The Impact of Incident Vertebral and Non-Vertebral Fragility Fractures on Health-Related Quality of Life in Established Postmenopausal Osteoporosis: Results from the Teriparatide Randomized, Placebo-Controlled Trial in Postmenopausal Women

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ABSTRACT. ***Objective.*** To report the combined impact of both vertebral and non-vertebral fractures on decreased health-related quality of life (HRQOL) in postmenopausal women (mean age 70.7) with osteoporosis who participated in a clinical trial to examine the anti-fracture efficacy of teriparatide [rhPTH(1-34)] injection.

Methods. Patients were randomly assigned to 1 of 3 study arms: placebo, 20 µg or 40 µg of teriparatide by daily self-injection. All patients received daily calcium (1000 mg) and vitamin D (400-1200 U) supplements. Patients were followed for a median of 21 months. Incident vertebral fractures were assessed by lateral spinal radiograph. Incident non-vertebral fractures were ascertained by patient self-report and verified by a review of radiological reports. HRQOLwas assessed at baseline and annually until study termination using the Osteoporosis Assessment Questionnaire (OPAQ), a validated disease-targeted instrument.

Results. Of the 365 women in the HRQOL sub-study, 53 had an incident vertebral or non-vertebral fracture during the study period. Compared to women without incident fractures, women who fractured reported significant declines in physical functioning, emotional status, and symptoms (all $p < 0.05$). Similarly, when analysis was limited to patients with significant loss in HRQOL, patients with incident fracture accounted for a greater proportion of those patients with decreased physical function, emotional status, and increased symptoms (all $p < 0.05$).

Conclusion. Our results confirm and extend previous findings to show that a composite endpoint of incident vertebral and non-vertebral fractures in women with postmenopausal osteoporosis was associated with significant decreases in HRQOL. (J Rheumatol 2003;30:1579–83)

Key Indexing Terms:
HEALTH-RELATED QUALITYOF LIFE INCIDENTFRACTURE OSTEOPOROSIS OPAQ

Osteoporosis, which has been defined as a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk, is associated with an enormous morbidity burden[1]. It is estimated that over 200 million people worldwide currently have low bone mass and that the global number of osteoporotic hip fractures will increase from 1.7 million annually to over 6 million by the year 2050[2]. In the United States alone, osteoporosis accounts for over 1.3 million vertebral and nonvertebral fractures resulting in an estimated 2,486,272 physician visits, 432,447 hospitalizations, and 179,222 nursing home stays annually[3,4]. Osteoporotic fractures can lead to further fractures, chronic pain, disability, increased dependence on others for some activities of daily living, deformities of the spine, need for nursing home care, depression, and death[5,6].

In addition to the clinical manifestation of the fractures themselves, investigators are increasingly becoming interested in the burden of osteoporotic fractures on health-related quality of life (HRQOL)[7,8]. HRQOL is a multi-dimensional concept that incorporates a patient's perceived physical, social, emotional, and functional well-being into their overall health status measurement[9]. In osteoporosis intervention studies, HRQOL is more commonly included as an outcome measure alongside bone mineral density (BMD) measurements and the assessment of frac-

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ture incidence[10]. Within the past decade, several disease-targeted instruments have been developed to assess HRQOL in the osteoporotic population, particularly postmenopausal women[11]. Previous clinical trials with raloxifene (Evista™) have demonstrated that postmenopausal women with osteoporosis who have experienced vertebral fractures have decreased HRQOL compared to osteoporotic women without fractures[10,12].

We report the combined impact of both incident vertebral and non-vertebral fragility fractures on HRQOL in an English-speaking subset of postmenopausal women with osteoporosis who participated in a double-blind, randomized, placebo-controlled trial to evaluate the anti-fracture efficacy of daily subcutaneous injections of the recombinant human parathyroid hormone (1-34), teriparatide.

MATERIALS AND METHODS

Study participants. A detailed description of this study has been described[13]. Briefly, study participants included 1637 postmenopausal women recruited from 99 centers in 17 countries. Only women with established osteoporosis as defined by a history of one moderate or at least 2 mild atraumatic vertebral fractures documented by spinal radiograph were included in the study. Study participants were randomized to receive either placebo, 20 µg, or 40 µg of teriparatide daily by self-administered injection. They were followed for a median of 21 months. In addition, all women received 1000 mg of calcium and 400 to 1200 IU of vitamin D.

