The Burden of Prevalent Fractures on Health-Related Quality of Life in Postmenopausal Women with Osteoporosis: The IMOF Study

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ABSTRACT. ***Objective.*** Vertebral fractures are a common complication of osteoporosis and may have a negative effect on health-related quality of life (HRQOL). We investigated the effect of prevalent vertebral fractures on HRQOL in patients with osteoporosis.

Methods. A cross-sectional multicenter study was carried out among postmenopausal women with primary osteoporosis attending primary care centers and hospital outpatient clinics: 234 women with vertebral fractures and 244 asymptomatic women. Women with secondary osteoporosis or taking medications that affect bone metabolism were excluded. All patients were questioned using the mini-Osteoporosis Quality of Life Questionnaire (mini-OQLQ), Medical Outcomes Study Short Form-36 (SF-36), and the EuroQuol-5D, after assessment of all clinical variables and anthropometric data. To assess comorbidity we used the Self-Administered Comorbidity Questionnaire (SCQ). Diagnosis of osteoporosis was confirmed in all patients by bone mineral density using dual energy x-ray absorptiometry. Radiographic evaluation was performed by a musculoskeletal radiologist. A total of 483 postmenopausal women, randomly matched for age out of 1579 healthy controls, were chosen to compare the SF-36 scores with respect to patients with and without vertebral fractures due to osteoporosis. A multivariable regression analysis was conducted to identify the strongest determinant for low HRQOL, adjusted for potential confounding variables such as comorbid conditions, education level, and psychosocial status.

Results. The vertebral fracture group had significantly lower scores than patients without fractures and controls in all domains of the generic and specific questionnaires. Women with only 1 prevalent fracture had statistically significantly lower HRQOL scores than those without fractures on SF-36 measures of bodily pain, physical functioning, and role function physical (all $p < 0.01$). HRQOL scores were lower in women with lumbar fractures compared with women with thoracic fractures only when the physical functioning and bodily pain dimensions approached statistical significance. Based on the multivariate analysis, the strongest determinant for low HRQOL was physical functioning (explained by number of vertebral fractures) followed by comorbidity score and age. Adjusted R^2 in the final model was 35.9%. Using the SF-36 summary scales, comorbid conditions predominantly affected either mental or physical health ($p < 0.0001$). A significant correlation ($p < 0.0001$) was found between total score on the mini-OQLQ and the mean SCQ comorbidity score.

Conclusion. Our results confirm previous findings that HRQOL, assessed by generic and osteoporosis-specific instruments, is decreased in patients with vertebral fractures due to osteoporosis as a function of the number of vertebral fractures, presence of comorbid conditions, and age. (First Release May 15 2007; J Rheumatol 2007;34:1551–60)

Key Indexing Terms:
VERTEBRAL FRACTURE
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QUESTIONNAIRE

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Osteoporosis is a disease characterized by low bone mineral density (BMD) and microarchitectural deterioration of the bone, resulting in loss of bone strength and therefore an increase in fracture risk[1]. Vertebral fractures are the most common clinical manifestation of osteoporosis: > 30% of women aged 75 years and 50% of women aged ≥ 85 years have experienced a nontraumatic vertebral fracture[2]. Prevalent vertebral fracture has a strong predictive value for future fractures, even after adjustment for age and BMD. The relative risk of future vertebral fractures increased progressively in patients with severe vertebral fractures and in those with multiple vertebral fractures — from 3.1 in those with one fracture to 10.6 in those with ≥ 3 vertebral fractures[3]. However, according to recent estimates, only about one-third of vertebral fractures come to medical attention[4]. Studies also describe that the progression of spinal osteoporosis with vertebral fractures resulted in a progressive decline in the patient's health-related quality of life (HRQOL)[5-9]. Vertebral fractures also cause postural deformities that induce chronic back pain and disability in physical activities, loss of self-esteem, and depression[10,11]. The societal burden of these fractures, in terms of costs and reduction in survival and HRQOL for the individuals affected, makes osteoporosis an important and increasing public health issue[12]. Assessment of HRQOL plays an increasingly important role in evaluating the burden of osteoporosis in a patient's daily life. HRQOL is defined as "the value assigned to life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, and treatment." It is commonly assessed using generic or disease-specific questionnaires. Generic HRQOL instruments such as the Medical Outcomes Study Short Form-36 (SF-36)[13], the Sickness Impact Profile[14], the Nottingham Health Profile[15], and the EuroQuol-5D (EQ-5D)[16] have revealed a reduction in physical functions in patients with vertebral fractures[5,7,9], and a disease-specific quality of life questionnaire of the European Foundation for Osteoporosis (QUALEFFO)[17] designed for use in clinical trials has demonstrated a relationship between increasing numbers of prevalent vertebral fractures and a reduction in HRQOL[6,9]. Severity of vertebral fracture is a significant predictor of back pain and back-related disability[10,18]. Other osteoporosis-targeted quality of life questionnaires such as the Osteoporosis Quality of Life Questionnaire (OQLQ)[19], the Osteoporosis Assessment Questionnaire[20], the Osteoporosis-Targeted Quality of Life[21], and the ECOS-16, developed to assess physical difficulties, fears, and adaptations to daily living in a cohort of women in the community[22], also confirmed reports of impaired psychological and physical function in women with osteoporosis and vertebral fractures[5,6,8-11,18].

We assessed the effect of prevalent vertebral fractures on HRQOL in patients with postmenopausal osteoporosis in comparison with asymptomatic osteoporotic subjects and with healthy controls. We employed the generic SF-36 and EQ-5D instruments for their validation qualities and capacity for comparisons between different diagnoses. A secondary aim was to identify the strongest determinant for low HRQOL.

