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Prevalent vertebral fractures and minor vertebral deformities analyzed by vertebral fracture assessment (VFA) increases the risk of incident fractures in postmenopausal women: the FRODOS study

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Abstract

Summary The incidence of vertebral fractures (VF) by vertebral fracture assessment (VFA) was 6.6% in postmenopausal women (FRODOS cohort) after 4 years of follow-up, increasing with prevalent VF and minor vertebral deformities, age, lower bone mass, glucocorticoid use, and rheumatoid arthritis. This study supports the usefulness of VFA to identify VF.

Purpose Vertebral fracture assessment (VFA) is increasingly used to identify spine fractures, but few cohort studies have used this method in prevalence and incidence assessment. We previously reported the prevalence of vertebral fractures (VF) and minor vertebral deformities (MVD) by morphometric VFA in a population-based cohort of postmenopausal women (FRODOS study). Therefore, the aim of this study was to analyze the incidence of VF, the associated risk factors, and particularly the role of MVD in this cohort of subjects.

Methods We performed a longitudinal analysis of 2510 women aged 59–70 years participating in the FRODOS prevalence study (2006–2009) with evaluable VFA 4 years later. VFA at baseline and in the present study was assessed by quantitative vertebral morphometry and by visual semiquantitative measurement. The multivariate Poisson regression model was performed, and relative risks with confidence interval of 95% were calculated for the incidence of VF. Bone mineral density (BMD) and an osteoporosis questionnaire were collected.

Results Overall, the incidence of VF was 6.6%, increasing with prevalent VF (24.5%) and in women with prevalent MVD (17.7%). Age and low BMD were also associated risk factors as were the presence of rheumatoid arthritis and exposure to glucocorticoids and bisphosphonates.

Conclusions The presence of prevalent VF assessed by VFA is associated with further incident spinal fractures in postmenopausal women. In addition, having MVD confers an increased risk of new VF.

Keywords Incidence · Prevalence · Vertebral deformities · Vertebral fracture assessment

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Introduction

The central role of vertebral fractures (VF) in postmenopausal osteoporosis is indisputable, and the finding of an incident VF, either clinical or morphometric, constitutes one of the main outcome measures in clinical trials and epidemiological studies in this field [1, 2]. Although there is still no consensus on the best diagnostic imaging of VF, the radiology-based visual semiquantitive (SQ) method proposed by Genant et al. [3] is the most widely implemented, and its use in conjunction with quantitative morphometry techniques has been recommended by the International Society of Clinical Densitometry (ISCD) [4].

With the Genant approach, VF are classified into grades 1, 2, and 3 corresponding to a 20–25%, 26 to 40%, and more than 40% reduction in vertebral heights, respectively. Vertebra

labeled as grade 2 fractures and especially those with grade 3 show the highest degree of either intraobserver or interobserver agreement and are considered as "true" fractures [5]. On the other hand, there are more discrepancies regarding mild grade 1 VF as there is no agreement as to whether these deformities correspond to anatomical or degenerative changes [6, 7] or they represent not fully developed osteoporotic fractures [8, 9]. However, from a clinical point of view, the most relevant question is whether these grade 1 fractures are associated with an increased risk of future VF [10, 11].

In recent years, the use of DXA-assisted vertebral fracture assessment (VFA) to detect VF has significantly increased. Nevertheless, most of these studies are intended to analyze the prevalence of VF [12, 13]. Although there are only a few studies assessing the incidence of VF by VFA [14–16], this method seems to be sensitive for detecting new, and especially moderate and severe, VF. Therefore, more prospective studies are needed to confirm the usefulness of this technique in clinical practice.

In 2014, our group reported the prevalence of VF and minor vertebral deformities (MVD) by morphometric VFA in a population-based cohort of postmenopausal women (FRODOS study), analyzing their relationship with the prevalence of low bone mass and the factors related to the development of VF [8]. In this study, we observed a higher frequency of MVD in patients with VF and those with osteoporosis, indicating the need to evaluate this type of mild deformity as a risk factor for further fractures. Therefore, the aim of this longitudinal study was to analyze the incidence of VF by VFA during a 4-year follow-up period, the associated risk factors for VF development, including the evaluation of bone mass, and the particular role that the presence of MVD may play in the risk of incident of VF in this cohort of subjects.