Measurements. Incident vertebral fractures were ascertained by a comparison of anteroposterior and lateral radiographs of the thoracic and lumbar spine taken at baseline and study endpoint. Radiographs were read at a central location by radiologists who were blinded to the treatment assignment. Per described techniques, vertebrae were graded as normal (i.e., normal vertebral height), mild (20-25% decrease in vertebral height), moderate (26-40% decrease in vertebral height), and severe (> 40% decrease in vertebral height)[14]. An incident vertebral fracture was defined as deterioration in a previously normal vertebra of at least one grade from baseline. A worsening of pre-existing deformities was not included in this analysis. Non-vertebral fragility fractures were ascertained by patient self-report and verified by a review of radiological reports. For the purposes of our analyses, we used a composite endpoint of incident fractures that included both vertebral and non-vertebral fragility fractures.

The Osteoporosis Assessment Questionnaire (OPAQ) has demonstrated reliability and validity as a disease-targeted instrument in postmenopausal osteoporosis[11]. The OPAQ version 2.0 is a validated, self-administered instrument consisting of 49 questions in 14 domains that can be grouped into 4 composite health status dimensions: physical function, emotional status, symptoms, and social interactions[15]. In addition, there are 6 individual questions and 12 domain-weighting questions. The OPAQ can be scored by individual domain or by the 4 composite health status dimensions. At the time of study design, the OPAQ version 2.0 was available in a validated English translation only. With the exception of the United Kingdom, OPAQ version 2.0 was administered to all study participants from the English-speaking countries of Australia, Canada, New Zealand, and the United States at baseline, month 12, and at study endpoint. Our results focus on the 4 health status dimension scores.

Statistical analysis. Each OPAQ domain and dimension was scored according to a published algorithm[15]. Within each domain, missing values were imputed with the mean of the non-missing values only if at least one-half of the questions were answered or were otherwise left blank. All summary scores were transformed into a range of 0 to 100 to allow for comparability. Higher OPAQ scores indicate a better HRQOL.

The analyses of incident fractures were based on longitudinal data obtained at baseline and followup at a median of 21 months. An OPAQ change score was calculated by subtracting the baseline score from the score at study endpoint. The difference in mean OPAQ change scores were compared between women who did and did not experience an incident fracture using an analysis of covariance model adjusting for baseline OPAQ scores. The proportion of women who experienced a significant loss in HRQOLwas compared between women who did and did not experience an incident fracture using Pearson's chi-square test. Significant HRQOL loss was defined as a loss of greater than one standard deviation (SD) from baseline.

All differences were tested at a 2-sided significance level of 0.05. All statistical analyses were performed using SAS (SAS Institute, Inc., Cary, NC, USA)[16].

RESULTS

Seventeen countries (n = 1,637) participated in the teriparatide randomized, placebo controlled trial[13]. Four English-speaking countries (n = 521) participated in the OPAQ sub-study. Baseline vertebral fractures and lumbar spine BMD values were summarized in Table 1 for English and non-English speaking countries. Patients from English speaking countries had greater baseline BMD values and fewer vertebral fractures.

Among the 521 English-speaking patients who participated in the OPAQ sub-study, only 365 qualified for the analysis. To qualify for the HRQOL analysis, patients were required to meet each of the following conditions: (1) have both baseline and followup radiographs; (2) have both baseline and followup OPAQ assessments; and (3) the followup OPAQ assessments should occur after the radiographic assessment of vertebral fracture in order to assess the potential impact of vertebral fractures on quality of life. Among the 521 patients in the HRQOL sub-study, 417 patients met condition 1. Of these, 366 patients also met condition 2. Of the 51 patients who met condition 1 but not condition 2, 46 had baseline OPAQ data but no followup data. Five patients had followup OPAQ assessments but no baseline assessments. Finally, 1 of the 366 patients did not meet condition 3. Overall, 150 of the 156 patients did not qualify for the HRQOL analysis because of early study discontinuation. Baseline characteristics were similar between the overall study population and the English-speaking HRQOL subset with the exception of current smoking status (18.1% overall vs 12.8% in the HRQOL subset). Table 2 summarizes the demographic and clinical characteristics of the 365 patients who participated in the HRQOL assessment.

