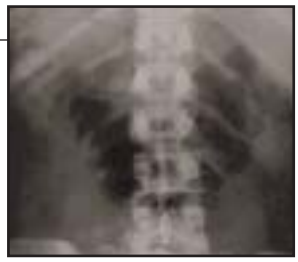


The Significance of Vertebral Fractures

Both the prevalence and the clinical significance of vertebral fractures has been greatly underestimated by physicians. Vertebral fractures are much more important than we have previously thought and we now have the tools to prevent a large proportion of them.

By David A. Hanley, MD, FRCPC

Vertebral fractures are the hallmark of postmenopausal osteoporosis. The stereotypical presentation is that of an elderly woman with marked thoracic kyphosis. This spinal deformity has been given the eponym "Dowager's Hump," a term which is not only politically incorrect, but medically misleading, as it ignores the importance of osteoporosis in men. Vertebral compression fractures are not unique to women and dorsal kyphosis is not an unusual finding in older men. In the Canadian Multicentre Osteoporosis Study (CaMos), vertebral spinal deformities were present in approximately 25% of all men and women over the age of 50.[1]

The overall prevalence of vertebral fractures has been greatly underestimated by physicians, and the clinical importance of these fractures has shared a similar fate. Vertebral compression fractures are often ignored when radiologists are interpreting chest X-rays, and many clinicians regard them as nothing more than a cosmetic problem. Surveys have suggested that the change in appearance associated with osteoporotic fractures of the spine is much more frightening to younger women than the prospect of a hip fracture due to osteoporosis. This focus on the changes in appearance caused by vertebral fractures is not surprising. The loss of height and curved spine of vertebral osteoporosis can be seen in individuals who seem otherwise healthy. Evidence is now accumulating, however, to indicate that vertebral frac-

Vertebral Fractures

tures are much more than a "cosmetic problem." The common misconception that these fractures are clinically unimportant probably stems from the fact that many patients with significant vertebral compression fracture deformities cannot recall isolated incidents of back pain associated with the fracture. However, the clinical relevance of vertebral fractures expresses itself in two ways:

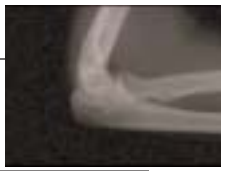
- The presence of a vertebral fracture predicts a high risk of more vertebral fractures, as well as non-vertebral fractures.
- Vertebral fractures are associated with significant morbidity and mortality.

This article will review some of the more recent papers which have examined the clinical manifestations of vertebral fractures and conclude with the important findings in recent clinical trials of osteoporosis pharmacologic therapies.

David A. Hanley, MD, FRCPC is professor and head of the division of endocrinology and metabolism, department of medicine, at the University of Calgary

What is a Vertebral Fracture?

The vertebral fracture is probably the most common fracture that occurs in patients with osteoporosis. A reasonable summary of the many epidemiology studies in this area would suggest that probably one woman in three over the age of 50 will experience a compression fracture of the spine.[2] Although the data are not as complete for men, the figure would probably range from between one in four and one in six. Clinicians commonly differentiate between "asymptomatic" vertebral fractures and "clinical" vertebral fractures. Asymptomatic vertebral fractures



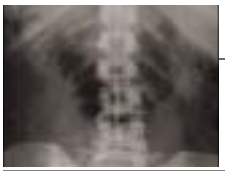
might be discovered either through height loss documented on clinical examination, or as an incidental finding on an X-ray of the spine or chest. Asymptomatic fractures discovered by X-ray are also called "radiographic fractures" and a variety of formulae have been developed to define them.[3-5] Most of these methods can be adapted to computer analysis and quantitative assessment of vertebral deformity can be carried out. The methods measure the height of a vertebral body at its centre, anterior and posterior edge, and look for any decrease in one of these measurements compared to the others in the same vertebral body or an average of the two vertebral bodies immediately adjacent (above and below) to the one in question. Some methods are more conservative than others, and while CaMos found deformities in about 25% of subjects over age 50, the European Vertebral Osteoporosis Study found an incidence of 12% in men and women aged 50 to 79 years.[6] No matter what criteria are used for defining radiographic vertebral fracture deformities, it is clear the problem is common in our elderly population.

Clinical vertebral fractures would be those which present with a history of acute onset of pain in the back, severe enough to cause the patient to seek a physician's attention, resulting in the ordering of an X-ray and discovery of a fracture. These are the fractures which are usually documented in epidemiologic studies of vertebral fractures reported through hospital and health care records. It is estimated, however, these only account for about one-quarter to one-third of all vertebral fractures.[7]

No matter what the criteria for defining radiographic vertebral fracture deformities, it is clear the problem is common in our elderly population.