MATERIALS AND METHODS

Recruitment of patients. In this cross-sectional multicenter study we investigated 478 postmenopausal women (mean age 68.5 yrs, range 48–89 yrs) with primary clinically stable osteoporosis (no change in treatment and no new clinical deformities in the last 12 mo) attending primary care centers and hospital outpatient clinics. The patient group included 234 women (mean age 69 yrs, range 48–89) who had vertebral fractures due to osteoporosis, and a group of 244 asymptomatic osteoporotic women matched for age with the patients with vertebral fractures. The women were screened in 5 rheumatology centers in Northern and Central Italy. A simple algorithm, the OPERA[23], based on age, weight, history of previous low impact fracture, early menopause, and corticosteroid therapy, was used as a prescreening tool to help clinicians identify which women are at increased risk for osteoporosis. Diagnosis of osteoporosis was confirmed by bone mineral density (BMD) using dual-energy x-ray absorptiometry (DEXA). Osteoporosis was defined as a T score lower than –2.5 (the difference between the measured BMD and the mean value of young adults, expressed in standard deviations), according to the World Health Organization Study Group definition[24]. All measurements at the left femoral neck and lumbar spine (L1–L4), in the anteroposterior position, were obtained using the Hologic scanner (Hologic QDR 4500; Hologic, Bedford, MA, USA). One of the inevitable limitations of the study was the use of different densitometry machines, yielding noncomparable BMD data. Thus, machines at each participating center were cross-calibrated at the beginning of the study using the same spine phantom (supplied by the manufacturer). Each phantom was scanned 10 times at each study center. Quality control procedures were followed according to the manufacturer's recommendations. T scores were based on a large European and US reference database for BMD[25]. Radiographic evaluation was performed centrally (at the Department of Radiology of the Università Politecnica delle Marche) by an experienced musculoskeletal radiologist. Total spine radiographs in lateral standing views in neutral/flexion/extension and in the lateral decubitus position in flexion/extension were taken with a film–tube distance of 1.8 m. The anterior, central, and posterior heights of each of the vertebral bodies from T4 to L5 in a neutral standing radiograph were measured using calipers. Vertebral fracture was considered present if at least one of 3 height measurements (anterior, middle, posterior) of one vertebra had decreased by more than 20% compared with the height of the nearest uncompressed vertebral body[26]. Vertebrae that could not be evaluated radiographically because of kyphosis, fusion, or other structural anomalies (such as severe degenerative changes) were excluded. Fractures caused by other diseases such as cancer were not included. Other exclusion criteria were as follows: (1) concurrent systemic inflammatory rheumatic disease or other disease that might explain the patient's back pain (such as severe scoliosis, lumbar spondylolisthesis, lumbar disc disease, or fibromyalgia); (2) history of metabolic bone disease (including hyperparathyroidism, osteomalacia, Paget's disease); (3) medical comorbidity that would render the patient unable to participate fully in study procedures (e.g., terminal conditions such as endstage renal disease, heart failure, or malignancy); (4) severe psychiatric emotional, cognitive, or speech impairments that would prevent them answering questionnaires; (5) hip fracture in the previous year with impaired walking; and (6) patients with recent (previous 6 mo) clinical vertebral fractures or who had had total hip prosthesis surgery in the previous 6 months for non-osteoporotic reasons. In addition, women who had recently been prescribed bisphosphonates, fluoride, or calcitonin were excluded.

Further, 483 postmenopausal women (mean age 69.1 yrs, range 50–87) randomly matched for age out of 1579 healthy controls were chosen for comparison of SF-36 scores of patients with and without vertebral fractures due to osteoporosis. Subjects with fibromyalgia, chronic back pain, and vertebral or other fractures were excluded. As acquisition of radiographs in the control group study was considered unethical in the context of the study, inclusion in this group depended on oral confirmation that the individual had never received a clinical diagnosis of vertebral or other fracture. This sample was selected from a previous cross-sectional population-based study, the MAPPING (MArche Pain Prevalence INvestigation Group) study[27].

All patients and healthy controls provided informed consent, and the appropriate review committees approved the study.

Background and illness-related variables. Demographic and socioeconomic information was assessed from patient interviews. Education level was separated into 3 categories based on the Italian school system: 1 = primary school, 2 = secondary school, and 3 = high school or university. The body mass index (BMI, body weight/height^2) was used to assess overweight. In all patients the presence of comorbidities was also assessed through patient self-reports using the Self-Administered Comorbidity Questionnaire (SCQ)[28], a modification of the widely used Charlson Index[29]. The SCQ uses patient interview or questionnaire responses rather than chart abstraction for assessment of comorbidity and is in excellent agreement with the chart-based Charlson Index[28]. We evaluated the rate of endorsement of each of 12 specific conditions as well as the number of conditions endorsed. We also calculated a score with 1 point if the condition was endorsed and additional points if the subject reported currently receiving treatment for it, or if it limited activities. Each condition could, therefore, contribute 0 to 3 points for a maximum of 36 points.

HRQOL questionnaires. The mini-OQLQ[30], SF-36[13], and EQ-5D[16] were administered in all patients, and all clinical variables and sociodemographic variables were taken into account.

Mini-Osteoporosis Quality of Life Questionnaire. The Italian version of the mini-OQLQ was used to measure HRQOL[31]; it was derived from the original 30-item OQLQ[19,30] to enhance its usefulness in clinical practice. It includes the 2 items from the OQLQ with the highest impact in each of the 5 domains (symptoms, physical functioning, emotional functioning, activities of daily living, and leisure), for a total of 10 items, each associated with a 7-point scale. The total score can vary from 10 to 70, while the domain scores can vary from 2 to 14. To standardize all scores, the total and domain scores were divided by the number of items that were used to generate the values. A standardized rating of 1 represents the worst possible function (extreme difficulties, constant fear, extreme distress) and a rating of 7 the best possible function (no difficulties, no fear, no distress).

