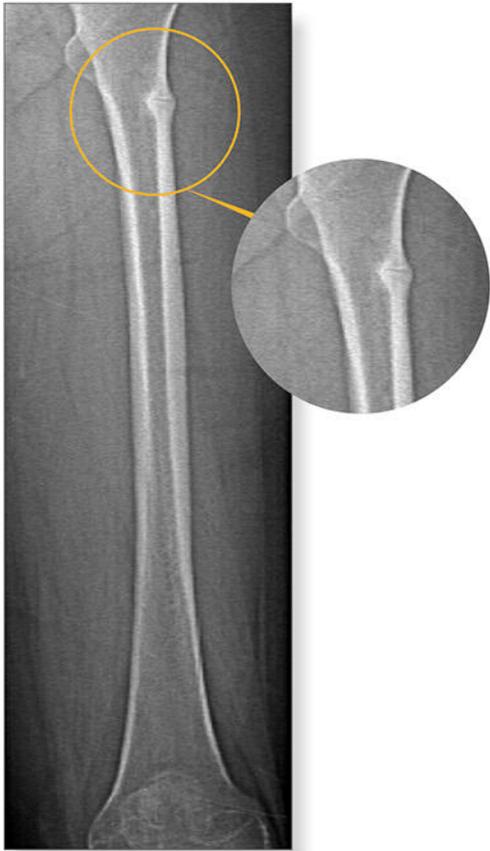


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Adding Lateral Spine Imaging for Vertebral Fractures to Densitometric Screening: Improving Ascertainment of Patients at High Risk of Incident Osteoporotic Fractures

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ABSTRACT

The current diagnosis of osteoporosis is limited to a T -score ≤ -2.5 . However, asymptomatic vertebral fractures (VF) are known to predict a high risk of subsequent fractures and pharmaceutical intervention is known to reduce future fracture risk in these individuals. In a prospective, population-based cohort of ambulant older women, we sought to evaluate the role of VF detection by screening densitometric lateral spine imaging (LSI) for VF at time of bone density testing to the effect on the magnitude of fracture risk. A total of 1084 women (mean age 75 years \pm SD 3 years) had baseline LSI that identified 100 (9%) women with VFs and 89 (8%) with femoral neck (FN) T -score osteoporosis ≤ -2.5 . Follow-up identified incident clinical spine fracture in 73 (7%), 305 (28%) with any fracture-related hospitalization, and 121 (11%) with a hip fracture-related hospitalization. Compared with those without baseline VF, in those with baseline VF, relative risk (RR) for incident clinical spine, hip, and any fracture were 3.46 (95% confidence interval [CI] 2.14–5.60, $p < 0.001$); 1.72 (95% CI 1.09–2.71, $p = 0.02$), and 1.4 (95% CI 1.07–1.84, $p = 0.02$), respectively. In 675 (62%) of women with femoral neck osteopenia (T -score < -1 to > -2.5), 61 (9%) also had a VF. Compared with those without baseline VF, RR for any incident fragility fractures and fractures at spine and hip in those with baseline VF were 1.6 (95% CI 1.2–2.1, $p < 0.01$), 3.9 (95% CI 2.2–6.9, $p < 0.01$), and 1.6 (95% CI 0.9–2.8, $p = 0.10$), respectively. On basis of the prognosis, older women with LSI VF with osteopenia should be diagnosed with osteoporosis and should be considered for pharmaceutical intervention. © 2018 American Society for Bone and Mineral Research.

KEY WORDS: ABMD; DXA; FRACTURE IDENTIFICATION; LATERAL SPINE IMAGING; VERTEBRAL FRACTURE ASSESSMENT

Introduction

Evaluation of fracture risk is central to deciding who will benefit from pharmacological interventions to reduce the risk of future fracture.⁽¹⁾ Screening using dual-energy X-ray absorptiometry (DXA) is currently one of the most common methods to evaluate fracture risk in a number of countries such as Australia, Canada, and the United States. However, the majority of older individuals who experience clinical

fractures do not have osteoporosis as defined by areal bone mineral density (aBMD) T -score of ≤ -2.5 .⁽²⁾

Spine fractures identified on standard lateral spine radiographs in aging populations strongly predict subsequent fractures and are themselves associated with increased morbidity and mortality.^(3,4) Furthermore, many randomized controlled trials (RCTs) have identified pharmacological interventions that substantially reduce fracture risk in these individuals.^(5–9) However, in clinical practice, as

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many as three-quarters of individuals with vertebral fractures do not present with symptoms sufficiently prominent to prompt spine imaging and establishment of a clinical diagnosis.^(10,11)