Diagnosis of Vertebral Fractures

A basic and simple diagnostic tool for the assessment of vertebral fractures should be available in every physician's office. This is the measurement of height. Although we lack studies with careful documentation of how much height loss is required to diagnose a vertebral compression fracture, most clinicians would suggest a loss of more than two to three centimeters of height from young adulthood or from a previous exam should raise the question of a vertebral fracture having occurred. The diagnosis of vertebral compression fractures must be confirmed by a spinal X-ray. As noted above, many fractures are asymptomatic and back pain is such a common symptom in the general population that it is not specific for vertebral fracture. When a vertebral fracture is discovered on X-ray and there is question as to whether it is



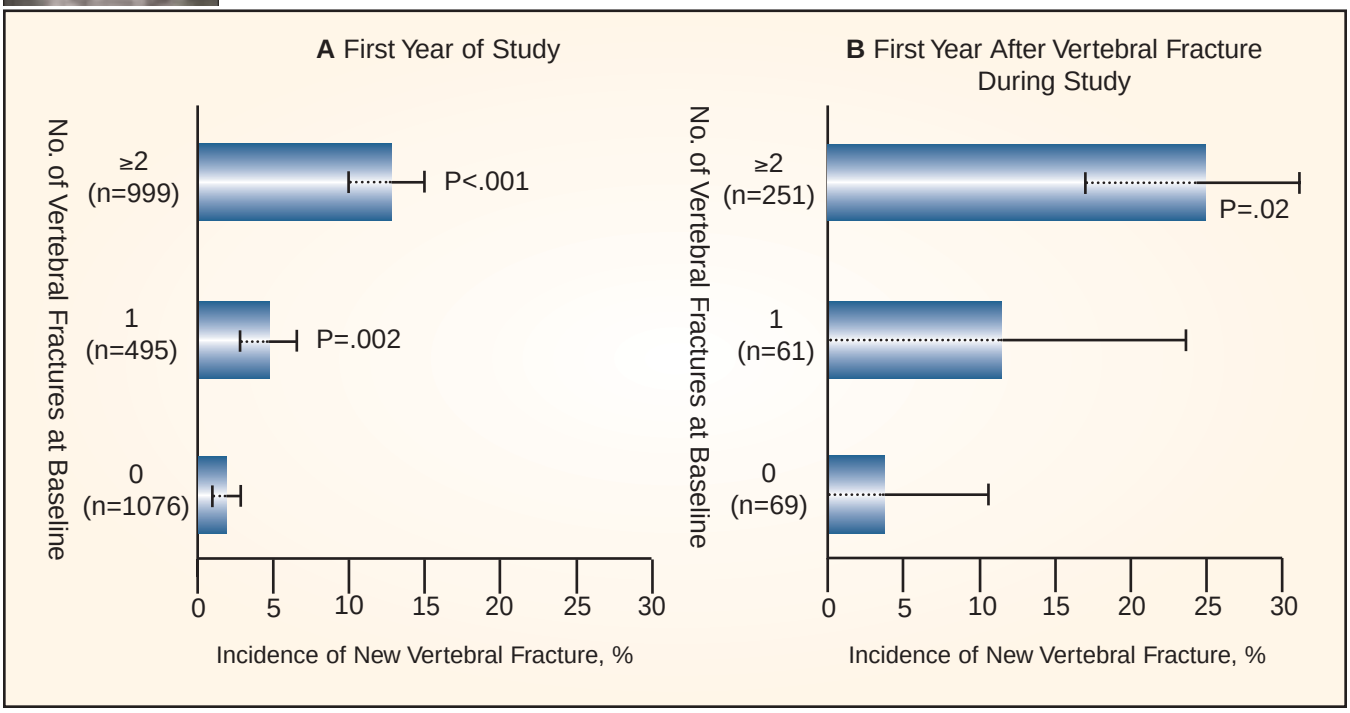


Figure 1. Incidence of Vertebral Fracture by Number of Baseline Vertebral Fractures. Incidence is based on Kaplan-Meier estimates of the survival function. Error bars represent 95% confidence intervals. Adapted from Lindsay R, Silverman SL, Cooper C, et al: JAMA. 2001; 285:320-3.

recent or remote, a bone scan can often identify any fracture which has occurred in the past six months.

