Bone Mineral Density and Health Related Quality of Life: a 3-Year Follow-Up Study of Osteoporotic Postmenopausal Women

Olivier Bruyere*, Caroline De Cock, Rita Deroisy and Jean-Yves Reginster

Department of Epidemiology, Public Health and Health Economics, University of Liege, 4020 Liege, Belgium

Abstract: *Objective*: The objective of this study was to evaluate the relationship between change in bone mineral density (BMD) and change in health related quality of life (HRQoL) over a 3-year period, in patients without incident of osteoporotic fracture.

Materials and Methods: Prior to the present study, two randomized controlled trials had been carried out to assess the efficacy of a new anti-osteoporotic drug. From the placebo group of those two trials, we selected for the present study 1838 osteoporotic postmenopausal women aged over 50 years, and followed their progress for a period of 3 years. BMD was measured at the lumbar spine and the proximal femur by dual-energy X-ray absorptiometry. Each patient received calcium and vitamin D supplements. HRQoL was assessed using 2 questionnaires: the generic tool Short Form 36 items (SF-36; including mental and physical components) and the specific Quality of Life Questionnaire in Osteoporosis (QUALIOST).

Result: At baseline, after adjustment for body mass index (BMI), age, number of vertebral fractures and number of peripheral fractures, multivariate regression analysis showed a significant association between the lumbar BMD and the mental component of the SF-36 ($p<0.001$). However, the relationship was not significant with the global score of the QUALIOST ($p=0.098$) and the physical component of the SF-36 ($p=0.051$). Multivariate regressions did not show a significant relationship between HRQoL and proximal femur BMD at baseline. After 3 years of follow-up, multivariate regression analysis showed no significant association between change in lumbar BMD and the main HRQoL items (global score of the QUALIOST, physical and mental components of the SF-36; p between 0.437 and 0.942). No significant relationships were found between change in femoral BMD and change in the global score of the QUALIOST ($p=0.088$) or change in the mental component of the SF-36 ($p=0.222$). However, a significant positive association ($p=0.031$) appeared between change in the physical component of the SF-36 and femoral BMD change.

Conclusion: In osteoporotic postmenopausal women receiving calcium and vitamin D, few relationships were found between BMD and HRQoL. However, these results were not strong enough to indicate a real clinically interesting relationship between HRQoL and BMD. Other studies would need to be performed to verify these results.

Keywords: Health related quality of life, bone mineral density, osteoporosis, postmenopausal women, prospective study.

BACKGROUND

The concept of health related quality of life (HRQoL) emerged as a means of measuring outcomes that are relevant to the patient [1]. Indeed, quality of life is a subjective multidimensional construct [2]. During the last few years, HRQoL has been assessed during interventional studies for patients with osteoporosis [3, 4]. It is often used as an outcome measure complementary to bone mineral density values and fracture incidence. In daily clinical practice, HRQoL tools help enhance patient-physician communication, monitoring response to therapy and detecting physical or psychological problems [5-7]. Several osteoporosis disease specific target instruments have been developed to evaluate HRQoL in patients who suffer from this chronic condition [8-13].

*Address correspondence to this author at the Department of Epidemiology, Public Health and Health Economics, University of Liege, 4020 Liege, Belgium; E-mail: Olivier.Bruyere@ulg.ac.be

Osteoporosis is a chronic condition that increases bone fragility and causes an increased risk of fracture. Osteoporosis and its complications have a considerable impact on health related quality of life (HRQoL) [5, 9, 10, 14, 15], partly due to pain [16], restriction on activity [17] and alteration in mood [18]. Moreover, Hawker *et al.* showed that fractures give rise to bone deformation, dorsal fatigue and respiratory disorder [19]. Osteoporosis also robs older women of many of their social roles because it limits their physical and functional capability [20]. Depression may also be considered as an important psychological dimension associated with osteoporosis [21-23]. All these elements contribute to a deterioration of the HRQoL in patients with osteoporosis [15, 24].

Some studies have assessed, cross-sectionally, the relationship between osteoporosis (mainly assessed by fractures) and HRQoL. They assessed HRQoL in patients with osteoporotic fractures or compared the HRQoL of postmenopausal women with and without osteoporotic fractures

1874-8279/09

[6, 25-32]. Some of these studies showed an impairment of HRQoL in patients with vertebral fractures [31, 32] but also the influence of number, type or severity of these on HRQoL [30, 31, 33]. For example, Oleksik *et al.,* in a multicentric (7 countries) study involving 751 postmenopausal European women aged up to 80 years, showed that QUALEFFO scores increased significantly (impairment of HRQoL), progressively with an increase in vertebral fractures ($p<0.001$). The authors also showed a difference in HRQoL between patients with or without vertebral fractures ($p<0.05$). Adachi *et al.* evaluated the association of several types of fracture (hip, pelvis and wrist) with HRQoL in 3394 postmenopausal women aged over 50 years in the Canadian Multicenter Osteoporosis Study (CaMos) [31]. They showed an association between hip or pelvis osteoporotic fractures and impairment of HRQoL (measured using the health utility index Marx 2 and 3) but the relationship was unclear for upper body fractures. Dolan *et al*. showed a minimal impact of Colles' fractures on loss of HRQoL in 50 UK women (aged 52-91 years) using EQ-5D [34]. The author suggested that the loss of HRQoL was associated with Colles' fractures in about 2% of cases. In the OFELY study, the measurement of femoral neck BMD and HRQoL (with the self-administered osteoporosis targeted quality of life survey instrument - OPTQoL) was carried out in 756 French women (mean age of 59 years) with and without osteoporosis or osteoporotic fractures. The adaptation and fears domain scores were significantly worse among women with BMD in the osteoporotic range (T score $\leq$- 2.5 SD; $p<0.05$) in comparison with non osteoporotic patients.