Medical Outcomes Study Short Form-36. The SF-36 is a generic instrument with scores based on responses to individual questions that are summarized in 8 scales, each of which measures a health concept[13], i.e., bodily pain, physical functioning, general health perception, role function–physical aspect, role function–emotional aspect, vitality, social functioning, and mental health[13]. These 8 scales, weighted according to normative data, are scored from 0 to 100, with higher scores reflecting a better quality of life. The SF-36 has been validated for use in Italy[32] and it can be completed within 15 min by most people. Recently, the creators of the SF-36 have developed algorithms to calculate 2 psychometric summary measures: the physical component summary scale score (PCS) and the mental component summary scale score (MCS)[33]. The PCS and MCS provide greater precision, reduce the number of statistical comparisons needed, and eliminate the floor and ceiling effects noted in several of the subscales[33]. Normative values for the SF-36 were obtained from a large local population study in Italy, made up of 483 women, from whom age and sex-matched controls were selected randomly[27].

EUROQoL-5D. The EQ-5D is a standardized self-administered questionnaire that classifies the patient in one of 243 health states[16]. It describes HRQOL in terms of 5 dimensions: mobility, self-care, usual activities (work, study, housework, family or leisure), pain/discomfort, and anxiety/depression. Each dimension is subdivided into 3 levels indicating no problem, a moderate problem, or an extreme problem. Different health states can be described using a 5-digit code number relating to the relevant level of each dimension. A perception of "own health state" as measured by visual analog scale (VAS) is also part of the EQ-5D but is scored separately. The anchors for this graduated 20 cm scale (0–100 points) are "worst immaginable health state" at 0, and "best imaginable health state" at 100. Respondents classify and rate their health on the day of the survey. Thus, data from EQ-5D can be represented in 3 distinct forms; Part 1 may be presented either as a profile ($EQ\text{-}5D_{profile}$), based on the unweighted responses indicating a patient's level of problem in each of the 5 domains, or as a health index ($EQ\text{-}5D_{utility}$), by applying a suitable weighting system such as the utilities obtained from the UK national survey. The VAS rating in Part 1 can be interpreted directly as a quantitative measure of the patient's evaluation of their own global health status ($EQ\text{-}5D_{VAS}$). The validity and reliability of the EQ-5D have proved acceptable for different populations and patient groups[6,27].

Statistical analysis. Parametric techniques may be applicable for certain ordinal level data; however, our data were generally not normally distributed (Kolmogorov-Smirnov test for normal distribution) and therefore the use of nonparametric techniques provided a more conservative estimate of statistical significance. Where appropriate, median and interquartile ranges are given, as well as mean and standard deviations. The differences among the groups were computed by the Mann-Whitney U-test and Kruskal-Wallis one-way analysis of variance for continuous variables or ordinal scaled scores and Fisher's exact test for categorical variables. To identify fracture locations that had the strongest association with HRQOL, patients were divided into 3 groups: no fracture, thoracic (T4–T12) fracture only, and lumbar (L1–L4) fracture only. Women with fractures in both the lumbar and thoracic spine regions were excluded from this fracture location analysis. This analysis included only women with ≥ 2 vertebral fractures. Intraobserver reproducibility was determined by the unweighted kappa (k) statistics. Correlations between variables were analyzed using Spearman rho correlation coefficients. Finally, to investigate which variables correlated best with HRQOL, multiple regression analysis was undertaken with dependent variables: 8 SF-36 dimensions and the summary scores. Independent variables were age, BMI, lumbar spine BMD (T score), comorbidity score by SCQ questionnaire, years postmenopause, and number of fractures. All differences were tested at a 2-sided significance level of $p < 0.05$. All data were stored in a FileMaker 7.0 relational database for Macintosh and processed with SPSS (v. 11.0) and MedCalc (v. 9.0) statistical software for Windows XP.

RESULTS

The mean age of the entire study group was 68.5 ± 7.8 years (range 48–89). Their formal education level was generally low: 51.3% had only a primary school education, and 22.9% had a high school education. A total of 59.3% of patients were married. Overall, 201 patients (42.1%) reported one or 2, and 112 patients (23.4%) reported 3 or more (range 3–7) comorbid conditions. The most frequently reported comorbid conditions were cardiovascular disorders (27.3%), chronic pulmonary disease (19.1%), metabolic disorders (13.7%), and gastrointestinal diseases (9.2%). Table 1 shows the main sociodemographic characteristics of patients with or without vertebral fractures and healthy controls. Statistically significant differences ($p < 0.01$) were found for a number of comorbid conditions ($p < 0.001$), average score of the SCQ questionnaire ($p < 0.001$), and for lumbar BMD obtained by DEXA ($p < 0.01$). Among study subjects, 244 had no vertebral fractures and 234 had at least one vertebral fracture, 147 had one to 3 fractures, 61 had 4 to 6 fractures, and 26 had > 6 fractures). The majority of women (142 patients, 60.7%) had thoracic fractures only, 49 (20.9%) had lumbar fractures only, and 43 (18.4%) had fractures in both the lumbar and thoracic spine regions. The intraobserver reproducibility (k) of spine evaluation, assessed on 77 radiographs, was 0.93 (95% CI 0.89–0.97) at the lumbar spine and 0.83 (95% CI 0.79–0.88) at the thoracic spine. The presence of prevalent vertebral fracture, as compared with subjects without prevalent vertebral

Table 1. Sociodemographic variables and clinical characteristics of 478 osteoporotic (OP) patients with and without vertebral fractures and 483 healthy controls. Percentages are rounded to the nearest decimal place.