Risk Factors for Vertebral Fractures

There are three major risk factors that can be applied to a general patient population—age, low bone density, and previous vertebral fracture. Other important risk factors which have been identified for osteoporosis have been well documented in many textbooks and reviews.[8] Of particular note would be early menopause (before age 45), hypogonadism in a male, glucocorticoid therapy, low dietary calcium intake, smoking, significant family history of osteoporosis, excessive caffeine intake and low body mass (under 57 kg).[8]

Importance of Previous Vertebral Fracture as Predictor of Subsequent Fracture

The last decade has seen the establishment of large randomized, placebo-controlled clinical trials as the standard for evaluation of osteoporosis therapy. These studies have focused on vertebral fractures, not only because they are the most common osteoporotic fracture, but they are relatively easy to document and quantify objectively with digital analysis of spinal X-rays. The largest trials have been of the selective estrogen receptor modulator raloxifene, of the potent bisphosphonates alendronate and risedronate and of the nasal spray salmon calcitonin. All of these studies have shown a significant reduction in vertebral fractures, and the bisphosphonate trials have demonstrated the

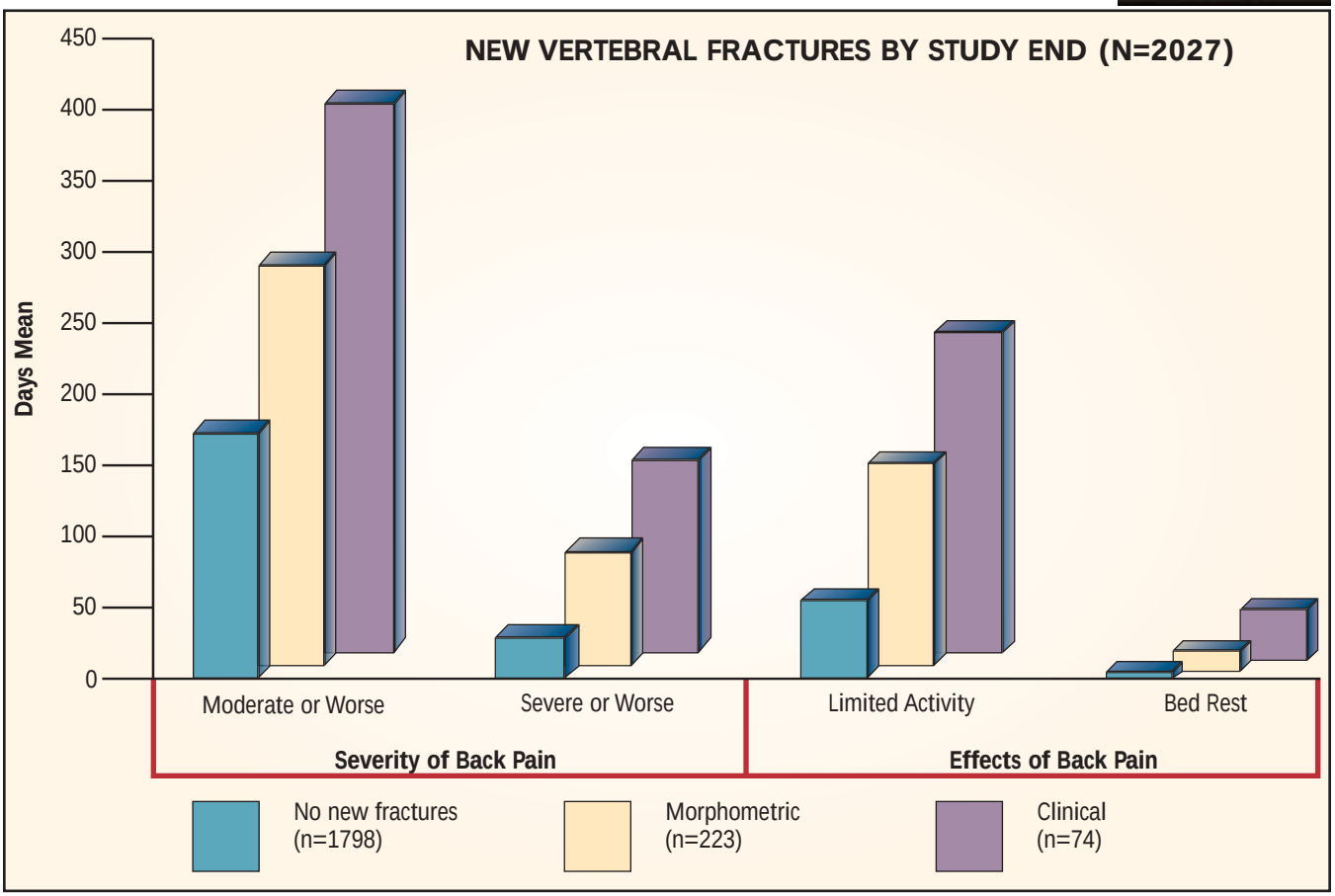
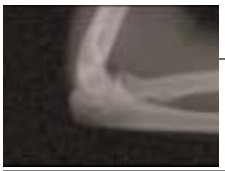


Figure 2a. Mean Number of Days With Back Pain Observed Among Women During Follow-up Period (Three Years) by Vertebral Fracture Status at the End of the Study. All women had at least one prevalent morphometric fracture at baseline. Morphometic fractures were diagnosed by digital analysis of routine X-rays, while clinical fractures were those in which back symptoms caused an X-ray to be taken. Adapted fromNevitt MC, Thompson DE, Black DM, et al: Arch Intern Med. 2000; 160:80.

treatment will also reduce the incidence of non-vertebral fractures, including hip fractures. These clinical trials have also been extremely informative with respect to the importance of vertebral fractures as predictors of future vertebral fractures, as well as all any other fracture related to osteoporosis.

