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Association of Severe Vertebral Fractures With Reduced Quality of Life

Reduction in the Incidence of Severe Vertebral Fractures by Teriparatide

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Objective. **The association between vertebral fracture severity and health-related quality of life (HRQOL) was investigated in a subset of patients in the Fracture Prevention Trial. We sought to determine whether vertebral fracture severity was associated with HRQOL scores, and if so, to determine the effects of teriparatide (recombinant human parathyroid hormone 1-34) on vertebral fracture grades that most strongly impact HRQOL in postmenopausal women with osteoporosis.**

Methods. **Vertebral fracture severity was assessed by the visual semiquantitative (SQ) method. A subset of 444 patients with a baseline radiograph completed the Osteoporosis Assessment Questionnaire. Baseline HRQOL scores were modeled as a function of maximum baseline vertebral fracture grade, while controlling for age, bone mineral density, body mass index, and back pain.**

Results. **The effect of baseline vertebral fracture grade on baseline HRQOL was statistically significant, while interactions between vertebral fracture grade and the other variables were not statistically significant. SQ grade 3 (SQ3) vertebral fractures were associated with a significantly lower overall HRQOL score and with significantly lower physical function, symptoms, and emotional status dimension scores. After a median of 19 months of therapy, new or worsening SQ3 vertebral fractures occurred in 21 of 448 patients (4.7%) in the placebo group compared with 3 of 444 patients (0.7%) in the 20 μg/day teriparatide group. The risk of developing a new or worsened SQ3 vertebral fracture was reduced by 86% ($P < 0.001$) in patients treated with 20 μg/day teriparatide.**

Conclusion. **Compared with prevalent fractures of lesser severity, SQ3 vertebral fractures were associated with reduced HRQOL. Teriparatide treatment significantly reduced the risk of new or worsening SQ3 vertebral fractures. These findings suggest, but do not directly demonstrate, a benefit of teriparatide on HRQOL.**

Osteoporosis is a chronic disease defined by low bone mass, diminished bone strength, and increased skeletal fragility, which increase the risk for future fractures (1). Vertebral fractures are the most common clinical manifestation of osteoporosis (2), since >30% of women age 75 years and 50% of women age 85 years and older have experienced a nontraumatic vertebral fracture (3). Patients having vertebral fractures are at much greater risk for future vertebral fractures. Additional vertebral fractures may result in further loss of height and kyphosis (4–6). Spinal deformity is often permanent following osteoporotic vertebral fracture. Potential long-term consequences of vertebral fractures include impaired physical functioning, immobility, loss of self-esteem, and depression (7–9). These chronic symptoms occur in 10% of postmenopausal women with radio-

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graphically defined vertebral fractures (10–12) and may significantly affect health-related quality of life (HRQOL) (9,13). Less than one-third of patients with radiographically defined vertebral fractures come to clinical attention (14). Population studies suggest that undiagnosed vertebral fractures are associated with diminished physical and functional status, diminished ability to perform activities of daily living, and overall decline in a patient's well-being (2,7,8,11,15,16).

HRQOL is a multidimensional assessment of a patient's perceived pain, functional limitations, and emotional status (17). The Osteoporosis Assessment Questionnaire (OPAQ) is one of several disease-targeted validated instruments for measuring HRQOL in osteoporosis clinical trials (18). Previous studies have shown that increasing numbers of prevalent vertebral fractures in postmenopausal women are associated with significant reductions in HRQOL (19–21). Severity of vertebral fracture is a significant predictor of back pain and back-related disability (10,22). We investigated the relationship between vertebral fracture severity and HRQOL using data from the Fracture Prevention Trial (23). We sought to determine whether there was an association between baseline HRQOL and baseline vertebral fracture severity, and if so, to determine the effects of teriparatide (recombinant human parathyroid hormone 1-34) on vertebral fracture grades that most strongly impact HRQOL in postmenopausal women with osteoporosis.