To the best of our knowledge, very few studies have dealt with the relationship between bone mineral density (BMD) and quality of life over the long-term [35]. In a recent study, Dhillon showed that female patients with osteoporosis have a reduced HRQoL compared with the age-matched female, irrespective of a history of prior fracture [36]. Another study documented fears and psychological disability in women who had osteoporosis but were free of fractures [37]. A direct relationship between HRQoL and BMD could be hypothesized to explain these results. Moreover, treatment of low BMD in osteoporotic individuals seems be associated with improved HRQoL [38].

The main purpose of this study was to assess 1) the relationship between HRQoL and BMD at baseline 2) the impact of changes in BMD on change in HRQoL score after 3 years.

METHOD

We used placebo data from two randomized, double blind, placebo-control trials assessing the effect and safety of a new anti-osteoporotic drug [39, 40]. The two studies were: the treatment of peripheral osteoporosis study (TROPOS) and spinal therapeutic osteoporosis intervention (SOTI). Women were eligible for the SOTI study if they were at least 50 years old, had been postmenopausal for at least five years, had had at least one prevalent vertebral fracture confirmed by spinal radiography and had a lumbar spine BMD of 0.840 g/cm^2 or less (corresponding to a T-score < -2.5). In the TROPOS study, the criteria for eligibility were a femoral neck BMD of 0.600 g/cm^2 or less (corresponding to a T-score < -2.5), an age of 74 years or older, or an age of between 70 and 74 years with at least one additional risk factor for fracture. In these studies, women were ineligible if they had a severe disease or condition that might interfere with bone metabolism or if they used anti-osteoporotic treatment. For this particular study, we included patients who had not had new fractures during the 3-year follow-up period in order to see the real impact of BMD change on HRQoL. Patients received daily calcium supplements at lunchtime to maintain a daily calcium intake above 1500 mg and vitamin D supplements (400 to 800 IU, depending on their baseline serum concentration of 25-OHD). After a run-in period of 2 to 24 weeks, depending on the severity of the deficiency of calcium and vitamin D, the subjects in the placebo group received a placebo powder for 3 years (2 gr a day of powder, which they mixed with water). The protocol of this study was approved by the Ethics Committee of the University of Liege.

BMD was estimated at lumbar spine and at proximal femur by dual-energy X-ray absorptiometry at baseline and at six-month intervals (by Hologic). A quality control programme, including serial measurements of a spine phantom and daily quality controls, was conducted throughout the study [41]. This procedure was detailed in the main publications of both studies [39, 40].

In this particular study, the specific QUAlity of LIfe questionnaire in OSTeoporosis (QUALIOST) [13] was used as a complement to the generic questionnaire medical outcome study Short Form 36 items (SF-36). The SF-36 measures quality of life using 36 items grouped into eight domains: physical functioning, role - physical, bodily pain, general health, vitality, social functioning, role - emotional and mental health. From these eight domains, two summary scores can be calculated: the physical and the mental component summary index [42, 43]. The score ranges from 100 (best) to 0 (worst).

The QUALIOST was designed for use as a complement to the SF-36 to measure established osteoporosis-specific quality of life. It includes 23 items and 8 multi functioning dimensions [13]. A total score (global score QUALIOST) can be calculated by summing the items. Scores vary between 0 (the worst score) and 100 (the best score representing perfect Quality of Life). This is except for back pain, climbing pain and general quality of life, for which scores vary between 1 and 5, with 1 corresponding to perfect HRQoL score for this item. This specific quality of life questionnaire was only used in a subgroup of the participants from SOTI.

Statistical analyses were performed using STATISTICA (version 7.1; StatSoft Inc). Normality of distribution was checked using the Shapiro-Wilk test. The correlation coefficient estimates were made using the Spearman correlation coefficient. The effect of BMD (for lumbar or femoral BMD) on HRQoL was assessed using multiple regression analysis adjusting for age, body mass index (BMI), number of prevalent fractures and, for change analysis, BMD at baseline, and HRQoL item value at baseline). For secondary analysis, patients were divided into groups during follow-up: patients with a BMD decrease higher than or equal to 3% and the others (Δ BMD >-3% or Δ BMD $\leq$-3%). This cut-off value is frequently used in clinical trials [44, 45]. The mean

changes in HRQoL scores in the different groups were tested using the student T-test. P-values < 0.05 were regarded as statistically significant in all statistical tests. The minimal detectable change [46] (defined as one half of standard deviation at baseline) was considered as a clinically significant change for items with a score of between 0 and 100.

Table 1. General Baseline Characteristics of the Study Population (n= 1838)

Characteristics	Mean (S.D)
Age (years)	73.7 (6.2)
Body mass index (kg/m²)	25.7 (4.0)
T-Score lumbar	-2.9 (1.5)
T-Score femoral	-2.9 (0.6)
Number of osteoporotic vertebral fractures	1.1 (1.9)
Number of osteoporotic peripheral fractures	0.5 (0.9)

RESULTS

This study included data from 1838 (1350 from TROPOS and 488 from SOTI) osteoporotic postmenopausal women. It should be pointed that only 63.5% (1168) of the 1838 subjects had both BMD and HRQoL values at baseline and after 3 years of follow-up. Moreover, only a fraction of the patients (432) received both the SF-36 and QUALIOST questionnaires.

