. Details regarding the bone densitometry measurements have been published previously [21,27,28].

Analysis of Hand Radiographs using Digital X-ray Radiogrammetry

Automated DXR (Pronosco X-posure System Pronosco, Vedbaek, Denmark) was used to calculate BMD (DXR-BMD, g/cm^2) of the forearm. Computation of DXR-BMD by the Pronosco X-posure System involves digitization of a single plain radiograph of the hand and subsequent image analysis of the digitized image. The system uses a completely automated procedure to calculate cortical thickness and overall bone width for the second through fourth metacarpals. The determination of DXR-BMD has been described previously [8] and will be only briefly summarized here.

To locate the bones in the radiograph the Pronosco X-posure System used a model-based algorithm based on the Active Shape Model [29]. The Active Shape Model algorithm was adapted to find the diaphysis of the three middle metacarpals in the hand. After each diaphysis was identified, a region of interest (ROI) was determined automatically for each metacarpal (Fig. 1a). The height of the ROI was fixed to 2.0 cm, 1.8 cm and 1.6 cm for the second, third and fourth metacarpals, respectively. The algorithm then couples the three ROIs from each metacarpal with each other, and moves them along the bone shaft to a position identified by the minimum combined bone width (Fig. 1b). The average cortical thickness (t_i) and bone width (W_i) were determined for the metacarpal i, and the bone volume per projected area

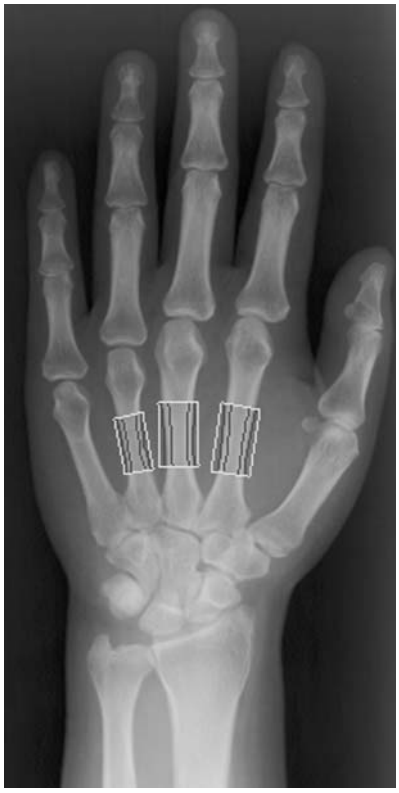

Fig. 1. Image of a hand radiograph with regions of interest outlined (**a**) and a magnified view of the metacarpals (**b**).

(VPA, cm) was computed for each metacarpal assuming a cylindrically shaped bone:

$$\mathrm{VPA_i} = \pi \times t_i \times (1 - t_i/W_i)$$

The total VPA for the metacarpals was defined as a weighted average:

$$\mathrm{VPA_{mc}} = (\mathrm{VPA_2} + \mathrm{VPA_3} + 0.5\ \mathrm{VPA_4}) / 2.5$$

DXR-BMD of the forearm was calculated as $\mathrm{VPA_{mc}} \times (1-P) \times c$, where P is the estimated three-dimensional porosity, chosen to be the fraction of the cortical bone volume that is not occupied by bone [30], and c is a scaling factor chosen to 'calibrate' the estimated DXR-BMD value so that it best corresponds to proximal forearm BMD, as assessed by dual-energy X-ray absorptiometry [8].

The metacarpal index (DXR-MCI) for each bone was defined as

$$\text{DXR-MCI}_i = 2 \times t_i / W_i$$

and the total DXR-MCI for the three metacarpals was computed as the weighted average:

$$\text{DXR-MCI}_{mc} = (\text{DXR-MCI}_2 + \text{DXR-MCI}_3 + 0.5\text{DXR-MCI}_4)/2.5$$

Statistical Analysis

Standard descriptive statistics were computed for each of the fracture (case) and no-fracture subcohorts. Mean values for the case and the cohort samples were compared using Student's *t*-test and chi-square analyses. We used proportional hazards models that accounted for the case–cohort sampling design (Stata Corporation, College Station, TX) to analyze predictors of wrist and hip fractures, and logistic regression analysis (SAS Institute, Cary, NC) to analyze predictors of vertebral fractures. Predictors of hip fracture were also analyzed separately for cervical and intertrochanteric hip fractures. In the analysis of hip fracture types, women with the other type of fracture were included as controls. For example, women who suffered a femoral neck fracture were included as controls for the analysis of intertrochanteric hip fractures. We used linear correlation analysis to compare DXR-BMD with BMD measurements obtained by the other techniques.