In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, patients were recruited on the basis of low bone density, and were sub-grouped into those patients who had a vertebral fracture on X-ray on entry into the trial and those who did not. Over the first three years of this study, more than 20% of the patients who entered the study with a previous vertebral fracture suffered a new one, in spite of adequate treatment with calcium and vitamin D supplementation. Almost 5% of the patients who entered the study with low bone density, but no prior vertebral fracture, also suffered a vertebral fracture during the three years of the study.[9]

In the Prevent Recurrence of Osteoporotic Fractures (PROOF) study of nasal spray calcitonin, the subjects averaged more than two vertebral fractures on entry. Over 25% of the control subjects suffered new vertebral fractures during the five years of the study. This high fracture rate was in spite of



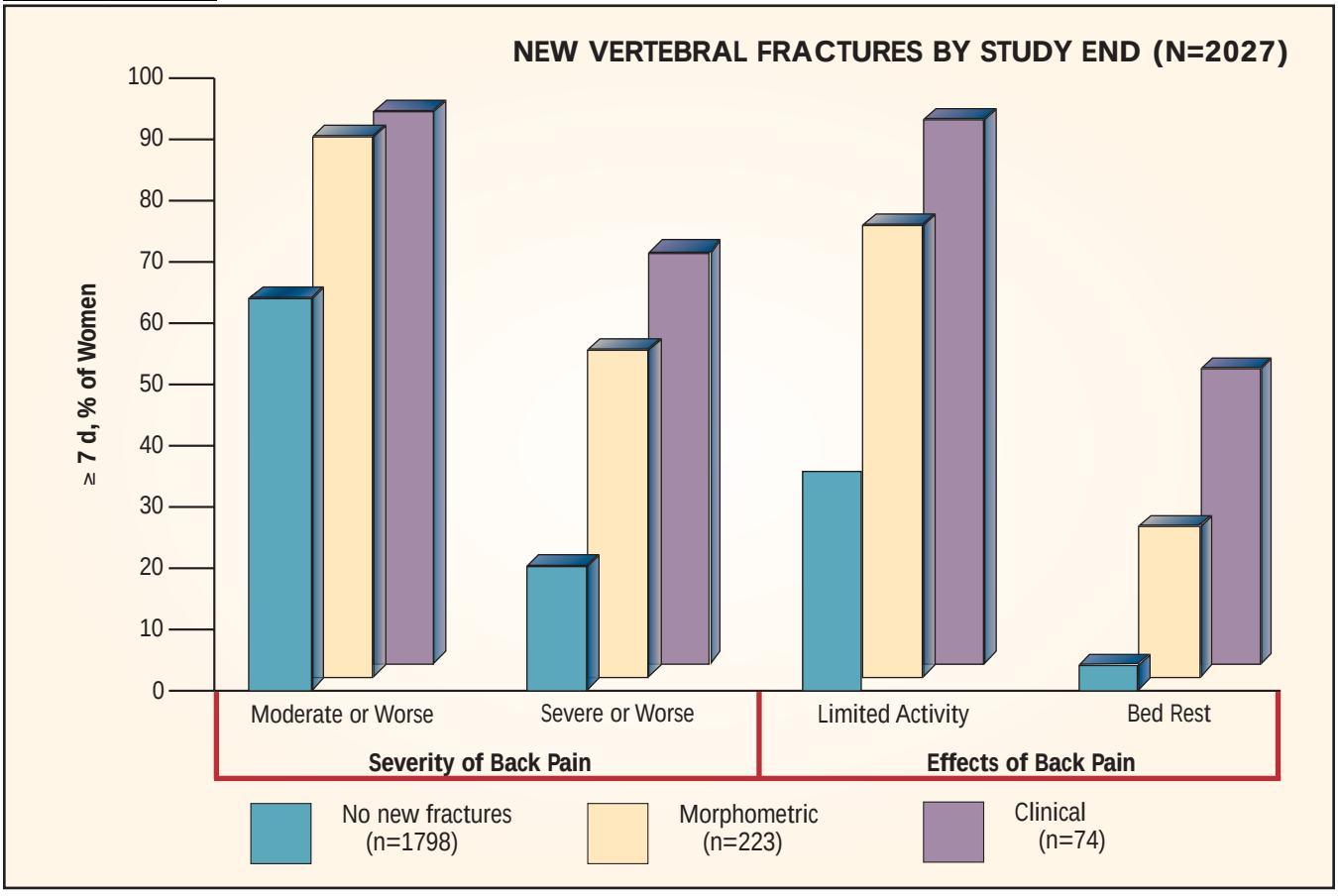


Figure 2b. Percentage With Back Pain Lasting Seven Days or More Observed Among Women During Follow-up Period (Three Years) by Vertebral Fracture Status at the End of the Study. All women had at least one prevalent morphometric fracture at baseline. Morphometic fractures were diagnosed by digital analysis of routine X-rays, while clinical fractures were those in which back symptoms caused an X-ray to be taken. Adapted fromNevitt MC, Thompson DE, Black DM, et al: Arch Intern Med. 2000; 160:80.