Methods

The Fractures Osteoporòtiques D'Osona (FRODOS) study is an observational, community-based study with the main goal of determining risk factors for fragility fractures (vertebral and non-vertebral) in postmenopausal women. A more detailed description of the cohort has been described elsewhere [8, 17]. Briefly, between the end of 2006 and the first half of 2009, of the 4015 women invited to participate, 2958 (74%) completed the prevalence study. Four years later, from January 2011 to July 2013, these 2958 participants were invited to participate in the second phase of the study (incidence study) (Fig. 1).

The project was undertaken at the Hospital Universitari of Vic, the only public reference facility of the Osona district, (70 km NW of Barcelona, Spain). All the participants signed the written informed consent to participate. The present study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and was reviewed and approved by the Institutional Ethics in Research Committee.

In addition to a structured interviewer-administered questionnaire regarding their general health status and the presence of clinical risk factors for osteoporosis and fractures, DXA-BMD assessment and VFA were performed in the same session.

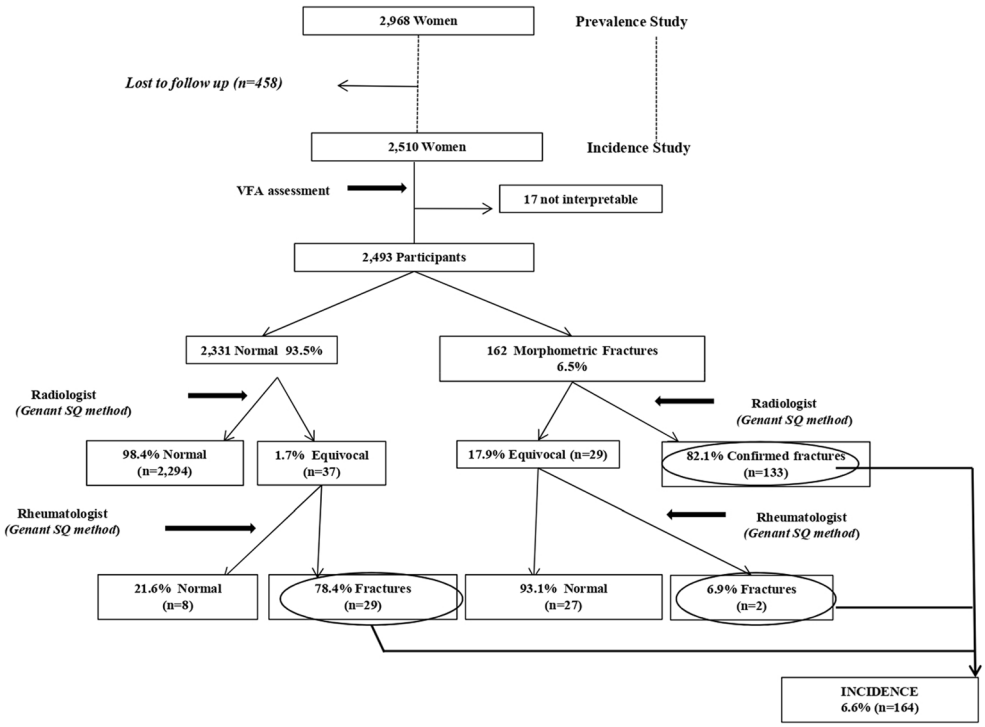

Fig. 1 Flowchart of the study

Inclusion and exclusion criteria

Candidates for inclusion were all women that completed the cross-sectional phase. As in the first study, individuals taking antiosteoporotic therapy were included and specifically registered.

Exclusion criteria were refusal to participate or the presence of a severe disease preventing mobilization.

Bone mineral density determination

Bone mineral density (BMD) of the lumbar spine (L1–L4) femoral neck and total hip was measured at baseline by dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy Advance, GE Medical Systems) with reference values adapted to the Spanish population [18]. Coefficients of variation were 1.5% for the lumbar spine and 1.5% for the femoral neck and total hip.

Vertebral fracture assessment

The same procedures performed in the baseline assessment were followed in the present study: a lateral scan of the spine (T6–L4) was acquired using DXA (Lunar Prodigy Advance, GE Medical Systems). The scans were obtained by a single trained technician using the standard software (version 9.30.044), which automatically places six points at the superior, middle, and inferior vertebral endplates. These points can be manually corrected. Anterior (Ha), middle (Hm), and posterior heights (Hp) were measured, and Ha/Hp and Hm/Hp ratios were obtained automatically (Fig. 2).