Results

Compared with subjects who did not suffer a fracture, those who suffered a wrist, hip, or vertebral fracture were more likely to have a prior history of fracture and to have a baseline vertebral fracture (Table 1). In addition, women who suffered an incident hip or vertebral fracture were older and thinner than unfractured control subjects (Table 1). Furthermore, at all skeletal sites, baseline BMD measurements were 7–16% lower ($p<0.0001$ for all) in women who suffered an incident fracture than in those who did not suffer a fracture (Table 2).

According to the case–cohort analysis, women with decreased BMD had an increased risk of subsequent wrist, hip and vertebral fracture. All BMD measurements were similar for prediction of wrist and vertebral fractures. After adjusting for age, the relative hazard of wrist fracture for a 1 SD decrease in BMD ranged from 1.5 for lumbar spine BMD to 2.1 for distal radius BMD (Table 3). Similarly, the age-adjusted odds ratio for vertebral fracture for a 1 SD decrease in BMD ranged from 1.8 for DXR-MCI and proximal radius BMD to 2.5 for femoral neck BMD (Table 3).

Hip fracture risk was best predicted by femoral neck BMD, whereas the predictions of hip fracture risk by all other BMD measurements were similar (Table 4). Specifically, the relative hazard (RH) for a 1 SD decrease in BMD was 3.0 for the femoral neck, and ranged from 1.5 to 1.9 for all other measurements. When hip fractures were analyzed separately according to fracture type, 107 were classified as femoral neck fractures and 87 as intertrochanteric fractures. (Note that 2 fractures were identified as both types, and therefore are included in both groups, whereas 3 of the fractures were not identified as either femoral neck or trochanteric.) Femoral neck BMD predicted both femoral neck and intertrochanteric hip fractures (RH = 2.1 and 2.5, respectively, Table 4). However, in contrast to femoral neck BMD, peripheral BMD measurements were much better predictors of intertrochanteric hip fracture (RH = 1.9–2.5) than of femoral neck hip fracture (RH = 1.1–1.3). Nonetheless, all peripheral BMD measurements were similar to each other in their ability to predict both femoral neck and intertrochanteric hip fractures.

None of the peripheral BMD measurements was better than any other for prediction of wrist, hip and vertebral fracture risk. Moreover, the inverse relationship between BMD and the risk of fracture was similar for calcaneus BMD, distal radius BMD and DXR-BMD (Fig. 2).

DXR-BMD was most strongly correlated with distal radius BMD ($r = 0.68$), proximal radius BMD ($r = 0.75$)

Table 1. Baseline characteristics of women with incident wrist, hip, and vertebral fractures compared with unfractured controls

Characteristic	Wrist fracture		Hip fracture		Vertebral fracture	
	Fx (n = 195)	No Fx (n = 392)	Fx (n = 195)	No Fx (n = 398)	Fx (n = 193)	No Fx (n = 392)
Age 65–69, n (%)	88 (45.1)	147 (37.5)	34 (17.4)	150 (37.7)	49 (25.4)	166 (42.3)
Age 70–74, n (%)	52 (26.7)	127 (32.4)	56 (28.7)	130 (32.7)	77 (39.9)	129 (32.9)
Age 75–79, n (%)	35 (18.0)	69 (17.6)	53 (27.2)	72 (18.1)	42 (21.8)	65 (16.6)
Age $\geqslant$80, n (%)	20 (10.3)	49 (12.5)	52 (26.7)	46 (11.6)	25 (13.0)	32 (8.2)
Prior history of Fx, n (%)	96 (50.0)**	143 (36.7)	111 (57.5)***	141 (35.6)	99 (51.3)***	135 (34.4)
Baseline vertebral Fx, n (%)	50 (25.9)*	71 (18.3)	78 (41.5)***	65 (16.4)	101 (52.3)***	65 (16.6)
Age (years), mean (SD)	71.7 (5.6)	72.1 (5.3)	75.5*** (6.1)	72.0 (5.2)	73.2*** (5.4)	71.3 (4.8)
Height (cm), mean (SD)	159.7 (5.7)	159.0 (6.1)	158.1 (6.9)	159.1 (6.1)	158.1** (6.1)	159.7 (6.1)
Weight (kg), mean (SD)	66.2 (12.5)	67.3 (12.5)	63.3*** (11.8)	67.5 (12.4)	64.5** (11.6)	68.0 (12.1)

Fx, fracture.
*$p<0.05$ compared with control subjects; **$p<0.01$ compared with control subjects; ***$p<0.0001$ compared with control subjects.

