ORIGINAL ARTICLE

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Grade 1 Vertebral Fractures Identified by Densitometric Lateral Spine Imaging Predict Incident Major Osteoporotic Fracture Independently of Clinical Risk Factors and Bone Mineral Density in Older Women

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ABSTRACT

Because prevalent vertebral fracture (VF) is a strong predictor of future fractures, they are important to identify in clinical practice as osteoporosis medications are effective and can be used to reduce fracture risk in postmenopausal women with VF. Lateral spine imaging (LSI) with dual-energy X-ray absorptiometry (DXA) can be used to diagnose VFs accurately but is not widespread in clinical practice. The prognostic value of grade 1 (20% to 25% compression) VFs diagnosed by LSI with DXA has been insufficiently studied. The aim of this study was to determine if grade 1 VF is associated with incident fracture in older women. Sahlgrenska University Hospital Prospective Evaluation of Risk of Bone Fractures (SUPERB) is a population-based study of 3028 older women from Gothenburg, Sweden. Included women were 75 to 80 years of age at baseline, answered questionnaires, and were scanned with DXA (Discovery A, Hologic, Waltham, MA, USA). LSI was used to diagnose VFs, which were classified using the Genant semiquantitative method. Cox regression models were used to estimate the association between VFs at baseline and X-ray–verified incident fractures, with adjustment for confounders. Women with a grade 1 VF (n = 264) or a grade 2–3 VF (n = 349) were compared with women without any fracture (n = 1482). During 3.6 years (median, interquartile range [IQR] 1.5 years) of follow-up, 260 women had any incident fracture and 213 a major osteoporotic fracture (MOF). Women with only grade 1 VF had increased risk of any fracture (hazard ratio [HR] = 1.67; 95% confidence interval [CI] 1.18–2.36) and MOF (HR = 1.86; 95% CI 1.28–2.72). For MOF, this association remained after adjustment for clinical risk factors and femoral neck bone mineral density (BMD). In conclusion, grade 1 VFs were associated with incident MOF, also after adjustment for clinical risk factors and BMD, indicating that all VF identified by DXA should be considered in the evaluation of fracture risk in older women. © 2020 The Authors. *Journal of Bone and Mineral Research* published by American Society for Bone and Mineral Research..

KEY WORDS: MILD VERTEBRAL FRACTURE; VERTEBRAL FRACTURE ASSESSMENT; DXA; INCIDENT FRACTURE; OLDER WOMEN

Introduction

It is well known that the prevalence of any prior fracture is a predictor of future fractures,[1–5] independently of bone mineral density (BMD).[6] Vertebral fracture (VF) is the most common osteoporotic fracture[7] and one of the strongest predictors for sustaining a new fragility fracture, particularly new VFs.[2,4,5] Osteoporosis medications are particularly effective in reducing the risk of VFs in postmenopausal women, and it is therefore of utmost importance that VFs come to clinical attention.[8,9] Spine imaging is required for the diagnosis of VF and the clinical challenge is to identify and diagnose the asymptomatic two-thirds of

Received in original form November 26, 2019; revised form May 22, 2020; accepted June 7, 2020; accepted manuscript online June 7, 2020.
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Additional Supporting Information may be found in the online version of this article.
Journal of Bone and Mineral Research, Vol. 35, No. 10, October 2020, pp 1942–1951.
DOI: 10.1002/jbmr.4108

individuals with VF,[10] in addition to detect VFs not reported correctly by the radiologist.[11]

Vertebral fracture assessment (VFA) is a well-established and validated method for detecting VFs from lateral spine imaging (LSI) with dual-energy X-ray absorptiometry (DXA).[12,13] Despite lower radiation dose and cost in comparison to conventional radiography and that several studies advocate its utility,[14,15] VFA is still not widespread in clinical practice, which could be attributable to occasional poor image quality and additional cost of the examination. Studies have shown that VFA accurately identifies moderate and severe VFs,[13,15–19] but also mild fractures can be identified with good agreement to conventional radiography.[20,21] Some reports, using conventional radiography, conclude that greater severity of the prevalent VF is associated with a higher risk for vertebral and non-vertebral fracture,[22,23] whereas others have found that also mild prevalent VF found on radiographs predicts subsequent vertebral and non-vertebral fracture risk.[24–26]

Less is known on how well VFA-detected prevalent VF can predict subsequent fractures. The first study on this issue, a large high-quality study from 2008,[27] concluded that prevalent VFs identified by VFA predict subsequent clinical fractures independent of age, weight, and BMD; however, VFs were not graded according to severity. Recently, two studies confirmed that prevalent VFs, diagnosed by LSI by DXA, were associated with incident fractures, independently of clinical risk factors and BMD.[28,29] Methods used to diagnose VFs were the modified algorithm-based qualitative method (mABQ)[28] and the Genant semiquantitative method (GSQ)[29] and incident fractures were collected from health databases and diagnosis codes. The fracture risk increased with the severity of VFA-detected VF, but the predictive value of mild grade 1 fractures could not be verified.[29] Thus, the ability of grade 1 VFs identified by LSI by DXA to predict fracture has been insufficiently studied, and none of the previous studies have been conclusive. If VFA, a method performed in conjunction with DXA and with considerably lower radiation and cost than conventional radiography, can identify mild grade 1 VF and improve fracture prediction, use of VFA could confer considerable clinical value.

Therefore, the aim of the current study was to investigate if grade 1 VFs, identified by VFA, are associated with incident fractures in older women, independently of clinical risk factors and BMD.

