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CLINICAL RESEARCH

Undiagnosed Vertebral Fractures Influence Quality of Life in Postmenopausal Women With Reduced Ultrasound Parameters

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Abstract

Background Osteoporosis, a multifactorial systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to increased bone fragility, is a worldwide public health problem. Vertebral fractures affect approximately 20% of postmenopausal women and are a hallmark of osteoporosis, but they may pass unnoticed, although they may lead to long-term immobility and disability.

Questions/purposes The aims of the present study were (1) to determine the prevalence and the severity of vertebral fractures in a large cohort of Italian women aged 60 years or older with reduced values of quantitative ultrasound parameters; and (2) to assess whether vertebral fractures and other variables may be associated with health-related quality of life.

Methods A total of 2450 women without back pain aged 60 years or older, after the completion of the Quality of Life Questionnaire of the European Foundation for Osteoporosis QUALEFFO, underwent quantitative ultrasound evaluation of the calcaneus; in those with a stiffness t-score of ≤ -2 (n = 1194), radiographic evaluation of the thoracic and lumbar spine was carried out and then quantitative morphometry was performed by dedicated software (MorphoXpress). The radiographic analysis was carried out on 885 women who presented films of adequate quality. Multivariate regression was used to adjust for confounding variables.

Results Of those who underwent radiographic analysis, 681 had no vertebral fractures, and 204 women (23.1%) had one or more previously undiagnosed vertebral fractures. The prevalence of previously undiagnosed vertebral fractures increased with advancing age with more than 30% of women older than 75 years having at least one fracture. Older age, body mass index, and severe vertebral fractures were independently associated with a worse total QUALEFFO score.

Conclusions We found that approximately one in four women showed evidence of undiagnosed vertebral fractures, and there was a strong age effect trend. Moreover, the severity grade of vertebral fractures, more than the number of fractures, was associated with a worsening of health-related quality of life as assessed by QUALEFFO. These findings confirm the clinical relevance of an early diagnosis of vertebral fractures and seem to support the usefulness of quantitative ultrasound measurements in the stratification of postmenopausal women at increased fracture risk.

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.
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Level of Evidence Level III, prognostic study. See the Guidelines for Authors for a complete description of levels of evidence.

Introduction

Osteoporosis, a multifactorial systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to increased bone fragility, is a worldwide public health problem [25]. The clinical and economic burden of osteoporosis is primarily the result of fractures and consequent morbidity [3]. Osteoporosis occurs primarily in women (80%) with postmenopausal women being at particularly high risk. Osteoporosis has a major economic impact with an estimated two million osteoporosis-related fractures occurring in the United States alone, consuming $17 billion in direct care costs [1]. Fractures resulting from osteoporosis are most frequent in the proximal femur, the distal radius, and the vertebrae. Vertebral fractures affect approximately 20% of postmenopausal women and are a hallmark of osteoporosis [27]. Vertebral fractures may be minor and pass unnoticed or they may lead to long-term immobility and disability.

It has been estimated that only one-in-three to one-in-five vertebral fractures come to clinical attention [27]. It has been reported that postmenopausal women with prior or incidental vertebral fractures are at higher risk of both vertebral and nonvertebral fractures than women without previous fractures independent of bone density [17, 20]. In particular, Lindsay et al. [20] reported that the occurrence of an incidental vertebral fracture markedly increases the risk of a second one within 12 months. Several other studies have shown that in postmenopausal women the consequences of vertebral fractures are markedly influenced by the number and severity of prior vertebral fractures [7, 27]. It has been reported that patients with multiple fractures are at increased risk of morbidity and mortality [2, 14]. Therefore, the recognition of vertebral fractures is critical for the prediction of possible future fractures. Several longitudinal studies have suggested that new vertebral fractures, even those not coming to clinical attention, may be associated with a substantial increase in back pain and functional limitation [26, 32]. A fracture may also decrease mobility and social interaction and cause emotional problems with consequent worsening of the health-related quality of life [22]. At present, the literature does not draw any definitive conclusions regarding whether osteoporosis, in the absence of known fracture, causes a worsening of the health-related quality of life [29, 34].

Although the presence of vertebral fractures as an independent risk factor for fractures is universally accepted, currently screening spine radiographs are not recommended in the guidelines of fracture risk assessment, except in those individuals who are known to be at increased risk [15, 24]. For this purpose, the last two decades have seen increased interest in using quantitative ultrasound techniques for the identification of subjects at increased risk of osteoporosis and fragility fractures [12, 19]. Moreover, several studies have clearly documented the ability of quantitative ultrasound measurements at calcaneus to predict fragility fracture risk independently of bone mineral density [16, 19, 23].