To evaluate the reproducibility of the vertebral height measurements, the scans of 90 women were repeated between 1 and 2 weeks later by the same technician blinded to the first assessment. Due to the length of the study, this procedure was performed in January 2011 (30 participants), January 2012 (30 participants), and January 2013 (30 participants); a new scan was performed for every subject in this precision study. The coefficients of variations of the repeated scans were 1.5% for Ha, 1.8% for Hm, 2.4% for Hp, and 2.3 and 2.7% for Ha/Hp and Hm/Hp, respectively.

Definition of vertebral fracture

A VF was defined according to the criteria described in our previous study [8]. Briefly, (a) at least one vertebra was required to have either of the two ratios (Ha/Hp and Hm/Hp) 3 standard deviations (SD) below the normalized [19] values of that ratio and/or the Hp should be 3 SD below the Hp of the adjacent non-fractured vertebra. (b) An experienced radiologist (JGB) with no knowledge of the previous procedures also assessed all the VFA scans using the Genant visual semiquantitative (SQ) method. (c) In case of disagreement between the morphometric and the SQ findings, a rheumatologist with expertise in VF evaluation definitively classified participants as having or not having a VF using also the Genant approach.

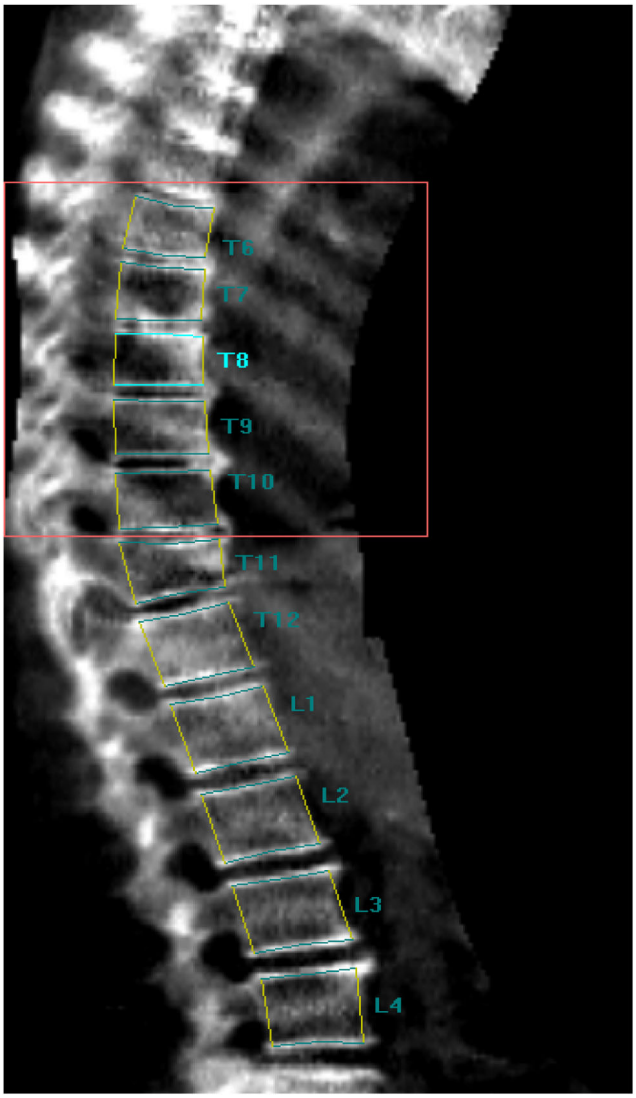

Fig. 2 Representative image of the VFA lateral scan

Participants with vertebral height ratios between − 2 and − 2.99 SD below the reference, i.e., those that did not meet the predefined criteria of morphometric fractures, were categorized as women with MVD.

Prevalent VFA status

Participants were classified into three mutually exclusive groups: (a) women with prevalent VF (with or without other vertebrae with MVD), (b) women with MVD, and (c) women with normal VFA status.

Definition of incident VF

A woman was classified as having an incident VF when according to the above described definition, a VF which was not present in the baseline evaluation was detected in the follow-up assessment.