Subjects and Methods

Subjects

The Sahlgrenska University Hospital Prospective Evaluation of Risk of Bone Fractures (SUPERB) study is a population-based study of 3028 older women from the greater Gothenburg area in Sweden, recruited via the Swedish population register between March 2013 and May 2016. Included women were 75 to 80 years of age at baseline and were followed from the baseline exam until May 24, 2018. They had to be ambulant (with or without walking aid), understand Swedish, and have at least one hip that could be evaluated for aBMD. The inclusion process has been described earlier.[30] The participants underwent DXA including VFA, and standardized self-reported questionnaires were used to collect data regarding lifestyle factors influencing the risk of osteoporosis and fractures, medical history, medication, and prior fracture.[31] Height and weight were measured twice, using standardized equipment, and the mean values were used in the analyses. A third measurement was performed if the body height differed more than 5 mm and the mean between the two most similar measurements was used. Of 3028 women, 90 (3%) women's VFA could not be analyzed because of poor image quality and 15 (0.5%) women were not able to undergo a lateral spine scan. All examinations took place at the Osteoporosis Clinic, Department of Geriatrics, Sahlgrenska University Hospital, Mölndal, Sweden. The ethical review board at the University of Gothenburg approved the study and all the study participants gave their written informed consent.

DXA

Detailed bone phenotyping was performed using the same DXA device for most participants ($n = 2995$) (Discovery A S/N 86491; Hologic, Waltham, MA, USA). Because of a temporary machine failure, a small proportion of women ($n = 33$) was measured with another Discovery A Hologic DXA device. A cross-calibration was performed between the two machines and has been reported elsewhere.[30] The areal BMD (aBMD) (g/cm^2) of the femoral neck (FN) and lumbar spine (LS) and trabecular bone score (TBS) were used in the analyses. Vertebrae that were fractured and/or contained osteosynthesis materials in the LS (L_1 to L_4) were excluded. The LS aBMD and TBS were calculated as the mean of L_1 to L_4 if at least two vertebrae were assessable. The coefficients of variation (CV) were for aBMD FN, aBMD LS, and TBS 1.3%, 0.7%, and 2.12%, respectively.

VFA

LSI at baseline, performed by DXA with the participant in the supine position, was used to diagnose VFs, using the software program Physician's Viewer (Hologic). With this software, the ability to visualize each vertebra is enhanced given the options to adjust the grayscale, brightness, magnification, and contrast of the image. After assessment of the anteroposterior LS image, the DXA operator marked the fourth lumbar vertebra. The lateral spine images were analyzed by the two examiners (LJ analyzed two-thirds and KR one-third of the 2923 scans) by manually placing six markers on each vertebra T_4 to L_4 visualizing the shape of each vertebral body.[32] The VFs were first classified according to the degree of compression as mild (grade 1), moderate (grade 2), or severe (grade 3) (height reduction 20% to 25%, >25% to 40%, and >40%, respectively) and then also according to shape, as wedge, biconcave, or crush, using the GSQ method.[33] Because of poor image quality, all vertebrae could not be visualized (T_4 to L_4). In the control group and in the group with grade 1 VF and grade 2–3 VF, 3225 (16.7%), 521 (15.2%), and 607 (15.3%) vertebrae, respectively, were not assessable. In total, 4353 (16.3%) vertebrae were not assessable, of which the majority (56%) were in the upper thoracic spine (T_4 to T_7). The presence of scoliosis was noted using the anteroposterior LS image and whole-body image, which was considered when markers were placed, in order to avoid falsely classifying a vertebral biconcave fracture. Differential diagnosis of other morphologic deformities of vertebral bodies included short vertebral height, degenerative scoliosis, Scheuermann's disease, Schmorl's nodes, and Cupid's bow deformities.[34] The most controversial and difficult differential diagnosis to consider is short vertebral height (SVH).[35] Criterion for SVH is reduction in one or more heights (anterior, middle, or posterior) of ≥15% to 20% of expected height without any endplate depression or cortical break.[36] SVH occurs with increasing degenerative changes. In SQ analysis of Genant, presence of a few vertebral morphologic changes should be checked for: lack of parallelism

of end plates, end plate depression, buckling of cortices, and loss of vertical continuity with adjacent vertebrae.[33] By using the GSQ method requiring 20% height reduction (for grade 1 VF) and investigating presence of the specified morphologic changes, SVH can be distinguished from grade 1 VF.

The risk of misclassifying SVH as a VF is at greatest around 20% height reduction. Recent studies have shown that SVH is not associated with low bone density.[35,36] Independent samples *t* test was used to examine if the women with grade 1 VF with height reduction just above 20% (20.0% to 22.5%) had lower BMD compared with women without fracture.

None of the assessors had any information regarding incident fracture status at the time of VFA analysis. The reproducibility was tested on 51 women on a vertebral level using ordinal variables (T_4 to L_4). Of these 51 women, 32 (63%) had no VF. In total, 552 vertebrae were assessable and 111 vertebrae were rated as not assessable (by one of the raters or both) and therefore excluded from the analysis. Of 552 assessable vertebrae, 543 (98.4%) were concordant in scoring. Of the 111 vertebrae that could not be assessed, 48 (43.2%) were concordant and 63 (56.8%) were not. Of the 63 vertebrae where examiners disagreed, 5 vertebrae were diagnosed as fractured by one of the examiners and not assessable by the other. In total, 46 (90.2%) participants were given the same overall category (maximum grade). Of the 5 women with discordant ascertainment, the error no fracture versus grade 1 VF and grade 1 VF versus grade 2–3 VF was found in 4 and 1 women, respectively. The intraobserver agreements for the two examiners were 98.9% and 97.8%, and kappa scores were 0.85 and 0.67, respectively. When separating grade 1 VFs from grade 2–3 VFs, the interobserver agreement and kappa score for grade 1 was 99.1% and 0.66, and for grade 2–3 99.4% and 0.84. Of the two assessors, one had substantial experience (LJ) and one had very limited experience (KR) in VF diagnosis. However, both had taken part in the instructional online International Society of Clinical Densitometry (ISCD)/International Osteoporosis Foundation (IOF) course on VFA reading (www.iofbonehealth.org), and one assessor (LJ) had also taken the course "Identification of vertebral fracture" at the Mellanby Centre, The University of Sheffield, UK (www.mellanbycentre.org).