Women included in this study were aged [mean (± S.D.)] 73.5 (6.2) years and more than 95% of the study population was aged 60 years or older. The mean BMD was 0.785 (0.145) g/cm² at lumbar spine and 0.577 (0.071) g/cm² at proximal femur. The number of fractures varied from 0 to 7 regarding peripheral fractures and from 0 to 13 regarding vertebral fractures. In our population, 697 (37.9%) of patients had no fractures. More characteristics of the study population are presented in Table **1**. Mean scores of HRQoL at baseline were 41.24 (23.26) for global QALIOST, 39.38 (10.18) for the standardized physical component of the SF-36 and 47.09 (11.94) for the standardized mental component of the SF-36 (Table **2**). Women with a fracture had a lower HRQoL than women without a fracture (Table **3**).

Relationship at Baseline Between BMD and HRQoL

In univariate analysis, some weak but significant positive correlations appeared between lumbar BMD and different items of the HRQoL at baseline (Table **4**): physical score of the QUALIOST (p<0.001), global score of the QUALIOST (p=0.012), intensity of back pain when climbing/walking (p<0.001), standardized mental component of the SF-36 (p<0.001), social functioning (p=0.006), role - emotional (p=0.049) and mental health (p<0.001). Surprisingly, significant negative correlations appeared between lumbar BMD and the standardized physical component of the SF-36 (p=0.027) and the physical function item of the SF-36

Table 2. Quality of Life Score at Baseline

Tools	Quality of Life Items	Mean (SD)
SF-36	Standardized physical component	39.3 (10.1)
	Standardized mental component	47.0 (11.2)
	Physical functioning	58.6 (24.9)
	Role - physical	51.2 (42.3)
	Bodily pain	53.1 (25.5)
	General health perception	55.4 (20.7)
	Vitality	51.5 (20.5)
	Social functioning	73.3 (24.6)
	Role - emotional	62.0 (42.2)
	Mental health	64.3 (21.1)
QUALIOST	Global score QUALIOST	39.9 (21.8)
	Psycho QUALIOST	41.2 (23.2)
	Physical QUALIOST	38.3 (22.7)
	Back pain (1-5)	3.0 (1.1)
	Pain when climbing/walking (1-5)	2.5 (1.2)
	General quality of life (1-5)	3.4 (0.8)

Table 3. Baseline Health-Related Quality of Life Scores in Women With or Without Prevalent Fracture

Tools	Quality of Life Items	Without Prevalent Fracture (N=697)	With Prevalent Fracture (N=1141)	p-Value
SF-36	Standardized physical component	41.5 (9.74)	38.0 (10.22)	<0.001
	Standardized mental component	48.6 (10.53)	46.1 (11.64)	<0.001
	Physical functioning	64.2 (23.60)	55.2 (25.13)	<0.001
	Role - physical	59.1 (41.40)	46.3 (42.16)	<0.001
	Bodily pain	57.3 (24.74)	50.6 (25.77)	<0.001
	General health perception	58.9 (20.71)	53.2 (20.55)	<0.001
	Vitality	55.6 (19.63)	49.1 (20.64)	<0.001
	Social functioning	78.0 (22.71)	70.5 (25.42)	<0.001
	Role - emotional	66.6 (40.26)	59.2 (43.24)	<0.001
	Mental health	68.2 (19.33)	61.9 (21.82)	<0.001
QUALIOST	Global score QUALIOST	30.2 (18.32)	41.4 (22.05)	<0.001
	Psycho QUALIOST	31.1 (19.40)	42.7 (23.47)	<0.001
	Physical QUALIOST	28.9 (20.48)	39.8 (22.81)	<0.001
	Back pain	2.8 (1.22)	3.0 (1.13)	0.193
	Pain when climbing/walking	2.0 (1.07)	2.6 (1.25)	<0.001
	General quality of life	3.1 (0.80)	3.4 (0.88)	0.038

Table 4. Baseline Unadjusted Coefficient Correlations Between Lumbar Bone Mineral Density and Health-Related Quality of Life

Tools	Quality of Life Items	Coefficient r	p-Value
SF-36	Standardized physical component	-0.056	0.027
	Standardized mental component	0.117	<0.001
	Physical functioning	-0.064	0.009
	Role - physical	0.005	0.847
	Bodily pain	-0.020	0.413
	General health perception	0.026	0.286
	Vitality	0.022	0.368
	Social functioning	0.067	0.006
	Role - emotional	0.049	0.049
	Mental health	0.093	<0.001
QUALIOST	Global score QUALIOST	0.121	0.012
	Psychological QUALIOST	0.074	0.124
	Physical QUALIOST	0.158	<0.001
	Back pain	0.084	0.079
	Pain when climbing/walking	0.162	<0.001
	General quality of life	0.044	0.364

(p=0.009). We also observed significant correlations between femoral BMD at baseline and the physical score of the QUALIOST (p=0.045), intensity of back pain when climbing/walking (p=0.012) and bodily pain (p=0.029) measured at baseline.

Multivariate regressions showed a significant relationship between the standardized mental component of the SF-36 and lumbar BMD ($p<0.001$) after adjustment for age, BMI and number of prevalent fractures (vertebral and peripheral). The association was not significant for lumbar BMD and global score QUALIOST ($p=0.098$) and for the standardized physical component of the SF-36 ($p=0.051$).

Multivariate regressions did not show a significant relationship between the main quality of life score and BMD at femoral neck ($p=0.286$ for global score QUALIOST; $p=0.821$ for the standardized physical component of the SF-36 and $p=0.272$ for standardized mental component of SF-36).