Compared with standard lateral spine radiographs, densitometric lateral spine imaging (LSI) has been shown to identify moderate to severe prevalent vertebral fractures accurately.^(12–14) Densitometric LSI is preferable to radiographic LSI for screening purposes because it is less expensive than standard lateral spine radiographs, exposes patients to substantially lower radiation,⁽¹⁵⁾ and can be undertaken on the same machine at the time of aBMD testing. This should allow identification of prevalent vertebral fractures to be incorporated into bone density measurement to improve estimates of patients' risk of subsequent fractures and to identify appropriate candidates for pharmacological therapy.⁽¹⁶⁾ Currently, lateral spine imaging at the time of bone density testing is rarely undertaken and is considered experimental by some third-party payers, in a large part because of the paucity of data from prospective studies demonstrating that prevalent vertebral fractures identified on densitometric LSI predict future fractures, independent of aBMD.⁽¹⁷⁾

Thus, our objectives were to assess the predictive value of vertebral fracture captured by densitometric LSI at the time of aBMD measurement using the same bone density machine on incident clinical vertebral fractures and low-trauma fracture hospitalization risk, focusing on patients with osteopenia defined by femoral neck *T*-score <−1 to >−2.5.

Materials and Methods

At baseline, written informed consents were obtained from all participants for the study and follow-up of electronic health records. The Human Ethics Committee of the University of Western Australia approved the study protocol and consent form (approval number 05/06/004/H50). The Human Research Ethics Committee of the Western Australian Department of Health (DOHWA HREC) also approved the data linkage study (approval number #2009/24). Because for the first 5 years of the study participants were randomized to calcium or placebo, the study was registered in the Australian New Zealand Clinical Trials Registry ACTRN12615000750583.

Study population

Participants were recruited in 1998 to a prospective, randomized controlled trial of oral calcium supplements to prevent osteoporotic fractures, the Calcium Intake Fracture Outcome Study (CAIFOS).⁽¹⁸⁾ Women were recruited from the Western Australian (WA) general population of women aged 70 years and older by mail using the Electoral Roll, which is maintained for all Australian citizens enrolled to vote in WA.⁽¹⁸⁾ Of 5586 women approached, 1500 women enrolled in the study. All participants were ambulant with an expected survival beyond 5 years and were not receiving any medication including hormone-replacement therapy known to affect bone metabolism. Baseline disease burden and use of non-bone active medications were comparable between these participants and the general population of similar age, although these participants were more likely to be from higher socioeconomic groups.⁽¹⁸⁾ In the first 5 years of the study, participants received either 1.2 g of elemental calcium as calcium carbonate daily or a matching placebo, whereas a substudy of the original 1500 ($n = 39$)

received calcium plus 1000 IU of vitamin D2 daily.⁽¹⁹⁾ Participants were invited to continue to participate in study follow-up, without intervention, for a subsequent 10 years, entitled the Perth Longitudinal Study of Aging in Women (PLSAW).⁽²⁰⁾ In 1998 or 1999, as part of bone structural assessment, 1140 participants had lateral spine imaging of which 1084 images were readable for prevalent vertebral fractures (95%). Of these individuals, 1057 also had femoral neck aBMD reports available.

Baseline data

Participants provided their previous medical history and current medications, verified by their general practitioner (GP) where possible. Prior osteoporotic fracture was defined as a participant-reported fracture after age 50 years that occurred with minimal trauma, ie, falling from a height of 1 m or less, but excluded fractures of the face, skull, fingers, or toes. Weight was assessed using digital scales with participants wearing light clothes and no shoes. Height was assessed using a stadiometer and the body mass index was calculated in kg/m². Femoral neck bone mineral density (FN aBMD) was measured by DXA using the same Hologic Acclaim 4500A fan beam densitometer that was used to capture the lateral spine images (Hologic Corp, Waltham, MA, USA) in 1998 or 1999 in 1057 of 1084 women (98%). The coefficient of variation at the femoral neck was 1.4% in our laboratory.