Incident fracture assessment

Incident fractures were X-ray verified. Images and/or X-ray reports were retrieved from a regional digital X-ray archive that included all 49 municipalities (covering an area of 25,000 square kilometers) in the Västra Götaland region surrounding Gothenburg. Three research nurses reviewed all the radiology reports performed between the baseline exam until May 24, 2018. All reported fractures were recorded. All radiographs without available radiology reports or reports with uncertain fracture diagnosis were manually reviewed by an orthopedic surgeon (LJ).

Biochemical determinations

Blood samples were drawn from all study participants, and serum was separated, aliquoted, and stored at −80°C until analyses. Serum calcium, 25-hydroxyvitamin D, and parathyroid hormone (PTH) were analyzed at the Department of Clinical Chemistry (Swedac accredited no. 1342), Linköping University Hospital, Sweden, and all samples were assayed with reagents from the same batch. Serum 25-hydroxyvitamin D was measured on the DiaSorin LIAISON XL analyzer with the 25-hydroxyvitamin D total chemiluminescence immunoassay (DiaSorin, Stillwater, MN, USA), which demonstrates 100% cross-reactivity for 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3. This assay has an assay performance of analytical range 10 to 375 nmol/L, and total CVs of 8.8%, 6.4%, and 6.8% at levels 25 nmol/L, 68 nmol/L, and 150 nmol/L, respectively. Serum intact PTH was determined with the Elecsys electrochemiluminescence immunoassay on a Roche Cobas e601 platform (Roche Diagnostics Scandinavia AB, Gothenburg, Sweden), with an assay performance of analytical range 0.13 to 530 pmol/L, and total CVs of 4.0% and 2.9% at levels 1.9 pmol/L and 8.6 pmol/L, respectively.

Statistical analyses

Continuous variables at baseline were analyzed by ANOVA followed by Bonferroni post hoc test to compare means between women without fracture and women with increasing severity of vertebral fracture. Results are presented as mean ± standard deviation (SD). Categorical variables at baseline were analyzed by chi-square test. Significance was defined by a p value <0.05. Cox proportional hazard models were used to investigate the association between VF and incident fracture, with adjustments for confounders. Each participant's follow-up time was used in the Cox regression model. Cox analyses were performed for any fracture (fractures of the skull, face, hand, and foot were excluded), MOF (fracture of the hip, spine, forearm, proximal humerus, and pelvis), and VF. Incidence per 1000 person-years was calculated as number of events divided by total follow-up time (until fracture, death, or censored) per 1000 years. Adjustments for confounders were performed in three steps with increasing numbers of covariates included. In model 1, we adjusted for age, height, and weight, whereas model 2 was also adjusted for all FRAX parameters, including self-reported previous fracture (after the age of 50 years, fractures of the skull and face excluded), family history of hip fracture, current smoking, oral glucocorticoid use (daily treatment with at least 5 mg prednisolone or equivalent for 3 months or more ever), rheumatoid arthritis, excessive alcohol intake (21 or more standard units per week), and osteoporosis medication (current treatment with bisphosphonates, teriparatide, or denosumab). In addition to the covariates used in model 2, model 3 also included FN BMD. Post hoc statistical power analyses were performed showing >80% power for incident any fracture and MOF. Using time-dependent Cox models with a linear interaction term between time and VF (grade 1 VF and grade 2–3 VF separately) and by visually reviewing the log (−log[survival]) versus log(time) curves for each outcome (any fracture, MOF, VF), the Cox models satisfied the proportionality assumption. In a subanalysis, TBS was divided into tertiles and combined into groups according to VF status at baseline. Associations between tertiles of TBS and grade 1 VF and the risk of MOF were investigated using Cox proportional hazard models. The results are presented as hazard ratios (HR) with 95% confidence interval (CI) (Supplemental Table S1). All statistical analyses were performed with SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA).

Results

Characteristics

Of 2923 women, 1482 (50.7%) did not have any VFA-verified VF or self-reported prior fracture and were therefore included in

the control group. Seven hundred six (24.2%) of the women had any VFA-verified VF. Ninety-three women had grade 1 VF in combination with grade 2 VF and/or grade 3 VF. Because the aim of the study was to investigate associations between grade 1 VF and incident fractures, these 93 women with both grade 1 VF and grade 2–3 VF were not included in the analyses. The remaining 613 women with VFs were divided into two groups. In the group with grade 1 VFs (n = 264), 233 had one grade 1 VF, 28 had two grade 1 VFs, and 3 had three grade 1 VFs. The number of grade 1 VFs according to vertebral level (T_4 to L_4) is presented in Fig. 1. The women with more severe fractures comprised 349 women with either grade 2 VFs (n = 224), grade 3 VFs (n = 82), or a combination of grade 2 and grade 3 VFs (n = 43). Characteristics of women without fracture (control group) and women with grade 1 VF and women with grade 2–3 VF at baseline are presented in Table 1. Women with VF were older and shorter compared with women without VF. FN and LS BMD as well as TBS were lower in women with VF compared with women without fracture. Presence of a self-reported prior fracture was more common among those with grade 2–3 VF compared with grade 1 VF. Serum levels of 25-hydroxyvitamin D, proportion of women with a fall accident last year, women using osteoporosis medication, and self-reported osteoporosis all increased with the severity of VF ($p < 0.05$). Of 3028 subjects, 126 (4.2%) died during the follow-up time. In the control group (n = 1482), grade 1 VF group (n = 264), and grade 2–3 VF group (n = 349), 58 (3.9%), 14 (5.3%), and 16 (4.6%) died, respectively. Because all women were followed using health registers, there was no loss to follow-up.

