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# Evaluation of Vertebroplasty with a Validated Outcome Measure: The Roland-Morris Disability Questionnaire

Andrew T. Trout, David F. Kallmes, Leigh A. Gray, Barbara A. Goodnature, Sandra L. Everson, Bryan A. Comstock, and Jeffrey G. Jarvik

**BACKGROUND AND PURPOSE:** Vertebroplasty is rapidly disseminating as a treatment for vertebral compression fractures, but its efficacy has not been assessed with a well-validated, back pain–specific instrument. We report the use of the Roland-Morris Disability Questionnaire (RDQ) in patients undergoing vertebroplasty for painful osteoporotic compression fractures.

**METHODS:** Retrospective review of patients treated with vertebroplasty who completed the RDQ and 2 verbal pain scales (0–10) for pain at rest and pain with activity at baseline, 1 week, 1 month, 6 months, and 1 year post-vertebroplasty. Changes in outcome measures were analyzed by using a paired *t* test and correlations were assessed with Spearman  $\rho$ . Multiple linear regression was used to analyze the relationship between baseline scores and independent variables.

**RESULTS:** One hundred thirteen patients were treated at 164 vertebral levels. At baseline, RDQ scores were associated with rest and activity pain ( $P < .001$  and  $P = .002$ , respectively) but were not associated with other independent variables. All 3 outcome scores decreased by 1 week and remained improved through maximal follow-up ( $P < .001$ ). RDQ scores improved by a mean of 7.0 points at 1 week and remained improved at 1 year ( $P = .02$ ). RDQ scores correlated with both rest and activity pain, but the absolute correlation was slightly better ( $+0.15$  on average) with activity pain.

**CONCLUSIONS:** Patients who underwent vertebroplasty experienced relief of back pain and symptoms, as shown by improvement in verbal pain and RDQ scores. The RDQ correlates well with measures of pain, shows clinically significant improvement and is responsive to changes across time. More important, the RDQ provides an easily administered, well-validated, back pain–specific outcome measure that could be adopted to assess vertebroplasty outcomes.

First used in the United States in the 1990s, vertebroplasty has rapidly approached standard of care for treatment of medically refractory, painful vertebral compression fractures. Because of difficulties in study design and execution there have been no randomized, blinded, controlled studies comparing vertebroplasty to placebo or conservative therapies. Instead, investi-

gators have sought to validate use of the procedure through changes in measures of perceived pain. These studies have shown significant improvement in pain and other symptoms as assessed by these instruments (1–3). There is no continuity, however, in the type of instrument used or the symptom variables that have been assessed in the vertebroplasty literature.

A critical review of the vertebroplasty literature reveals that, to this point, there exists a dearth of studies that have used validated outcome measures to assess the efficacy of this treatment. Visual analog scoring of perceived pain is the most common method of assessment. Although this addresses the patient's pain and provides a well-validated variable for assessment of pain control (4), this instrument fails to address the other symptoms and disabilities experienced by the patient. Because vertebroplasty aims at improving both the pain and disability experienced by the patient, both of these elements should be in-

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cluded in outcome measures when determining treatment efficacy.

We report the application of a widely applied, back pain-specific, well-validated outcomes instrument, the Roland-Morris Disability Questionnaire (RDQ), to a consecutive cohort of patients undergoing vertebroplasty for the treatment of painful, osteoporotic compression fractures. In addition, we correlated the RDQ with 2 11-point graded pain scales and tracked these measures across time. We believe that the RDQ should be used as the primary outcome measure for vertebroplasty research and practice.

## Methods

We performed a retrospective review of 113 patients who underwent vertebroplasty between April 21, 2003, and September 27, 2004, at our institution. Institutional review board approval was obtained for this study. Vertebroplasty typically was offered to patients with radiologic evidence of acute or subacute vertebral compression fractures of thoracic or lumbar vertebrae. Exclusion criteria included improvement with conservative management, technical contraindications, and non-correlating pain. Patients included in this study were limited to those with compression fractures due to underlying osteoporosis.