The aim of the present study was twofold: first, to determine the prevalence and the severity of vertebral fractures in a large cohort of Italian women aged 60 years or older with reduced values of quantitative ultrasound parameters at the calcaneus; and second, to assess whether vertebral deformities, stiffness index, and other variables may be associated with health-related quality of life.

Patients and Methods

Study Sample

A total of 55 Italian centers located in both academic and nonacademic general hospitals dealing with diseases relevant to internal medicine, and equipped with facilities for the diagnosis of osteoporosis, were invited to participate in the Fracture Evaluation by Digital Radiography Observational (FEDRO) study. In each center, experienced clinicians recruited up to 50 ambulatory postmenopausal women referred by their family physicians as outpatients for their specialist visit and who satisfied the following inclusion criteria: age 60 years or older and in menopause (spontaneous or surgical) for at least 5 years. The women were excluded if they had been referred by physicians for acute back pain, if they were taking glucocorticoids or antiosteoporotic drugs (apart from calcium/vitamin D supplements), and if they had a previous diagnosis of osteoporosis or vertebral fractures. Other exclusion criteria were presence of malignancy, history of alcohol abuse ($>$ 400 g/week), cognitive problems that could prevent reliable completion of the questionnaire, any treatment in the last 12 months with drugs known to influence bone metabolism, and a history of fractures over the preceding 12 months. Each woman underwent a structural medical interview (including questions on the presence of comorbidities, use of specific drugs, major risk factors for osteoporosis), the administration of the Italian version of the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO), and the evaluation of bone status by using quantitative ultrasound (QUS) at calcaneus. The comorbidities taken into consideration were

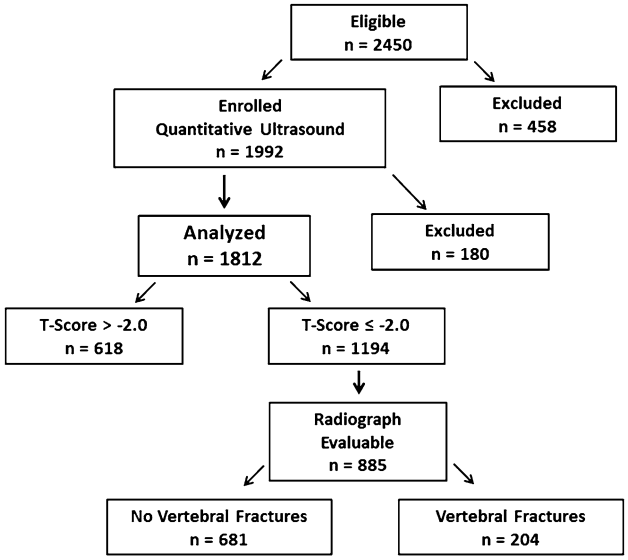

Fig. 1 The figure shows the diagrammatic representation of the study population.

diabetes, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, hypertension, cerebrovascular diseases, peptic ulcer, depression, and Parkinson disease.

Of the 2450 eligible postmenopausal women (age range, 60–86 years), 458 were eliminated as a consequence of stringent inclusion/exclusion criteria (n = 292), impossible or inadequate completion of the QUALEFFO questionnaire (n = 122), or inadequate evaluation of quantitative ultrasound parameters at calcaneus for edema, deformities, or movement artifacts (n = 44). Moreover, 180 subjects were discarded due to the lack or incompleteness of data. Of the remaining 1992 women, 618 presented a stiffness t-score of > -2 and 1194 a stiffness t-score of ≤ -2. These women were asked to undergo radiographic evaluation of the thoracic and lumbar spine; 1045 of them accepted, but 146 were disqualified for the study as a result of inadequate radiographic quality and in 14 women, the radiographs were lost during the process of centralized evaluation. Therefore, the analysis was carried out on the remaining 885 postmenopausal women (Fig. 1).

Measurement

The quantitative ultrasound measurements were carried using the Achilles Express apparatus (GE-Lunar, Madison, WI, USA). Before the study began, a protocol to standardize the methodology of the measurement was sent to each participating center. All instruments were calibrated daily in accordance with the manufacturer's recommendations, and in each center, all measurements were taken by the same operator. Quantitative ultrasound measurements were performed at the right os calcis; in the case of a previous fracture within the right lower extremity, the contralateral calcaneus was measured. The broadband ultrasound attenuation (BUA) and speed of sound (SOS) were measured. The Stiffness Index (SI), a composite parameter obtained by a mathematical combination of BUA and SOS, was calculated by the software of the device and expressed as a percentage of values for young subjects.