VF and associations to incident fracture

The incident fractures were divided into three groups: any fracture, MOF, and VF (Table 2).

Incident any fracture

During 3.6 years (median, interquartile range [IQR] 1.5 years) of follow-up, 260 women suffered any fracture. The proportion of incident any fracture was 9.5% (n = 141) in the no fracture group and increased to 16% (n = 42) and 22% (n = 77) among those with grade 1 VF, and grade 2–3 VF, respectively. The incidence rate per 1000 person-years in the no fracture group, grade 1 VF, and grade 2–3 VF were 28.2, 47.2, and 68.0, respectively.

According to the analysis with Cox proportional hazard models, women with grade 1 VF at baseline had 67% increased risk for suffering any fracture (HR = 1.67; 95% CI 1.18–2.36). This association remained after adjustment for clinical risk factors (HR = 1.59; 95% CI 1.03–2.45) but not after adjustment also for FN BMD, although the association was of borderline significance (HR = 1.51; 95% CI 0.98–2.34). When adjustment was performed for LS BMD instead of FN BMD in model 3, grade 1 VF was significantly associated with incident any fracture (HR = 1.57; 95% CI 1.01–2.43). In a subanalysis, women with only one grade 1 VF (n = 233) had 87% increased risk for any fracture (HR = 1.87; 95% CI 1.32–2.65), and this association remained after adjustment for clinical risk factors and FN BMD (HR = 1.70; 95% CI 1.09–2.65) (Table 3).

Incident major osteoporotic fracture (MOF)

A total of 213 women suffered a MOF during the follow-up time of 3.6 years (no previous fracture group: n = 109 [7.4%]; grade 1 VF: n = 36 [14%]; and grade 2–3 VF: n = 68 [19%]). Incidence rates per 1000 person-years increased from 21.5 in the no fracture group to 40.1 and 59.1 in those with grade 1 VF and VF 2–3, respectively (Table 2).

Women with grade 1 VF at baseline had 86% increased risk for MOF (HR = 1.86; 95% CI 1.28–2.72; Fig. 2*A*), and this association remained after adjustment for clinical risk factors and FN BMD (HR = 1.72; 95% CI 1.08–2.76). Adjustment for LS BMD instead

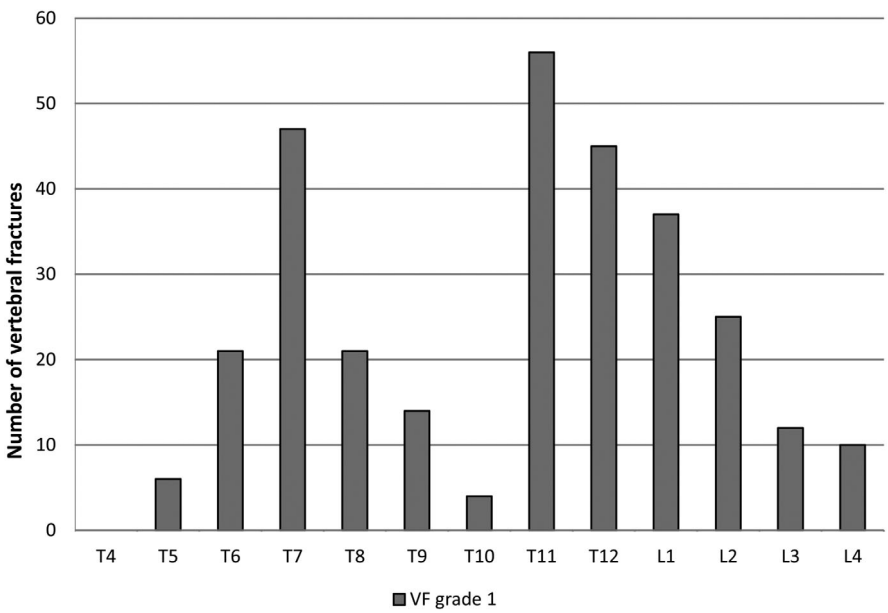

Fig 1. The number of grade 1 vertebral fractures presented according to vertebral level (T_4 to L_4) and vertebral fracture assessment in women aged 75 to 80 years.

Table 1. Characteristics of Older Women Without VFA-Diagnosed VF and With Increasing Severity of VFs