Relationship Between Change in HRQoL and Change in BMD

After 3 years of follow-up, we had BMD data and at least one HRQoL item value for 1168 subjects. In our population, the global score QUALIOST increased by 14.9 (68.8)% ($p=0.655$), the standardized physical component of the SF-36 decreased by 0.33 (26.2)% ($p<0.001$), the standardized mental component of the SF-36 decreased by 1.21 (30.9)% ($p<0001$), lumbar BMD decreased by 0.25 (6.09)% ($p=0.241$) and femoral BMD decreased by 2.3 (5.30)% ($p<0.001$). Between 29.8 and 51.2% of patients achieved the minimal detectable change (Table **5**).

After 3 years of follow-up, in unadjusted analysis, we found no significant correlation between change in lumbar BMD and change in different items of HRQoL (p between 0.25 and 0.99) except in the case of change in the standardized physical component of the SF-36 ($p=0.029$) and general health perception ($p=0.042$). After adjusting for age, BMI, number of prevalent vertebral and peripheral fractures, BMD at baseline and value of HRQoL at baseline, multiple regressions did not show a significant relationship between change in the main HRQoL items and lumbar BMD change (p between 0.465 and 0.884). We also compared HRQoL scores between patients with a decrease in lumbar BMD of 3% or more and other patients. No statistically significant difference appeared between the groups (Table **6**).

In univariate analysis, no significant relationship appeared between femoral BMD and HRQoL except for one negative significant correlation with change in the physical item of the QUALIOST ($p=0.019$). When considering change in femoral BMD and change in HRQoL items, multiple regressions (after adjusting for age, BMI, number of prevalent vertebral and peripheral fracture, BMD at baseline and value of HRQoL at baseline) showed a significant relationship between change in femoral BMD and change in the standardized physical component of the SF-36 ($p=0.031$; $r^2=0.214$). No significant difference regarding HRQoL change was observed when we compared patients with a decrease in femoral BMD of 3% or more to the other patients (Table **7**).

DISCUSSION

This study is, to the best of our knowledge, one of the first assessing, prospectively, the associations between BMD (measured at two different sites) and HRQoL in women without incident of fracture.

Very few studies have dealt with the influence of BMD alone on HRQoL [35, 47]. Some studies suggest that osteoporosis decreases HRQoL [35]. They also observed better HRQoL scores in normal subjects compared to osteopenic or osteoporotic patients ($p<0.05$) for domains exploring general health perception and mental function. Recently, in a prospective trial of 325 women (96%) and men aged [mean (± S.D.)] 60 (±11) years, Dhillon *et al.* demonstrated a decreasing HRQoL (measured with EQ-5D, a generic self-report questionnaire) in osteoporotic women compared to the non

Table 5. Minimal Detectable Change (MCD) of the Health-Related Quality of Life Items

Tools	Quality of Life Items	MCD	% of the Population With Value Over MCD
SF-36	Standardized physical component	5.0	33.1
	Standardized mental component	5.6	34.9
	Physical functioning	12.4	34.0
	Role - physical	21.1	42.8
	Bodily pain	12.7	32.5
	General health perception	10.3	29.9
	Vitality	10.2	29.8
	Social functioning	12.3	51.2
	Role - emotional	21.1	35.2
	Mental health	10.5	35.9
QUALIOST	Global score QUALIOST	10.9	45.1
	Psychological QUALIOST	11.6	31.8
	Physical QUALIOST	11.3	34.6

Table 6. Change in Health Related Quality of Life Scores After 3 Years Between Women With Decrease of Lumbar Bone Mineral Density ≥ 3% and Other Patients

Tools	Quality of Life Items	Decrease in Lumbar Bone Mineral Density ≥ 3% (N= 332)	Decrease in Lumbar Bone Mineral Density < 3% (N=836)	p-Value
SF-36	Standardized physical component	-1.9 (8.8)	-0.7 (8.8)	0.052
	Standardized mental component	-1.3 (10.9)	-2.1 (10.4)	0.264
	Physical functioning	-4.3 (21.9)	-3.5 (21.9)	0.571
	Role - physical	-6.8 (46.9)	-6.3 (46.6)	0.887
	Bodily pain	-2.8 (23.3)	-0.8 (22.2)	0.165
	General health perception	-2.6 (17.9)	-1.4 (16.2)	0.266
	Vitality	-2.2 (19.14)	-2.4 (17.57)	0.852
	Social functioning	-7.2 (25.1)	-6.7 (25.9)	0.750
	Role - emotional	-5.5 (46.2)	-8.5 (45.1)	0.312
	Mental health	-	-	-
QUALIOST	Global score QUALIOST	1.6 (15.1)	-0.9 (17.7)	0.173
	Psycho QUALIOST	0.5 (16.7)	-1.9 (18.3)	0.224
	Physical QUALIOST	2.7 (17.1)	0.0 (20.2)	0.213
	Back pain	-0.1 (1.1)	-0.1 (1.2)	0.782
	Pain when climbing/walking	0.1 (1.1)	0.0 (1.2)	0.382
	General quality of life	0.1 (0.8)	0.1 (0.7)	0.955

Table 7. Change in Health Related Quality of Life Scores After 3 Years Between Women With Decrease of Femoral Bone Mineral Density ≥ 3% and Other Patients