Risk factors for incident fractures

Baseline information was collected in the prevalence study including clinical and anthropometric characteristics, BMD and VFA status, and previous clinical fragility fractures, among others, which were considered as risk factors [8]. In addition, due to the influence of antiosteoporotic treatment either at baseline and/or during follow-up on VF outcome, this was also considered as an independent factor, and thus, participants were further categorized into two groups: (a) unexposed and (b) exposed (baseline and/or follow-up users, baseline users but withdrawal during follow-up). Since the most frequent antiosteoporotic treatment used was bisphosphonates, only this type of treatment was included in the analysis.

Statistical analysis

The results for categorical variables were expressed as absolute and relative frequencies and results for continuous variables as means and standard deviations (SD). The survival time (years) for each participant was the time interval between the baseline and the follow-up survey. The annual incidence of VF was expressed as the number of women who had at least one incident vertebral fracture for every 1000 women-years (person-years at risk [PY]), and their 95% confidence interval was also calculated. To analyze the factors associated with VF and MVD prevalence, the chi-squared test was performed for the categorical variables, while for the quantitative variables an analysis of the variance was performed.

To identify the univariate risk factors associated with incident VF with a value of $p < 0.05$, Poisson regression was used, and subsequently with the factors associated with the incidence, the multivariate Poisson regression model was performed. Through these analyses, relative risks (RRs) were calculated with a confidence interval of 95% (95% CI) for the incidence of VF.

The kappa method was used for the analysis of the concordance between the morphometric VFA assessment and the Genant method.

Statistical significance was considered when the p value was less than 0.05. Statistical analyses were performed using SPSS v18 and Stata v8.

Analysis of non-participation/mortality

The baseline characteristics of the 458 candidate women who did not participate in the incidence study were compared with those of the women who completed this phase. Forty-five women died during the study (1.5% rate).

Results

The study was completed by 2510 women (2510/2968, participation rate 84.5%). Of these, 17 (0.7%) had no assessable VFA; thus, the results of 2493 women were finally analyzed (Fig. 1). The mean follow-up period was 4.22 ± 0.3 years (2.7–5.7 years) with a follow-up of 3.7 to 4.7 years in 95% of the cases.

Table 1 shows the baseline characteristics of the 2493 participants classified as women with prevalent VF, women with prevalent MVD, and women with normal vertebral status. At baseline, the prevalence of VF and MVD was 4.1% ($n = 102$) and 15.6% ($n = 338$), respectively. Compared with women without prevalent VF, participants with VF were older, had had previous fragility fracture, were more frequently taking bisphosphonates and glucocorticoids, and also had a lower T-score ($p < 0.05$) (Table 1). Likewise, women with prevalent VF had more MVD (35.3% vs. 16.2%, $p < 0.001$).

Similarly, women with prevalent MVD were older, had also had more fractures since menopause, and showed a lower T-score than participants with normal VFA ($p < 0.05$).

Agreement between morphometric and Genant semiquantitative classifications

The kappa index between the morphometric assessment and the radiologist evaluation (Genant method) was 0.787 (good agreement), and the same index between morphometric assessment and the rheumatologist (Genant method) was 0.816 (very good agreement).

Incidence of VF

At follow-up, 164 women (6.6%) presented at least one new VF (Fig. 1). This represents an incidence rate of 15.55 women/10^3 PY. Altogether, there were 196 VF: 137 women sustained one VF, 23 women sustained 2 VF, 3 participants presented 3 fractures, and 1 woman sustained 4 VF. Of these 164 women with incident fractures, 37.8% were clinically symptomatic. Of the 196 incident VF, 68.5% were localized in the thoracic spine and 31.5% in the lumbar spine, with T11 (13.8%), T12 (13.3%), and L1 (20.4%) being the most frequently affected vertebrae.

Table 1 Baseline clinical characteristics of the 2493 participants according to prevalent VFA status