	No fracture $n = 1482$	Grade 1 VF $n = 264$	Grade 2–3 VF $n = 349$	p Value[a,b]
Age (years)	77.7 ± 1.6	78.0 ± 1.5[c]	78.1 ± 1.6[d]	**0.000**
Height (cm)	162.0 ± 5.7	161.8 ± 5.6	161.0 ± 6.0[d]	**0.009**
Weight (kg)	68.8 ± 12.1	69.2 ± 11.4	68.8 ± 12.5	0.850
Body mass index (kg/m^2)	26.2 ± 4.4	26.4 ± 3.9	26.5 ± 4.5	0.351
Femoral neck BMD (g/cm^2)	0.68 ± 0.11	0.65 ± 0.10[c]	0.63 ± 0.10[d]	**0.000**
Lumbar spine BMD (g/cm^2)	0.96 ± 0.18	0.93 ± 0.17[c]	0.91 ± 0.16[d,e]	**0.000**
TBS	1.22 ± 0.11	1.19 ± 0.11[c]	1.18 ± 0.11[d,e]	**0.000**
Fall accident within the last year, % (n)	26.0 (385)	24.6 (65)	33.8 (118)	**0.008**
Self-reported prior fracture, % (n)[f]	0 (0)	38.4 (101)	54.0 (188)	**0.000**
Heredity of hip fracture, % (n)	16.3 (238)[g]	17.6 (46)	19.4 (66)	0.386
Current smoking, % (n)	6.1 (90)	3.0 (8)	5.4 (19)	0.138
Excessive alcohol consumption, % (n)[h]	0.7 (10)	0.8 (2)	0.3 (1)	0.674[i]
Blood biochemistry				
Calcium (mmol/L)	2.47 ± 0.10	2.47 ± 0.11	2.47 ± 0.10	0.629
25-hydroxyvitamin D (nmol/L)	60.6 ± 20.5	62.7 ± 20.1	64.9 ± 21.2[d]	**0.001**
Parathyroid hormone (pmol/L)	5.03 ± 2.24	4.97 ± 2.02	5.05 ± 2.25	0.893
Medications				
Glucocorticoid use, % (n)[j]	2.9 (43)	3.0 (8)	5.2 (18)	0.102
Osteoporosis medication, % (n)[k]	4.9 (73)	10.6 (28)	23.2 (81)	**0.000**
Medical history				
Rheumatoid arthritis, % (n)	3.7 (55)	4.5 (12)	4.3 (15)	0.754
Hyperthyroidism, % (n)	5.4 (80)	4.9 (13)	4.6 (16)	0.809
Osteoporosis, % (n)	10.3 (152)	24.2 (64)	35.8 (125)	**0.000**
Hypertension, % (n)	53.0 (785)	51.1 (135)	51.9 (181)	0.826
Stroke, % (n)	6.1 (90)	8.7 (23)	6.9 (24)	0.268
Myocardial infarction, % (n)	4.2 (62)	4.2 (11)	6.0 (21)	0.320
Angina, % (n)	5.1 (75)	4.5 (12)	7.2 (25)	0.243
Heart failure, % (n)	7.6 (113)	9.5 (25)	10.0 (35)	0.256
Type 2 diabetes, % (n)	10.5 (154)[l]	9.2 (24)	9.2 (32)	0.680
Chronic bronchitis, asthma, emphysema, % (n)	9.1 (135)	9.8 (26)	12.3 (43)	0.190
Cancer, % (n)	19.4 (288)	22.3 (59)	20.9 (73)	0.500
Glaucoma, % (n)	8.4 (124)	7.6 (20)	7.2 (24)	0.628

VFA = vertebral fracture assessment; VF = vertebral fracture; BMD = bone mineral density; TBS = trabecular bone score.

Values are presented as mean ± standard deviation for continuous variables and as percentage and number for categorical variables. Significance was defined by $p < 0.05$, and significant values are presented in bold.

[a]Continuous variables one-way ANOVA followed by Bonferroni post hoc test.

[b]Categorical variables chi-square test.

[c]Grade 1 VF versus no VF.

[d]Grade 2–3 VF versus no VF.

[e]$n = 336$.

[f]After age 50 years, fractures of the skull and face are excluded.

[g]$n = 1460$.

[h]21 or more units per week.

[i]Fisher's exact test.

[j]Daily oral treatment with at least 5 mg for 3 months or more ever.

[k]Current treatment with bisphosphonates, teriparatide, or denosumab.

[l]$n = 1471$.

of FN BMD in model 3 resulted in a highly similar association (HR = 1.78; 95% CI 1.11–2.85). Having only one grade 1 VF was associated with a 92% increased risk for MOF after adjustment for clinical risk factors and FN BMD (HR = 1.92; 95% CI 1.18–3.10) (Table 3). In a fully adjusted model, women with grade 2–3 VF had 86% increased risk for MOF (HR = 1.86; 95% CI 1.20–2.89; Fig. 2*B* and Table 2).

Incident VF

During the follow-up time of 3.6 years, 101 women suffered a VF, with the lowest proportion in the no fracture group ($n = 45$, 3%) and with increasing proportion in the groups depending on severity of VF ($n = 15$, 5.7% in grade 1 VF, and $n = 41$, 12% in grade 2–3 VF). The incidence rate per 1000 person-years increased from 8.7 in the no fracture group to 15.9 and 34.0 in the grade 1 VF and grade 2–3 VF group, respectively (Table 2).

Women with grade 1 VF at baseline had 83% increased risk for VF (HR = 1.83; 95% CI 1.02–3.28), but this association did not remain after adjustment for clinical risk factors (HR = 1.56; 95% CI 0.73–3.32) and FN BMD (HR = 1.52; 95% CI 0.71–3.25). Having only one grade 1 VF at baseline resulted in a two times increased risk for VF, but this association did not remain when adjusted for clinical risk factors and FN BMD (Table 3).

Table 2. Associations Between VF Identified Using LSI With DXA and Fracture Risk in Older Women

	No fracture n = 1482	Grade 1 VF n = 264	Grade 2–3 VF n = 349
Any fracture[a]			
n (%)	141 (9.5)	42 (15.9)	77 (22.1)
Per 1000 person-years	28.1	47.2	68.0
Time at risk, median (IQR), years	3.36 (1.72)	3.55 (1.39)	3.47 (1.68)
HR (95% CI)			
Adjusted for age, height, weight	1 [Reference]	**1.67 [1.18–2.36]**	**2.40 [1.81–3.17]**
+FRAX clinical risk factors	1 [Reference]	**1.59 [1.03–2.45]**[b,c]	**1.94 [1.30–2.91]** [c,d]
+FN BMD	1 [Reference]	1.51 [0.98–2.34][e,f]	**1.67 [1.11–2.51]**[f,g]
MOF			
n (%)	109 (7.4)	36 (13.6)	68 (19.5)
Per 1000 person-years	21.5	40.1	59.1
Time at risk, median (IQR), years	3.46 (1.69)	3.56 (1.28)	3.52 (1.64)
HR (95% CI)			
Adjusted for age, height, weight	1 [Reference]	**1.86 [1.28–2.72]**	**2.72 [2.00–3.69]**
+FRAX clinical risk factors	1 [Reference]	**1.79 [1.12–2.87]**[b,c]	**2.14 [1.38–3.32]**[c,d]
+FN BMD	1 [Reference]	**1.72 [1.08–2.76]**[e,f]	**1.86 [1.20–2.89]**[f,g]
VF			
n (%)	45 (3.0)	15 (5.7)	41 (11.7)
Per 1000 person-years	8.7	15.9	34.0
Time at risk, median (IQR), years	3.53 (1.65)	3.60 (1.09)	3.61 (1.49)
HR (95% CI)			
Adjusted for age, height, weight	1 [Reference]	**1.83 [1.02–3.28]**	**3.83 [2.50–5.86]**
+FRAX clinical risk factors	1 [Reference]	1.56 [0.73–3.32][b,c]	**3.00 [1.66–5.43]**[c,d]
+FN BMD	1 [Reference]	1.52 [0.71–3.25][e,f]	**2.61 [1.43–4.74]**[f,g]