Densitometric lateral spine imaging

Digitally enhanced lateral single-energy images of the thoracolumbar spine were collected using a Hologic 4500A machine (Hologic) in a randomly selected subgroup of the original cohort in 1998 (18%) and 1999 (82%). A single experienced investigator (JTS) read all images and scored vertebral fractures using the Genant semiquantitative method that scores fractures on a variety of imaging features including the degree of compression.⁽²¹⁾ The scoring system was modified in that grade 1 fractures were considered fractures only if there was clear endplate depression or cortical discontinuity, as described in a prior publication.⁽²²⁾ This investigator, who was blinded to all study participant characteristics, has previously been documented to ascertain vertebral fractures on both densitometric and standard radiographic lateral spine images with high reliability.^(22,23)

Prospective fracture events

Hip and all osteoporotic fracture-related hospitalizations over a 14.5-year period from 1998 to 2013 were identified using the Hospital Morbidity Data Collection (HMDC), linked via the Western Australian Data Linkage System (WADLS). This system allows complete identification of all admissions and discharge events from all hospitals in Western Australia; patients of this age rarely leave the state. Diagnosis codes were defined using the International Classification of Diseases, Injuries, and Causes of Death: Clinical Modification (ICD-9-CM) codes 1998–1999⁽²⁴⁾ and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM) for 1999–2013.⁽²⁵⁾ Codes used for identification were S02-S92, M80, T02, T08, T10, T12, and T14.2. Fractures of the face (S02.2–S02.6), fingers (S62.5–S62.7), and toes (S92.4–S92.5) and traumatic fractures caused by motor vehicle accidents were excluded (external cause of injury codes V00–V99).

Because vertebral fractures rarely result in hospitalizations, minimally traumatic symptomatic vertebral fractures were identified from patient-completed adverse event diaries. To identify adverse events, participants completed a paper-based diary in which they listed the date and reason for attendance by a health care professional at the time of the attendance. Every 4 months for the first 5 years of the study and every 6 months during the subsequent 10 years of follow-up, adverse event diaries were mailed to our study center and the data entered into an electronic database. If a spine fracture was identified at the time of data entry, further verification from the radiological report and/or GP record was requested. If these confirmed the report, a new clinical spine fracture event was recorded.

Statistical analysis

Baseline data are presented as either mean \pm SD for continuous variables with a normal distribution, median, and interquartile range (IQR) for continuous variables with a non-normal distribution, or number and percent (%) for categorical variables. The unadjusted relative risk (RR) of incident fractures in women with baseline densitometric LSI vertebral fracture (VF) compared with those without was reported using differences in proportion in the two populations. Cox regression analyses adjusted for age, treatment assignment (calcium or placebo), and FN aBMD were also undertaken. Cox proportional hazards assumptions were tested with the Schoenfeld residuals, and no violations were detected. For self-reported analysis, data were censored at date of withdrawal from the clinical follow-up or death. For hospital discharge fracture data, the Hospital Morbidity Data Collection provided event information for all women who remained in Western Australia and was censored at the date of death, supplied by the Data Linkage Branch.

Although assessing improvements to risk prediction compared with age and aBMD was not the primary goal of this study, we undertook area under the curve–receiver operating characteristic (AUC-ROC) analysis, category-free net reclassification improvement (cfNRI), and integrated discrimination improvement (IDI). The cfNRI counts the direction of the change

in risk for each participant (event, no event, and overall). The IDI reflects the extent of the change in risk and not only the direction. For both net reclassification improvement (NRI) and integrated discrimination improvement, we used bootstrapping ($n = 1000$) to report 95% CI for events, non-events, and overall as opposed to p values⁽²⁶⁾ using the *incrisk* module in Stata. Hosmer–Lemeshow tests were undertaken to determine how well the predicted models fit the observed incident fractures (calibration). Secondary analyses to investigate the potential relevance of the competing risk of death were also undertaken using a stratified proportional subdistribution hazard model.⁽²⁷⁾ All analyses were undertaken using IBM SPSS Statistics version 22 (2012, IBM Corp, Armonk, NY, USA), Stata (version 13, StataCorp LP, College Station, TX, USA), or SAS (version 9.4, SAS Institute Inc., Cary, NC, USA).

Results

Baseline data

From the cohort of 1500 women, 1084 (70%) had lateral spine images captured in 1998 or 1999 (Fig. 1). The baseline characteristics of the 416 women who did not have LSI were similar to those with LSI except being an average of 0.8 year older (Supplemental Table S1).

The proportion of interpretable vertebrae for fracture from the lateral spine images varied from 83% at T₄ to 99% to 100% from T₉ to L₄. Of the 100 women with densitometric LSI vertebral fractures, 39 women had grade I (mild), 48 women grade II (moderate), and 13 women grade III (severe) fractures; 82 women had 1 fractured vertebra, 15 had 2 fractured vertebrae, and 3 had 3 fractured vertebrae. The 293 (27%) women who reported a fracture between the ages of 50 years and entry into the study were more likely to have a prevalent vertebral fracture and had lower femoral neck aBMD (Table 1). Nine women reported a prior history of vertebral fracture before baseline, of which 5 reports were incorrect, and 4 reports were confirmed on the lateral spine images; the remaining 96 women (96%) with prevalent VF were not aware of having had a vertebral fracture.