The 365 women were predominantly Caucasian (97.0%) with a mean age of 70.7 years. Women in the incident fracture group were older and had spent more years postmenopause compared to women in the no-fracture group.

Fifty-three women experienced at least one incident vertebral or non-vertebral fragility fracture during the study period. Table 3 shows the association between the composite endpoint of incident fractures and HRQOL. From baseline to endpoint, women who experienced incident fractures reported significant declines in the OPAQ health status

Table 1. Baseline BMD and fractures. English-speaking countries versus non-English-speaking countries.

Factor	English Speaking Countries* (n = 521)	Non English Speaking Countries** (n = 1,114)	p (ANOVA)
Lumbar spine BMD, mean (g/cm^2)	0.85	0.81	< 0.001
Number of vertebral fractures, mean	2.1	2.4	0.003

* Australia, Canada, New Zealand, United States. ** Argentina, Austria, Belgium, Czech Republic, Denmark, Finland, Hungary, Israel, Italy, Norway, Poland, Sweden, The Netherlands.

Table 2. Study population demographics and clinical profile. The differences between women with and without incident fractures were statistically significant ($p < 0.05$) at baseline for the following factors: age, body mass index, and years postmenopausal.

Factor	No Incident Fracture	≥ 1 Incident Fracture	Overall
Sample Size (n)	312	53	365
Age (mean)	70.3	72.9	70.7
Body mass index (mean)	26.8	25.4	26.6
Years postmenopausal (median)	22.0	26.0	23.0
Current smokers (%)	12.8	13.2	12.9
Alcohol (%)	43.9	52.8	45.2
Caucasian (%)	97.4	94.3	97.0
Country (n)			
USA	227	45	272
Canada	57	4	61
Australia	15	2	17
New Zealand	13	2	15
Lumbar Spine BMD (g/cm^2)	0.86	0.81	0.86

Table 3. Association between incident fractures and mean change in HRQOL. All OPAQ scores are presented on a 100-point scale. The differences between the two groups were compared by analysis of covariance adjusting for baseline OPAQ scores. Compared to women without incident fractures, women with incident fractures reported significant decreases in the following OPAQ domains: walking/bending, dressing/reaching, household/self-care, transfers, back pain, and fatigue (all $p < 0.05$).

OPAQ Dimensions	No Incident Fracture (N = 312)	≥ 1 Incident Fracture (N = 53)	p
Physical Function	–0.9 (11.5)	–3.6 (18.0)	0.024
Emotional Status	0.4 (9.9)	–1.8 (11.9)	0.038
Symptoms	2.1 (14.2)	–4.1 (17.2)	0.002
Social Interaction	1.2 (14.3)	1.3 (14.7)	0.917

dimensions of physical function, emotional status, and symptoms versus women who did not fracture. The OPAQ domains of walking/bending, dressing/reaching, household/self-care, transfers, back pain, and fatigue were all significantly and negatively associated with incident fracture (all $p < 0.05$).

Women with incident fractures represented a substantially higher proportion of those patients who reported significant loss (> 1 standard deviation decrease in OPAQ dimension scores from baseline) in the physical function, emotional status, and symptoms dimensions (Table 4). There was no association between social interaction and incident fractures seen in this sub-study population with OPAQ

Regardless of treatment group, no statistically significant differences were detected between treatment arms with respect to HRQOL.

DISCUSSION

In the MORE trial, we showed that the endpoints of both incident vertebral and non-vertebral fracture were associated with lower HRQOLscores[12]. Only 22% of women with incident vertebral fractures had significant loss in HRQOL[12]. Recent phase 3 clinical trials have begun to use all osteoporotic fractures as an endpoint for efficacy. This study confirms that a composite endpoint of incident osteoporotic fractures defined as both vertebral and non-vertebral

Table 4. Association between incident fractures and proportion of women with a significant loss in HRQOL. A significant loss in HRQOLis defined as a decrease of one standard deviation (SD) or more from baseline to study endpoint. The baseline SD are 17.3 (physical function), 17.1 (emotional status), 19.7 (symptoms), and 15.5 (social interaction). The percentages of women who suffered a significant loss in HRQOL were compared by Pearson's chi-square test. Compared to women without incident fractures, a substantially higher proportion of women with incident fractures reported significant loss in the following OPAQ domains: dressing/reaching, household/self-care, back pain, and fatigue (all $p < 0.01$).