PATIENTS AND METHODS

Study group. The methods used during the Fracture Prevention Trial have been previously reported (23). Briefly, women who were postmenopausal for at least 5 years were randomly assigned to receive daily subcutaneous injections of 20 μg teriparatide (n = 541), 40 μg teriparatide (n = 552), or placebo (n = 544) in addition to daily calcium (1,000 mg) and vitamin D (400–1,200 IU) supplements. The median duration of treatment was 19 months. To be included in the study, patients had to have at least 2 mild atraumatic prevalent vertebral fractures or 1 moderate atraumatic vertebral fracture. Patients with fewer than 2 moderate vertebral fractures were required to have bone mineral density (BMD) at the hip or lumbar spine that was at least 1 SD below the mean for normal premenopausal Caucasian women (age range 20–35 years) for study eligibility. Exclusion criteria included diseases known to affect bone or calcium metabolism, urolithiasis within 2 years, serum creatinine level >2 mg/dl, alcoholism, drug abuse, or use of medications known to alter bone metabolism.

Each patient gave written informed consent for study participation, and Institutional Review Board approval was obtained at all study sites. All study methods and procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki.

Vertebral fracture assessment. Radiographs of the spine were obtained from all participants at baseline and at the conclusion of the study. Radiographic evaluation was performed centrally (at the Osteoporosis and Arthritis Research Group and the University of California, San Francisco) by a radiologist who was blinded to treatment group assignment but not to temporal sequence. Vertebrae were graded on a scale of 0–3 using a visual semiquantitative (SQ) method (SQ grade 0 [SQ0] = no fracture, SQ1 = mild fracture, SQ2 = moderate fracture, and SQ3 = severe fracture) (24). A mild fracture was defined as an ~20–25% reduction in anterior, middle, or posterior vertebral height. Moderate and severe vertebral fractures were defined as an ~25–40% reduction and an ~>40% reduction, respectively, in vertebral height. New vertebral fracture was defined as a postbaseline SQ grade of 1, 2, or 3 in a vertebra that was graded 0 at baseline, while worsening fracture was defined as a postbaseline increase in SQ grade in a vertebra having an SQ grade of 1 or 2 at baseline. Vertebrae that could not be evaluated radiographically because of kyphosis, being fused, or other anomalies were not graded.

HRQOL questionnaire. OPAQ version 2.0 is a self-administered, osteoporosis-specific, validated instrument consisting of 49 questions grouped into 14 domains that can be subgrouped into 4 composite health status dimensions (physical function, emotional status, symptoms, and social interactions) and a single overall question on HRQOL (18). The physical function dimension comprises 6 domains: walking/bending, standing/sitting, dressing/reaching, household/self care, transfers, and usual work. The emotional status dimension comprises 4 domains: fear of falling, level of tension, body image, and independence. The symptoms dimension includes 2 domains: back pain and fatigue. The social interactions dimension comprises 2 domains: social activity and support of family and friends.

During the Fracture Prevention Trial, a validated version of OPAQ version 2.0 was only available in English. Therefore, the OPAQ was administered only to English-speaking participants from Australia, Canada, New Zealand, and the US at baseline, month 12, and study end point. For each participant, OPAQ scores were obtained for the 4 composite health status dimensions, 14 domains, and overall HRQOL. Dimensions are scored on a scale with a ceiling of 100, with higher scores representing better overall HRQOL.

Statistical analysis. Among the patients to whom the OPAQ was administered, the number who had incident vertebral fractures was insufficient for us to assess the impact of incident fracture severity on HRQOL. Therefore, we investigated the relationship between baseline vertebral fracture SQ grade and baseline OPAQ score via analysis of variance (ANOVA) modeling. Using this approach, the statistical modeling did not have to account for therapy. We performed separate ANOVAs for each HRQOL domain and dimension score, modeling HRQOL outcome as a function of maximum baseline SQ grade, while controlling for other potentially important predictor variables, such as back pain, femoral neck BMD, lumbar spine BMD, body mass index (BMI), and age. All first-order interactions between the maximum baseline SQ grade and the other factors modeled were considered. For

Table 1. Baseline demographics of the study population from the Fracture Prevention Trial with radiographic and OPAQ HRQOL assessments, stratified by baseline vertebral fracture grade*