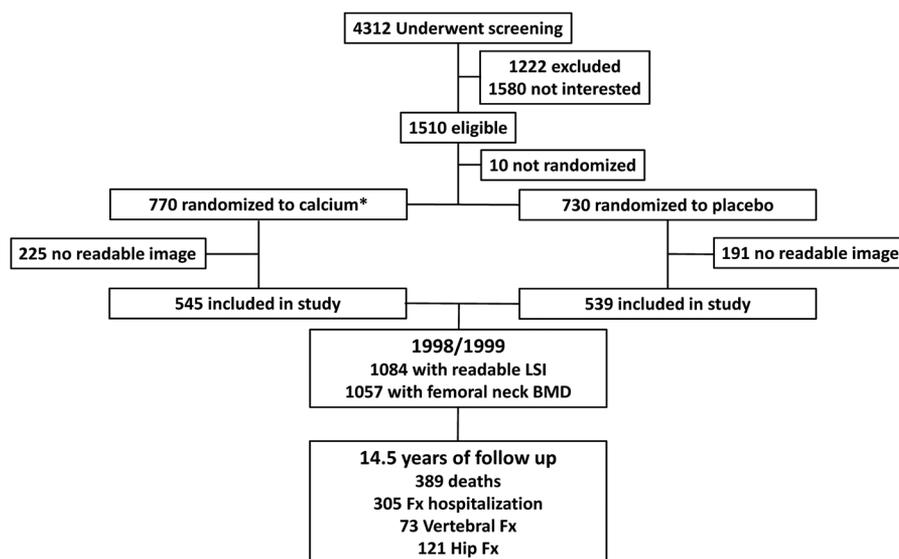


Fig. 1. Flow diagram of study. LSI = lateral spine imaging; Fx = fracture.

Table 1. Baseline Characteristics and 14.5-Year Fracture Outcomes in Study Participants by Grade of Vertebral Fractures at Baseline

	No VF <i>n</i> = 984 (90.8%)	Baseline VF <i>n</i> = 100 (9.2%)	Grade 1 only <i>n</i> = 39 (3.6%)	Grade 2 or more <i>n</i> = 61 (5.6%)
Baseline data				
Age (years)	74.9 ± 2.6	75.1 ± 2.7	74.6 ± 2.7	75.5 ± 2.7
Body mass index (kg/m ²)	27.2 ± 4.5	27.1 ± 4.2	27.5 ± 4.0	26.8 ± 4.3
Randomized to calcium supplements, <i>n</i> (%)	493 (50.1)	52 (52.0)	18 (46.2)	34 (55.7)
Femoral neck aBMD (g/cm ²)	0.691 ± 0.102	0.667 ± 0.116^a	0.676 ± 0.102	0.661 ± 0.125
Femoral neck T-score (units)	−1.39 ± 0.85	−1.59 ± 0.97^a	−1.51 ± 0.85	−1.64 ± 1.03
Self-reported fracture history at baseline				
Any low-trauma fracture, yes, <i>n</i> (%)	248 (25.2)	45 (45.0)^a	15 (38.5)^b	30 (49.2)^b
Vertebral fracture, yes, <i>n</i> (%)	5 (0.5)	4 (4.0)^a	0 (0)	4 (6.6)
Incident clinical spine fracture, <i>n</i> = 73				
Vertebral fracture, yes, <i>n</i> (%)	54 (5.5)	19 (19.0)^a	3 (7.7)^b	16 (26.2)^b
HR for vertebral fracture	1 (ref.)	3.81 (2.26–6.43)^c	1.49 (0.47–4.78)	5.40 (3.08–9.46)^c
Incident hip fracture hospitalization, <i>n</i> = 121				
Hip fracture, yes, <i>n</i> (%)	103 (10.5)	18 (18.0)^a	6 (15.4)^b	12 (19.7)^b
HR for hip fracture	1 (ref.)	1.77 (1.07–2.92)^c	1.50 (0.66–3.41)	1.95 (1.07–3.55)^c
Incident low-trauma fracture hospitalization, <i>n</i> = 305				
Any fracture, yes, <i>n</i> (%)	267 (27.1)	38 (38.0)^a	12 (30.8)^b	26 (42.6)^b
HR for any fracture	1 (ref.)	1.54 (1.09–2.16)^c	1.17 (0.66–2.09)	1.79 (1.20–2.68)^c

Data expressed as mean ± SD or no. (%).

aBMD = areal bone mineral density; ref. = referent; VF = vertebral fracture; HR = hazard ratio.