Tools	Quality of Life Items	Decrease in Femoral Bone Mineral Density ≥ 3% (N= 496)	Decrease in Femoral Bone Mineral Density < 3% (N=665)	p-Value
SF-36	Standardized physical component	-1.3 (9.1)	-0.88 (8.6)	0.423
	Standardized mental component	-2.3 (10.16)	-1.6 (10.8)	0.348
	Physical functioning	-4.8 (22.09)	-2.9 (21.8)	0.156
	Role - physical	-8.6 (47.84)	-4.9 (45.5)	0.185
	Bodily pain	-1.8 (22.6)	-1.0 (22.5)	0.533
	General health perception	-1.3 (16.3)	-2.0 (17.0)	0.543
	Vitality	-2.6 (17.0)	-2.2 (18.8)	0.684
	Social functioning	-7.7 (25.6)	-6.2 (25.89)	0.317
	Role - emotional	-10.2 (43.9)	-5.8 (46.4)	0.102
	Mental health	-2.1 (17.1)	-1.8 (18.9)	0.759
QUALIOST	Global score QUALIOST	1.7 (15.6)	-1.1 (17.4)	0.133
	Psycho QUALIOST	0.8 (16.9)	-2.2 (18.2)	0.131
	Physical QUALIOST	2.9 (18.2)	-0.2 (19.4)	0.137
	Back pain	-0.1 (1.1)	-0.2 (1.2)	0.776
	Pain when climbing/walking	0.1 (1.1)	0.0 (1.2)	0.603
	General quality of life	0.1 (0.7)	0.0 (0.7)	0.718

osteoporotic population, irrespective of a history of prior fracture [36]. They showed an association between hip or pelvis osteoporotic fractures and impairment of HRQoL (measured using the health utility index Marx 2 and 3) but the relationship was unclear for upper body fractures. Dolan *et al.* showed a minimal impact of Colles' fractures on loss of HRQoL in 50 UK women (aged 52-91 years) using EQ-5D [47]. Their study, involving 1129 postmenopausal patients [mean age 67.2 (11.9) years] showed that several modifiable factors (for example: smoking, medication, diabetes…) influenced HRQoL in patients with vertebral fractures. However, they did not assess the influence of BMD in their study [47]. In their study, Romagnoli *et al.* showed that both vertebral fracture and a reduced BMD impairs some aspects of HRQoL perception (measured using QUALEFFO) in 361 asymptomatic ambulant women [48-50] but not consistently reported [35] to be associated with low BMD of the spine. However, it has not been clearly proven whether this potential association might be related to psychiatric disorder alone or to the hormonal or nutritional disorders associated with depression. Moreover, early in the disease process, women report high levels of anxiety caused in large part, by their very real fear of future fractures [51, 52]. Generally, a score of $\leq$35 for the mental component of the SF-36 is considered as indicating mental distress [53]. Our results do not show the relationship between change in BMD and change in mental health items after 3 years of follow-up.

Change in lumbar BMD was positively correlated with change in the standardized physical component of the SF-36 and change in general health perception in our population. Osteoporosis sometimes causes a restriction on social and leisure activities and may severely affect a woman's mood [5, 18].

In the study of Romagnoli *et al.*, administration of the QUALEFFO questionnaire to women suggested that low femoral neck BMD was associated with poorer physical functioning [35]. Our results confirm this observation. Multiple regression definitely showed a significant relationship between change in femoral BMD and change in the standardized physical component of the SF-36 (p=0.031; r^2=0.214).

One of the strengths of this study is that it involves a large population, and this reinforces the reliability of our results. Moreover, the women in the study had no disease or condition that could interfere with bone metabolism at baseline and they did not use anti-osteoporotic treatment except for calcium and vitamin D supplements. Analysis was based on validated tools (DXA, SF-36, and QUALIOST), which were collected during a large prospective placebo-controlled trial. These results were robust to adjustment for known prior fracture history.

Multiple regression analysis was performed with adjustment for age, BMI, number of prevalent vertebral and peripheral fractures, BMD at baseline and value of HRQoL at baseline. However, we did not have data concerning different factors that could influence HRQoL values; smoking status, other disease conditions or exercise level. We only knew that the patients did not have a pathology or other condition that could interfere with bone metabolism and that they were not using anti-osteoporotic treatment [39, 40].

We did not find any statistically significant differences concerning the HRQoL score between patients with a decrease in BMD of 3% or more and the others for the two BMD sites measured (except for one borderline significant difference). However, it was shown that, with age, the presence or worsening of degenerative conditions of the spine, such as osteophytes and endplate sclerosis, could contribute to a variation in lumbar spine BMD measurement [54].

The patients in this study received calcium and vitamin D supplements, which may have a positive effect on bone health and could possibly have modified our result [55-57].

It is also possible that a placebo effect affected our results [58, 59]. For example in their study involving 1896 women and men aged 35 to 60 year, Bouchet *et al.* showed a significant effect of placebo on improving the physical, mental and pain dimension of the SF-36 (p=0.02 to 0.04) compared to a control group [59]. An interesting study [60], published some years ago suggests a positive effect of participation in a clinical trial on HRQoL. Perhaps our second HRQoL score was affected because of participation in the trial.

The choice of tools used in this study could also have affected our results. The generic quality of life questionnaire chosen for our study was the Short Form 36 items (SF-36). This questionnaire has been widely adopted [25, 28, 61] and has been well validated for use in many countries and for many disease processes, including osteoporosis [62-66]. One of the strongest attributes of the SF-36 is its consistently high levels of reliability (test-retest and internal consistency) and validity (content, concurrent, criterion, construct and predictive) [63, 67]. This questionnaire is obviously not specific to osteoporosis. In our population, we observed that a minority of patients seemed to demonstrate a clinically significant change for items after 3 years of follow-up.