VF = vertebral fracture; LSI = lateral spine imaging; DXA = dual-energy X-ray absorptiometry; IQR = interquartile range; HR = hazard ratio; CI = confidence interval; FN = femoral neck; BMD = bone mineral density; MOF = major osteoporotic fracture.

Associations were studied using Cox proportional hazard models. HR and 95% CI are presented. Model 1 = adjusted for age, height, and weight; Model 2 = adjusted for age, height, weight, and the FRAX clinical risk factors (previous fracture, family history of hip fracture, current smoking, oral glucocorticoid use, osteoporosis medication, rheumatoid arthritis, excessive alcohol intake); Model 3 = adjusted for the same as model 2 with the addition of FN BMD.

[a]Without fractures of the skull, face, hand, and foot.

[b]n = 261.

[c]No VF n = 1452.

[d]n = 340.

[e]n = 260.

[f]No VF n = 1445.

[g]n = 338.

VF with TBS and associations to MOF

When TBS was included as a covariate (as a continuous variable) in the Cox regression, TBS and grade 1 VF were both independent predictors for MOF when adjusted for clinical risk factors (HR = 0.83; 95% CI 0.70–0.99 and HR = 1.79; 95% CI 1.12–2.86, respectively). An interaction term between TBS (as a continuous variable) and prevalent VF status (three-level ordinal variable [no VF, grade 1 VF, grade 2–3 VF]) and the risk of MOF was tested in a Cox regression model with adjustment for clinical risk factors. The interaction term was not significant. In a subanalysis, TBS was divided into tertiles and combined with grade 1 VF or grade 2–3 VF to examine the role of TBS and VF combined in the prediction of the risk of incident MOF. The combination of grade 1 VF and lowest TBS tertile was associated with a significant increase in the risk for MOF compared with the combination of grade 1 VF and moderate or high TBS, also after adjustment for clinical risk factors and FN BMD (HR = 2.30; 95% CI 1.11–4.75). This risk (grade 1 VF and lowest TBS tertile) was similar to the combination of grade 2–3 VF and lowest TBS tertile also after adjustment for clinical risk factors and FN BMD (HR = 2.44; 95% CI 1.40–4.25; Supplemental Table S1).

VF or SVH

Of the 264 women with grade 1 VF, 150 women had a height reduction (anterior, middle, or posterior) of 20.0% to 22.5% (mean ± SD height reduction 21.3% ± 0.72%). Independent t test was used to compare means of FN BMD and LS BMD between women without fracture and women with grade 1 VF 20.0% to 22.5% reduction. FN BMD was significantly lower in women with grade 1 VF 20% to 22.5% reduction (0.65 g/cm^2 compared with 0.68 g/cm^2 in women without fracture; p = 0.000), but LS BMD was not significantly lower (0.94 g/cm^2 compared with 0.96 g/cm^2; p = 0.080).

Discussion

In this prospective population-based study of older women, we found that mild VFs, identified using VFA by DXA, were associated with incident MOFs independently of clinical risk factors and FN BMD.

To our knowledge, this is the first study showing that also mild VF, detected by VFA, is a predictor of new fractures. A few previous reports have questioned the reliability of VFA for detecting

Table 3. Associations Between One Single Grade 1 VFs Identified Using LSI with DXA and Risk for MOF in Older Women

	No fracture $n = 1482$	One grade 1 VF $n = 233$
Any fracture[a]		
n (%)	141 (9.5)	41 (17.6)
Per 1000 person-years	28.1	52.6
Time at risk, median (IQR), years	3.36 (1.72)	3.52 (1.45)
HR (95% CI)		
Adjusted for age, height, and weight	1 [Reference]	**1.87 [1.32–2.65]**
+FRAX clinical risk factors	1 [Reference]	**1.73 [1.11–2.71]**[b,c]
+FN BMD	1 [Reference]	**1.70 [1.09–2.65]**[d,e]
MOF		
n (%)	109 (7.4)	35 (15.0)
Per 1000 person-years	21.5	44.5
Time at risk, median (IQR), years	3.46 (1.69)	3.52 (1.39)
HR (95% CI)		
Adjusted for age, height, and weight	1 [Reference]	**2.08 [1.42–3.05]**
+FRAX clinical risk factors	1 [Reference]	**1.94 [1.20–3.15]**[b,c]
+FN BMD	1 [Reference]	**1.92 [1.18–3.10]**[d,e]
VF		
n (%)	45 (3.0)	15 (6.4)
Per 1000 person-years	8.7	18.0
Time at risk, median (IQR), years	3.53 (1.65)	3.64 (1.16)
HR (95% CI)		
Adjusted for age, height, and weight	1 [Reference]	**2.09 [1.17–3.77]**
+FRAX clinical risk factors	1 [Reference]	1.75 [0.82–3.75]
+FN BMD	1 [Reference]	1.74 [0.81–3.74]

VF = vertebral fracture; LSI = lateral spine imaging; DXA = dual-energy X-ray absorptiometry; MOF = major osteoporotic fracture; IQR = interquartile range; HR = hazard ratio; CI = confidence interval; FN = femoral neck; BMD = bone mineral density.