	OP with Vertebral Fractures, N = 234	OP without Vertebral Fractures, N = 244	Controls, N = 483	p
Age, yrs, mean (± SD)	69.0 (6.9)	68.1 (9.9)	69.1 (10.1)	NS
Range	48–89	50–87	49–86	
Years since menopause, mean (± SD)	19.8 (10.8)	22.1 (11.9)	20.4 (12.4)	NS
Range	5–46	6–48	4–42	
Education level, n (%)				
Primary school	128 (54.7)	117 (47.9)	249 (51.6)	NS
Secondary school	62 (26.5)	61 (25.0)	102 (21.1)	
High school/university	44 (18.8)	66 (27.1)	132 (27.3)	
Body mass index, mean (± SD)	25.4 (3.6)	24.9 (3.5)	25.9 (4.1)	NS
Range	18.1–44.8	17.5–45.1	18.1–43.9	
No. comorbid conditions, n (%)				
None	52 (22.2)	113 (46.3)	221 (45.7)	< 0.001
1–2	110 (47.0)	91 (37.3)	142 (29.4)	
3–4	54 (23.1)	34 (13.9)	86 (17.8)	
≥ 5	18 (7.7)	6 (2.5)	34 (7.1)	
Comorbidity score by SCQ, mean (± SD)	3.45 (2.1)	1.96 (2.4)	1.88 (1.9)	< 0.001
BMI, L1–L4, g/cm^2, mean (± SD)	0.811 (0.141)	0.842 (0.138)	—	< 0.01

SCQ: Self-Assessment Comorbidity Questionnaire, BMI: body mass index, NS: nonsignificant.

fractures, was associated with lower scores on the dimensions of the mini-OQOL, SF-36, and EQ-5D questionnaires. There were no differences in HRQOL scores between women who attended a primary care center or a hospital outpatient clinic. Table 2 shows results comparing osteoporotic patients with and without vertebral fractures. A significant difference (Mann-Whitney U-test) was found between the 2 groups for all dimensions considered. SF-36 scores in patients with vertebral fractures due to osteoporosis clearly showed a more significant impairment in quality of life than those of healthy controls (Figure 1). Women with only one prevalent fracture had statistically significantly lower HRQOL scores than those without vertebral fractures on the SF-36 for bodily pain, physical functioning, and role-physical (all $p < 0.01$). Patients with

Table 2. Comparison of the mini-OQOL, SF-36, and EUROQoL scores between postmenopausal women without and with vertebral fractures (Mann-Whitney U-test, independent sample).

	OP without Vertebral Fractures, n = 244			OP with Vertebral Fractures, n = 234			Mann-Whitney Test	
	Mean (SD)	Median	25–75 Percentile	Mean (SD)	Median	25–75 Percentile	z	p
Mini-OQOL								
Symptoms	5.072 (1.546)	5.000	4.000–6.500	3.564 (1.636)	3.250	2.000–4.500	–9.435	< 0.0001
Activities in daily life	4.955 (1.888)	5.000	3.500–6.500	3.113 (1.932)	2.500	1.500–5.000	–9.491	< 0.0001
Physical functioning	4.867 (1.736)	5.000	3.500–6.500	3.088 (1.950)	3.000	1.500–5.000	–9.447	< 0.0001
Leisure	4.764 (2.113)	5.000	3.000–7.000	3.197 (2.019)	3.000	1.500–5.000	–7.946	< 0.0001
Emotional functioning	5.316 (1.633)	5.500	4.000–7.000	3.882 (1.900)	4.000	2.000–5.500	–8.137	< 0.0001
Total score	4.995 (1.372)	5.000	4.200–6.050	3.383 (1.475)	3.300	2.000–4.500	–10.798	< 0.0001
SF-36								
Bodily pain	64.668 (23.927)	67.250	45.000–80.000	49.220 (22.604)	45.000	32.500–57.500	–7.262	< 0.0001
Physical functioning	70.861 (21.967)	75.000	55.000–90.000	50.406 (24.476)	50.000	30.000–70.000	–8.698	< 0.0001
General health perception	52.705 (18.857)	50.000	40.000–65.000	41.303 (19.136)	40.000	30.000–55.000	–6.143	< 0.0001
Role function-physical aspect	41.407 (29.442)	40.000	25.000–100.000	32.312 (37.917)	25.000	0.000–75.000	–6.570	< 0.0001
Role function-emotional aspect	64.118 (37.502)	66.700	33.300–100.000	37.885 (39.019)	33.300	0.000–66.700	–7.113	< 0.0001
Vitality	54.570 (15.867)	52.500	45.000–60.000	44.979 (16.449)	45.000	35.000–55.000	–5.487	< 0.0001
Social functioning	71.156 (21.904)	75.000	50.000–87.500	56.624 (23.252)	50.000	37.500–75.000	–6.518	< 0.0001
Mental health	57.590 (18.561)	60.000	46.000–68.000	51.731 (18.567)	52.000	40.000–64.000	–3.368	< 0.001
Physical component summary score (PCS)	43.654 (10.058)	42.815	36.175–53.540	35.656 (10.020)	33.160	29.510–42.300	–8.127	< 0.0001
Mental component summary score (MCS)	49.180 (8.924)	49.515	41.990–54.055	45.832 (9.142)	44.250	38.630–50.730	–3.617	< 0.005
EUROQoL-5D								
Utility	0.710 (0.1566)	0.701	0.624–0.806	0.567 (0.2220)	0.616	0.465–0.699	–7.906	< 0.0001
VAS	60.533 (19.011)	60.000	50.000–70.000	46.816 (22.255)	50.000	30.000–60.000	–7.052	< 0.0001

OP: osteoporosis, VAS: visual analog scale.