### *Vertebroplasty Procedure*

Vertebroplasties were performed by staff radiologists according to the methods outlined previously (5). Specifically, patients were treated by using intravenous conscious sedation. Biplane fluoroscopy was used in all cases. Local anesthesia was administered over the skin, subcutaneous tissues, muscular tissues, and periosteum of the targeted pedicle. Transpediculate or parapedicular trajectories were used in all cases. After local anesthetic administration, 11- or 14-gauge biopsy needles (Cook Inc., Bloomington, IN) were advanced into the central aspect of the vertebral bodies for unipediculate approaches, whereas placement of the needle was made into the midportion of the hemivertebra for bipediculate approaches.

The polymethylmethacrylate (PMMA) cement mixture was prepared under a vacuum hood. Approximately 30 g of PMMA powder (Codman Cranioplastic, Raynham, MA) was mixed with 12 g sterile barium sulfate (Cardinal Health, McGaw Park, IL) and 1 g gentamicin powder (Hawkins Inc., Minneapolis, MN). Liquid PMMA monomer was mixed with the powder mixture until the fluid reached a viscosity similar to that of cake glaze. The mixture was then loaded either into an injector device (Cook Inc.) or into 1-mL syringes and injected under continuous lateral and intermittent AP fluoroscopy. Cement injection was considered complete when the cement reached the posterior fourth of the vertebral body on the lateral projection. Injection was also terminated when epidural, venous, or transdiscal extravasation was noted. Following needle removal, patients were left on strict bed rest for 1 hour and then discharged.

A maximum of 4 vertebral levels were treated in a single session based on clinician comfort levels. Additional levels were treated in repeat sessions as required.

### *Outcome Measures*

The RDQ (appendix 1) and 2 verbal scales (scored 0–10) to assess “pain at rest” and “pain with activity” were administered in person by trained nurses at the time of evaluation for vertebroplasty. The original RDQ contained 24 questions and was derived from statements contained in the Sickness Impact Profile (6). Each question was selected on the basis of its

likelihood of being influenced by back pain and the qualification “because of my back pain” was added to further target the responses (7). The modified RDQ used in this study is that proposed by Patrick et al (8) and contains 23 yes/no questions. Nineteen of these 23 items are taken from the original RDQ, and 4 were derived from other statements in the Sickness Impact Profile (8). These modifications were suggested by the authors in an effort to reduce redundancy and add in items that were previously shown to better reflect changes in patient condition (8). The modified instrument takes approximately 3 minutes to complete and can be self-administered or administered via the telephone. It is scored from 0 to 23 on the basis of the number of “yes” responses. The authors have demonstrated that the modified version had a high level of internal consistency, construct validity, and responsiveness (8).

Follow-up data for all 3 outcome scales were gathered by telephone by the same trained nurses at 1 week, 1 month, 6 months, and 1 year post-vertebroplasty. Patients who were telephoned 3 times, without successfully obtaining follow-up data, were designated as nonrespondents for that time period. Nonrespondent status at a given time point did not preclude contacting that patient at the next designated time point.

### *Statistical Analysis*

Changes in pain scores across time were analyzed by using a paired *t* test comparison to the preceding time point. Correlation between outcome measures was assessed with the Spearman  $\rho$  correlation coefficient and differences in the strength of correlation were assessed through statistical bootstrapping of the data. Multiple linear regression was used to analyze the relationship between outcome scores and independent variables (age, sex, lumbar versus thoracic treatment, number of levels treated) at baseline and 1 week.

## Results

Data were collected from 113 patients who underwent vertebroplasty at 164 vertebral levels. Compression fractures in this population were all osteoporotic in origin. The mean patient age at the time of the procedure was 74 years (range, 28–96 years). Ninety (80%) of the 113 patients were women. As of this study, 113 patients were immediately post-vertebroplasty, 108 (96%) patients 1 week post-vertebroplasty, 93 (82%) patients 1 month post-vertebroplasty, 52 (46%) patients 6 months post-vertebroplasty, and 19 (17%) patients 1 year post-vertebroplasty. RDQ scores were available for 108 (96%) patients at baseline, 93 (86%) patients at 1 week, 73 (79%) patients at 1 month, 46 (89%) patients at 6 months, and 15 (79%) patients at 1 year. Four patients were excluded at 1 year because of secondary injury or processes that may have skewed their RDQ scores. Three of the excluded patients had falls resulting in pelvic fractures in one and new vertebral fractures in another. The fourth patient was excluded because of a subsequent diagnosis of fibromyalgia as the cause of her pain.