Table 2. Mean baseline bone mineral density and radiogrammetry characteristics of participants with incident wrist, hip and vertebral fractures compared with those of the respective control subjects who did not suffer a fracture[a]

Characteristic	Wrist fracture		Hip fracture		Vertebral fracture	
	Fx (n = 195)	No Fx (n = 392)	Fx (n = 195)	No Fx (n = 398)	Fx (n = 193)	No Fx (n = 392)
Femoral neck BMD (g/cm^2)	0.609	0.660	0.556	0.659	0.584	0.664
Lumbar spine BMD (g/cm^2)	0.802	0.865	0.797	0.864	0.753	0.869
Calcaneal BMD (g/cm^2)	0.371	0.410	0.344	0.411	0.356	0.416
Distal radius BMD (g/cm^2)	0.322	0.373	0.320	0.373	0.320	0.373
Proximal radius BMD (g/cm^2)	0.592	0.645	0.581	0.647	0.586	0.650
DXR-BMD (g/cm^2)	0.468	0.491	0.451	0.492	0.459	0.495
DXR-MCI	0.345	0.370	0.331	0.371	0.340	0.374

Fx, fracture.
[a]All BMD measurements were lower in subjects with fracture than in those with no fracture (p<0.0001 for all).

Table 3. Association between bone mineral density and risk of wrist and vertebral fracture using age-adjusted models: relative hazard and odds ratio for a 1 SD decrease in each bone measurement

Bone measurement	Standard deviation	Wrist fracture relative hazard (95% CI)	Vertebral fracture odds ratio (95% CI)
Femoral neck BMD (g/cm^2)	0.108	1.8 (1.4, 2.3)	2.5 (1.9, 3.2)
Lumbar spine BMD (g/cm^2)	0.156	1.5 (1.2, 1.9)	2.3 (1.8, 2.9)
Calcaneal BMD (g/cm^2)	0.092	1.7 (1.4, 2.0)	2.1 (1.7, 2.6)
Distal radius BMD (g/cm^2)	0.083	2.1 (1.7, 2.5)	1.9 (1.6, 2.4)
Proximal radius BMD (g/cm^2)	0.101	1.8 (1.5, 2.1)	1.8 (1.5, 2.2)
DXR-BMD (g/cm^2)	0.058	1.6 (1.3, 2.0)	1.9 (1.5, 2.3)
DXR-MCI	0.060	1.7 (1.4, 2.1)	1.8 (1.4, 2.2)

Table 4. Association between bone mineral density and risk of all hip fractures, femoral neck and intertrochanteric fractures using age-adjusted models[a]

Bone measurement	All hip fractures (n = 195)[b] Relative hazard (95% CI)	Femoral neck fractures (n = 107)[b] Relative hazard (95% CI)	Intertrochanteric fractures (n = 87)[b] Relative hazard (95% CI)
Femoral neck BMD (g/cm^2)	3.0 (2.1, 4.3)	2.1 (1.6, 2.8)	2.5 (1.7, 3.8)
Lumbar spine BMD (g/cm^2)	1.5 (1.2, 1.9)	1.0 (0.77, 1.4)	2.1 (1.5, 3.1)
Calcaneal BMD (g/cm^2)	1.9 (1.5, 2.4)	1.1 (0.89, 1.4)	2.5 (1.8, 3.4)
Distal radius BMD (g/cm^2)	1.8 (1.4, 2.2)	1.3 (1.0, 1.6)	2.1 (1.5, 3.0)
Proximal radius BMD (g/cm^2)	1.7 (1.4, 2.1)	1.2 (0.95, 1.6)	1.9 (1.5, 2.6)
DXR-BMD (g/cm^2)	1.8 (1.4, 2.2)	1.2 (0.92, 1.5)	2.3 (1.7, 3.0)
DXR-MCI	1.8 (1.4, 2.3)	1.2 (0.94, 1.6)	2.3 (1.7, 3.1)

[a]Cohort standard deviation shown in Table 3.
[b]The total number of hip fractures includes individuals identified with both fracture subtypes.

and DXR-MCI (r = 0.87), whereas it was moderately correlated with femoral neck BMD (r = 0.50), lumbar spine BMD (r = 0.44) and calcaneus BMD (r = 0.59).

