

Prevention and Management of Osteoporosis

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Osteoporotic fractures are a growing public health issue. Prevention and management of osteoporosis are becoming increasing concerns especially as the number of individuals reaching old age continues to grow, euphemistically “as the baby boomers come of age.” Identification of those individuals who are at an increased risk for fracture is important for planning and implementing proper prevention and management strategies. Although diagnostic tools are available for identifying decreased bone density and effective therapies exist for treatment of existing disease, clinical guidelines based on cost-effective approaches are still needed to more accurately identify which patients would benefit from early intervention (either prevention or treatment). Clinical Cornerstone® Supplement 2. Copyright © 2003 Excerpta Medica, Inc.

During the last decade, the prevention and management of osteoporosis have emerged as major clinical challenges for physicians, health care professionals, and patients. As the number of individuals reaching old age continues to swell, the impact of this “silent disease” will be far from silent. The disease is osteoporosis, the complication is fracture. Both men and women can suffer from osteoporosis. However, the majority of affected people—80%—are women. Therefore, this article focuses on the prevention and management of osteoporosis in women.

Morbidity and mortality associated with hip and vertebral fractures have an overwhelming impact on individual health needs as well as the demands placed on the health care system. Currently, in the United States an estimated 30 million women >50 years have or are at risk for osteoporosis (1). At least 90% of all hip and

spine fractures among elderly women can be attributed to osteoporosis (2). Of women who suffer a hip fracture, about half will spend some time in a nursing home, only one third will regain their prefracture level of function, which includes walking independently and performing basic activities of daily living, and an estimated 20% will die in the following year as an indirect consequence of the fracture (3,4). Vertebral fracture is associated with an increased risk of a subsequent fragility fracture and increases in back pain, disability, and physical deformity (5). Direct expenditures for osteoporotic fractures have increased from an estimated \$5 billion in 1985 to more than \$17 billion per year in 2001 (6,7).

IDENTIFYING PERSONS AT RISK

Osteoporosis is defined as “a systemic skeletal disease characterized by low bone mass and microar-

chitectural deterioration of bone tissue, with a consequent increase in bone fragility and a susceptibility to fracture.” (8) Bone density and bone structure determine the strength of bone tissue and correlate highly with load-bearing capacity and fracture risk. In fact, measurement of bone mineral density (BMD) is a more accurate predictor of fracture than hypercholesterolemia is at predicting myocardial infarction (9). In addition to BMD, other risk factors such as female sex, advanced age, personal history of fracture as an adult, history of fracture in a first-degree relative, low body weight (<127 lb), current cigarette smoking, estrogen deficiency, alcoholism, and inadequate physical activity, contribute to an individual’s fracture risk (10). While low BMD, identified most commonly through dual-energy x-ray absorptiometry screening, is an important risk factor, identification of other potentially contributing factors is also important to determine those persons at highest risk of fracture and those who may be candidates for treatment.

KEY POINT

At least 90% of all hip and spine fractures among elderly women can be attributed to osteoporosis. Of women who suffer a hip fracture, about half will spend some time in a nursing home, only one third will regain their prefracture level of function, and an estimated 20% will die in the following year as an indirect consequence of the fracture.

Women have several factors that place them at greater risk than men for osteoporosis and fracture risk. Women achieve a lower peak bone mass at middle age as a result of their smaller skeletal structure. Additionally, women experience a point of accelerated bone loss at the time of menopause where up to 20% of their mass could be lost over a

period of 5 years. Men, however, tend to show a gradual decline in mass over the years without any point of accelerated losses.

KEY POINT

Pharmacologic interventions that include prescription medications to reduce fractures should be part of a comprehensive patient management program in high-risk individuals.

PREVENTION

Osteoporosis, especially with early intervention, is a preventable disease, and it is possible that in the next century we will come to regard this disease historically much like rickets. However, in striving to eliminate the disease, the question of what we are trying to accomplish arises. What should the goal of prevention be? Is the goal simply to prevent any amount of bone loss, or to prevent development of the disease osteoporosis, or to prevent fracture?

The concept of bone loss is a universal phenomenon with aging. Skeletal growth and the majority of bone mass are achieved during the first 2 decades of life with a peak in bone density occurring around the age of 30. Between the ages of 30 and menopause, bone mass remains relatively stable (11). At menopause women have a period of 5 or more years during which there is an accelerated rate of bone loss. Some women will lose up to 5% of their bone mass per year during this time. In postmenopausal women who are taking estrogen therapy this accelerated rate of loss does not usually occur until the estrogen is stopped. With suspension of estrogen, bone will be lost at a rate similar to that seen at the time of natural menopause. After this period of rapid decline, the rate of bone loss tends to slow but continues indefinitely as long as a woman lives. If bone loss tends to be very slow then lifestyle changes might be enough to maintain an adequate bone mass. However, if the rate of decline is rapid, lifestyle changes may not be enough. Even with supplemental calcium and

exercise, for many women bone loss cannot be effectively halted without other therapeutic interventions (12).