the fact that all subjects received 1000 mg calcium and 400 I.U. of vitamin D daily.[10]

A recent analysis of the placebo (calcium plus or minus vitamin D) arm of the clinical trials of the new bisphosphonate, risedronate, has provided unequivocal evidence for the concept that vertebral fractures beget more vertebral fractures. In pooling the data from all the major clinical trials of risedronate, it was demonstrated that when a subject experienced a vertebral fracture during the period of observation in the clinical trial there was an average of a 20% likelihood of a second vertebral fracture within one year of the first (see Figure 1). All of these patients received 1000 mg of calcium per day and, if their vitamin D levels were documented to be low, they received up to 500 I.U. of vitamin D daily as well.[11]

Vertebral Fractures and Morbidity

Although the management of an acute clinical vertebral fracture clearly involves physician intervention, the asymptomatic vertebral fracture should not be ignored. It is increasingly well recognized that vertebral fractures have major long-term impli-

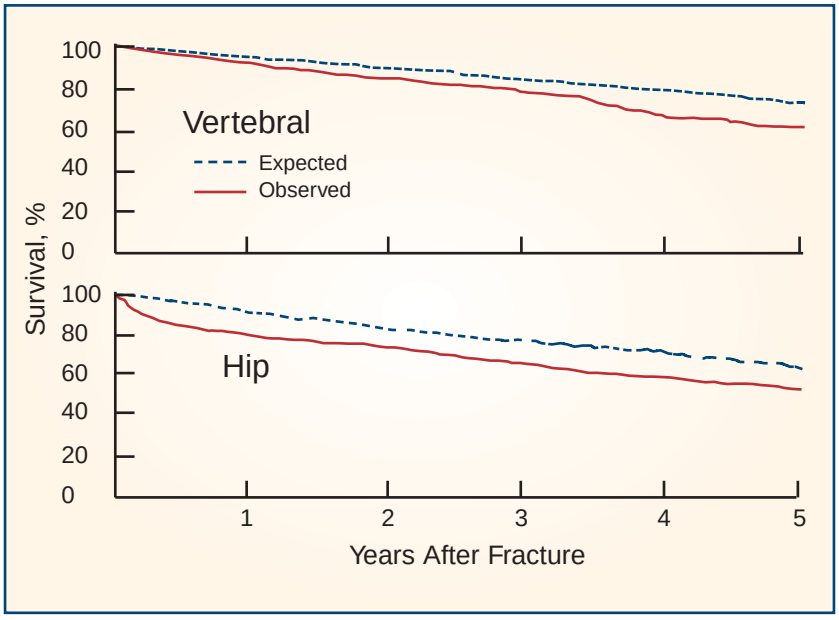


Figure 3. Survival rates after the diagnosis of a vertebral or hip fracture among residents of Rochester Minnesota. Both the observed survival and that expected using 1980 death rates of residents in the West North Central United States are shown. Adapted with permission from Cooper C, Atkinson EJ, Jacobsen SJ, et al: Am J Epidemiol. 1993; 137:1001-5.

cations for quality of life and morbidity, irrespective of whether they are labeled symptomatic or asymptomatic. Some of the best information in this regard comes from the work of Michael Nevitt and his colleagues examining the subjects in the Fracture Intervention Trial (FIT) of alendronate, and the Study of Osteoporotic Fractures. A recent analysis from the Study of Osteoporotic Fractures indicates that postmenopausal women with a vertebral fracture during an average 3.7 years of study had anywhere between a two- and eightfold increase in back pain, back related disability, bed rest days, and days of limited activity due to back pain. Furthermore, the new vertebral fractures that were documented by X-rays at the start and end of the study were associated with increased back pain and functional limitation irrespective of whether the patients had sought medical attention because of back pain or whether or not the fracture had been identified by a physician during the course of the study. In general, women who have had compression fractures will report difficulties with activities with daily living approximately five to 10 times more commonly than those who do not have fractures.[12-14]