Discussion

In this prospective study we showed that DXR-BMD, an estimate of forearm BMD computed using automated digital X-ray radiogrammetry, predicts wrist, vertebral and hip fracture risk as well as other peripheral BMD measurements. Each standard deviation (SD) decrease in DXR-BMD was associated with a 1.6- to 1.9-fold increase in fracture risk. In comparison, a 1 SD decrease in calcaneal or radial BMD was associated with a 1.7- to 2.1-fold increase in the risk of fracture, whereas a 1 SD decrease in femoral neck BMD was associated with a 1.8- to 3.0-fold increase in fracture risk.

Similar to previous reports [31–33], we found that

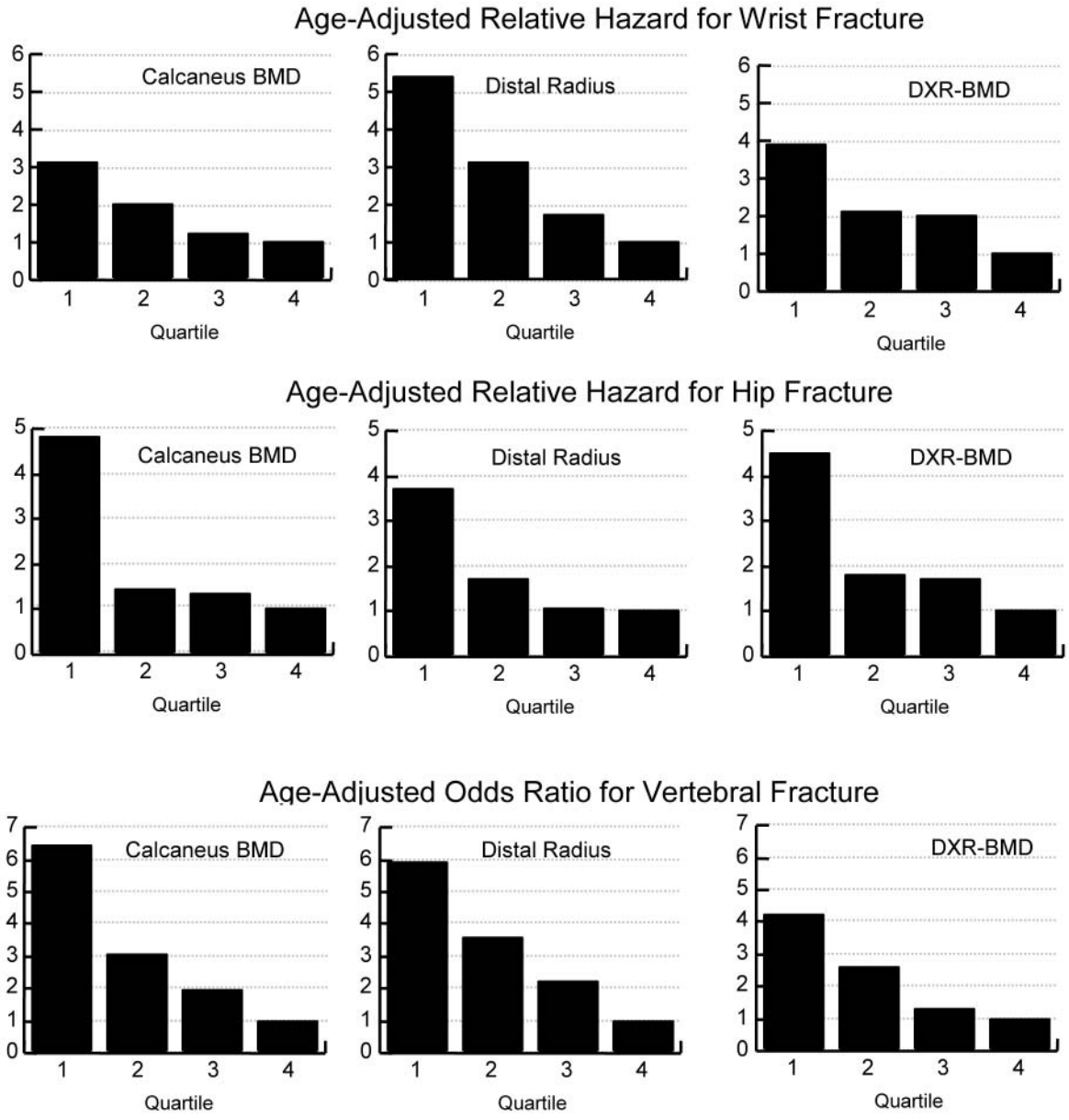

Fig. 2. Age-adjusted relative risk of wrist, hip and vertebral fracture by quartile of calcaneus BMD, distal radius BMD and DXR-BMD.