≥ 6 fractures had significantly reduced physical functioning ($p < 0.0001$), role-physical ($p < 0.0001$), bodily pain ($p < 0.001$), general health perception ($p < 0.01$), vitality ($p < 0.01$), social function ($p < 0.01$), role-emotional ($p < 0.001$), social function ($p < 0.01$), mental health ($p < 0.05$), and physical ($p < 0.001$) and mental ($p < 0.02$) health summary scores (Figure 2). HRQOL scores were lower in women with lumbar fractures than in women with thoracic fractures only, as the physical functioning and bodily pain dimensions approached statistical significance ($p = 0.021$, $p = 0.034$, respectively). No other dimension was found to be significant. In the women with vertebral fractures, the proportion reporting problems in each of the 5 health domains of the $EQ\text{-}5D_{profile}$ was significantly higher than the subgroup without vertebral fractures (Table 3).

Multivariate regression analyses were performed to analyze the effects of different factors that might influence the HRQOL (Table 4). According to these models, the strongest determinant for low HRQOL, measured using the SF-36 questionnaire, was physical functioning, explained by the number of vertebral fractures (ß coefficient = –12.07, standard error = 2.52, $p < 0.0001$) followed by comorbidity score by SCQ questionnaire (ß coefficient = –3.52, SE = 0.41, $p < 0.0001$) and age (ß coefficient = –0.46, SE = 0.18, $p = 0.012$). The adjusted R^2 in the final model was 35.9%. The role of comorbidity was also assessed by comparing the SF-36 PCS and MCS scores in patients with and without other health conditions. Figure 3 shows there was a significant inverse association (Kruskal-Wallis test, $p < 0.0001$) between the number of comorbidities and both PCS and MCS scores of the SF-36. Moreover, a significant correlation was found between the total score of the mini-OQLQ and the mean SCQ comorbidity score (rho = –0.308, $p < 0.0001$). Negative correlations are expected in the mini-OQLQ, indicating that subjects with more comorbidities have lower (worse) scores than subjects with fewer comorbidities (Figure 4). Stratification into 3 categories showed that increasing education was associated with higher bodily pain severity by SF-36 (Kruskal-Wallis test = 10.93, $p < 0.005$). Finally, testing for correlation between instruments we found that Spearman's rho correlation coefficients for the comparable subscales and dimensions of the mini-OQLQ and SF-36 ranged from 0.221 to 0.514 (Table 5). Generally, higher significant correlations were seen when comparing mini-OQOL to SF-36 scales with a high capability to measure pain and physical health, and lower significant correlations were seen when comparing mini-OQOL to SF-36 scales with high capability to measure mental health. The correlations between mini-OQOL total scores ($p < 0.0001$) and SF-36 PCS and MCS dimensions ($p < 0.0001$) are particularly interesting.

DISCUSSION

Among the different types of osteoporotic fractures, the clinical significance of vertebral fractures is increasingly acknowl-

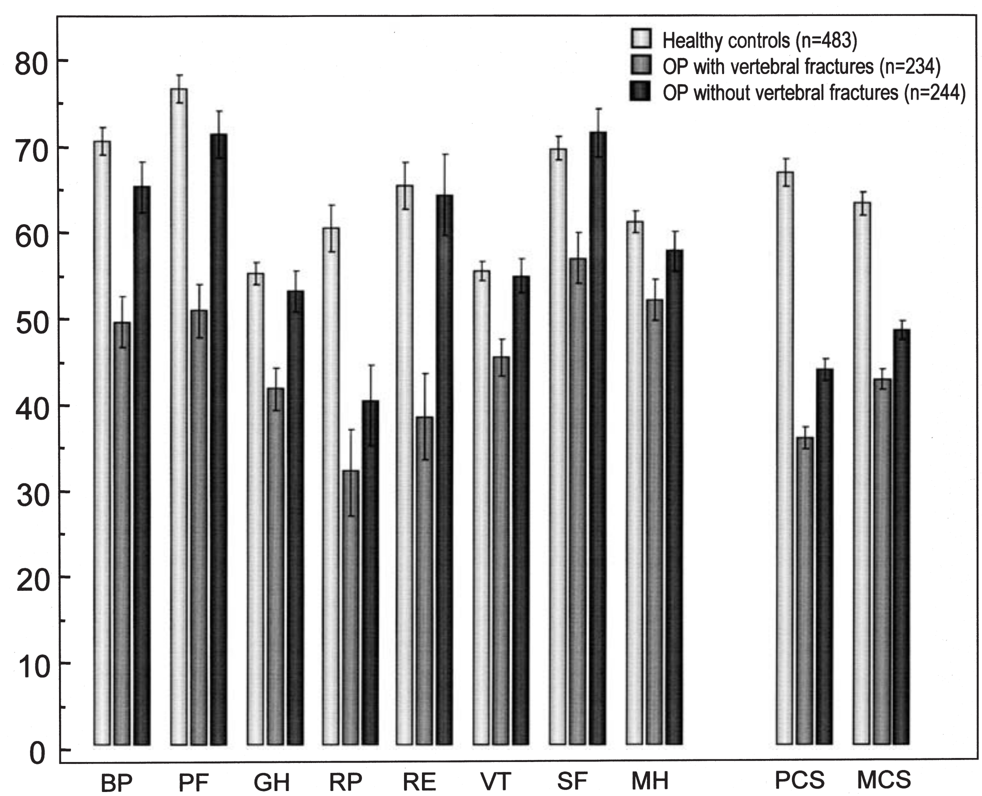

Figure 1. Comparison of SF-36 values among patients with and without prevalent vertebral fractures and healthy controls. OP: osteoporosis, BP: bodily pain, PF: physical functioning, GH: general health perception, RP: role-physical, RE: role-emotional, VT: vitality, SF: social functioning, MH: mental health, PCS/MCS: physical/mental summary scores.