Associations were studied using Cox proportional hazard models. HR and 95% CI are presented. Model 1 = adjusted for age, height, and weight; Model 2 = adjusted for age, height, weight, and the FRAX clinical risk factors (previous fracture, family history of hip fracture, current smoking, oral glucocorticoid use, osteoporosis medication, rheumatoid arthritis, excessive alcohol intake); Model 3 = adjusted for the same as model 2 with the addition of FN BMD.

[a]Without fractures of the skull, face, hand, and foot.

[b]$n = 230$.

[c]No VF $n = 1452$.

[d]$n = 229$.

[e]No VF $n = 1445$.

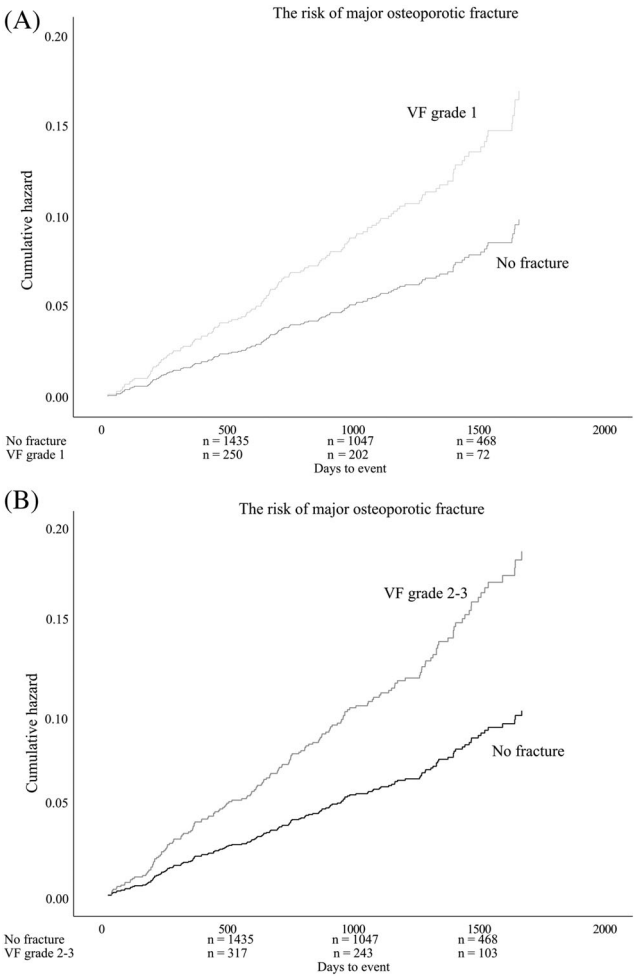

Fig 2. Relationship between cumulative hazard for predicted major osteoporotic fracture and days in older women without fracture at baseline and older women with grade 1 vertebral fracture (*A*) or grade 2–3 vertebral fracture (*B*) at baseline, adjusted for age, height, weight, previous fracture, family history of hip fracture, current smoking, oral glucocorticoid use, osteoporosis medication, rheumatoid arthritis, excessive alcohol intake, and femoral neck bone mineral density.

mild VFs.[16,17] The image quality by VFA is indeed inferior compared with conventional radiography, leading to more unreadable images or difficulties to clearly visualize the vertebrae, especially the upper thoracic vertebrae. In the present study, unreadable vertebrae at level T_7 and L_1 were common (21% and 6%, respectively). Given the fact that mild VFs are underdiagnosed with VFA because of unreadable vertebrae in the mid-thoracic spine and thoracolumbar junction, ie, the most common site of fractures, we believe that the prevalence of VFs may be underestimated in the present study.

Another aspect of detecting mild VFs is the validity. The chosen method for vertebral morphometry, regardless of the source of the image (VFA or conventional spinal radiographs), may impact the diagnosis. However, there is yet no consensus when a minor deformity should be classified as a fracture. Melton and colleagues[37] found that the prevalence of vertebral deformities ranged from 3% to 90% depending on which morphometric method that was used.[38] To reduce the focus on height reduction and the risk of misclassifying "short vertebral height" as a fracture, Jiang and colleagues[39] introduced the mABQ, which requires evidence of vertebral endplate fracture without a minimum threshold for reduction in vertebral height.[35] Although the mABQ method has advantages, there are also some limitations. First, VFs can deform the anterior vertebral

cortex without endplate disruption. Second, the vertebrae must be filmed in a perfect lateral projection for assessment of the central endplate and vertebral ring.[40] This is a substantial problem using conventional radiography with cone beam X-rays, due to the parallax phenomenon, but can also be a challenge when using VFA by DXA in the presence of scoliosis, resulting in rotated vertebrae. In a subanalysis, in the current study, women with grade 1 VF with height reduction just above 20% had lower BMD compared with women without fracture, indicating that grade 1 VFs in the current study are osteoporotic fractures and not SVH.

The GSQ method was used in the current study because it is the most widely used diagnostic method; however, this method requires training and expertise to minimize the risk of false-positive VFs. Therefore, the two examiners were well trained and fully aware of possible differential diagnoses, such as short vertebral height, degenerative scoliosis, Scheuermann's disease, Schmorl's nodes, and Cupid's bow deformity, in order to reduce the risk of misclassification. In general, multiple fractures increase the risk for subsequent fractures. The fact that hazard ratios describing the risk increase in the 233 women who only had one grade 1 VF (excluding the 31 women with two or more grade 1 VFs) were somewhat higher than for all women with any number of grade 1 VFs is somewhat puzzling. Because of the high degree of overlap between the investigated groups, with only 31 women differing in number of grade 1 VF, it is difficult to draw any certain conclusions of this finding. However, a possible explanation could be that there is an increased risk of misclassification in those with more than one grade 1 VF because of the presence of scoliosis, Scheuermann's disease, and degenerative changes, more commonly observed in multiple fractures.