OPAQ Dimensions	No Incident Fracture n = 312 (%)	≥ 1 Incident Fracture n = 53 (%)	p
Physical Function	6.5	15.2	0.040
Emotional Status	3.7	12.5	0.008
Symptoms	6.2	14.9	0.032
Social Interaction	9.8	4.1	0.196

fragility fractures combined also is associated with lower HRQOL scores using OPAQ. Compared to women without incident fracture, women with incident fracture suffered a significant loss in OPAQ dimensions of physical function, emotional status, and symptoms. All the women in this sub-study had at least one prevalent vertebral fracture at baseline, suggesting a sustained loss in HRQOL with new osteoporotic fractures.

The apparent lack of association in the social interaction dimension may suggest a lack of responsiveness in this OPAQ dimension. However, women in the incident fracture group made up a smaller proportion of patients reporting significant loss in the social interaction dimension compared to the non-fracture group, although the results were not significant (Table 4). This may suggest increased social support and interaction after fracture.

Even though teriparatide decreased the risk of new vertebral fracture by 69% in the full population, there were no differences between the treatment groups and placebo in any HRQOLdomain. A possible explanation for this is that only a small number of women in our study had incident fracture (15%) of which a minority (< 16%) had significant changes in physical functioning, emotional status, or symptoms (as defined by a 1 SD change). Significant losses in these same dimensions were also seen in 3-6% of patients without fracture. The incremental proportion of women with significant loss in HRQOL was therefore 8-10% in this study.

Another possible explanation is that with only 150 patients in each treatment group, our study was not adequately powered to detect an HRQOL difference between placebo and treatment. Even though there was a difference of 2.7 between patients with at least 1 fracture and patients without a fracture, most patients did not develop a fracture during the 18-month followup. Therefore, the difference between placebo and teriparatide was somewhat smaller than the difference between patients with and without fractures. Assuming a one-point difference between placebo and teriparatide in physical function, to detect a statistically significant difference (at alpha = 0.05) with 80% power, about 2300 patients are needed in each group. If the difference increases to 2, then only 570 patients are needed in each group.

This study is the second large, prospective, international clinical trial where HRQOLdata were routinely collected on a large sample of postmenopausal women using a validated OPAQ. Our results using a composite endpoint for all osteoporotic fractures confirm and further extend our findings from the MORE study, in which we reported a significant association between incident vertebral fracture and physical function, emotional status, and symptoms using OPAQ[12].

This study confirms that disease-targeted measures, such as OPAQ, appear to be sensitive to changes in HRQOLwith incident fracture.

Our sample size was too small to examine the independent relationships between incident vertebral or incident non-vertebral fractures and HRQOL. Nevertheless, our results show compelling evidence of an association between a composite endpoint of incident osteoporotic fracture (both vertebral and non-vertebral) and lower HRQOL scores in postmenopausal women. However, one must be cautious in drawing a causal relationship. The observed association of reduced HRQOLfor women with incident fractures may be related to other confounding factors. HRQOLin older populations can be affected by many other factors, including comorbidity, lifestyle, socioeconomic conditions, and other risk factors. In our analyses, we statistically adjusted only for baseline HRQOL scores.

The women in the sub-study were predominantly Caucasian, a group known to be at high risk for postmenopausal osteoporosis. Our results may not apply to men or other ethnic groups. The women were participating in a clinical trial, and may differ considerably in their perception of HRQOL compared to the general population. We did not know when the incident fracture exactly occurred within the median 21-month study period, limiting our ability to examine the relationship between acute incident fracture and acute HRQOL outcomes.

We studied women with a history of prevalent vertebral

fracture and confirmed the association of subsequent osteoporotic fracture and losses in HRQOL for women with prevalent vertebral fractures at baseline. We did not study the association of osteoporotic fracture and HRQOL for women without prevalent vertebral fractures at baseline.

We found that a composite endpoint of both incident vertebral and non-vertebral fragility fractures was associated with decreases in all dimensions of HRQOL with the exception of social interaction. Incident fractures seem to have an incrementally significant and negative impact on HRQOL that is detectable for patients who have prevalent vertebral fractures at baseline.

Patients with prevalent vertebral fracture have an increased risk of subsequent osteoporotic fractures. Our findings show that these patients may be at risk for further decreases in HRQOL with subsequent incident fractures.

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