	Baseline vertebral fracture grade†			
Baseline parameter	0 (n = 49)	1 (n = 153)	2 (n = 175)	3 (n = 67)
Age, years	68.76 ± 6.95	70.11 ± 6.99	70.89 ± 6.61	73.71 ± 6.49
BMI, weight (kg)/height (m^2)	27.45 ± 3.84	27.06 ± 4.86	26.18 ± 4.04	26.07 ± 5.13
Years postmenopausal	21.02 ± 9.27	23.08 ± 8.79	24.54 ± 9.12	27.49 ± 8.69
LS BMD, gm/cm^2	0.93 ± 0.17	0.89 ± 0.19	0.82 ± 0.17	0.79 ± 0.18
LS BMD T score	−1.37 ± 1.47	−1.68 ± 1.76	−2.34 ± 1.54	−2.57 ± 1.62
FN BMD, gm/cm^2	0.67 ± 0.10	0.65 ± 0.10	0.61 ± 0.09	0.57 ± 0.12
FN BMD T score	−1.94 ± 0.71	−2.08 ± 0.76	−2.44 ± 0.73	−2.67 ± 0.93
Back pain, no. (%)	16 (32.7)	43 (28.1)	65 (37.1)	33 (49.3)

* Except where indicated otherwise, values are the mean ± SD. OPAQ = Osteoporosis Assessment Questionnaire; HRQOL = health-related quality of life; BMI = body mass index; LS = lumbar spine; BMD = bone mineral density; FN = femoral neck.
† Semiquantitative grades of vertebral fracture were as follows: 0 = no fracture, 1 = mild fracture, 2 = moderate fracture, and 3 = severe fracture.

each HRQOL variable, a stepwise selection procedure was used to determine the final model, and the estimated differences between the SQ grades (SQ3 versus SQ2, SQ3 versus SQ1, SQ3 versus SQ0, SQ2 versus SQ1, SQ2 versus SQ0, and SQ1 versus SQ0) were calculated. In addition, to determine whether the number of prevalent vertebral fractures corresponding to each respective SQ grade influenced HRQOL, additional statistical modeling was performed using as covariates the number of mild fractures, number of moderate fractures, and number of severe fractures a patient had at baseline. First-order interaction terms were also considered.

Baseline characteristics were compared among patients with different baseline SQ grades. Continuous variables were compared using ANOVA, while categorical variables were compared using Fisher's exact test. Because SQ3 vertebral fractures were found to have the greatest impact on HRQOL at baseline in the OPAQ subset of the Fracture Prevention Trial, we compared the incidences of new or worsening SQ3 vertebral fractures in the entire placebo (n = 448), 20 μg/day teriparatide (n = 444), and 40 μg/day teriparatide (n = 434) treatment arms of the Fracture Prevention Trial for which there were evaluable baseline and followup radiographs. The relative risks of new or worsening SQ3 vertebral fractures and corresponding *P* values are reported.

RESULTS

Baseline demographics of the study population, stratified by baseline vertebral fracture severity, are shown in Table 1. There were statistically significant differences at baseline in age, BMD, BMI, and incidence of back pain among the vertebral fracture SQ grade groups. Patients tended to be older, to have lower BMD and BMI, and to have a greater incidence of back pain as the severity of vertebral fracture increased.

Table 2 shows the final ANOVA modeling results for each HRQOL dimension and domain. There were no statistically significant interactions between SQ grade and the other factors for each HRQOL outcome modeled. For the physical function dimension, patients with prevalent SQ3 vertebral fractures reported significantly lower HRQOL scores ($P < 0.01$) compared with patients without SQ3 fractures. The estimated physical function score differences were −9.6, −8.0, and −7.8 for patients with SQ3 fractures compared with patients with SQ0, SQ1, and SQ2 fractures, respectively (Figure 1A). Estimated differences in physical function scores among patients with SQ0, SQ1, or SQ2 vertebral fractures were not statistically significant (Figure 1A). Similarly, estimated differences in emotional status and symptoms dimension scores were significantly ($P < 0.05$) reduced in patients with prevalent SQ3 vertebral fractures com-