^a*p* < 0.05 compared with no vertebral fracture by chi-square test, Fisher's exact test, or Student's *t* test where appropriate.

^b*p* < 0.05 compared with no vertebral fracture by Mantel-Haenszel test of trend (dichotomous) or Tukey's post hoc test (continuous) where appropriate.

^c*p* < 0.05 by Cox regression compared with referent category adjusted for age and calcium/placebo treatment.

Association with incident fractures in the whole cohort (Table 1)

During the study, 73 women sustained a clinical spine fracture of which 19 (19.0%) occurred in the 100 women with baseline VF and 54 (5.5%) occurred in the 984 without baseline VF. Thus women with baseline VF had a relative risk for incident clinical spine fracture of 3.46 (95% CI 2.14–5.60, *p* < 0.001). The relevant hazard ratios (HR) adjusted for age and calcium or placebo treatment are shown in Table 1.

During the study, 121 women experienced a hip fracture hospitalization of which 18 (18.0%) occurred in those with baseline VF and 103 (5.5%) occurred in those without baseline VF. Compared with those without VF, those with VF had a RR of 1.72 (95% CI 1.09–2.71, *p* = 0.02) for hip fractures. The relevant HRs adjusted for age and calcium or placebo treatment are shown in Table 1.

During the study, 305 women sustained a fracture-related hospitalization of which 38 (38.0%) occurred in those with baseline VF and 267 (5.5%) occurred in those without baseline VF. Compared with those without VF, women with baseline VF had a RR for fracture hospitalizations of 1.4 (95% CI 1.07–1.84, *p* = 0.02). The relevant HRs adjusted for age and calcium or placebo treatment are shown in Table 1.

For all incident fracture outcomes, the effect size was larger in participants with grade 2 VFs compared with the less frequent grade 1 VF (grade 1, 39%; grade 2, 61%). However, in absolute terms, the rate of fractures in grade 1 VF participants was higher than in individuals with no baseline VF.

A competing risk of death analysis is shown in Supplemental Table S2 in which the association between prevalent LSI VFs and incident fractures was analyzed using subdistribution hazards models. The results were similar to the HR risks shown in Table 1.

Sensitivity and specificity for incident fractures in the whole cohort

Osteoporosis (T-score less than −2.5) had a sensitivity for clinical vertebral fractures of 19.7% (95% CI 11.2–30.9%) and a specificity of 92.4% (95% CI 90.6–94.0%). Prevalent VF had a similar sensitivity for incident clinical vertebral fractures of 26.0% (95% CI 16.5–37.6%) and a specificity of 92.0% (95% CI 90.1–93.6%). The combination of osteoporosis (T-score less than −2.5) or prevalent VF had a sensitivity for clinical vertebral fractures of 39.4% (95% CI 28.0–51.8%) and a specificity of 85.1% (95% CI 82.8–87.3%).

Osteoporosis (T-score less than −2.5) had a sensitivity for fracture hospitalization of 13.2% (95% CI 9.6–17.6%) and a specificity of 93.4% (95% CI 91.4–95.1%). Prevalent VF had a similar sensitivity for fracture hospitalization of 12.5% (95% CI 9.0–16.7%) and a specificity of 92.0% (95% CI 89.9–93.8%). The combination of osteoporosis or prevalent VF had a sensitivity for fracture hospitalization of 24.0% (95% CI 19.2–29.3%) and a specificity of 86.4% (95% CI 83.8–88.7%).

Incident fracture data by baseline aBMD

A prespecified analysis to examine the association between prevalent baseline LSI-detected VF with fracture outcomes, stratified by baseline T-score categories, was undertaken (Fig. 2). Importantly, compared with women with osteopenia but without LSI fracture, those with osteopenia and LSI fracture sustained a significantly higher absolute risk of clinical spine and all osteoporotic fractures with risk similar to older women with osteoporosis FN T-score < −2.5. A more detailed analysis is presented in Table 2. In the 27.7% of participants with FN T-score ≥ −1, the presence or absence of baseline VF did not alter the