In the analysis of FIT, Nevitt has recently demonstrated that vertebral fractures that are only detected by morphometric changes on X-ray (no acute clinical pain syndrome causing them to seek medical attention) are still associated with a significant increase in number of days of back pain, number of days of limited activity, and number of days with bed rest (see Figures 2a and 2b). With either clinical or "asymptomatic" radiographic fractures, the likelihood of having at least seven days of bed rest was increased by approximately 25-fold. The patients who suffered clinical fractures had an even greater impact on days of back pain, days of limited activity, and days of bed rest. By reducing the incidence of compression fractures of the spine, the treatment with alendronate caused a significant reduction in severity of all of these parameters.[15]

A Canadian study found that up to 87% of women with symptomatic vertebral fractures reported difficulties with simple daily activities such as carrying, walking, house-

work and shopping.[16] The impact of vertebral fractures on quality of life is now being studied in a number of epidemiologic investigations, including the Canadian Multicentre Osteoporosis Study.

Vertebral Fractures and Mortality

It is now becoming increasingly apparent that vertebral fractures are associated with an increased mortality. There are three studies that are particularly notable in identifying this link. The first was a small study of the population living near the Mayo Clinic[17] in which the observed mortality with documented clinical vertebral fracture was almost 20% higher than the expected mortality rate over an observation period of five years. This increased mortality is more gradual, but not any less than the excess mortality seen after hip fracture (see Figure 3).[17]

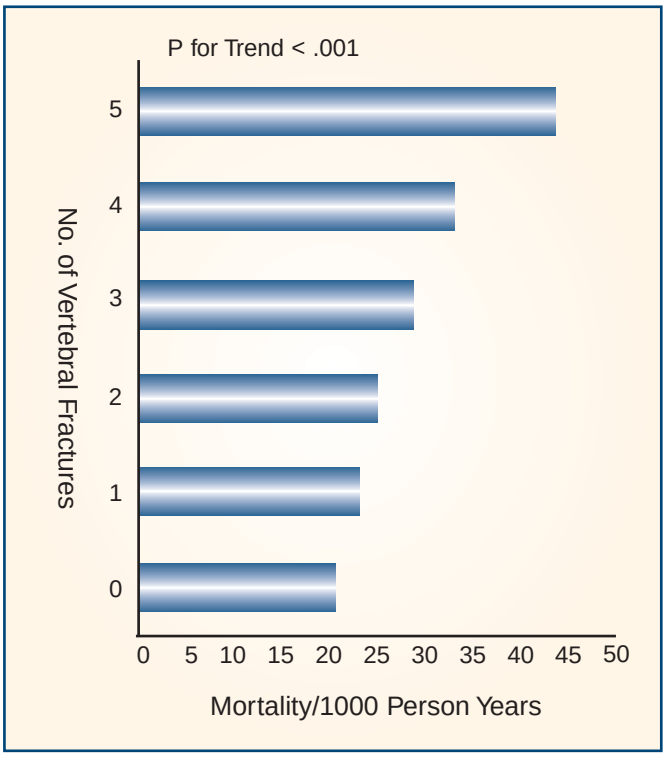
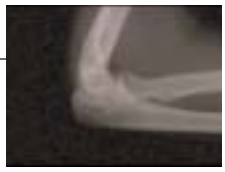


Figure 4. Age standardized mortality by number of fractures. Adapted from Kado DM, Browner WS, Palermo L, et al: Arch Intern Med. 1999; 159:1215-20.

In the Study of Osteoporotic Fractures, patients with vertebral fractures also had an increase in observed over expected mortality.[18] The mechanism is not entirely clear, but an obvious link with respiratory disease can be made when one considers the effect of vertebral fractures on the anatomy of the chest. Kado *et al* demonstrated a direct relationship between number of vertebral deformities and death due to pulmonary cause (hazard ratio, 2.1; 95% confidence interval, 1.4 to 3.0).[18] Mortality rose significantly (P for trend <.001) from 19 per 1000 woman-years with no fractures to 44 per 1000 woman-years in those with five or more fractures (see Figure 4).[18] In particular, vertebral fractures were related to the risk of subsequent cancer (hazard ratio, 1.4; 95% confidence interval, 1.1 to 1.7) and pulmonary death (hazard ratio, 2.1; 95% confidence interval, 1.4 to 3.0). In the subset of women who underwent thoracic curvature measurements, severe kyphosis was also related to pulmonary deaths (hazard ratio, 2.6; 95% confidence interval, 1.3 to 5.1).