Table 2. Analysis of variance modeling results*

OPAQ variable	Significant main effects ($P < 0.05$)
Overall QOL	SQ grade, back pain
Physical function	SQ grade, back pain, FN BMD, BMI
Symptoms	SQ grade, back pain
Emotional status	SQ grade, back pain, FN BMD
Social interactions	Back pain
Body image	SQ grade, back pain†
Back pain	SQ grade, back pain
Dressing/reaching	SQ grade, back pain†
Fear of falling	Back pain, FN BMD, age, BMI
Fatigue	Back pain
Household/self care	SQ grade, back pain, FN BMD
Independence	SQ grade, back pain, FN BMD
Level of tension	Back pain, FN BMD, age
Social activity	None
Support of family and friends	SQ grade
Standing/sitting	SQ grade, back pain
Transfers	Back pain, FN BMD, BMI
Usual work	SQ grade, back pain, FN BMD
Walking/bending	SQ grade, back pain, FN BMD, BMI

* SQ grade = semiquantitative grade (of vertebral fracture) (see Table 1 for other definitions).
† $P < 0.10$ for SQ grade.

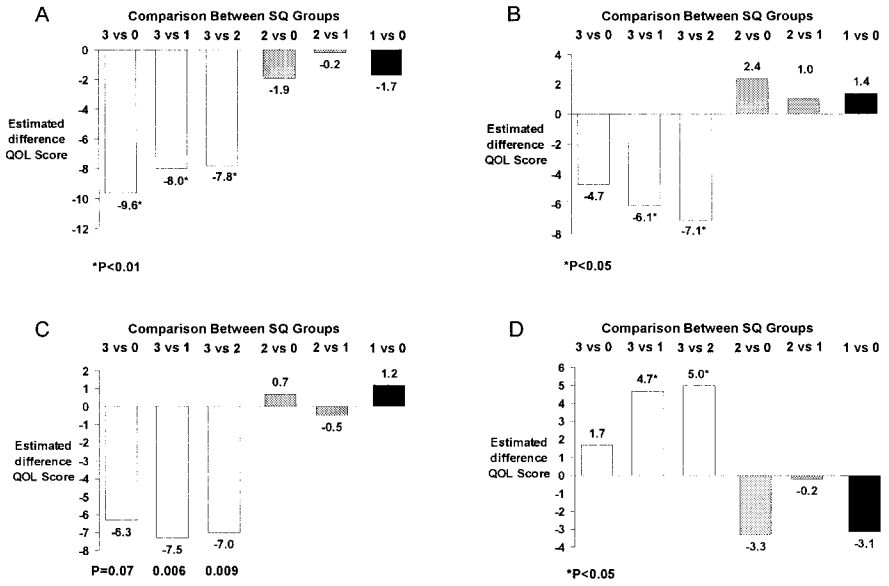

Figure 1. Baseline Osteoporosis Assessment Questionnaire dimension scores as a function of maximum semiquantitative (SQ) grade of vertebral fracture. Shown are estimated differences in quality of life (QOL) scores between patients grouped according to their grade of vertebral fracture (SQ grade 0 [SQ0] = no fracture, SQ1 = mild fracture, SQ2 = moderate fracture, and SQ3 = severe fracture). **A,** Physical function dimension scores. **B,** Emotional status dimension scores. **C,** Symptoms dimension scores. **D,** Social interactions dimension scores.

pared with patients with SQ1 or SQ2 fractures (Figures 1B and C). In contrast, patients with SQ3 fractures tended to score higher on the social interactions dimension (Figure 1D). Overall HRQOL was also reduced in patients with at least 1 baseline SQ3 vertebral fracture, since these patients reported significantly reduced ($P < 0.001$) overall HRQOL scores of −12.1, −10.1, and −10.1, respectively, compared with patients with SQ0, SQ1, or SQ2 vertebral fractures (Figure 2).

We also assessed the impact of the number of SQ1, SQ2, and SQ3 vertebral fractures on each HRQOL dimension. The number of SQ3 vertebral fractures, but not the numbers of SQ1 or SQ2 vertebral fractures, significantly predicted changes in each HRQOL dimension. First-order statistical interactions between numbers of SQ1, SQ2, and SQ3 vertebral fractures were not significant. These findings suggest that a greater number of SQ3 vertebral fractures was associated with greater changes in HRQOL. However, increasing numbers of SQ1 or SQ2 fractures did not significantly affect HRQOL, and among women with SQ3 fractures, additional fractures of lesser severity did not impact HRQOL.