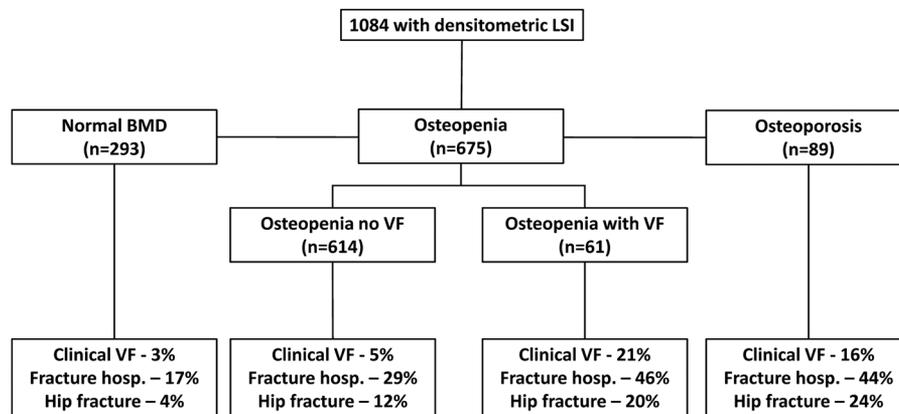


Fig. 2. Relationship between baseline femoral neck bone mineral density category and lateral spine imaging (LSI) determined vertebral fractures (VF).

relatively low fracture risk of the whole group. However, in the 63.8% of participants with osteopenia (FN T -score < -1 to > -2.5), compared with those without prevalent VF, individuals with LSI VF had substantially higher RRs for clinical vertebral fractures and all fracture hospitalization (RR = 3.9, 95% CI 2.2–6.9, $p < 0.01$; RR = 1.6, CI 1.2–2.1, $p = 0.01$, respectively) but not hip fracture hospitalization (RR = 1.61, 95% CI 0.93–2.79, $p = 0.10$). The 8.4% of women with FN T -score ≤ -2.5 were already at higher risk of fracture than the other two categories. If they also had evidence of a baseline spine fracture, they had a higher risk of subsequent clinical spine fracture compared with those without a spinal fracture (RR = 2.98, 95% CI 1.17–7.56, $p = 0.03$) but not for other fracture categories. Adjusted Cox proportional hazards regression analyses for the whole cohort, women with normal T -scores, and osteoporotic women are presented in Supplemental Table S3. The addition of VF to age, treatment, and FN aBMD in risk prediction models suggested VF improved risk prediction for clinical spine fractures but not fracture

hospitalizations compared with age, treatment, and femoral neck T -scores (continuous) (Supplemental Table S4).

Osteopenic women

The HR analysis is shown in Table 3. Adjusting for age and therapy for the first 5 years with or without the adjustment for baseline FN aBMD identified similar risks to the RR calculations that were significant for clinical spine fracture and all fracture hospitalization categories but not hip fracture hospitalization. The HRs for fracture were substantially higher in the two-thirds of participants with grade 2 or higher baseline LSI VFs.

Sensitivity and specificity for incident fractures in osteopenic women

Prevalent VF had a sensitivity for clinical vertebral fractures of 27.7% (95% CI 15.6–42.6%) and a specificity of 92.4% (95% CI 90.0–94.3%). Prevalent VF had a sensitivity for fracture

Table 2. Number of Incident Self-Reported Fractures and Fracture Hospitalizations Over 14.5 Years Categorized by Baseline FN T -Scores and Presence and Grade of LSI Baseline Vertebral Fractures in 1057 Participants With FN aBMD Data

14.5-Year incident fracture outcome	No baseline VF	Baseline VF	Grade 1 only	Grade 2 or more
Participants' T -score ≥ -1 , $n = 293$ (27.7% of total cohort)				
No. (%) of participants' T -score ≥ -1	271 (92.5)	22 (7.5)	11 (3.8)	11 (3.8)
Clinical spine fracture, yes, n (%)	9 (3.3)	1 (4.5)	0 (0.0)	1 (9.1)
Hip fracture hospitalization, yes, n (%)	11 (4.1)	1 (4.5)	1 (9.1)	0 (0.0)
Low-trauma fracture hospitalization, yes, n (%)	47 (17.3)	3 (13.6)	1 (9.1)	2 (18.2)
Participants' T -score < -1 to > -2.5 , $n = 675$ (63.8% of total cohort)				
No. (%) of participants' T -score < -1 to > -2.5	614 (91.0)	61 (9.0)	21 (3.1)	40 (5.9)
Clinical spine fracture, yes, n (%)	34 (5.5)	13 (21.3)^a	2 (9.5)^b	11 (27.5)^b
Hip fracture hospitalization, yes, n (%)	75 (12.2)	12 (19.7)	5 (23.8)	7 (17.5)
Low-trauma fracture hospitalization, yes, n (%)	178 (29.0)	28 (45.9)^a	10 (47.6)^b	18 (45.0)^b
Participants' T -score ≤ -2.5 , $n = 89$ (8.4% of total cohort)				
No. (%) of participants' T -score ≤ -2.5	75 (84.3)	14 (15.7)	5 (5.6)	9 (10.1)
Clinical spine fracture, yes, n (%)	9 (12.0)	5 (35.7)^a	1 (20.0)^b	4 (44.4)^b
Hip fracture hospitalization, yes, n (%)	16 (21.3)	5 (35.7)	0 (0.0)	5 (55.6)
Low-trauma fracture hospitalization, yes, n (%)	33 (44.0)	6 (42.9)	0 (0.0)	6 (66.7)

FN = femoral neck; LSI = lateral spine imaging; aBMD = areal bone mineral density; VF = vertebral fracture. Lateral spine images taken in 1998 or 1999.