In a five-year prospective cohort study done between 1989 and 1994, of all residents aged 60 years and older (2,413 women and 1,898 men) in Dubbo, Australia, a strong association between low trauma osteoporotic fractures and mortality was observed.[19] In both women and men, mortality was increased in the first year after all major osteoporotic fractures. This might be expected for hip fractures, but the association was almost as strong for vertebral fractures. In women, age-standardized mortality ratios were 2.18 (95% confidence



interval 2.03 to 2.32) for the proximal femur, and 1.66 (1.51 to 1.80) for vertebral fractures. In men, the age-standardized mortality ratios were 3.17 (2.90 to 3.44) for proximal femur, and 2.38 (2.17 to 2.59) for vertebral fractures. A ratio of 1.00 would be expected if there was no association of a fracture with mortality. This excess mortality spanned all age groups in the study, suggesting an osteoporotic fracture increases mortality, even in relatively young patients. This increased risk applies at least as much to men as to women.

Taken together, these studies provide strong evidence that we have been gravely (pardon the play on words) underestimating the clinical significance of vertebral fractures.

Importance of Early Institution of Osteoporosis Therapy in Patients with Vertebral Fractures

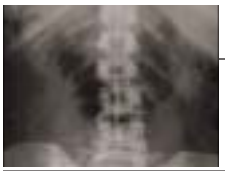
In reviewing all of the major clinical trials, it is clear that a vertebral fracture is the warning sign that a cascade of future vertebral fractures may occur, with obvious implications for morbidity and mortality. The above studies indicate the critical importance of identifying and treating osteoporotic fractures aggressively. We now have a number of therapeutic interventions available which are clearly effective in reducing the risk of future fractures by approximately 40 to 50% or more.[9,10,20-22] **A failure to recognize osteoporotic fractures as a clear indication for the institution of therapy is likely to become an issue for lawyers specializing in medical malpractice.**

Prompt diagnosis and institution of osteoporosis therapy can have relatively rapid benefits. Treatment of osteoporosis can have a major impact on fracture risk even in the first year after initiating therapy. This is most clearly seen in the randomized placebo-controlled clinical trials of risedronate.[21,22] These studies were specifically designed to examine the effect of treatment on the time to first fracture, and, because spine X-rays were done each year, the fracture benefits were clear and consistent at the end of the first year of treatment. Risedronate 5 mg daily reduced the incidence of new vertebral fractures in the first treatment year by over 60%.

Retrospective analysis of the major clinical trials of alendronate and raloxifene also have shown a significant reduction in clinical vertebral fractures in the first year of therapy. These studies were not specifically designed to assess subjects with spine X-rays in the first year of treatment. However, if the patient complained of new onset of back pain, an X-ray would likely be taken, and in the first year of the MORE trial and the first year of the FIT study, the placebo arm had significantly more painful clinical fractures than the raloxifene or alendronate treated subjects, respectively.[23]

A number of centres with skilled interventional radiologists have started to offer vertebroplasty to selected patients.

Can other osteoporosis therapies be effective in the first year? The trials of nasal spray calcitonin, cyclical etidronate and estrogen were not powered to assess the effect on fractures in the first year of therapy. Although a first-year benefit is possible, in one of the key



For the patient with established osteoporosis and prior vertebral fractures, we must offer effective therapies to prevent further fractures.

trials of cyclical etidronate, a reduction in fracture rate (not number of patients with fractures) was only seen when the first year was eliminated from the analysis, suggesting that cyclical etidronate might not prevent vertebral fractures in the first year of use.[24]

There is only one small study of estrogen showing vertebral fracture prevention, using the 100 microgram estradiol patch in a one-year randomized placebo-controlled trial.[25] This study showed fewer vertebral fractures in the treatment group but, like the studies of cyclical etidronate, it did not meet today's basic clinical trial standard of demonstrating a reduction in the number of patients with fractures (*i.e.* one patient with several fractures could make the difference between a positive and negative result of the study).

Although first-year fracture benefit data are lacking, calcitonin has immediate analgesic properties for patients with symptomatic vertebral fractures.

Vertebroplasty: The next leap forward?

For the patient with a recent or chronically painful vertebral compression fracture, a new therapeutic modality is achieving preliminary success. A number of centres with skilled interventional radiologists have started to offer vertebroplasty to selected patients. This procedure features the expansion of a crushed vertebral body by injection with polymethylmethacrylate. This material hardens to the same or greater strength than bone and, often, the deformity and pain can be at least partially corrected. Some results are dramatic. This technique has not been studied in a controlled clinical trial, but seems to be gaining interest and acceptance in some centres in the United States and Canada. It is not recommended for all vertebral fractures, but may be able to help where conventional therapy has failed.[27,28]

Conclusion

The conclusion to be drawn from all of these studies is that vertebral fractures are much more important than had been previously thought. We now have the tools to prevent a large proportion of them. All of the currently approved osteoporosis therapies have been

shown to prevent vertebral fractures in randomized placebo-controlled clinical trials. However, the level of evidence for estrogen and cyclical etidronate is lower than for alendronate, risedronate raloxifene or calcitonin.