Results for individual OPAQ domain and dimension scores were consistent. That is, compared with patients with less severe vertebral fractures, patients with prevalent SQ3 vertebral fractures scored significantly lower in domains comprising the physical function, symptoms, and emotional status dimensions, and

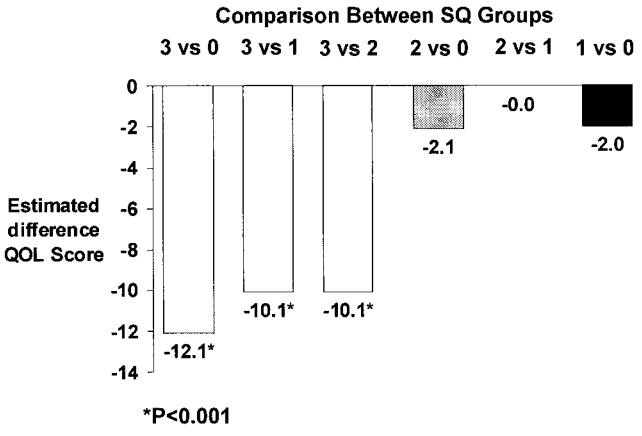

Figure 2. Baseline Osteoporosis Assessment Questionnaire overall health-related quality of life (HRQOL) scores as a function of the maximum semiquantitative (SQ) grade of vertebral fracture. Shown are estimated differences in overall HRQOL scores between patients grouped according to their grade of vertebral fracture (SQ0 = no fracture, SQ1 = mild fracture, SQ2 = moderate fracture, and SQ3 = severe fracture).

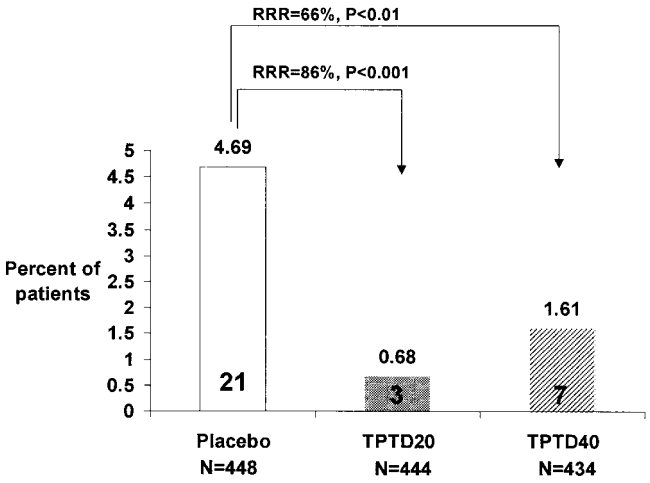

Figure 3. New or worsening semiquantitative grade 3 (severe) vertebral fracture in patients randomly assigned to receive 20 μg/day teriparatide (TPTD20), 40 μg/day teriparatide (TPTD40) or placebo during the Fracture Prevention Trial. RRR = relative risk reduction.

they tended to score higher in the domains comprising the social interactions dimension.

Because SQ3 vertebral fractures had the greatest impact on HRQOL at baseline in the OPAQ subset of the Fracture Prevention Trial, the incidence of new or worsening SQ3 vertebral fractures was compared in the placebo and 20 μg/day teriparatide treatment arms during the Fracture Prevention Trial. In the placebo group (n = 448), 14 patients experienced new SQ3 fractures and 8 patients experienced worsened SQ3 fractures, including 1 patient who experienced both 1 new and 1 worsened SQ3 fracture. In the 20 μg/day teriparatide group (n = 444), no patients experienced new SQ3 fractures and 3 patients experienced worsened SQ3 fractures. In the 40 μg/day teriparatide group (n = 434), 3 patients experienced new SQ3 fractures and 4 patients experienced worsened SQ3 fractures. Overall, new or worsening SQ3 vertebral fractures occurred in 21 patients (4.7%) in the placebo group compared with 3 patients (0.7%) in the 20 μg/day teriparatide group and 7 patients (1.6%) in the 40 μg/day teriparatide group (Figure 3). Thus, compared with placebo, daily treatment with 20 μg and 40 μg teriparatide significantly reduced the risk of new or worsening SQ3 vertebral fractures by 86% ($P < 0.001$) and 66% ($P < 0.01$), respectively (Figure 3).

