

Original Article

Prevalent Vertebral Deformity Predicts Incident Hip though not distal Forearm Fracture: Results from the European Prospective Osteoporosis Study

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Abstract. The presence of a vertebral deformity increases the risk of subsequent spinal deformities. The aim of this analysis was to determine whether the presence of vertebral deformity predicts incident hip and other limb fractures. Six thousand three hundred and forty-four men and 6788 women aged 50 years and over

were recruited from population registers in 31 European centers and followed prospectively for a median of 3 years. All subjects had radiographs performed at baseline and the presence of vertebral deformity was assessed using established morphometric methods. Incident limb fractures which occurred during the follow-up period were ascertained by annual postal questionnaire and confirmed by radiographs, review of medical records and personal interview. During a total of 40 348 person-years of follow-up, 138 men and 391

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women sustained a limb fracture. Amongst the women, after adjustment for age, prevalent vertebral deformity was a strong predictor of incident hip fracture, (rate ratio (RR) = 4.5; 95% CI 2.1–9.4) and a weak predictor of ‘other’ limb fractures (RR = 1.6; 95% CI 1.1–2.4), though not distal forearm fracture (RR = 1.0; 95% CI 0.6–1.6). The predictive risk increased with increasing number of prevalent deformities, particularly for subsequent hip fracture: for two or more deformities, RR = 7.2 (95% CI 3.0–17.3). Amongst men, vertebral deformity was not associated with an increased risk of incident limb fracture though there was a nonsignificant trend toward an increased risk of hip fracture with increasing number of deformities. In summary, prevalent radiographic vertebral deformities in women are a strong predictor of hip fracture, and to a lesser extent humerus and ‘other’ limb fractures; however, they do not predict distal forearm fractures.

Keywords: Incidence; Limb fracture; Osteoporosis; Vertebral deformity; Vertebral osteoporosis

Introduction

There is clear evidence that the presence of a vertebral deformity increases the risk of future spine fractures [1]. Less is known, however, about the predictive risk of a vertebral deformity on future limb fractures and particularly the hip and wrist. Longitudinal studies in women with clinically apparent vertebral deformities suggest that these are associated with a subsequent increased risk of nonvertebral fractures including a 1.8- to 3.8-fold increased risk of hip fracture [2–6]. Even higher risks are observed in men and women admitted to hospital following a vertebral fracture [7]. However, clinically apparent deformities represent about one third of all vertebral deformities and the extent to which these findings may be generalized is unclear [8]. One study suggested that individuals with severe radiographic spinal deformity had an increased risk of future nonvertebral fractures; however, the numbers of cases were small and the risk of the individual fracture types was not reported [9]. In a more recent American study among a large group of elderly women, radiographic vertebral deformity was associated with an increase in the risk of future hip and any nonvertebral fracture, though, after adjusting for age and BMD, no increase in the risk of future wrist fracture was observed [10]. To our knowledge there are no data from population studies about the relationship of radiographic vertebral deformity and the risk of subsequent limb fracture in men. A better understanding of the relationship between radiographic vertebral deformity and the risk of future types of limb fracture may enable more effective targeting of fracture intervention programs.

The aim of this analysis was to determine whether the presence of radiographic vertebral deformity predicts incident limb fracture in European men and women and

to confirm whether the magnitude of any increased risk is similar at individual fracture sites.

Subjects and Methods

Subjects

The subjects included in this analysis were recruited for participation in the European Vertebral Osteoporosis Study (EVOS). The detailed methods have been described elsewhere [11]. In brief, men and women aged 50 years and over were recruited from population registers in 36 European centers. Stratified sampling was used with the aim of recruiting equal numbers of men and women in each of six 5-year age bands: 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, and 75 years and over. Subjects were contacted by letter of invitation which included information about the study. Those who consented to take part were interviewed using a structured interview which included questions about previous fragility fractures. Lateral spinal radiographs were performed. The radiographs were evaluated morphometrically by one of three observers and the presence of vertebral deformity determined using the McCloskey–Kanis method [12].

The subjects recruited in 29 of the EVOS centers have been followed prospectively by annual postal questionnaire, and in a further 3 by telephone or personal interview (European Prospective Osteoporosis Study, EPOS). Subjects were asked to record details of any fractures sustained in the intervening period, and to mark on a body manikin (included with the postal questionnaire) the site of any fractures. Fractures reported were confirmed at each of the participating centers by the principal investigator by review of radiographs, medical record or subject interview. In addition the investigator confirmed the site of the reported fracture. From these sources contemporary data to confirm or refute the occurrence and site of fracture were not available in 9% of cases. In these cases the site of fracture was determined from the area marked by the subject on the manikin [13]. Because of a low follow-up rate (in part a consequence of large-scale population mobility) the data from one center (Zagreb, Croatia) were excluded from this analysis. The data coordination for the study was in Manchester and Lubeck (Germany). Ethics approval was obtained centrally and at individual participating centers.