peripheral BMD measurements, including DXR-BMD, are better predictors of the risk of intertrochanteric hip fracture than of femoral neck fracture. For example, in an earlier analysis of the entire SOF cohort, Seeley and colleagues [31] reported that the hazard ratios for the association between intertrochanteric fractures and BMD at the calcaneus, distal radius and proximal radius were 2.78, 1.99, and 1.80, respectively. In contrast, the associations between appendicular BMD and femoral neck fracture risk were much weaker, with hazard ratios ranging from 1.10 to 1.25. Our results, using a sample of the entire SOF cohort, are consistent with these data, as we found age-adjusted relative hazards for a 1 SD decrease in peripheral BMD measurements ranging from 1.9 to 2.5 for intertrochanteric hip fractures, and from 1.0 to 1.3 for femoral neck fractures. The reasons for this discrepancy in the ability of peripheral BMD measurements to predict femoral neck versus intertrochanteric hip fracture risk are not well understood. It is likely that whereas overall fracture risk is well predicted by peripheral BMD measurements, the distribution of bone mass in various regions in the proximal femur that predispose to a certain type of hip fracture [34–37] is not captured by peripheral BMD measurements. It is interesting to note, however, that peripheral measurements, including DXR-BMD, are nearly as strong predictors of intertrochanteric fractures as is femoral neck BMD.

The DXR-BMD technique (and radiogrammetry techniques in general) primarily measure cortical bone at skeletal sites distinct from the common fracture sites, which are comprised of both trabecular and cortical bone regions. Therefore, theoretically, these measurements may not be useful for prediction of fracture risk at clinically relevant sites. However, previous retrospective studies found that radiogrammetry measurements of the metacarpals and radius are lower in individuals with prevalent vertebral and wrist fractures [9,13–16]. In addition, both retrospective and prospective studies demonstrated an association between BMD of the phalanges computed using radiographic absorptiometry and fracture risk [38–40]. Thus, these previous studies, taken together with the results of the current study, confirm that BMD measurements of the hand and wrist, including those derived from automated digital X-ray radiogrammetry, traditional radiogrammetry, radiographic absorptiometry and bone densitometry, are associated with fracture risk at the wrist, spine and hip.

Due to the protocol for acquisition of the radiographs in the SOF, DXR-BMD was computed using the second through fourth metacarpals, instead of being computed from the metacarpals, radius and ulna, as is done with the initial version of the Pronosco X-posure System [8]. However, in a retrospective analysis Black and colleagues [20] reported that the association with fracture risk for DXR-BMD computed from the metacarpals was similar to that for DXR-BMD computed from the metacarpals, radius and ulna. In addition, re-evaluation of radiographs acquired in their study showed that DXR-BMD computed from the metacarpals was strongly correlated with DXR-BMD computed from the metacarpals, radius and ulna (r = 0.94, unpublished data). Thus, these data indicate that the results from the present study are also applicable to DXR-BMD measurements that are computed from the metacarpals, radius and ulna.

Another potential limitation of the study was the relatively short period of follow-up (4–5 years) for fractures. Thus, the ability of DXR-BMD to predict fractures over a longer time period is not known. However, Duppe and colleagues [41] have shown that a single forearm BMD measurement predicts fracture risk over a 25-year period. Although the predictive ability decreased slightly compared with a previous study in the same population with a follow-up period of 11–13 years, the associations with hip and vertebral fracture risk were still strong and significant. For example, among women aged 40–70 years at the initial BMD measurement, the relative risk associated with 1 SD decrease in forearm BMD was 1.66 for hip fractures and 1.79 for vertebral fractures. These data suggest that DXR-BMD measurements, since they are strongly correlated with forearm BMD, are likely to predict fracture risk over a longer time period than was assessed in the present study.

In summary, in a prospective evaluation of elderly women we found that DXR-BMD predicts wrist, hip and vertebral fracture risk as well as BMD measurements at the forearm, heel and spine. These data provide strong evidence for the use of DXR-BMD as an alternative to peripheral dual-energy and single-energy X-ray absorptiometry measurements for prediction of fracture risk, and suggest that DXR-BMD may be useful for prediction of fracture risk in clinical settings where hip BMD is not available.

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