VFA status	Normal $n = 2003$ (80.3%)	MVD $n = 388$ (15.6%)	VF $n = 102$ (4.1%)	p
Age, mean ± SD	65.2 ± 3.5	65.8 ± 3.7	67.1 ± 3.6	< 0.001
Age of menopause, mean ± SD	49.6 ± 5.4	49.4 ± 5.3	48.6 ± 6.2	0.168
BMI, mean ± SD	28.4 ± 4.7	28.6 ± 4.9	29.3 ± 4.8	0.920
Previous fragility fracture, *n* (%)	325 (16.2%)	92 (23.7%)	43 (42.2%)	< 0.001
First-degree family history of fractures, *n* (%)	439 (22.5%)	97 (25.6%)	24 (23.8%)	0.134
Smokers, *n* (%)	55 (2.7%)	8 (2.1%)	4 (3.9%)	0.549
Alcohol use, *n* (%)	29 (1.4%)	7 (1.8%)	2 (2.0%)	0.764
Bisphosphonate users, *n* (%)	165 (8.2%)	38 (9.8%)	28 (27.5%)	< 0.001
Glucocorticoids use, *n* (%)	104 (5.2%)	20 (5.2%)	13 (12.7%)	0.005
Rheumatoid arthritis, *n* (%)	11 (0.5%)	2 (0.5%)	0 (0%)	0.754
T-score femoral neck, mean ± SD	− 1.20 ± 0.96	− 1.38 ± 0.96	− 1.70 ± 0.82	< 0.001
Lowest T-score, mean ± SD	− 1.83 ± 1.11	− 2.07 ± 1.15	− 2.34 ± 1.12	< 0.001

VFA vertebral fracture assessment, *MVD* minor vertebral deformities, *VF* vertebral fractures

Table 2 shows the characteristics of the patients with incident VF and those without new VF. As shown in the table, women with incident VF were slightly older, had more prevalent VF (15.3% vs. 3.3%, $p < 0.001$), and also had more prevalent MVD (38.4% vs. 14%, $p < 0.001$) than participants without incident VF. Furthermore, these participants had had more fragility fractures since menopause (26.8 vs. 17.9%, $p = 0.004$), were more frequently receiving treatment with bisphosphonates and glucocorticoids, and had also a lower T-score.

Risk factors for a new vertebral fracture

The incidence of VF in women with prevalent VF was 24.5% compared to 5.8% of those without previous VF ($p < 0.05$) (Table 2).

Minor vertebral deformities

As a whole, women with MVD at baseline had more incident VF than participants without these deformities (17.7% vs. 4.3%, $p < 0.001$) (Fig. 3a). Furthermore, when the role of MVD was analyzed taking into account the presence of previous VF, it was observed that women with both prevalent VF and MVD had a 33.3% incidence of VF whereas in women without MVD this figure was 19.7% ($p = 0.126$) (Fig. 3b). In participants without prevalent VF, those with MVD showed a greater incidence of VF compared to women without MVD (16.2% vs. 3.8%, $p < 0.001$) (Fig. 3c).

Bisphosphonate therapy

At baseline, 231 (9.2%) individuals were taking bisphosphonates, with this proportion being significantly higher (28% vs. 9.2%; $p < 0.001$) in women with prevalent VF ($n = 104$) (Table 1). At follow-up, the number of bisphosphonate-exposed women raised up to 507 individuals (19.5% of the participants). Again, among those who had developed an incident VF ($n = 52$), the proportion of bisphosphonate users was higher (31.7% vs. 19.5%; $p < 0.001$) (Table 2).

Applying the multivariate Poisson regression model (Table 3) and after adjusting for variables which were significant in the univariate model, the incidence of VF was associated with the prevalence of both VF, RR 5.35 (95% CI 3.37–8.51), and MVD, RR 3.94 (95% CI 2.82–5.52). The age of the participants, RR 1.05 (1.01–1.10), a diagnosis of rheumatoid arthritis, RR 4.18 (95% CI 1.33–13.13), and the lowest T-score, RR 0.81 (95% CI 0.70–0. 93), were also significant associated risk factors.

Non-participation analysis

Compared to the 2510 women who completed the two phases of the study, women who did not participate in the incidence study, $n = 458$ (15.4%), were older (66.1 ± 3.6 vs. 65.4 ± 3.5, $p < 0.001$), had had more previous fractures (23.8% vs. 18.5%, $p = 0.008$), were more frequently smokers (5.5% vs. 2.7%, $p = 0.002$), and less commonly received bisphosphonate treatment (15.3% vs. 19.6%, $p = 0.029$).