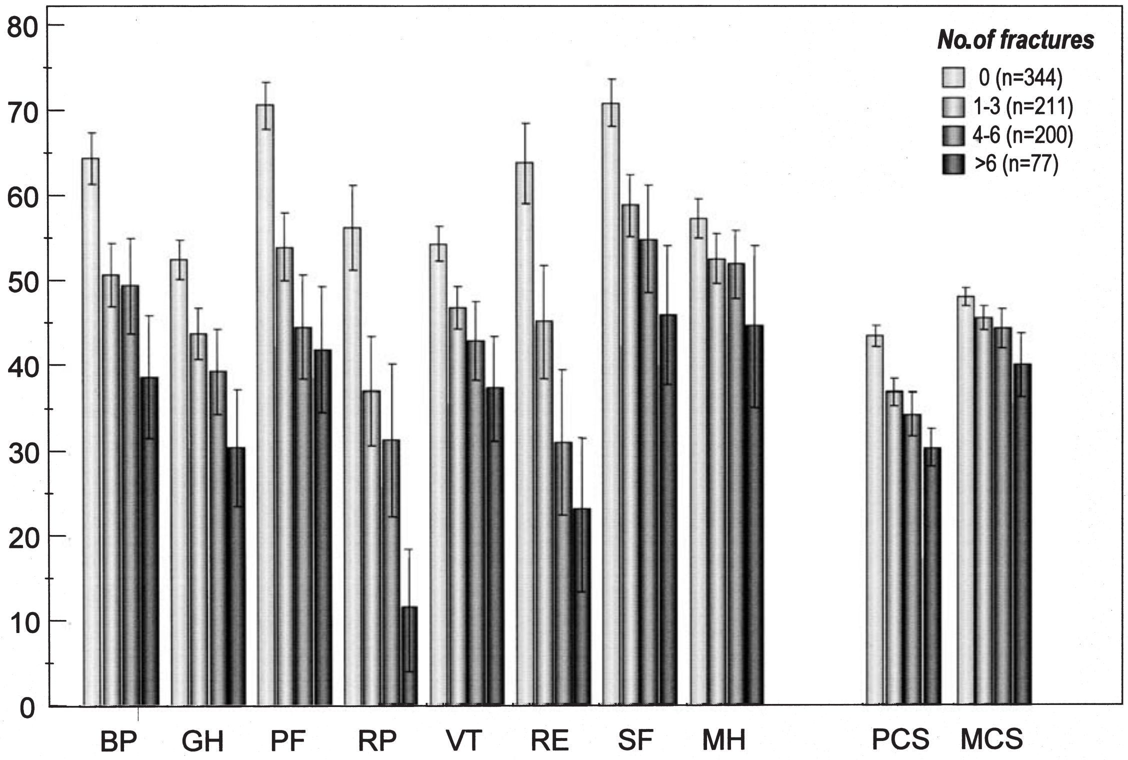

Figure 2. Effect of number of prevalent vertebral fractures on different domains of the SF-36 questionnaire. Definitions as for Figure 1.

Table 3. Health profile: percentage of patients with osteoporosis without and with vertebral fractures reporting some or severe problems in each domain of the EQ-5D profile.

EQ-5D Domain	All Patients, n = 478	Without Vertebral Fractures, n = 244	With Vertebral Fractures, n = 234	p*
Mobility, %	46	40	52	< 0.05
Self-care, %	16.5	12	21	< 0.05
Usual activities, %	35.5	26	45	< 0.01
Pain/discomfort, %	65	51	79	< 0.01
Anxiety/depression, %	48.5	39	58	< 0.01

* Fisher's exact test.

Table 4. Multiple regression analysis. Dependent variables: SF-36 and component summary scores. Independent variables: 1: age, 2: body mass index, 3: lumbar spine BMD (T score), 4: comorbidity score, 5: years postmenopause, 6: number of fractures.

Independent Variables	Dependent Variables	Adjusted R^2 % for Model	p for Model
4, 6	Bodily pain	23.6	< 0.001
4, 6	General health perception	27.2	< 0.0001
2, 4, 6	Role function-physical	27.3	< 0.0001
1, 4, 6	Physical functioning	35.9	< 0.0001
4, 6	Social functioning	23.5	< 0.001
4, 6	Role function-emotional	21.2	< 0.001
1, 4, 5, 6	Vitality	23.8	< 0.001
4, 6	Mental health	10.7	< 0.001
4, 6	Physical component summary score	34.6	< 0.0001
4, 6	Mental component summary score	14.9	< 0.001

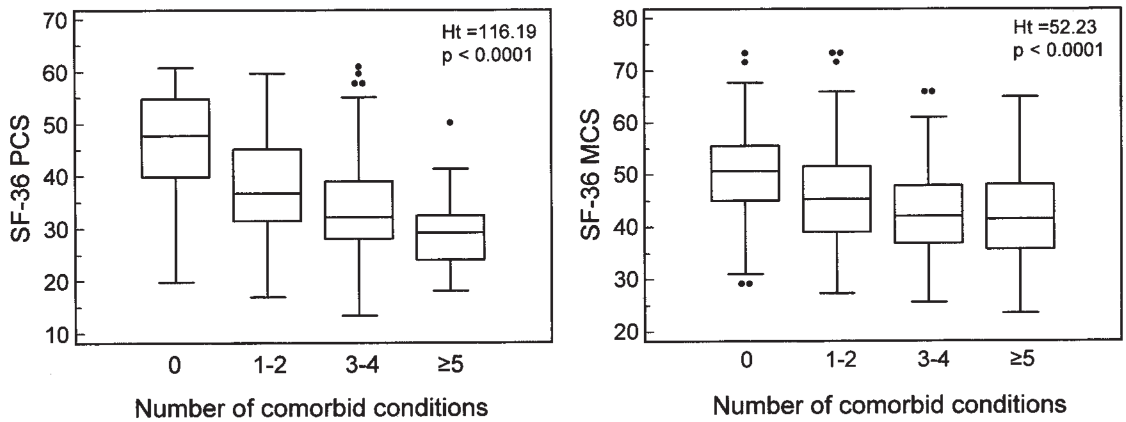

Figure 3. Median SF-35 physical (PCS) and mental (MCS) summary scores according to number of comorbid conditions. Plots provide information on the symmetry of a distribution, the numerical measures of central tendency, and the variability and spread of data in the tails of a distribution. Plots show median values (horizontal line within the box), 25th and 75th percentiles, and 90th percentiles. The Kruskal-Wallis test was carried out across all 4 groups.