All 3 outcome measures (rest pain, activity pain, and RDQ score) showed a significant decrease at 1 week ( $P < .001$ ), with RDQ scores improving by a mean of 7.0 points. These improvements in all 3 outcome measures persisted through 1-year follow-up (Fig 1). Absolute values continued to decline at each time point, but the changes between time points were not statistically significant. There was a statistically

FIG 1. Mean RDQ and pain scores, with SDs, across follow-up. There is significant improvement in all 3 outcome measures at 1 week that persists throughout follow-up.

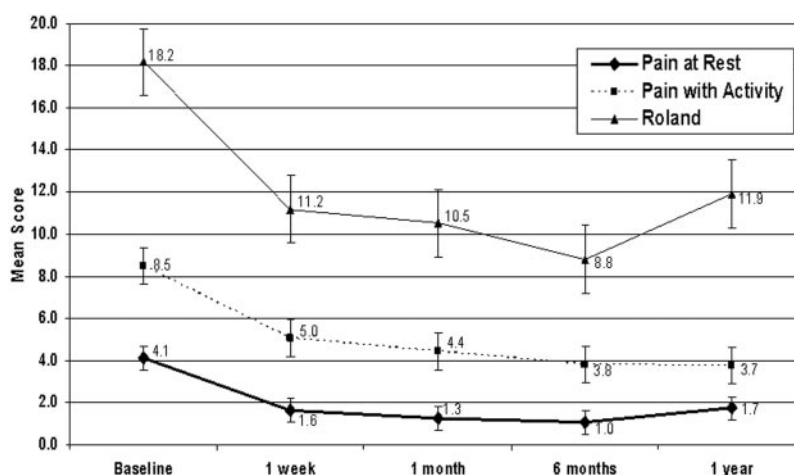


TABLE 1: Correlation between Roland score and pain scales at each time point throughout follow-up

	Pain at Rest	Pain with Activity
Baseline	0.30	0.47
1 week	0.57	0.52
1 month	0.44	0.40
6 months	0.31	0.63

TABLE 2: Linear regression of baseline Roland and pain with activity scores

Covariate	Baseline, Roland	Baseline, Pain with Activity	Baseline, Pain at Rest
Pain with activity	<.001		.06
Pain at rest	.002	.06	
Roland score		<.001	.04
Age	.09	.58	.30
Sex (male)	.06	.20	.99
Level			
Lumbar	.50	.38	.12
Thoracic	.64	.29	.18
Number of levels treated	.45	.43	.35

Note.—Columns indicate *P* values.

significant increase in RDQ scores at 1 year ( $P = .003$ ), but the score remained significantly improved over that at baseline ( $P = .02$ ).

RDQ scores correlated with both rest pain and activity pain at all time points (Table 1). On average, the correlation between RDQ scores and activity pain scores was +.15 better than that with rest pain scores. This difference approached but did not reach statistical significance ( $P = .07$ ).

Multiple linear regression analysis of outcome measures showed an association between baseline RDQ scores and baseline activity pain and rest pain ( $P < .001$  and  $P = .002$ , respectively) but showed no significant correlation with other patient or procedural variables (Table 2). Scores at 1 week were not found to be associated with baseline scores or any of the other variables.

## Discussion

Although vertebroplasty is rapidly disseminating as a treatment for vertebral compression fractures, the evidence for efficacy is weighed largely on symptomatic improvement in perceived pain from case series. Although pain control is an important element of vertebroplasty, the procedure is also designed to reduce disability in the treated individual. Few investigations have used validated outcome measures to address the impact of vertebroplasty on patient disability.

In the current study, we applied the RDQ to the practice of vertebroplasty. We selected the RDQ because it fulfills criteria that are important for outcome measures used to evaluate the efficacy of vertebroplasty: (1) back pain-specific measurement; (2) well validated in the literature; and (3) easily administered by telephone to elderly patients. The RDQ was specifically designed to assess physical disability due to lower back pain (6). In addition, this instrument was determined to be reliable and well validated when it was initially proposed and has been validated in many studies since that time (7, 9).