The QUALIOST was developed as a specific module of a generic questionnaire (SF-36), in order to focus on domains related to osteoporosis that were not already covered by the generic instrument [13]. The QUALIOST has demonstrated good reliability and good construct and criterion validity [52]. However, this questionnaire has not been widely used in epidemiological studies. The specific items of the QUALIOST were generated simultaneously in French and in English and the questionnaire was subject to a psychometric evaluation in 140 osteopenic British and French women [52]. Moreover, low responsiveness is described in the literature for the physical and emotional components and for the total score of the QUALIOST (effect size 0.15-0.17) regarding vertebral fractures [13]. Moreover, when we compare HRQoL scores for patients with or without incident of fracture at baseline, QUALIOST showed results quite the opposite of those of the SF-36. The use of another specific HRQoL questionnaire from those that have been developed for use in patients with osteoporosis [9, 11, 12, 68, 69], including the Ecos-16 [68], the Osteoporosis Quality of Life Questionnaire [5, 69], the mini-Osteoporosis Quality of Life Questionnaire [5] and the Questionnaire of the European Foundation for Osteoporosis [9], could perhaps have changed our results. After 3 years of follow-up, few patients seemed to obtain clinically significant changes with QUAL-

IOST (between 3.9 and 29.9% of patients, depending on the items).

Despite the high number of patient (1838) included in this study, it should be acknowledged that only 63.5% (1168) of them had both BMD and HRQoL values at baseline and after 3 years of follow-up. Moreover, only a fraction of the patients (432) received both the SF-36 and QUALIOST questionnaires. As a consequence, the statistical power of this study was sometimes low for some of the analyses (generally <30%). However, Dennison *et al*. pointed out the same problem in the Hertfordshire cohort study [70].

CONCLUSION

In conclusion, our results suggest that BMD could partly affect HRQoL, but the exact mechanisms of action are unknown. However, these results were not enough to indicate a real clinically interesting relationship between HRQoL and BMD. Other studies would need to be performed in order to verify and explain these results.

DECLARATION OF INTEREST

The authors declare that they have no competing interest. No industry funding was received for the study.

AUTHOR CONTRIBUTION

All authors contributed to the design and writing of the study, and to the literature review. CD and OB performed the statistical analyses. All the authors read and approved the final manuscript.

ACKNOWLEDGEMENT

The authors would like to thank Servier for providing access to their database.

REFERENCES

[1] Ethgen O, Tellier V, Sedrine WB, De Maeseneer J, Gosset C, Reginster JY. Health-related quality of life and cost of ambulatory care in osteoporosis: how may such outcome measures be valuable information to health decision makers and payers? Bone 2003; 32: 718-24.

[2] Ethgen O, Reginster JY. Quality of life assessment in clinical trials: a holistic approach to health. Rev Med Liege 2002; 57: 695-700.

[3] Reginster JY, Compston JE, Jones EA, *et al.* Recommendations for the registration of new chemical entities used in the prevention and treatment of osteoporosis. Calcif Tissue Int 1995; 57: 247-50.

[4] Lombardi I, Jr., Oliveira LM, Mayer AF, Jardim JR, Natour J. Evaluation of pulmonary function and quality of life in women with osteoporosis. Osteoporos Int 2005; 16: 1247-53.

[5] Cook DJ, Guyatt GH, Adachi JD, *et al.* Development and validation of the mini-osteoporosis quality of life questionnaire (OQLQ) in osteoporotic women with back pain due to vertebral fractures. Osteoporosis Quality of Life Study Group. Osteoporos Int 1999; 10: 207-13.

[6] Adachi JD, Ioannidis G, Olszynski WP, *et al.* The impact of incident vertebral and non-vertebral fractures on health related quality of life in postmenopausal women. BMC Musculoskelet Disord 2002; 3: 11.

[7] Detmar SB, Muller MJ, Schornagel JH, Wever LD, Aaronson NK. Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. JAMA 2002; 288: 3027-34.

[8] Helmes E, Hodsman A, Lazowski D, *et al.* A questionnaire to evaluate disability in osteoporotic patients with vertebral compression fractures. J Gerontol A Biol Sci Med Sci 1995; 50: M91-98.

[9] Lips P, Cooper C, Agnusdei D, *et al.* Quality of life as outcome in the treatment of osteoporosis: the development of a questionnaire for quality of life by the European Foundation for Osteoporosis. Osteoporos Int 1997; 7: 36-8.

[10] Lips P, Cooper C, Agnusdei D, *et al.* Quality of life in patients with vertebral fractures: validation of the quality of life questionnaire of the European foundation for osteoporosis (QUALEFFO). working party for quality of life of the European foundation for Osteoporosis. Osteoporos Int 1999; 10: 150-60.

[11] Lydick E, Zimmerman SI, Yawn B, *et al.*Development and validation of a discriminative quality of life questionnaire for osteoporosis (the OPTQoL). J Bone Miner Res 1997; 12: 456-63.

[12] Randell AG, Bhalerao N, Nguyen TV, Sambrook PN, Eisman JA, Silverman SL. Quality of life in osteoporosis: reliability, consistency, and validity of the Osteoporosis Assessment Questionnaire. J Rheumatol 1998; 25: 1171-9.

[13] de la Loge C, Sullivan K, Pinkney R, Marquis P, Roux C, Meunier PJ. Cross-cultural validation and analysis of responsiveness of the QUALIOST: QUAlity of Life questionnaire In OSTeoporosis. Health Qual Life Outcomes 2005; 3: 69.

[14] Garnero P, Sornay-Rendu E, Chapuy MC, Delmas PD. Increased bone turnover in late postmenopausal women is a major determinant of osteoporosis. J Bone Miner Res 1996; 11: 337-49.