By using European normative data, the stiffness value of 72% corresponds to a -2 t-score, as assessed by World Health Organization criteria. The women with a t-score of > -2 did not undergo further evaluations, whereas in those with a t-score of ≤ -2, two radiographs of the thoracic and lumbar spine in lateral projection were obtained according to standardized procedures.

The study protocol was prepared according to the Declaration of Helsinki and subsequent relevant integrations. Written consent was obtained from all participants, and the study was approved by the local ethical committee of each center.

The QUALEFFO questionnaire was developed and validated in different languages including Italian in a multicenter international study showing adequate test–retest reliability, internal consistency, and discriminatory ability between patients with vertebral fractures and control subjects [21, 22]. This tool includes five domains: pain, physical function (divided into three subdomains: activities of daily living, jobs around the house, and mobility), social function, general health perception, and mental function. The individual item scores for each domain are averaged, and the mean score for each domain is transformed linearly onto a 0 to 100 score, where 0 corresponds to best health-related quality of life and 100 to worst health-related quality of life. Finally, the QUALEFFO total score was calculated as an average of the transformed domain scores. Therefore, the five domains were presented individually and as a total score. To limit possible biases related to disease awareness, QUALEFFO was administered before quantitative ultrasound measurement and radiographic evaluation.

Assessment of Vertebral Fractures

All radiographs were examined centrally (at San Giovanni Rotondo, FG, Italy) for the presence of any vertebral deformities by an experienced radiologist (GG) who was unaware of the patients' characteristics. First, a qualitative evaluation was made to exclude vertebral deformity causes other than osteoporotic fractures and poor radiographs. Subsequently, the vertebrae were identified and morphometry was performed from the fourth thoracic vertebra (T4) to the fourth lumbar vertebra (L4) by using dedicated software for quantitative morphometry (MorphoXpress;

P&G Pharmaceuticals, Egham, UK). The characteristics and performance of MorphoXpress have been reported in detail in a recent paper by one of the authors (GG) [11]. In brief, MorphoXpress operates as follows: analysis is initialized by the manual targeting of the centers of upper and lower vertebrae to be analyzed. The software then automatically finds the positions of landmarks for a standard six-point morphometry measurement. The software then allows these points to be moved by the operator, if deemed necessary, before the points are confirmed as being correct [11]. Then the anterior (Ha), midvertebral (Hm), and posterior (Hp) heights of each vertebra were measured and the three ratios, Ha/Hp, Hm/Hp, and Hp/Hp-below, were calculated.

The fractures were defined as mild, moderate, or severe based on a height ratio decrease of 20% to 25%, 25% to 40%, and over 40%, respectively, according to Genant et al.'s graduation [9]. In all patients, we also evaluated the Spinal Deformity Index (SDI). SDI is an assessment tool similar to the Genant semiquantitative (SQ) approach, which integrates both the number and the severity of vertebral fractures. SDI is obtained by summing the vertebral fracture grades along the spine from T4 to L4 where SQ0 indicates absence of fracture and SQ1, SQ2, and SQ3 indicate mild, moderate, or severe fracture, respectively [6]. Therefore, for each subject, the SDI was calculated by summing up the SQ grade for each of the 13 vertebrae from T4 to L4 (SDI = SQT4+…+SQT12+SQL1…+SQL4) [6].

Statistical Analysis

All analyses were performed with the Statistical Package for Social Sciences, for Windows, Version 16.0 (SPSS, Inc, Chicago, IL, USA). Continuous variables were expressed as means and SDs, unless differently specified, and categorical variables as percentages. Differences in demographic, anthropometric, and clinical characteristics between women with and without morphometric vertebral fractures were evaluated by using the Mann Whitney test, whereas the chi–square test for trend (Mantel–Haenszel extension) was calculated to assess a significant increase/decrease in prevalence of previously undiagnosed vertebral fractures across age groups by fracture severity.

Patients' characteristics significantly associated with total QUALEFFO score at univariate analysis were entered into the multiple linear regression model (Method: Enter) in which the primary outcome was total QUALEFFO and the presence of severe fractures (yes/no) the main predictor while adjusting for potential confounders, including age, body mass index, age at menopause, number of pregnancies, comorbidities (yes/no), and stiffness. All assumptions underlying the multiple regression analysis were satisfied and the collinearity diagnostics (VIF and Condition index) confirmed the independence of covariates included in the model.