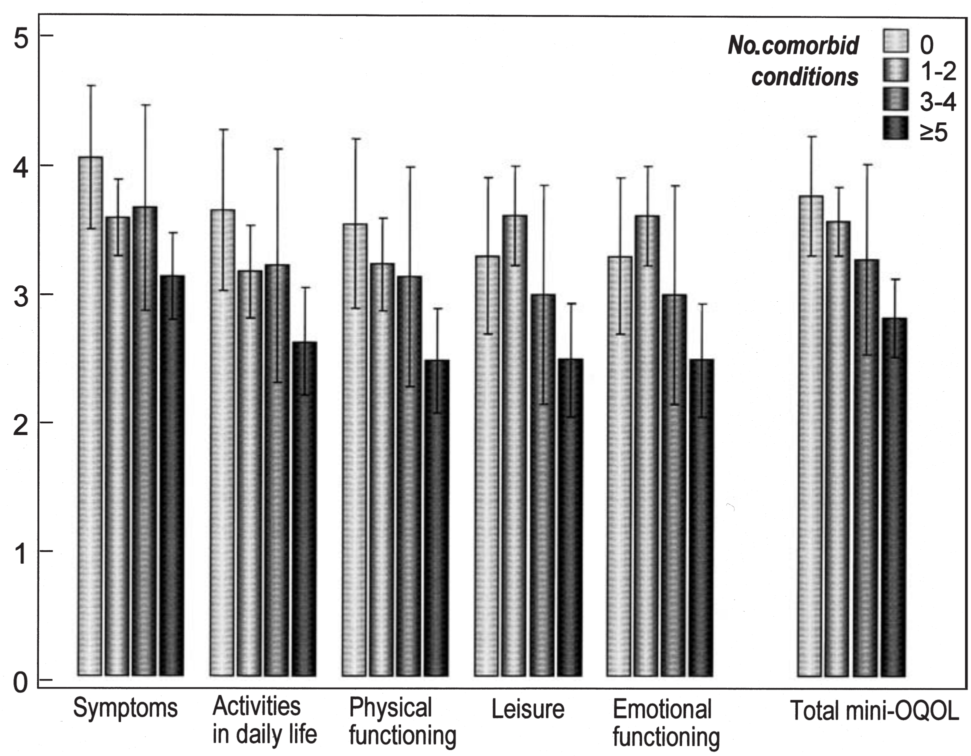

Figure 4. Effects of number of comorbid conditions on different domains of the mini-OQOL questionnaire.

edged, as these have physical, psychological, and social consequences that can affect HRQOL profoundly[5-9]. Health status and HRQOL are core components of health outcomes. Health status is a measure of how a person feels and functions, and includes assessment of the severity of symptoms, the effects of symptoms and activity limitations on functioning, and the effect of illness on a person's ability to participate in life. HRQOL is an even broader concept that includes health status, but also incorporates an evaluative component that assesses a person's satisfaction with his or her current health status. Measurement of the effect of disease on HRQOL is, therefore, of importance since it allows a broad assessment of effects on health domains that are not always recorded in standard clinical or disease-specific assessments. It also allows the measurement of "health utility," which forms the basis for the estimation of quality-adjusted life-years (QALY), and is an important part of health economic assessment.

Our results show compelling evidence of an association

Table 5. Correlation matrix (Spearman's rho) of mini-OQLQ questionnaire vs SF-36 domains and dimensions.

	Mini-OQLQ Questionnaire					
	Symptoms	Activities of Daily Living	Physical Functioning	Leisure	Emotional Functioning	Total Score
SF-36						
Bodily pain	0.472	0.408	0.428	0.329	0.318	0.488
Physical functioning	0.451	0.439	0.474	0.375	0.388	0.514
General health perception	0.327	0.319	0.321	0.259	0.313	0.364
Role function-physical aspect	0.402	0.366	0.392	0.329	0.298	0.437
Role function-emotional aspect	0.352	0.324	0.340	0.293	0.325	0.402
Vitality	0.331	0.329	0.346	0.269	0.301	0.380
Social functioning	0.422	0.425	0.422	0.312	0.385	0.469
Mental health	0.285	0.280	0.286	0.221	0.282	0.304
Physical component summary score	0.458	0.433	0.473	0.347	0.349	0.498
Mental component summary score	0.293	0.282	0.277	0.44	0.321	0.341