^a $p < 0.05$ compared with no vertebral fracture by chi-square test or Fisher's exact test where appropriate.

^b $p < 0.05$ compared with no vertebral fracture by Mantel-Haenszel test of trend (dichotomous).

Table 3. Fracture Outcomes Over 14.5 Years for Women ($n = 675$) With Osteopenia T -score < -1 to > -2.5

	No VF $n = 614$ (91%)	Baseline VF $n = 61$ (9.0%)	Grade 1 only $n = 21$ (3.1%)	Grade 2 or more $n = 40$ (5.9%)
Clinical spine fracture				
HR for vertebral fracture (age, treatment adj.)	1 (ref.)	4.37 (2.30–8.28)^a	1.82 (0.44–7.60)	5.85 (2.96–11.56)^a
HR for vertebral fracture (age, treatment, aBMD adj.)	1 (ref.)	4.14 (2.17–7.89)^a	1.75 (0.42–7.34)	5.50 (2.77–10.93)^a
Hip fracture hospitalization				
HR for hip fracture (age, treatment adj.)	1 (ref.)	1.64 (0.89–3.02)	1.97 (0.80–4.88)	1.46 (0.67–3.17)
HR for hip fracture (age, treatment, aBMD adj.)	1 (ref.)	1.53 (0.83–2.84)	1.92 (0.78–4.77)	1.34 (0.61–2.92)
Low-trauma fracture hospitalization				
HR for any fracture (age, treatment adj.)	1 (ref.)	1.86 (1.25–2.78)^a	1.83 (0.97–3.46)	1.88 (1.16–3.06)^a
HR for any fracture (age, treatment, aBMD adj.)	1 (ref.)	1.54 (1.09–2.16)^a	1.76 (0.93–3.33)	1.67 (1.02–2.73)^a

Data expressed as mean \pm SD or no. (%).

VF = vertebral fracture; HR = hazard ratio; ref. = referent; aBMD = areal bone mineral density.

^a $p < 0.05$ by Cox regression compared with referent category with covariates as listed.

hospitalization of 13.6% (95% CI 9.2–19.0%) and a specificity of 93.0% (95% CI 90.3–95.1%).

The addition of VF or grade 2 or worse VF to age, treatment, and FN aBMD in risk prediction models suggested VF improved risk prediction for clinical spine fractures but not fracture hospitalizations compared with age, treatment, and femoral neck T -scores (continuous) (Supplemental Table S4).

Discussion

In this study, elderly women with VFs identified on densitometric lateral spine images at baseline had up to a 3.8 times increased HR for incident fractures, particularly incident clinical spine fractures, that have been shown in other studies to be associated with substantial morbidity, pain, loss of mobility comparable to hip fractures, and increased mortality.^(3,4,28,29) Second, identifying VF using a bone density machine categorized women at higher risk of clinical spine fracture and fracture hospitalizations independently of aBMD. This was particularly evident in women with osteopenia (T -score < -1 to > -2.5) who might not be considered candidates for pharmacologic fracture prevention therapy. Third, adding VF to BMD T -score ≤ -2.5 substantially improved sensitivity by identifying women who would suffer a clinical spine fracture or fracture hospitalizations with little change to specificity. Using formal clinical prediction methods, the addition of VF to hip BMD improved the ROC, NRI, and IDI for future spine fracture but not for other fractures.

This study also confirmed that the magnitude of the fracture risk increased with the grade of LSI VF as previously shown by others using spine radiography.⁽³⁰⁾ These results extend the findings of previous studies by showing the robustness of the association between vertebral fracture detected on densitometric LSI and incident clinical spine fractures and fracture-related hospitalizations, even after adjustment for the competing risk of mortality.