Table 2 Baseline clinical characteristics of the subjects according to the development of incident vertebral fractures

	Incident VF $n = 164$ (6.6%)	No incident VF $n = 2329$ (93.4%)	p
Normal MVD	76 (46.3%) 63 (38.4%)	1927 (82.7%) 325 (14.0%)	< 0.001
Prevalent VF	25 (15.3%)	77 (3.3%)	
Age, mean ± SD	66.5 ± 3.7	65.3 ± 3.5	< 0.001
Age of menopause, mean ± SD	49.4 ± 4.9	49.5 ± 5.5	0.801
BMI, mean ± SD	29.1 ± 4.8	28.5 ± 4.7	0.100
Previous fragility fracture, *n* (%)	44 (26.8%)	416 (17.9%)	0.004
First-degree family history of fractures, *n* (%)	40 (24.7%)	520 (22.9%)	0.311
Smokers, *n* (%)	6 (3.7%)	61 (2.6%)	0.447
Alcohol use, *n* (%)	2 (1.2%)	36 (1.5%)	0.792
Bisphosphonate exposed, *n* (%)*	52 (31.7%)	455 (19.5%)	< 0.001
Glucocorticoids use, *n* (%)	16 (9.8%)	121 (5.2%)	0.013
Rheumatoid arthritis, *n* (%)	3 (1.8%)	10 (0.4%)	0.016
T-score femoral neck, mean ± SD	− 1.51 ± 0.96	− 1.23 ± 0.96	< 0.001
Lowest T-score, mean ± SD	− 2.30 ± 1.18	− 1.86 ± 1.11	< 0.001

MVD minor vertebral deformities, *VF* vertebral fractures

*Baseline and/or follow up users

Discussion

This study provides valuable information about the assessment of postmenopausal women at risk for the development of VF. Our results support not only the usefulness of VFA in the identification of VF but also the additional function of MVD as a risk factor for further fractures. After 4 years of follow-up of 2510 postmenopausal women from the population-based FRODOS study, the cumulative incidence rate of VF assessed by VFA was 6.6%, representing an incidence rate of 15.55 women/10^3 PY. Besides confirming the relevance of several well-known risk factors for the incidence of VF such as age, prevalent VF status, and densitometric osteoporosis, the study emphasizes the role of the so-called mild or MVD. The FRODOS cohort is a population-based study designed to determine risk factors for osteoporotic fractures (especially VF) with a good to very good participation rate at both recruitment (71.1%) and follow-up (84.5%). In the two phases, a quantitative VFA approach with normalized reference values was complemented by a second assessment using the Genant method to assess the presence of VF.

The use of VFA in the appraisal of VF has substantially increased in recent years [12], but it not was until 2008 that McCloskey at al. [20], in a clinical trial including more than 5000 women, reported that prevalent VF (14.5%) identified by VFA were associated with a twofold increase in the relative risk of new osteoporotic fractures. Nevertheless, the data on incident VF was mainly obtained from a radiologic-based study, in which only a subset of subjects with baseline VF was evaluated for incident VF after 3 years.

The specific relationship between prevalent and incident VF using the VFA approach has only been reported in three series: the Japanese Population-based Osteoporosis (JPOS) Cohort Study [14], a subset of participants from the Osteoporosis and Ultrasound "OPUS" Study [15], and a subset of midlife women from the SWAN study [16]. The Japanese study included more than 700 women between 50 and 79 years of age with an initial prevalence of VF of 13.8% who were followed up for 6 years, showing an incidence of VF of 10.3% (16.7/10^3 PY). Both the Japanese and our study were population-based cohort studies with similar inclusion criteria, data collection, and VFA methodology and definition of prevalent and incident VF. In our study, however, the prevalence of VF, a key factor for new spinal fractures, was much lower (4.1%); consequently, the overall incidence (6.6%) and the incident rate (15.5/10^3 PY) of VF were also lower than what was reported in the Japanese cohort [14]. These differences could be partly explained by several factors, such as the higher rates of VF reported in Japanese population [2], the normalized ratios used for VF definition in our study, and/or the differences in the sample size of the age groups included in the two studies (2510 vs. 246 postmenopausal women aged 60–70 years), among others. Again, both studies confirmed the relevance of prevalent VF as a determinant risk factor for new fractures. Thus, baseline VF was associated with a fivefold increase in the RR for new VF in the two studies (24% in FRODOS vs. 32% in JPOS) whereas in women without prevalent VF these figures were 5.8% and 7.6%, respectively.