Analysis

Subjects contributed follow-up time (person-years) from the date of the baseline survey until limb fracture, death or the end of the study. Fractures were classified using the 9th edition of the International Classification of Diseases [14] into the following categories: hip (neck of femur), ICD code 820; distal forearm, ICD code 813; humerus, ICD code 812; ‘other’ limb, ICD codes 814–817, 821–826. Cox regression analysis was used to

assess the predictive risk of vertebral deformity on future limb fractures [15]. Analysis was undertaken looking initially at ‘any’ limb fracture and then separately by fracture site. In subjects who sustained more than one fracture of the same type, the time to the first fracture event was used in the analysis. Adjustments were made for age and subsequently for previous low-trauma fragility over the age of 50 years (yes/no). To determine whether there was a trend toward an increased risk of limb fracture with increasing numbers of vertebral deformities, the analyses were repeated after categorization of subjects by number of vertebral deformities (none/single/two or more) and a test of trend performed. All analyses were undertaken separately in men and women. The proportional hazards assumption underlying the Cox regression model was checked visually using Aalen plots [16]. Analyses were performed using the statistical package STATA [17].

Results

Subjects

Six thousand three hundred and forty-four men, mean age 64.2 (SD = 8.4) years, and 6788 women, mean age 63.6 (SD = 8.4) years, were followed for a median of 3 years (range 0.4 – 5.9 years), a total of 40348 person-years of follow-up. As previously reported [12] the prevalence of vertebral deformity was similar in men and women (11.7% vs 11.8%). Multiple vertebral deformities (≥ 2 deformities) were present in 3.4% of men and 3.8% of women. Compared with the men, a greater proportion of the women reported a history of previous fragility fracture (after age 50 years) (13.2% vs 5.1%).

Limb Fractures

In total, 138 men and 391 women sustained a limb fracture during the follow-up period (Table 1). Of these,

Table 1. Number of subjects with incident limb fracture by sex

	Men	Women
Hip	19 (14%)	28 (7%)
Distal forearm	32 (23%)	150 (38%)
Humerus	15 (11%)	43 (11%)
‘Other’ limb	74 (53%)	178 (45%)
Any limb fracture ^a	138 (100%)	391 (100%)

^aNumbers in cells do not add up because 10 subjects incurred more than one type of limb fracture.

the majority were fractures of the distal forearm. Ten subjects sustained more than one type of limb fracture.

Vertebral Deformity and Incident Limb Fractures

Table 2 presents the crude and age-adjusted rate ratios (RR) for the association between baseline prevalent vertebral deformity and future limb fracture in men and women. Among women, after age adjustment, those with a prevalent vertebral deformity had a modestly increased risk of sustaining ‘any’ limb fracture: rate ratio (RR) = 1.6 (95% confidence interval (CI) 1.2–2.1). In contrast, among men, there was no association between baseline deformity and subsequent ‘any’ limb fracture: RR = 1.0 (95% CI 0.6–1.7).

In women, prevalent vertebral deformity was associated with a significant increase in the risk of subsequent hip fracture: (RR = 4.5; 95% CI 2.1–9.4), a weak increase in the risk of ‘other’ limb fractures (RR = 1.6; 95% CI 1.1–2.4) and a weak though nonsignificant increase in the risk of humerus fracture (RR = 1.6; 95% CI 0.7–3.3). Thirty-six per cent of women with hip fracture had a baseline vertebral deformity. There was no association with distal forearm fracture. In men, prevalent vertebral deformity was associated with a weak though nonsignificant increase in the risk of hip fracture (RR = 1.7; 95% CI 0.6–5.1). There was no

Table 2. Relationship between prevalent vertebral deformity and incident limb fracture in men and women