We showed substantial improvement in RDQ scores that persisted with time. Mean improvements were on the order of 7–9 points at all follow-up intervals. This level of improvement far exceeds the change of 2–3 points that is considered clinically important by the authors of the instrument (7). Further, we showed that RDQ scores correlate with the well-established 11-point verbal pain scales frequently used in the literature. Both RDQ scores and pain scale measurements improved significantly at 1 week and remained improved over baseline through 1-year follow-up. Last, we found the RDQ instrument to be highly user-friendly, generating acceptable response rates and facilitating telephone follow-up with vertebroplasty patients. These findings are relevant because they show that the RDQ is well suited to measure vertebroplasty outcomes as it is both sensitive to change across time and correlates well with the patient's level of pain and disability.

Previous authors have applied a variety of validated outcomes scales to vertebroplasty and have shown



TABLE 3: Results of previous outcome measure studies

Study	<i>n</i>	Instrument	Result
Zoarski et al (18)	30 patients, 54 fractures	MODEMS (includes SF-36)	Improvement in all 4 MODEMS modules ( $P < .0001$ , $P < .0001$ , $P < .0004$ , $P < .0009$ )
Perez-Higueras et al (19)	13 patients, 37 fractures	McGill-Melzack Pain Questionnaire	Improvement in scores following treatment ( $P < .001$ ), but worsening at follow-up (mean of 65 months)
Legroux-Gerot et al (12)	16 patients, 21 fractures	McGill-Melzack Pain Questionnaire	Decrease in scores at 6 months with no change through maximal follow-up (mean of 35 months) ( $P < .05$ )
		Nottingham Health Profile	Decrease in quality of life ( $P = .05$ ); increase in social isolation ( $P < .05$ ), otherwise no change
Cortet et al (20)	16 patients, 20 fractures	McGill-Melzack Pain Questionnaire	Decrease in score at days 3, 30, 90, and 180 (all $P < .005$ )
		Health Profile	Decrease in 5 of 6 dimensions ( $P < .001$ , $P < .05$ , $P < .05$ , $P < .05$ ), not sleep
Winking et al (14)	38 patients	ODI	Decrease in mean score at day 2, which persisted to 6 weeks ( $P < .01$ )

Note.—MODEMS indicates Musculoskeletal Outcomes Data Evaluation and Management Scale; ODI, Oswestry Low Back Pain Disability Questionnaire.

improvement in measured disability and symptoms (Table 3). With the exception of the Oswestry Low Back Pain Disability Questionnaire (ODI), however, these instruments do not focus on the most relevant criteria in tracking outcomes in vertebroplasty patients. Back pain specificity is the most important of these criteria. Many of the patients who receive vertebroplasty have coincident health problems that influence their overall level of health and functioning. Back pain and symptom data that are gathered through global health measures are likely confounded by the influence of other health conditions on these assessments.

The SF-36, McGill Mezack questionnaire, and Nottingham Health Profile were designed as generic measurements of health and are not specific to back pain (10–12). It is important to note that the RDQ shows more responsiveness to change than the SF-36 and thus may be more useful in assessing outcomes (13). Also the McGill Mezack questionnaire is more complex than other instruments both to administer and to score.

The ODI might be considered to be the most appropriate instrument that has been previously used in the literature to assess outcomes after vertebroplasty. This instrument was specifically designed to describe back pain and disability and has been found to be both reliable and valid (7). It has also been effectively administered in person and by telephone. The only study in the literature to use the ODI in vertebroplasty outcomes assessment is the study by Winking et al (14), which enrolled 38 patients and tracked their outcomes for 1 year. The authors showed a significant decrease in ODI score 2 days postvertebroplasty that persisted unchanged to 6 weeks. Although ODI scores were tracked out to 1 year, statistics were only given on these data out to 6 weeks, and thus the authors could not comment on long-term outcomes.

Comparisons of the RDQ to the ODI have shown small but important differences. Stratford et al (9)

found an increased rate of incomplete responses with the ODI when compared with the RDQ. This may be inherent in the instrument or may reflect the fact that the ODI has more questions specific to “sex life,” “social life,” and “travel,” which may be less relevant in the day-to-day function of the elderly population. Regarding the applicability of the 2 instruments, Roland and Fairbank (7) concluded that the RDQ may be better suited to settings in which patients have mild to moderate disability that is expected to improve, whereas the ODI is suited to situations in which patients have persistent severe disability. These 2 conclusions lead us to believe that the RDQ is not only more appropriate in vertebroplasty patients who are expected to rapidly improve, but also may generate more complete responses and data.