The SWAN study included 1446 midlife women from different American states with a mean follow-up of 6.8 years and

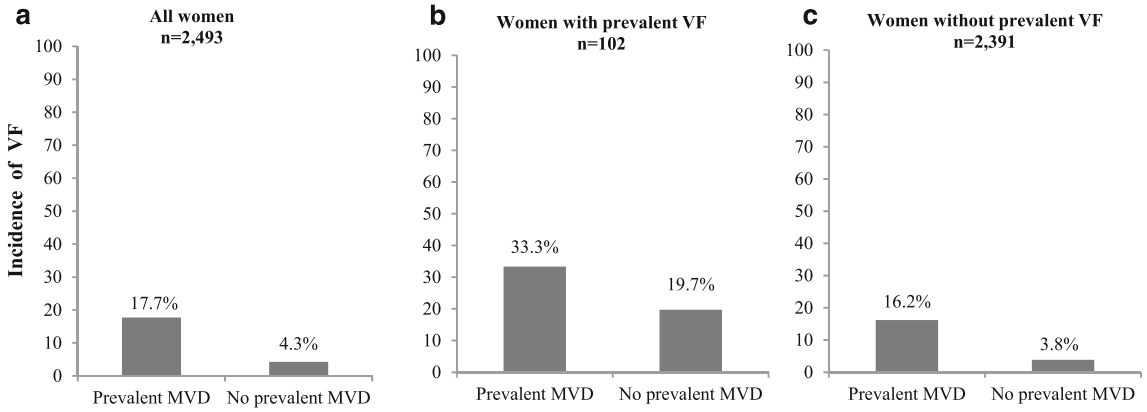

Fig. 3 Incident vertebral fractures in subjects with or without prevalent minor deformities. The figure shows the baseline prevalence of minor vertebral deformities (MVD) in the participants of the study who developed incident vertebral fractures (VF): **a** in all participants, **b** in women with prevalent VF, and **c** in women without prevalent VF

aged between 49 and 62 years [16]. This study evaluated VF with VFA using the Genant method. In this series, the prevalence of VF was similar to our results, with 3.2% of subjects having VF at baseline. Conversely, the incidence of VF was very low, $1.98/10^3$ PY, a finding probably related to the younger age of the subjects, who were mainly under 60. The authors of this study pointed out the difficulties in evaluating VF with VFA in the upper spine, especially from T4 to T6, and the possible underestimation of mild vertebral deformities (grade 1) which constituted about two-thirds of the VF of this study [16].

The OPUS study included 600 European women aged 55–80 years assessed at baseline and after 6 years. This study used another method to identify the presence of VF, the algorithm-based qualitative methodology (ABQ) [15], resulting in a prevalence of VF of 6.82%, which was slightly higher than ours, with an incidence of 5%. Again, and similar to previous and our results, the authors reported a significant increased risk for incident VF in older participants and those with lower hip BMD and with prevalent VF [15]. Notably, only moderate–severe VF contributed to this association since the presence of mild VF showed no significant results.

Table 3 Relative risk of incident vertebral fracture by Poisson's regression analysis

Characteristic	RR (CI 95%) Crude	RR (CI 95%) Adjusted
Normal	1	1
MVD	4.28 (3.06–5.98)	3.94 (2.82–5.52)
VF	6.46 (4.11–10.15)	5.35 (3.37–8.51)
Age	1.10 (1.05–1.14)	1.05 (1.01–1.10)
Previous fragility fractures	1.62 (1.15–2.29)	
Bisphosphonate exposed*	1.82 (1.31–2.53)	
Glucocorticoids users	1.86 (1.10–3.11)	
Rheumatoid arthritis	3.55 (1.14–11.14)	4.18 (1.33–13.13)
Lowest T-score	0.737 (0.620–0.876)	0.81 (0.70–0.93)

MVD minor vertebral deformities, *VF* vertebral fractures

*Baseline and/or follow-up users

In our series, we also analyzed the presence of MVD (a type of vertebral deformity that we have previously reported to be related to prevalent VF) [8] and its role as a risk factor for further VF. Remarkably, in the present study, the presence of MVD, independently of the prevalence of VF, markedly increased the likelihood of new VF. In addition, these subjects presented similar characteristics to those with VF, such as having more prevalent fragility fractures and lower BMD values. Moreover, it should be noted that the subjects with VF and concomitant MVD presented the highest incidence of VF, 33.3%. All of this supports the role of MVD in the vertebral fracture cascade [21]. Indeed, the multivariate analysis confirmed that besides low BMD and prevalent VF, MVD was associated with the risk of new VF.