Median score differences in total QUALEFFO and pain, physical function, social function, general health perception, and mental health domains by type of fracture were analyzed by the Kruskal–Wallis test. A two-tailed p value < 0.05 was considered statistically significant.

Results

Of the 885 postmenopausal women who underwent imaging of the spine because of low quantitative ultrasound scores and with radiographic films of adequate quality, 681 (76.9%) had no vertebral fractures, and 204 women (23.1%) had one or more vertebral fractures. The demographic, clinical, and ultrasonographic characteristics of the 885 women grouped according to the presence of any previously undiagnosed vertebral fractures were similar (Table 1). However, the women with asymptomatic vertebral fractures were older than those without (69.7 versus 68.3 years, $p < 0.01$). Grouping the 885 postmenopausal women by a 5-year age interval, we found that prevalence of previously undiagnosed vertebral fractures increased with advancing age ($p < 0.001$) with more than 30% of women older than 75 years demonstrating at least one previously undiagnosed vertebral fracture (Table 2). The distribution of vertebral fractures along the spine showed a peak at T7 to T9; a second less prominent peak was observed at L1 (Fig. 2). It is evident that whereas moderate/severe fractures were homogeneously distributed along the spine, mild fractures were notably prevalent at the thoracic level.

Table 1. Demographic, anthropometric, and clinical characteristics of 885 postmenopausal women with or without morphometric vertebral fractures

Characteristics	No vertebral fractures (n = 681)	Vertebral fractures (n = 204)	p value
Weight (kg)	66.4 ± 11.4	65.8 ± 11.1	0.06
Height (cm)	158.2 ± 6.3	157.9 ± 6.1	NS
Body mass index (kg/m^2)	26.6 ± 4.6	26.3 ± 4.4	NS
Age at menopause (years)	48.6 ± 5.4	48.4 ± 5.2	NS
Stiffness (%)	65.0 ± 11.5	64.1 ± 11.2	NS
Stiffness (t-score)	−2.5 ± 0.8	−2.6 ± 0.8	NS
Comorbidities, number/total number (%)	547/681 (80.4%)	177/204 (83.7%)	NS

NS = nonsignificant.

Table 2. Prevalence of asymptomatic vertebral fractures in 885 postmenopausal women according to age and fracture severity

	Age (years)					
Vertebral fracture	60–64	65–69	70–74	75–79	≥ 80	p value
No fracture (%)	81.7	79	77.2	69.8	66.2	0.0001
Mild fracture (%)	13.2	15.5	16.3	19.5	19.1	0.99
Moderate fracture (%)	4.1	4.3	5.5	9	11.7	0.004
Severe fracture (%)	1	1.2	1	1.6	3	0.12

Results are presented as the frequency and severity of fracture (%) for each quinquennium.

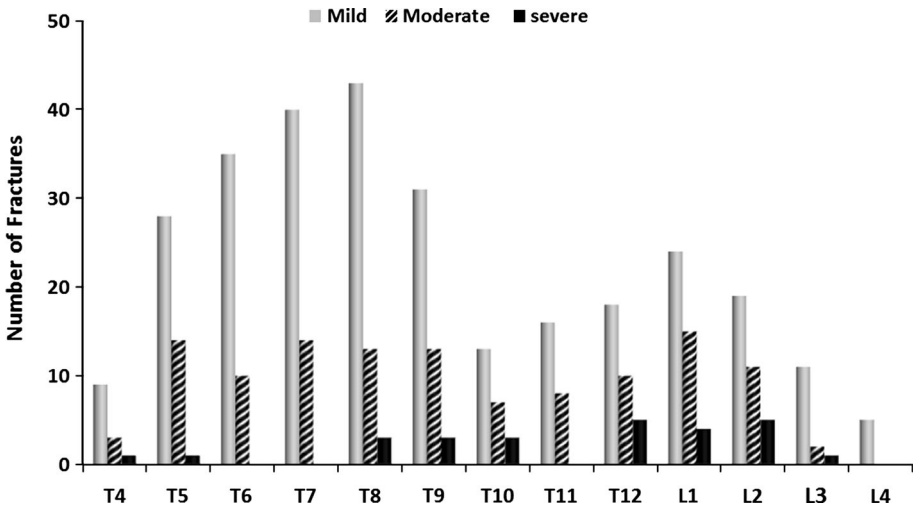

Fig. 2 Distribution of asymptomatic vertebral fractures in 885 postmenopausal women is shown according to vertebral level and fracture severity.