In our practice, we have observed substantial clinical utility for the RDQ. Primarily, the RDQ is more useful than pain scores for assessment of the impact of vertebral fractures on the patient's daily life. Pain scores are influenced by the patient's perception and tolerance for pain and the reported value relates only loosely to functional limitation. The RDQ, however, gives care providers an objective assessment of the functional limitation suffered by the patient. This is useful both for the treating physician and for ancillary health staff. For the physician, thinking of RDQ scores in categories similar to those defined by Patrick et al (8)—10.8 = low; 15.7 = mild; 17.5 = moderate; 19.0 = severe—allows informal categorization of the severity of the patient's impairment and provides some basis for treatment and management decisions. For ancillary health staff, specific limitations indicated in the RDQ can provide a basis for physical/occupational therapy or other directed lifestyle interventions. Finally, tracking both specific items on the RDQ and the RDQ score in general, allows effective monitoring of a patient's progress following vertebroplasty.

Although our study is the first to apply the RDQ to

vertebroplasty patients and the first to show long-term improvement in a validated, back pain-specific outcome measure, several substantial limitations remain. This study was both retrospective and lacking a control group. Ultimately, to validate the efficacy of vertebroplasty, prospective controlled studies are needed to show significant improvement over conservative management (15). Another potential limitation to this study is that follow-up was done by telephone. Although we felt that one of the characteristics of a good outcome measure was ease of telephone administration, other investigators argue that administering an instrument by telephone introduces a bias to the data (16, 17). This is a valid concern, but the increased response rates and the ability for fragile and significantly disabled patients to complete the instrument outweigh the potential bias. In addition, we took steps to minimize this bias by having designated vertebroplasty nurses administer the RDQ in person and by telephone according to a strict protocol. The low response rate at 1 year is also problematic, with only 17% of subjects achieving that duration of follow-up by the time of this study. On the basis of the small data set, the results for 1 year may be less reliable than those at earlier time points. Finally, a potential issue with our data collection is that our nonrespondents were not carefully tracked. For the purpose of outcomes data, it would be useful to differentiate between patients who were unwilling or unable to complete the instrument versus those who were simply lost to follow-up.

This study undertook to address an underlying deficiency in the vertebroplasty literature and demonstrate the use of a validated outcome measure. It provides useful and valid data about vertebroplasty outcomes but does not preclude the necessity to undertake additional prospective, controlled studies. If we are to draw larger conclusions across studies and populations, it is important that we standardize our outcome assessments.

## Conclusion

Patients undergoing vertebroplasty for osteoporotic compression fractures had less pain and symptoms after the procedure. On the basis of background data and the results of this study, the RDQ appears well suited as a standardized measure of the efficacy of vertebroplasty. It is longitudinally validated and back pain-specific, and we have shown it to be effective in assessing outcomes following vertebroplasty. It is our assertion that the RDQ should be adopted as the outcome measure of choice to monitor the long-term efficacy of vertebroplasty.

## Appendix 1

### Modified RDQ (6, 8)

When your back hurts, you may find it difficult to do some of the things that you normally do. This list contains sentences that people have used to describe

themselves when they have back pain. When you read them, you may find that some stand out because they describe you *today*. As you read the list, think of yourself *today*. When you read a sentence that describes you today, put a tick against it. If the sentence does not describe you, then leave the space blank and go on to the next one. Remember, only tick the sentence if you are sure it describes you today.