Limb fracture	Men				Women			
	Baseline vertebral deformity				Baseline vertebral deformity			
	No (n = 5601) n (%) ^a	Yes (n = 743) n (%) ^b	Rate ratio, crude (95% CI)	Rate ratio, age-adjusted (95% CI)	No (n = 5989) n (%) ^a	Yes (n = 799) n (%) ^b	Rate ratio, crude (95% CI)	Rate ratio, age-adjusted (95% CI)
Hip	15 (0.3%)	4 (0.5%)	2.0 (0.7–6.2)	1.7 (0.6–5.1)	15 (0.3%)	13 (1.6%)	6.6 (3.2–13.9)	4.5 (2.1–9.4)
Distal forearm	29 (0.5%)	3 (0.4%)	0.8 (0.2–2.6)	0.8 (0.2–2.6)	131 (2.2%)	19 (2.4%)	1.1 (0.7–1.8)	1.0 (0.6–1.6)
Humerus	15 (0.3%)	0	†	†	34 (0.6%)	9 (1.1%)	2.0 (1.0–4.2)	1.6 (0.7–3.3)
Other limb	65 (1.2%)	9 (1.2%)	1.2 (0.5–2.1)	1.2 (0.6–2.4)	146 (2.4%)	32 (4.0%)	1.7 (1.1–2.4)	1.6 (1.1–2.4)
Any limb	122 (2.2%)	16 (2.2%)	1.0 (0.6–1.7)	1.0 (0.6–1.7)	318 (5.3%)	73 (9.1%)	1.8 (1.4–2.3)	1.6 (1.2–2.1)

^aNumber and percentage of individuals without vertebral deformity with individual limb fracture type.

^bNumber and percentage of individuals with vertebral deformity with individual limb fracture type.

†Too few events.

Table 3. Relationship between number of prevalent vertebral deformities and incident limb fracture in men and women

	Men Rate ratio ^a (95% CI)					Women Rate ratio ^a (95% CI)				
	Hip	Distal forearm	Humerus	Other	'Any' limb	Hip	Distal forearm	Humerus	Other	'Any' limb
No vertebral deformity ^b	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1 vertebral deformity	1.2 (0.3–5.4)	0.7 (0.2–3.1)	†	0.9 (0.4–2.2)	0.8 (0.4–1.6)	2.8 (1.0–7.7)	0.9 (0.5–1.6)	1.2 (0.3–5.4)	1.3 (0.8–2.2)	1.2 (0.9–1.7)
2+ vertebral deformities	2.7 (0.6–11.7)	0.9 (0.1–6.4)	†	1.9 (0.7–5.1)	1.5 (0.7–3.3)	7.2 (3.0–17.3)	1.2 (0.6–2.6)	2.7 (0.6–11.7)	2.4 (1.4–4.1)	2.4 (1.7–3.4)
<i>p</i> trend	<i>p</i> = 0.2	<i>p</i> = 0.7	–	<i>p</i> = 0.4	<i>p</i> = 0.6	<i>p</i> < 0.001	<i>p</i> = 0.8	<i>p</i> = 0.1	<i>p</i> = 0.002	<i>p</i> < 0.001

^aAdjusted for age. ^bIndividuals without prevalent vertebral deformity form the referent group in all analyses.

†Too few events.

increase in the risk of any of the other limb fracture types in men.

Adjustment for previous low-trauma fractures slightly reduced the strength of the association between vertebral deformity and subsequent hip fracture in women (RR = 4.2; 95% CI 2.0–9.0) and in men (RR = 1.6; 95% CI 0.5–4.9), though it did not influence the strength of the associations for the other fracture types (data not shown).

Influence of Number of Vertebral Deformities

In both sexes, increasing number of vertebral deformities was associated with an increased risk of all types of limb fracture except distal forearm fracture (Table 3). The increase in risk was greatest for hip fracture and more marked in women than in men (2+ deformities vs no deformity: women RR = 7.2; 95% CI 3.0–17.3, and men RR = 2.7; 95% CI 0.6–11.7).

Discussion

In this prospective study, radiographic vertebral deformities in women predicted hip fracture and to a lesser extent humerus and 'other' limb fracture, though not distal forearm fracture. In men there was a weak though statistically nonsignificant association with hip fracture only.

There are relatively few data concerning the relationship between radiographic vertebral deformity and future limb fracture. Vertebral fractures which come to clinical attention are associated with a 2- to 3-fold increased risk in future fragility fractures including a 1.8- to 3.8-fold risk of sustaining a hip fracture [2–6]. Such clinically apparent fractures, however, account for about one third of all vertebral fractures [8], and the extent to which these findings may be generalized beyond this group is unclear. In a population-based study, Burger et al. [9] found that subjects with severe radiographic vertebral deformity had an increased risk of future nonvertebral fractures; however, the numbers of subjects were small

and the future risk of individual fracture types was not reported [9]. Fujiwara et al. [18] in a Japanese cohort reported a 2-fold increased risk of hip fracture associated with prevalent vertebral deformities. In a more recent large study of elderly American women, radiographic vertebral deformity was associated with an increased risk of hip and any nonvertebral fracture, with relative risks of 2.8 and 1.9 respectively [10]. In contrast, after adjusting for age and BMD no increased risk was observed for wrist fracture [10]. Our data confirm these findings with an increased risk of hip and 'any' limb, though not wrist fracture, in a cohort of younger European women though the magnitude of the increased risk of hip fracture was greater than that observed in the American study.