For the patient with established osteoporosis and prior vertebral fractures, we must offer effective therapies to prevent further fractures. The osteoporosis treatment for this kind of high-risk patient should be chosen on the basis of demonstrated effectiveness in the first year of therapy. Currently, only risedronate, alendronate and raloxifene have clear randomized, placebo-controlled clinical trial evidence for fracture prevention in the first year of therapy. **Dx**

References

1. Jackson SA, Tenenhouse A, Robertson L: Vertebral fracture definition from population-based data: preliminary results from the Canadian Multicenter Osteoporosis Study (CaMos). Osteoporos Int 2000; 11:680-7.
2. Cummings SR, Black DM, Rubin SM: Lifetime risks of hip, Colles', or vertebral fracture and coronary heart disease among white postmenopausal women. Arch Intern Med. 1989; 149:2445-8.
3. Black DM, Palermo L, Nevitt MC, et al: Defining incident vertebral deformity: a prospective comparison of several approaches. The Study of Osteoporotic Fractures Research Group.J Bone Miner Res 1999; 14:90-101.
4. Genant HK, Jergas M, Palermo L, et al: Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis The Study of Osteoporotic Fractures Research Group. J Bone Miner Res. 1996; 11: 984-96.
5. Black DM, Palermo L, Nevitt MC, et al: Comparison of methods for defining prevalent vertebral deformities: the Study of Osteoporotic Fractures. J Bone Miner Res. 1995; 10:890-902).
6. O'Neill TW, Felsenberg D, Varlow J, et al: The prevalence of vertebral deformity in european men and women: the European Vertebral Osteoporosis Study. J Bone Miner Res. 1996; 11:1010-8.
7. Ross PD: Clinical consequences of vertebral fractures. Am J Med 1997; 102(Suppl 6A):30S-43S.
8. Anonymous consensus document: Osteoporosis prevention, diagnosis, and therapy. JAMA 2001; 285:785-95.
9. Ettinger B, Black DM, Mitlak BH, et al: Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA. 1999; 282: 637-45.
10. Chesnut CH, Silverman S, Andriano K, et al: A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med. 2000; 109:267-76.
11. Lindsay R, Silverman SL, Cooper C, et al: Risk of new vertebral fracture in the year following a fracture. JAMA. 2001; 285:320-3.
12. 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.
13. Greendale GA, Barrett-Connor E, Ingles S, et al: Late physical and functional effects of osteoporotic fracture in women: the Rancho Bernardo Study. J Am Geriatr Soc. 1995; 43:955-61.
14. Huang C, Ross PD, Wasnich RD: Vertebral fracture and other predictors of physical impairment and health care utilization. Arch Intern Med. 1996; 156:2469-75.
15. Nevitt MC, Thompson DE, Black DM, et al: Effect of alendronate on limited-activity days and bed-disability days caused by back pain in postmenopausal women with existing vertebral fractures. Fracture Intervention Trial Research Group. Arch Intern Med. 2000; 160:77-85.
16. Cook DJ, Guyatt GH, Adachi JD, et al: Quality of life issues in women with vertebral fractures due to osteoporosis. Arthritis Rheum Jun; 36:750-6.
17. Cooper C, Atkinson EJ, Jacobsen SJ, et al: Population-based study of survival after osteoporotic fractures. Am J Epidemiol. 1993; 137:1001-5.
18. Kado DM, Browner WS, Palermo L, et al: Vertebral fractures and mortality in older women: a prospective study. Study of Osteoporotic Fractures Research Group. Arch Intern Med. 1999; 159:1215-20.
19. Center JR, Nguyen TV, Schneider D, et al: Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet. 1999; 353:878-82.
20. Black DM, Cummings SR, Karpf DB, et al: Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet. 1996; 348:1535-41.
21. Harris ST, Watts NB, Genant HK, et al: Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA. 1999; 282:1344-52.
22. Reginster J, Minne HW, Sorensen OH, et al: Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000; 11:83-91.
23. Black DM, Thompson DE, Bauer DC, et al: Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. J Clin Endocrinol Metab. 2000; 85:4118-24.
24. Storm T, Thamsborg G, Steiniche T, et al: Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med. 1990; 322:1265-71.
25. Lufkin EG, Wahner HW, O'Fallon WM: Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med. 1992; 117:1-9.
26. Lyritis GP, Paspati I, Karachalios T, et al: Pain relief from nasal salmon calcitonin in osteoporotic vertebral crush fractures. A double blind, placebo-controlled clinical study. Acta Orthop Scand Suppl. 1997; 275:112-4.
27. Levine SA, Perin LA, Hayes D, et al: An evidence-based evaluation of percutaneous vertebroplasty. Manag Care. 2000; 9: 56-60,63.
28. Grados F, Depriester C, Cayrolle G, et al: Long-term observations of vertebral osteoporotic fractures treated by percutaneous vertebroplasty. Rheumatology (Oxford). 2000; 39:1410-4.