1. I stay at home most of the time because of my back
2. I change position frequently to try and get my back comfortable
3. I walk more slowly than usual because of my back
4. Because of my back I am not doing any of the jobs that I usually do around the house
5. Because of my back, I use a handrail to get upstairs
6. Because of my back, I have to hold on to something to get out of an easy chair
7. I get dressed more slowly than usual because of my back
8. I only stand up for short periods of time because of my back
9. Because of my back, I try not to bend or kneel down
10. I find it difficult to get out of a chair because of my back
11. My back is painful almost all the time
12. I find it difficult to turn over in bed because of my back
13. I have trouble putting on my sock (or stockings) because of the pain in my back
14. I only walk short distances because of my back pain
15. I sleep less well because of my back
16. I avoid heavy jobs around the house because of my back
17. Because of my back pain, I am more irritable and bad tempered with people than usual
18. Because of my back, I go upstairs more slowly than usual
19. I stay in bed most of the time because of my back
20. Because of my back problem, my sexual activity is decreased
21. I keep rubbing or holding areas of my body that hurt or are uncomfortable
22. Because of my back, I am doing less of the daily work around the house than I would usually do
23. I often express concern to other people about what might be happening to my health

## References

1. Evans AJ, Jensen ME, Kip KE, et al. **Vertebral compression fractures: pain reduction and improvement in functional mobility after percutaneous polymethylmethacrylate vertebroplasty retrospective report of 245 cases.** *Radiology* 2003;226:366–372
2. McGraw JK, Lippert JA, Minkus KD, et al. **Prospective evaluation of pain relief in 100 patients undergoing percutaneous vertebroplasty: results and follow-up.** *J Vasc Interv Radiol* 2002;13:883–886
3. Diamond TH, Champion B, Clark WA. **Management of acute**

- osteoporotic vertebral fractures: a nonrandomized trial comparing percutaneous vertebroplasty with conservative therapy. *Am J Med* 2003;114:257–265
4. Huskisson EC. Measurement of pain. *Lancet* 1974;2:1127–1131
  5. Jensen ME, Evans AJ, Mathis JM, et al. Percutaneous polymethylmethacrylate vertebroplasty in the treatment of osteoporotic vertebral body compression fractures: technical aspects. *AJNR Am J Neuroradiol* 1997;18:1897–1904
  6. Roland M, Morris R. A study of the natural history of back pain. Part I. Development of a reliable and sensitive measure of disability in low-back pain. *Spine* 1983;8:141–144
  7. Roland M, Fairbank J. The Roland-Morris Disability Questionnaire and the Oswestry Disability Questionnaire. *Spine* 2000;25:3115–3124
  8. Patrick DL, Deyo RA, Atlas SJ, et al. Assessing health-related quality of life in patients with sciatica. *Spine* 1995;20:1899–1908; discussion 1909
  9. Stratford PW, Binkley J, Solomon P, et al. Assessing change over time in patients with low back pain. *Phys Ther* 1994;74:528–533
  10. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–483
  11. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975;1:277–299
  12. Legroux-Gerot I, Lormeau C, Boutry N, et al. Long-term follow-up of vertebral osteoporotic fractures treated by percutaneous vertebroplasty. *Clin Rheumatol* 2004;23:310–317
  13. Turner JA, Fulton-Kehoe D, Franklin G, et al. Comparison of the Roland-Morris Disability Questionnaire and generic health status measures: a population-based study of workers' compensation back injury claimants. *Spine* 2003;28:1061–1017; discussion 1067
  14. Winking M, Stahl JP, Oertel M, et al. Treatment of pain from osteoporotic vertebral collapse by percutaneous PMMA vertebroplasty. *Acta Neurochir (Wien)* 2004;146:469–476
  15. Jarvik JG, Kallmes DF, Mirza SK. Vertebroplasty: learning more, but not enough. *Spine* 2003;28:1487–1489
  16. Weinberger M, Oddone EZ, Samsa GP, et al. Are health-related quality-of-life measures affected by the mode of administration? *J Clin Epidemiol* 1996;49:135–140
  17. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. *Ann Intern Med* 1993;118:622–629
  18. Zoarski GH, Snow P, Olan WJ, et al. Percutaneous vertebroplasty for osteoporotic compression fractures: quantitative prospective evaluation of long-term outcomes. *J Vasc Interv Radiol* 2002;13:139–148
  19. Perez-Higueras A, Alvarez L, Rossi RE, et al. Percutaneous vertebroplasty: long-term clinical and radiological outcome. *Neuroradiology* 2002;44:950–954
  20. Cortet B, Cotten A, Boutry N, et al. Percutaneous vertebroplasty in the treatment of osteoporotic vertebral compression fractures: an open prospective study. *J Rheumatol* 1999;26:2222–2228