between prevalent vertebral osteoporotic fracture and lower HRQOL scores in postmenopausal women. Specifically, women with vertebral fractures reported poorer physical and mental health, as well as more role limitation (physical and emotional) and pain, than those without vertebral fractures and healthy controls. In agreement with previous studies[27,31,34], the SF-36 physical dimensions were more strongly affected than the psychological dimensions. Mini-OQLQ, SF-36 domain scores, and both dimensional scores (PCS and MCS) decreased progressively (that is, worse HRQOL) with increasing number of prevalent vertebral fractures, and the effect of the first fracture was already statistically significant. A progressive decline in HRQOL with increasing number of prevalent vertebral fractures was also found in other subpopulations of the Multiple Outcomes of Raloxifene Evaluation (MORE) study using the Osteoporosis Assessment Questionnaire[10,11,20] and with the QUALEFFO[6,9]. Similarly, correlation was found between the number of recent vertebral fractures and back pain or physical functioning[18]. However, one must be cautious in inferring a causal relationship. The association of reduced HRQOL observed for postmenopausal women with vertebral fractures may be related to other confounding variables, including socioeconomic conditions, psychosocial status, and other traditional risk factors. In addition, self-reported chronic pain or physical functions, common complaints of elderly people[27], may be a secondary symptom of another condition, such as ischemic heart disease, pain due to digestive diseases, or chronic peripheral neuropathic pain. Like Adachi, *et al*[5] and Hallberg, *et al*[7], we registered the occurrence of concomitant diseases in fracture patients, but a systematic study for comparison with nonfracture controls of these percentages remains difficult, however, as the definition of comorbidity and the number of comorbid conditions varied between the studies and different comorbidity measures were used[28,29]. Multiple instruments have been developed and validated to quantify comorbidity for purposes of statistical adjustment and clinical decision-making[28,29]. The majority of these use medical-record review or administrative data as sources of information; observation during clinical encounters and self-reports have also been used. These instruments have primarily been validated against "objective" health outcomes such as mortality, length of stay, and cost of care[29]. Self-reported information about comorbidity and the burden it imposes can provide information about the concurrent impact of multiple disease states on HRQOL outcomes[28]. Self-reported comorbidity information is also efficient in studies in which other information, such as HRQOL outcomes, is collected by survey. Using the SF-36 summary scales, we found that comorbid conditions predominantly affect either mental or physical health (Figure 3). Moreover, a significant correlation was found between total score of the mini-OQLQ and the mean SCQ comorbidity score. Knowledge of these effects may be very useful for clinicians in order to optimize treatment or even prevent adverse effects on HRQOL.

Osteoporosis has significant psychological and social consequences, including anxiety and depression as well as social withdrawal and isolation[18]. These factors can have a significant negative influence on HRQOL. That in our study 58% of the patients with vertebral fractures reported moderate or severe anxiety/depression on the $EQ\text{-}5D_{profile}$ confirms that mental function is impaired in these patients. In agreement with our results, Cook, *et al*[35] showed that emotional dysfunction is a serious problem in patients with spinal osteoporosis as a considerable proportion of their patients (> 50%) suffered from emotional dysfunction. We cannot exclude that this was a coincidental finding, since the mental function domain was the least discriminatory and responsive in other studies. In both our groups we found a strong positive correlation between the PCS and MCS scores of the SF-36; this could be explained in several ways: (1) limitations in physical functioning, physical roles, and self-care in general influence overall well-being and lead to deterioration of emotional status; (2) depression is associated with reduced mobility independently of the underlying cause; and (3) there may be no direct relationship between depression and functional limitations, indeed the association may be spurious, resulting from the influence of chronic pain on both elements. Recently, a stronger relationship has been found between HRQOL and the cost of ambulatory care in osteoporosis[36]. The mental dimension can play an important role in the determination of economic costs, therefore it should be taken into account when analyzing management strategies for osteoporosis[36].

Another important aspect underlined by our study was the presence of a significant relationship between back pain severity on the SF-36 and the level of formal education, suggesting that formal education should be included as a variable in clinical studies of vertebral fractures due to osteoporosis. A low level of formal education has been reported to be a risk factor for back pain and disability in the community[27]. This is in line with the results of other studies[37]. Previously, we found education was related to functional limitations measured by the Western Ontario and McMaster Universities Osteoarthritis Index[38], Arthritis Impact Measurement Scales (AIMS2)[39], and the Chronic Pain Grade Questionnaire[34] in patients with other musculoskeletal conditions[27]. The mechanism by which education influences pain disability or psychological process is unclear, but may be related to enhanced self-efficacy and sense of control, allowing the patient to take advantage of a greater number of pain-reducing modalities.

The strengths of this multicenter study include examination of prevalent vertebral fractures where HRQOL data were routinely collected from a large sample of postmenopausal women using validated generic and specific questionnaires. All participants were "real-life" patients who had been treated for osteoporosis in tertiary care settings and thus represented a homogeneous group. Our analysis was adjusted to take into account factors that may influence the quality of life such as comorbidities, education levels, and psychosocial status. However, other potential confounding variables, such as time since last vertebral fracture and use of antidepressant drugs or other concomitant medications, were not explicitily controlled for in our analyses. Our study has limitations, mainly inherent to its cross-sectional design and also to the assessment of risk factors that often depended on the accuracy of participants' recollections. This suggests potential recollection bias, as patients may perceive their quality of life to be better than it actually was, leading to overestimation of the loss in quality of life related to fracture. Further, it is possible that other conditions such as abnormal spinal alignment, back muscle weakness, or inflexibility may have contributed to a reduced quality of life in these patients. The exact source of back pain and disability in physical activities in people with osteoporosis is not clear and is likely to be multifactorial. Some studies have suggested kyphosis and vertebral compression fractures[40] as the underlying causes of back pain in osteoporosis, and both these factors influence balance and functional mobility[41]. Ryan and Fried[41] demonstrated in their cross-sectional study of 231 community-dwelling older individuals that kyphosis is associated with reduced gait and stair-climbing function. In a cross-sectional study comparing women with confirmed vertebral compression fracture with age and race matched controls without fractures, those with fractures had reduced maximal trunk torque, spine motion, functional reach, mobility skills, and gait speed[41]. Huang, *et al*[42] found that the number of recent vertebral fractures in 569 postmenopausal women was a significant predictor of poor performance in functional reach and gait speed. Finally, we studied only Caucasian women, a group known to be at risk for postmenopausal osteoporosis. Our results may not apply to men or to other ethnic groups.

Patients with prevalent vertebral fractures were found to be associated with a significant decline in HRQOL for most of the domains analyzed. In clinical trials, any vertebral radiological fracture, not just clinical fractures, should be considered as a primary endpoint with regard to HRQOL. The causal relationship, if any, between osteoporosis and reduced HRQOL remains unclear. It is possible that reduced HRQOL is multifactorial and due to comorbidities other than osteoporosis, which may in themselves contribute to the risk of bone loss and fracture.

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