The mean scores for the component domains of the QUALEFFO and total QUALEFFO score in women without vertebral fractures and in those with mild, moderate, or severe vertebral fractures have been reported (Table 3). The women with higher grades of vertebral deformity had a lower quality of life in all domains but the differences reached statistical significance only for the QUALEFFO total score ($p = 0.02$) and general health perception ($p = 0.04$). We also evaluated the scores of QUALEFFO in the 885 postmenopausal women grouped on the basis of SDI (SDI = 0; SDI = 1–2; SDI ≥ 3) and we found no significant differences. Multivariate regression analysis carried out to identify patients characteristics related to the QUALEFFO total score showed that severe vertebral fractures, age, and body mass index were independently associated with a worsening of total QUALEFFO score (Table 4).

Discussion

Although the presence of vertebral fractures as an independent risk factor for further vertebral or hip fractures is universally accepted, at present, spine radiographs are not recommended in current guidelines of fracture risk assessment but could be suggested only in the case of those individuals who are at increased risk [15, 24]. For this purpose, quantitative ultrasound techniques may represent an interesting tool for the identification of subjects at increased risk of fragility fractures [12, 19]. The major finding of this study was that approximately one in four postmenopausal women in apparently good health, but with reduced SI, had sustained at least one vertebral fracture. In accordance with previous surveys, we found that the prevalence and the severity of vertebral fractures in such women increase steadily with age [4, 7, 10, 13, 24, 27, 31, 35]. In addition, we found the presence of an undiagnosed osteoporotic vertebral fracture was an independent risk factor for inferior quality-of-life scores using the QUALEFFO tool.

Our study has some limitations, the most important of these being its cross-sectional nature, which does not allow for the establishment of any casual relationships between the parameters. Moreover, because radiographic evaluation was carried out only in women with reduced SI, any extension to a general population should be treated with

Table 3. Scores for the five QUALEFFO domains and the total QUALEFFO score in patients grouped according to the presence and type of vertebral fractures

Domain	No fracture	Mild	Moderate	Severe	p value*
Pain	39.9 (19.8–59.9)	39.9 (19.8–59.9)	39.9 (19.8–59.9)	39.9 (19.8–59.9)	0.161
Physical function	21.9 (9.6–41.6)	19.1 (7.8–40.1)	22.9 (8.4–42.6)	30.8 (16.1–48.0)	0.08
Social function	48.7 (31.3–66.1)	46.1 (33.3–60.0)	52.9 (30.6–72.0)	64.3 (47.7–76.1)	0.135
General health perception	56.3 (39.7–74.1)	58.3 (41.6–66.6)	58.3 (41.7–75.0)	75.0 (58.3–83.3)	0.043
Mental function	40.4 (23.7–55.3)	38.9 (22.2–50.1)	38.8 (26.4–51.3)	50.0 (35.4–63.9)	0.054
Total QUALEFFO score	38.7 (28.5–48.3)	36.6 (27.9–48.6)	42.3 (32.9–49.9)	50.7 (42.7–55.4)	0.024

All values are expressed as median (interquartile range); * Mann Whitney test; QUALEFFO = Quality of Life Questionnaire of the European Foundation for Osteoporosis.

Table 4. Patients characteristics influencing total QUALEFFO score in multivariate analysis (n = 885)

	Multivariate analysis		
Variables	β	SE	p
Fractures severe (yes/no)	10.37	5.2	0.046
Age (years)	0.54	0.18	0.004
Body mass index (kg/m^2)	0.55	0.17	0.001
Age at menopause (years)	0.02	0.15	0.884
Number of pregnancies	0.92	0.63	0.147
Comorbidities (yes/no)	1.86	1.8	0.304
Stiffness (%)	−0.51	0.07	0.463

QUALEFFO = Quality of Life Questionnaire of the European Foundation for Osteoporosis.

caution. Also, the lack of any information on vitamin D levels, calcium intake, and physical activity may represent a limitation. Moreover, data on comorbidities are based on patients' reports without any further validation of objectivity. Finally, the fact that in this study no intraobserver repeatability testing was carried out, the accuracy in the centralized evaluation of vertebral deformities was assured by the use of a reproducible semiautomatic method recently validated by one of the authors (GG) [11].