Aubry-Rozier and colleagues[41] investigated if the examiner's level of expertise could affect the reproducibility of VFA readings in a population-based cohort. When a VF diagnosis done by a non-expert reader, before and after instruction course, was compared with an expert reader, the reproducibility increased mostly because of fewer grade 1 VF diagnosed by the non-expert reader after an instruction course. Diacinti and colleagues found that a significant proportion of mild VFs were misdiagnosed by local radiologists compared with central expert radiologists even on standard radiographs.[42] With this in mind, we emphasize that appropriate training is needed for VFA readers and that in some cases also additional spine imaging, including interpretation done by expert radiologists, should be considered to confirm the VF diagnosis.

In our study, the prevalence of mild VF was 13% and the prevalence of all VFs 29%, which indicates that we had about the same prevalence as expected at this age in the general population of women in Scandinavia.[43] However, the prevalence of mild VFs was somewhat lower in our study in comparison with other studies, of which some used conventional radiography[23,25] and some used VFA.[17] This may indicate that we could have underdiagnosed VFs, rather than detecting false-positive mild VFs. In comparison, Prince and colleagues[29] used VFA and found an even lower prevalence of mild VFs and total VFs of 3.1% and 9.2%, respectively, but this is likely attributable to the lower fracture incidence in Australia compared with Sweden. They also used single-energy images from a Hologic device and identified VFs by the GSQ method. However, they applied a modified scoring system where clear endplate depression or cortical discontinuity needed to be present for grade 1 fracture diagnosis, which may have contributed to the low prevalence.[29] Women with VFs had 3.8 times (95% CI 2.3–6.4) increased risk for incident VFs and 1.5 (95% CI 1.1–2.2) times increased risk for any fracture, but when VFs were divided according to severity, the predictive value of mild grade 1 fractures could not be verified. The low number of women with grade 1 VF (n = 39) could have contributed to this finding.

The predictive value of mild grade 1 VFs for subsequent fractures detected by conventional radiography has been verified.[24–26,44] Lentle and colleagues[44] compared the GSQ and mABQ methods for radiologic identification of VF in a large population-based longitudinal cohort. They concluded that prevalent grade 1 VF, whatever method used, was associated with incident VF, although grade 1 GSQ VFs were not associated with incident non-vertebral fractures, and grade 1 mABQ VFs was more strongly associated with incident VFs than prevalent VFs adjudicated with GSQ. Consistent with this study, the data from the current study demonstrate that although grade 1 VFs predict fractures, grade 2–3 VFs are even more strongly associated with fracture outcomes.The mABQ method was also used in the study by Schousboe and colleagues[28] using VFA instead of conventional radiography to investigate the predictive value of VFA-verified VF on the risk for incident fractures. This was the first study to demonstrate the value of VFA in routine clinical practice (different DXA operators) for predicting incident fractures. However, it was a retrospective and not population-based study, the incident fractures were recorded from health databases, and VFs were not graded according to severity. The first study to report that prevalent VFs identified by VFA predict subsequent clinical fractures independent of age, weight, and BMD was performed by McCloskey and colleagues.[27] They used the McCloskey algorithm (quantitative morphometry) for identifying VFs, and concluded that multiple VFs meant a greater risk for sustaining a fracture, although they did not grade the VFs according to severity.

A large meta-analysis found that TBS was a significant predictor of fracture risk independently of FRAX and BMD.[45] In our cohort, the predictive value for incident MOF was even higher when grade 1 VF was combined with the lowest tertile of TBS (HR = 2.30), indicating that both grade 1 VF and deteriorated trabecular microstructure in the vertebrae independently contribute to fracture risk. However, there was no interaction between TBS and VF status.

The strengths of the current study are several. It is a large population-based study and all the incident fractures were X-ray verified. The VFA images were analyzed by only two examiners with good intra- and interobserver reliability, and the radiographs of incident fractures were analyzed by one examiner. A limitation that should be acknowledged is that even if the agreement between examiners was good concerning assessable vertebrae, there was a considerable difference whether vertebrae could be assessed. Furthermore, having a total of 51 subjects for a reliability test constitute a relatively small sample and may not be sufficiently large to capture the presumed larger variability among patients encountered in clinical practice. Another limitation is that we included relatively old women within a narrow age span (75 to 80 years of age). In this age group, vertebral fractures are highly prevalent due to a high prevalence of osteoporosis, which could limit the generalizability of the results to other age groups.

In conclusion, VFA identified grade 1 VFs were associated with incident MOF, also after adjustment for clinical risk factors and FN BMD, indicating that all VF identified using densitometric LSI should be considered when evaluating fracture risk in older women.

Disclosures

ML has received lecture fees from Amgen, Lilly, MEDA, Renapharma, and UCB Pharma, and consulting fees from Amgen, Radius Health, UCB Pharma, Renapharma, and Consilient Health. All other authors state that they have no conflicts of interest.

Acknowledgments

This study was funded by the Swedish Research Council (VR), the ALF/LUA grant from the Sahlgrenska University Hospital, the Swedish Society of Medicine, the Gothenburg Society of Medicine, the King Gustaf V's and Queen Victoria's Freemason Foundation, and the Inga-Britt and Arne Lundberg Foundation. We thank Diana Atanasova for excellent technical assistance with the biochemical measurements.

Authors' roles: Study design: LJ, DS, and ML. Study conduct: LJ, DS, AGN, and ML. Data collection: LJ, DS, AGN, PM, KR, and ML. Data analysis: LJ, DS, and ML. Data interpretation: LJ, DS, and ML. Drafting manuscript: LJ. Revising manuscript content: LJ, DS, AGN, PM, KR, DM, and ML. Approving final version of manuscript: LJ, DS, PM, KR, DM, and ML. LJ and ML take responsibility for the integrity of the data analysis.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1002/jbmr.4108.

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