DISCUSSION

Fractures are associated with pain and decreased physical function and emotional status. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was the first international clinical trial that used osteoporosis-targeted questionnaires, such as the quality of life questionnaire of the European Foundation for Osteoporosis and the OPAQ. In the MORE trial, prevalent vertebral fractures were associated with decreased quality of life (20,21). The first vertebral fracture was associated with statistically significant decreases in HRQOL dimensions of physical function, symptoms, and emotional status, and subsequent vertebral fractures were associated with marked decreases in these same HRQOL dimensions (20,21). Fractures of the lumbar spine had greater impact on HRQOL than did fractures of the thoracic spine (20,21).

A subset of patients in the Fracture Prevention Trial (n = 444) had both a spine radiograph and a completed OPAQ at baseline. It was previously reported that 54 of 374 women who completed the OPAQ yearly experienced an incident vertebral or nonvertebral fracture during the study period (19). Compared with women without incident fractures, women with incident fractures had worse HRQOL from baseline to end point in the symptoms dimension ($P = 0.008$) and in the back pain domain ($P = 0.023$).

We now report on the association between baseline vertebral fracture severity and quality of life as measured by the OPAQ in this subset of 444 women. Compared with vertebral fractures of lesser severity, SQ3 vertebral fractures were associated with a significantly greater reduction in HRQOL. SQ3 vertebral fractures were associated with a significantly lower overall HRQOL score and with significantly lower physical function, symptoms, and emotional status dimension scores. These reductions in HRQOL are substantial and clinically meaningful. In the subgroup of patients described here, fractures graded SQ2 and SQ1 were not associated with reduced HRQOL compared with fractures of lesser severity in these dimensions. A statistically significant increase in the social interactions dimension was noted when we compared SQ3 fractures with SQ1 or SQ2 fractures. While this was not expected based on observational studies (25), this finding may represent increased support from family and friends for patients with more symptomatic vertebral fractures. Although SQ1 and SQ2 prevalent vertebral fractures did not significantly impact HRQOL in this study, previously reported data from the MORE trial suggest that there is a corresponding decline in HRQOL with increasing SQ grade (26).

In the full population of the Fracture Prevention Trial, a 65% decrease in the relative risk of new verte-

bral fracture ($P \leq 0.001$) was reported in patients treated with 20 μg/day teriparatide (23). Because of the impact of SQ3 fractures on HRQOL, we analyzed the incidence of new or worsening SQ3 vertebral fractures in the placebo and teriparatide treatment arms of this trial. Teriparatide at 20 μg/day and 40 μg/day decreased the relative risk of new or worsening SQ3 vertebral fracture by 86% ($P < 0.001$) and 66% ($P < 0.01$), respectively.

This study is the second large, prospective international clinical trial in which HRQOL data were routinely collected from a large sample of postmenopausal women by use of a validated osteoporosis-targeted questionnaire. Our results confirm the impact of vertebral fracture on HRQOL, and they add to our knowledge of the association of vertebral fracture severity with HRQOL. This study confirms that disease-targeted instruments, such as the OPAQ, appear to be sensitive to changes in HRQOL with severity of fracture.

Our sample size was too small to examine the relationship between incident vertebral fracture severity and HRQOL. HRQOL in older populations is affected by many factors, including comorbidity, lifestyle, socioeconomic conditions, and other risk factors, and thus, the observed association of reduced HRQOL in women with SQ3 vertebral fractures may be related to other confounding factors not accounted for in the modeling. However, the observed associations remained significant after adjustment for age, BMD, BMI, and incidence of back pain. The patients in the substudy were predominantly Caucasian women, a group known to be at high risk for postmenopausal osteoporosis. Our results may not apply to men or to other ethnic groups. The women were participating in a clinical trial, and they may differ considerably from the general population in their perception of HRQOL.

In the Fracture Prevention Trial, compared with fractures of lesser severity, SQ3 vertebral fractures were associated with reduced HRQOL. Treatment with teriparatide significantly reduced the risk of new or worsening SQ3 vertebral fracture. These findings suggest, but do not directly demonstrate, a benefit of teriparatide on HRQOL.

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