The prevalence of unrecognized vertebral fractures (23%) in our study was higher than that observed in previous studies [35]. In fact, in the European Vertebral Osteoporosis Study (EVOS), the prevalence of fractures in postmenopausal women aged 50 to 79 years, randomly recruited from the general population, varied from 12.0% to 20.2% according to the McCloskey and Eastell method, respectively, and from 11.1% to 20% according to geographic differences [27]. Also, Clark et al. [4] in an age-stratified random sample of women aged 50 years or older from South America found a prevalence increasing from 6.9% in women aged 50 to 59 years to 27.8% in those aged 80 years or older. This difference may be the result of the fact that the age of our study population was a minimum of 60 years and that the morphometric evaluation was carried out only on those women with a quantitative ultrasound t-score ≤ -2.0 and therefore with a mild increase in fracture risk. On the other hand, other studies found a higher prevalence of vertebral fractures with respect to our population [31]. It is well known that the estimated prevalence rate of vertebral fractures in a population depends heavily on the diagnostic criteria used. For these reasons, we chose to use both the semiquantitative assessment derived by Genant et al. [9], which allows good differential diagnosis of vertebral deformities, and the quantitative morphometry using dedicated software, which guarantees high precision in the assessment of the height of the vertebrae.

In agreement with several studies [26], but in contrast to others [8], we have found that lumbar fractures present a higher impact on the quality of life. This could be explained by the fact that the ratio of moderate to severe/mild fractures is markedly higher in the lumbar spine than in the thoracic spine; therefore, the location of fractures seems to have a lower impact on health-related quality of life than the severity of the deformities. Another important finding of our study is that the severity of vertebral deformities has a markedly negative impact on health-related quality of life. In fact, in our study, the presence of moderate/severe fractures was associated with a worsening of QUALEFFO scores more than the presence of mild deformities. A possible explanation of this finding may be that some mild deformities are not true vertebral osteoporotic fractures but may be anatomic variants or degenerative abnormalities. Pluijm et al. [28] in a longitudinal study reported that, in contrast with more severe deformity, the presence of mild vertebral deformities only was not significantly associated with any of the outcome measures of functioning and well-being. In our study the domain "pain" did not show any differences between patients with or without vertebral fractures or among patients according to the number and grades of vertebral fractures. This finding is in agreement with some recent studies [8, 31] but in disagreement with others [22, 26], which found that pain domain was discriminant in

osteoporotic women. However, these latter studies enrolled patients on the basis of symptoms related to clinically apparent fractures and compared them with patients without back pain. Moreover, in the QUALEFFO questionnaire, the questions about back pain focus on current or recent pain and cannot capture episodes of back pain, which have been resolved [8]. It is well known that the pain associated with a fragility vertebral fracture progressively diminishes and reaches a stable level within 3 years [30]. In fact, chronic pain lasting more than 3 years is uncommon and can be observed only in patients with more severe fractures [8]. This seems to be confirmed by the fact that in our population, a nonsignificant worsening in pain domain was observed only in patients with a markedly elevated vertebral fracture load (SDI $\geq$ 3). The suggestion that the number of fractures is also an important determinant of the worsening of quality of life has been supported by the observation that the impact of any recent vertebral fracture is more marked in the patients who had already sustained a previous vertebral deformity [5]. Moreover, it is important to note that in elderly women, back pain is multifactorial and is often the result of osteoarthritis, a protruded disk, and muscle diseases [18, 33]. In our study population, we found that reduced values of stiffness are associated to a lowering of health-related quality of life; however, the association was no longer significant after adjusting for potential confounders such as age, comorbidities, and fractures.

We observed that in a large cohort of postmenopausal ambulatory women with reduced SI at the calcaneus, approximately one in four women evidenced undiagnosed vertebral fractures showing a strong age effect trend. Moreover, the severity grade of vertebral fractures, more than the number of fractures, was associated with a worsening of health-related quality of life as assessed by QUALEFFO. At present, a radiological screening for vertebral fractures is not possible for an entire elderly population but would be appropriate for those individuals who are known to be at increased risk. For this purpose, our findings seem to support the usefulness of quantitative ultrasound measurements in the stratification of vertebral fracture risk. The early identification of postmenopausal women with undiagnosed vertebral fracture may be relevant, because this may permit better treatment and could possibly avoid a further decrease in their quality of life later in life. Further studies are necessary to define the most suitable age for quantitative ultrasound screening and the cost-effectiveness of such a strategy.

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