Previous studies have identified spine X-ray as a way to detect prevalent vertebral fractures that improve prediction of future fractures.^(31–33) In a previous study of a low bone density population at high risk of fracture, the addition of baseline VF detection by X-ray-based LSI to aBMD and clinical risk factors improved fracture prediction.⁽³⁴⁾ McCloskey and colleagues also

report, in the setting of a randomized secondary prevention clinical trial of the bisphosphonate clodronate versus placebo, that those with one or more prevalent vertebral fractures on densitometric LSI had increased HRs for incident clinical fractures at any skeletal sites, independent of age, treatment, and femoral neck aBMD.⁽³⁵⁾ Notably, the strength of the associations with all incident fractures and clinical spine fractures reported in the McCloskey study and our data were as strong or nearly as strong as the associations shown in other large observational cohort studies of vertebral fractures identified on standard lateral spine X-rays and incident clinical and vertebral fractures.^(31–33) These findings suggest that this technology is useful to identify women at high fracture risk and stratification to guide treatment decisions, particularly in those without osteoporosis by BMD criteria.

There are several factors that need to be considered in generalizing these data. First, the study was in women older than 70 years where the prospective risk of incident fractures is higher than in younger women. Second, the 9.2% prevalence of vertebral fracture in this study was slightly lower than those identified in other population-based studies where the prevalence of vertebral fracture among women age 65 years and older is 10% to 15%.^(35–37) However, the prevalence is very similar to the 10.5% (95% CI 7.1–14.8) recently reported by Cosman and colleagues⁽³⁸⁾ in the NHANES 2013–2014 study with similar methods of detection of prevalent VF. Third, baseline LSI was not assessed in almost one-third of the recruited participants and so the risk of bias cannot be completely excluded, even though the characteristics of women without lateral spine images were similar to those included in the study. Fourth, lateral spine imaging using densitometers, even with newer technology, generally has poorer image quality of vertebrae superior to T₇ vertebrae than standard radiographs and is less accurate at detection of mild vertebral fractures. However, fractures superior to T₇ are relatively uncommon in older women, and the predictive value of mild grade 1 prevalent vertebral fractures is much weaker compared with moderate to severe prevalent vertebral fractures.⁽³⁹⁾ Fifth, although the presence of LSI VFs increased the RR for hip fracture prediction to RR = 1.6 (95% CI 1.2–2.1) in osteopenic patients, this did not reach conventional levels of significance possibly because of the relatively small

sample size. In comparison, the SOF study of 9704 women reported a similar bone density adjusted RR for hip fractures in those with prevalent vertebral fractures of 1.86 (95% CI 1.53–2.26, $p < 0.05$).⁽³⁴⁾ Sixth, although no effect of calcium supplementation treatment was identified, because the first 5 years of the study was a RCT of calcium supplements to prevent fractures, we cannot exclude a treatment effect between prevalent vertebral fracture and subsequent fractures. However, this is unlikely because the results of the RCT were null and we adjusted for treatment in all analyses. Finally, because we do not have the X-rays that were used to identify clinical spine fractures, we cannot rule out that these were existing spine fractures rather than incident spine fractures.

The strengths of this study include the population-based recruitment of the participants who are thus representative of older female populations often invited to undertake screening bone densitometry. Second, the assessment of prevalent vertebral fractures was undertaken by one experienced investigator (JTS) blinded to the study outcomes from lateral spine images acquired using a single-energy scanning densitometer with an effective radiation of 5 μ Sv dose, approximately 120 times lower than a lateral digital X-ray.⁽¹⁵⁾ Third, the study utilized two separate methods of fracture detection: 1) verified spine fractures identified from patient diaries provided to the investigators at regular intervals (selected because these fractures do not always result in hospitalization), and 2) complete ascertainment of fracture hospitalization records independent of self-report that may reflect the true utility of lateral spine imaging by removing the risks of recall and retention bias or loss to follow-up. Fourth, the study design involved a long and complete follow-up allowing identification of individuals at increased risk for many years. Finally, randomized controlled trials of currently available pharmacologic fracture prevention agents have shown that these therapies reduce subsequent fractures among women who either have a femoral neck aBMD T -score ≤ -2.5 or have a prevalent vertebral fracture with a femoral neck aBMD T -score of < -1.0 or -1.5 .^(5–9) Thus, there is strong evidence that once identified, these individuals can reduce their risk with the use of pharmaceutical therapy.

In conclusion, at the time of bone density measurement identifying women with prevalent vertebral fractures using low-radiation-dose lateral spine imaging further identifies individuals without osteoporosis who are at high fracture risk. Because these women can have their fracture risk reduced with pharmaceutical therapy, addition of this screening test to aBMD screening may improve clinical management in this age group.

Disclosures

KEW is an employee of Hologic, Inc. All time spent on this work was part of his employment. The other authors report no conflict of interest in this work.

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