[15] Gold DT. The clinical impact of vertebral fractures: quality of life in women with osteoporosis. Bone 1996; 18(3 Suppl): 185S-189S.

[16] Nevitt MC, Ettinger B, Black DM, *et al.* The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann Intern Med 1998; 128: 793-800.

[17] Cook DJ, Guyatt GH, Adachi JD, *et al.* Quality of life issues in women with vertebral fractures due to osteoporosis. Arthritis Rheum 1993; 36: 750-6.

[18] Ross PD. Clinical consequences of vertebral fractures. Am J Med 1997; 103: 30S-42S; discussion 42S-43S.

[19] Hawker GA. The epidemiology of osteoporosis. J Rheumatol Suppl 1996; 45: 2-5.

[20] Hallal JC. Osteoporotic fractures exact a toll. J Gerontol Nurs 1985; 11: 13-9.

[21] Coelho R, Silva C, Maia A, Prata J, Barros H. Bone mineral density and depression: a community study in women. J Psychosom Res 1999; 46: 29-35.

[22] Reginster JY, Deroisy R, Paul I, Hansenne M, Ansseau M. Depressive vulnerability is not an independent risk factor for osteoporosis in postmenopausal women. Maturitas 1999; 33: 133-7.

[23] Gold DT, Smith SD, Bales CW, Lyles KW, Westlund RE, Drezner MK. Osteoporosis in late life: does health locus of control affect psychosocial adaptation? J Am Geriatr Soc 1991; 39: 670-5.

[24] Picavet HS, Hoeymans N. Health related quality of life in multiple musculoskeletal diseases: SF-36 and EQ-5D in the DMC3 study. Ann Rheum Dis 2004; 63: 723-9.

[25] Hallberg I, Rosenqvist AM, Kartous L, Lofman O, Wahlstrom O, Toss G. Health-related quality of life after osteoporotic fractures. Osteoporos Int 2004; 15: 834-41.

[26] Begerow B, Pfeifer M, Pospeschill M, *et al.* Time since vertebral fracture: an important variable concerning quality of life in patients with postmenopausal osteoporosis. Osteoporos Int 1999; 10: 26-33.

[27] Oleksik A, Lips P, Dawson A, *et al.* Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. J Bone Miner Res 2000; 15: 1384-92.

[28] Randell AG, Nguyen TV, Bhalerao N, Silverman SL, Sambrook PN, Eisman JA. Deterioration in quality of life following hip fracture: a prospective study. Osteoporos Int 2000; 11: 460-6.

[29] Silverman SL, Minshall ME, Shen W, Harper KD, Xie S. The relationship of health-related quality of life to prevalent and incident vertebral fractures in postmenopausal women with osteoporosis: results from the multiple outcomes of raloxifene evaluation study. Arthritis Rheum 2001; 44: 2611-9.

[30] Fechtenbaum J, Cropet C, Kolta S, Horlait S, Orcel P, Roux C. The severity of vertebral fractures and health-related quality of life in osteoporotic postmenopausal women. Osteoporos Int 2005; 16: 2175-9.

[31] Adachi JD, Ioannidis G, Pickard L, *et al.* The association between osteoporotic fractures and health-related quality of life as measured by the health utilities index in the canadian multicentre osteoporosis study (CaMos). Osteoporos Int 2003; 14: 895-904.

[32] Cvijetic S, Mestrovic T, Crkvenac A, Davila S, Korsic M. Quality of life in osteoporotic patients with hip fracture and without fracture. Arh Hig Rada Toksikol 2002; 53: 257-62.

[33] Brenneman SK, Barrett-Connor E, Sajjan S, Markson LE, Siris ES. Impact of recent fracture on health-related quality of life in postmenopausal women. J Bone Miner Res 2006; 21: 809-16.

[34] Dolan P, Torgerson D, Kakarlapudi TK. Health-related quality of life of Colles' fracture patients. Osteoporos Int 1999; 9: 196-9.

[35] Romagnoli E, Carnevale V, Nofroni I, *et al.* Quality of life in ambulatory postmenopausal women: the impact of reduced bone mineral density and subclinical vertebral fractures. Osteoporos Int 2004; 15: 975-80.

[36] Dhillon V, Hurst N, Hannan J, Nuki G. Association of low general health status, measured prospectively by Euroqol EQ5D, with osteoporosis, independent of a history of prior fracture. Osteoporos Int 2005; 16: 483-9.

[37] Chandler JM, Martin AR, Girman C, *et al.*Reliability of an Osteoporosis-Targeted Quality of Life Survey Instrument for use in the community: OPTQoL. Osteoporos Int 1998; 8: 127-35.

[38] Yoh K, Tanaka K, Ishikawa A, *et al*. Health-related quality of life (HRQOL) in Japanese osteoporotic patients and its improvement by elcatonin treatment. J Bone Miner Metab 2005; 23: 167-73.

[39] Meunier PJ, Roux C, Seeman E, *et al.* The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004; 350: 459-68.

[40] Reginster JY, Seeman E, De Vernejoul MC, *et al*. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: treatment of peripheral osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005; 90: 2816-22.

[41] Slosman D, Meunier PJ, Delmas PD, Sebert JL, De Vernejoul MC, Reginster JY. The use of different dual X-ray absorptiometry brands in a multicenter clinical trial. J Clin Densitom 1999; 2: 37-44.

[42] Haley SM, McHorney CA, Ware JE, Jr. Evaluation of the MOS SF-36 physical functioning scale (PF-10): I. Unidimensionality and reproducibility of the Rasch item scale. J Clin Epidemiol 1994; 47: 671-84.