The concept of MVD is not new, but it has only been applied occasionally in large radiographic assessments for VF. In their excellent work about risk factors for a first incident VF, Nevitt and colleagues described that women with MVD but without prevalent VF had a significant increased risk for new VF [22]. Along the same line, a meta-analysis by Johansson et al. of the placebo arms of four clinical trials of antiosteoporotic drugs indicated that the presence of MVD conferred a greater risk for VF [10]. Conversely, other authors suggested that the presence of MVD does not provide relevant information [7].

In a prospective Canadian multicenter study (CaMos), Lentle et al. evaluated the X-ray images of 4465 women and 1771 men aged > 50 years for VF assessment, analyzing the prevalence and incidence of VF [23]. In this extensive cohort, the authors compared the ABQ and the Genant semiquantitative methods for the diagnosis of VF, as well as the role of grade 1 VF as a risk factor for further fractures according to

the diagnostic method. The overall prevalence and incidence of VF varied depending on the method used, ranging from a prevalence of 6.7% and incidence of 6.3/1000 PY when using the ABQ method to 16.4% and 10.2/1000 PY with the Genant method. Again, low BMD and prevalent VF were related to incident fractures with the two methods, with higher associations being observed with the ABQ. Of note, grade 1 VF were associated with incident VF with the two methods, although only grade 1 VF defined by ABQ was associated with incident non-VF, further confirming the relevance of low-grade vertebral deformities in the risk of new fractures. These latter data have influenced the indications suggesting the preferential use of morphological assessment in the diagnosis of VF [24]. Nonetheless, it should be noted that in the Rotterdam Study [25], 35% of the fractures identified by the ABQ method were observed in vertebrae without significant morphometric changes, thereby suggesting that a combination of both methods would probably be more adequated [26]. The different methods used in the definition of VF clearly influence the diagnosis of this type of fracture and consequently the data on its prevalence and incidence. Nonetheless, in spite of this assumption, in the present population, constituted by postmenopausal women over 60 years of age, the use of VFA was able to identify those with a higher risk for future VF fractures thereby confirming the usefulness of this method for evaluating subjects at risk. Indeed, we observed a high sensitivity and specificity of 82.3% and 98.8%, respectively, of the VFA morphometric method compared to Genant SQ evaluation with an overall accuracy of 97.8% for VF detection. This result is remarkable for VFA-based identification of patients with VF, at least in relation to the widely used Genant SQ. In addition, although fractures were evaluated morphometrically, in our study prevalent MVD were clearly related to incident VF, thereby showing that whatever method is used for the diagnosis of mild deformities, these deformities should probably be taken into account when evaluating osteoporotic subjects, since they confer an increased risk for further VF.

Our study however has some limitations, such as the use of specific devices and techniques per person and not per vertebra. Thus, a direct comparison of quantitative morphometry and Genant visual assessment could have improved the ability to understand the relative performance of the different methods used for assessment of VF; however, such a study was impracticable for logistic reasons. The inclusion of women receiving bisphosphonates constitutes another possible drawback, possibly influencing the predictive value of VF. Nonetheless, we think that this possibility does not limit the value of our findings, since we observed that this group of subjects, as expected, presented a higher risk for prevalent and incident VF, further confirming the usefulness of VFA for identifying high-risk subjects for VF. In addition, it should be noted that the incorporation of this variable was predetermined in the analysis. Finally, the narrow age range of the women and certain variability in the length of follow-up should also be noted. All of these aspects restrict the results for this age-range group of subjects and indicate the need to confirm the present results in other settings. Nonetheless, our study also has several strengths, which include an extensive cohort of subjects with a high index of participation in the follow-up study. Although it could be argued that there is a possible bias of the more severely affected subjects not participating in the incidence follow-up study, only 15% of subjects did not participate in this study. Additionally, the identification of VF by VFA was not only evaluated by quantitative morphometric analysis but also confirmed by the additional use of a visual score by an experienced radiologist, clearly improving the diagnostic accuracy of this method.

In conclusion, the presence of prevalent VF assessed by VFA is associated with further incident spinal fractures in postmenopausal women. In addition, our results indicate than MVD also increase the risk of further VF, and therefore, these findings should be taken into account when evaluating postmenopausal women at risk for fractures. Clearly, longer follow-up studies comparing several diagnostic criteria for VF definition would provide additional information on this relevant subject.

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Compliance with ethical standards

Ethical approval This study has been approved by the local Research and Ethics Committee, and it has been performed in accordance with the 1964 Declaration of Helsinki.

Conflicts of interest None.

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