What is the mechanism by which prevalent vertebral deformity increases the risk of future hip and other limb fractures? At least part of the explanation is that both fractures share similar underlying risk factors and in particular a reduction in bone mass [19–21]. In previous studies, however, the predictive risk of future nonvertebral fractures remained significant after adjusting for bone mass suggesting that other factors are also important [9,10]. In our study bone mass measurements were performed in a subsample (28%) of the study cohort. When we looked at 'any' limb fracture in this subsample, adjusting for BMD did not alter the strength of the observed associations. Poor bone quality, or an increased tendency to fall among those with prevalent vertebral deformity, may in part explain the increase in risk. Further studies are required in order to tease out the relative contribution of bone mass, quality and falls in explaining the increased risk.

In our study vertebral deformity did not predict future distal forearm fracture. It is possible that individuals who sustain a vertebral deformity may, because of symptoms (e.g., back pain), fear of falling or co-morbid factors, become less mobile and therefore in a fall are less likely to fall forward onto their outstretched hand and thus be less likely to sustain a distal forearm fracture [22]. Adjusting for time spent walking did not influence our findings, though it may be that other parameters of

physical activity such as walking frequency or speed, which were not assessed in our study, may be important [23,24].

We found no association between prevalent vertebral deformity and incident limb fractures in men. We have shown previously that very heavy activity undertaken during occupational or recreational life is linked with an increased risk of vertebral deformity – suggesting that trauma may be a factor in their pathogenesis [25]. The presence of multiple deformities is a stronger indicator of underlying osteoporosis than a single vertebral deformity [26] and this may explain the modest (though nonsignificant) increased risk of hip fracture which was observed in men with multiple deformities. Another possible reason for the absence of any significant associations is that compared with women a greater proportion of limb fractures in men are related to moderate or heavy trauma rather than osteoporosis [27,28].

Our study had several advantages: it was prospective, population-based and included both men and women. There are, however, several limitations which need to be considered when interpreting the results. This was a multicenter study and investigators were separately responsible for confirming the presence and site of self-reported fractures at their individual centers. It is possible errors may have arisen during this process resulting in misclassification of either fracture status or fracture type. It is likely, however, that the effect of any such misclassification would be random and tend to reduce the strength of the observed risks between vertebral deformity and subsequent limb fracture. Misclassification may also have arisen if incident limb fractures which occurred were not reported. The effect of such misclassification would again be to reduce the chance of finding significant associations. In a separate study at three of the participating centers, amongst 174 subjects with a known history of previous fracture, only 12 (7%) did not recall the event, and only 3% of subjects did not recall a hip or distal forearm fracture [13].

In 9% of fracture cases information about the presence and site of the fracture was available only from the postal questionnaire. This was in part due to inherent difficulties in access to radiographs and medical records that exist in some European countries. In some countries, for example, casualty radiographs are not routinely reported and individuals are permitted to keep their radiographs. The data on these self-reports is likely to be less accurate than reports which were confirmed. In EPOS, of those in whom verification of fracture was possible, fractures were not confirmed in 11%, though the proportion was lower for hip and wrist fractures [13]. However, restricting the analyses to those individuals in whom fractures were confirmed did not affect the results (data not shown).

In this analysis vertebral deformity was defined using a morphometric approach [12]. This approach does not distinguish between deformities due to osteoporosis and deformities due to other causes including osteoarthritis and trauma. Previous studies, however, suggest a

relatively strong association between a reduction in bone mass and morphometrically defined vertebral deformity in women and men, suggesting that osteoporosis is important in their pathogenesis in both sexes [19]. The inclusion of non-osteoporotic deformities would be likely to tend to reduce the chance of finding significant associations with future fractures. Certain deformity types appear to be more strongly associated with low bone mass than others; however, the numbers in our study were too small to permit stratification by individual deformity type [19].

Our data have important clinical and public health considerations. The results highlight the important predictive risk of radiographic vertebral deformity for future hip fracture, and also the aetiological heterogeneity of the different fracture types. Hip fracture is the major consequence of osteoporosis with significant morbidity and economic impact [29]. Vertebral fractures occur at an earlier age than hip fracture. Early identification and targeting interventions at such individuals may help to reduce the burden of morbidity due to hip fracture in later life.

In summary, we have shown that future limb fractures and particularly hip fracture are an important health outcome in women with prevalent vertebral deformities. Our data also highlight the aetiological heterogeneity of the different fracture types.

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