[43] Ware JE, Keller SD. SF-36 physical and mental health summary scales: a user's manual. Boston: The Health Institute 1994.

[44] Gallagher JC, Rosen CJ, Chen P, Misurski DA, Marcus R. Response rate of bone mineral density to teriparatide in postmenopausal women with osteoporosis. Bone 2006; 39: 1268-75.

[45] Adachi JD, Adami S, Kulkarni PM, Wong M, Stock JL. Similar proportions of women lose bone mineral density with raloxifene or alendronate treatment. J Clin Densitom 2005; 8: 273-7.

[46] Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003; 41: 582-92.

[47] Papaioannou A, Kennedy CC, Ioannidis G, *et al.* Determinants of health-related quality of life in women with vertebral fractures. Osteoporos Int 2006; 17: 355-63.

[48] Schweiger U, Deuschle M, Korner A, *et al.* Low lumbar bone mineral density in patients with major depression. Am J Psychiatry 1994; 151: 1691-3.

[49] Michelson D, Stratakis C, Hill L, *et al.* Bone mineral density in women with depression. N Engl J Med 1996; 335: 1176-81.

[50] Halbreich U, Rojansky N, Palter S, *et al.* Decreased bone mineral density in medicated psychiatric patients. Psychosom Med 1995; 57: 485-91.

[51] Gold DT, Bales CW, Lyles KW, Drezner MK. Treatment of osteoporosis. The psychological impact of a medical education program on older patients. J Am Geriatr Soc 1989; 37: 417-22.

[52] Marquis P, Cialdella P, De la Loge C. Development and validation of a specific quality of life module in post-menopausal women with osteoporosis: the QUALIOST. Qual Life Res 2001; 10: 555-66.

[53] Walsh TL, Hanscom B, Homa K, Abdu WA. The rate and variation of referrals to behavioral medicine services for patients reporting poor mental health in the national spine network. Spine 2005; 30: E154-160.

[54] Liu G, Peacock M, Eilam O, Dorulla G, Braunstein E, Johnston CC. Effect of osteoarthritis in the lumbar spine and hip on bone mineral density and diagnosis of osteoporosis in elderly men and women. Osteoporos Int 1997; 7: 564-9.

[55] Richy F, Deroisy R, Lecart MP, Hanssens L, Mawet A, Reginster JY. D-hormone analog alfacalcidol: an update on its role in postmenopausal osteoporosis and rheumatoid arthritis management. Aging Clin Exp Res 2005; 17: 133-42.

[56] Boonen S, Bischoff-Ferrari HA, Cooper C, *et al*.Addressing the musculoskeletal components of fracture risk with calcium and vitamin D: a review of the evidence. Calcif Tissue Int 2006; 78: 257-70.

[57] Boonen S, Body JJ, Boutsen Y, *et al*. Evidence-based guidelines for the treatment of postmenopausal osteoporosis: a consensus document of the Belgian Bone Club. Osteoporos Int 2005; 16: 239-54.

[58] Staats P, Hekmat H, Staats A. Suggestion/placebo effects on pain: negative as well as positive. J Pain Symp Manage 1998; 15: 235-43.

[59] Bouchet C, Guillemin F, Briancon S. Nonspecific effects in longitudinal studies: impact on quality of life measures. J Clin Epidemiol 1996; 49: 15-20.

[60] Kessenich CR, Guyatt GH, Rosen CJ. Health-related quality of life and participation in osteoporosis clinical trials. Calcif Tissue Int 1998; 62: 189-92.

[61] Rabenda V, Manette C, Lemmens R, Mariani AM, Struvay N, Reginster JY. Direct and indirect costs attributable to osteoarthritis in active subjects. J Rheumatol 2006; 33: 1152-8.

[62] Aaronson NK, Acquadro C, Alonso J, *et al.* International quality of life assessment (IQOLA) project. Qual Life Res 1992; 1: 349-51.

[63] McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 1994; 32: 40-66.

[64] Adachi JD, Loannidis G, Berger C, *et al.* The influence of osteoporotic fractures on health-related quality of life in community-dwelling men and women across Canada. Osteoporos Int 2001; 12: 903-8.

[65] Aranha LL, Miron Canelo JA, Alonso Sardon M, Del Pino Montes J, Saenz Gonzalez MC. Health-related quality of life in Spanish women with osteoporosis. Rev Saude Publica 2006; 40: 298-303.

[66] Razavi D, Gandek B. Testing Dutch and French translations of the SF-36 Health Survey among Belgian angina patients. J Clin Epidemiol 1998; 51: 975-81.

[67] Gandek B, Sinclair SJ, Kosinski M, Ware JE, Jr. Psychometric evaluation of the SF-36 health survey in Medicare managed care. Health Care Financ Rev 2004; 25: 5-25.

[68] Badia X, Prieto L, Roset M, Diez-Perez A, Herdman M. Development of a short osteoporosis quality of life questionnaire by equating items from two existing instruments. J Clin Epidemiol 2002; 55: 32-40.

[69] Osteoporosis Quality of Life Study Group. Measuring quality of life in women with osteoporosis. Osteoporos Int 1997; 7: 478-87.

[70] Dennison EM, Syddall HE, Statham C, Aihie Sayer A, Cooper C. Relationships between SF-36 health profile and bone mineral density: the Hertfordshire Cohort Study. Osteoporos Int 2006; 17: 1435-42.

Received: July 30, 2009 Revised: August 7, 2009 Accepted: September 10, 2009