Both the prevention and treatment of osteoporosis require interventions, earlier rather than later, that are safe, effective, and affordable. Optimal prevention and treatment call for the modification of those risk factors that are modifiable: maintaining a healthy lifestyle that includes a healthy diet with sufficient calcium and vitamin D; exercise to develop good muscle tone to help avoid falls and potential injury; not smoking cigarettes; and drinking alcohol in moderation. Pharmacologic interventions that include prescription medications to reduce fractures should be part of a comprehensive patient management program in high-risk individuals. For patients who already have established disease, medications indicated for treatment should be used.

KEY POINT

Drugs approved for the prevention of osteoporosis fall into 2 general categories: drugs that are considered bone-specific, which include the bisphosphonates, alendronate and risedronate, and drugs that have therapeutic effects in other medical conditions as well as in osteoporosis.

PHARMACOLOGIC THERAPY

Osteoporosis medications are approved for either prevention or treatment of the disease. A few medications have received approval for use in either situation. Targeting individuals who could ultimately benefit from pharmacologic treatments requires objective measures. BMD testing has become well established as the gold standard for the diagnosis of osteoporosis. According to the World Health Organization, bone density in postmenopausal women is characterized as normal, osteopenic (low BMD), or osteoporotic. Osteopenia exists if an individual has a BMD score between -1 and -2.5 SD below that of a “young normal” adult.

Osteoporosis exists if an individual has a BMD score that is 2.5 SD or lower (T-score at or below -2.5). Women in this group who have already experienced one or more fractures are deemed to have severe or “established” osteoporosis (13).

The goal of prevention and treatment is to prevent fractures. Women who have normal or low BMD are targeted for prevention measures, and women with established osteoporosis are targeted for treatment. When recommendations are made, it is important to recognize that while BMD has the strongest relation to fracture, many fractures occur in women who have normal or low BMD but have other risk factors.

The possibility of fracture increases when low bone density is combined with other factors, but the exact interaction of these factors is unclear (14). Because aspects of bone structure are not reflected in BMD, previous fracture significantly increases the risk for other fractures, even in patients with similar BMD measurements. A study conducted by Lindsay (15) demonstrates that women who develop a vertebral fracture are at substantial risk for additional fracture within the next year (Figure 1).

Pharmacologic interventions increase bone mass either by decreasing bone resorption, with a secondary gain in bone mass, or by a direct anabolic effect. Preferably they also increase bone strength and quality. Drugs that specifically act on bone by decreasing resorption are the bisphosphonates, calcitonin, estrogen, and selective estrogen receptor modulators (SERMs). Parathyroid hormone (PTH) has become the first FDA-approved skeletal anabolic agent for bone.

Drugs currently approved for the prevention of osteoporosis fall into 2 general categories: drugs that are considered bone-specific, which include the bisphosphonates, alendronate and risedronate, and drugs that have therapeutic effects in other medical conditions as well as in osteoporosis, including hormone therapy (HT), whose primary indication is the treatment of menopausal symptoms, and the SERM raloxifene, which appears in preliminary tests to substantially reduce the risk of estrogen receptor-positive breast cancer in clinical trials conducted with osteoporotic women (16). The bisphospho-

nates and raloxifene are approved for treatment as well as prevention of osteoporosis.

Bisphosphonates

Bisphosphonates act by blocking osteoclast action and thus prevent resorption during the remodeling cycle of bone turnover. The bisphosphonates risedronate and alendronate are effective agents for reducing vertebral and nonvertebral fracture risk. In large, randomized, controlled trials, alendronate showed consistent increases in BMD irrespective of the severity of the underlying bone density levels, and reduced both vertebral and nonvertebral fractures (17,18). Among women with osteoporosis, symptomatic vertebral fractures were decreased by 44% over 4 years and clinical fractures were reduced by 36% (17). Risedronate similarly reduced the incidence of vertebral fractures by 41% over 3 years (19) and was effective in reducing hip fracture by 40% in elderly women who had low BMD but not in women who had risk factors alone (20).

Calcitonin

Calcitonin is an endogenous inhibitor of bone resorption that acts by suppressing osteoclasts. Several studies on the effectiveness of calcitonin have shown positive effects in increasing BMD in

postmenopausal women; however, the effect on fracture reduction has been less predictable in clinical trials. In one study of postmenopausal women who used calcitonin daily, new vertebral fractures were decreased by 33% compared with placebo though only a small increase was noted in BMD (21).

Estrogen

For many years, HT had been the sole FDA-approved pharmacologic therapy for the prevention and treatment of osteoporosis. Later, labeling changes moved the FDA indication to prevention only, based on information from observational studies. The recent report from the Women's Health Initiative (WHI) study on HT provides the first large-scale, randomized controlled trial for the use of estrogen in preventing osteoporosis. Results from the study showed that HT reduced hip and vertebral fractures by 34% with an overall reduction in fracture risk of 24% (22). This finding is of particular note since the women in the WHI trial were not selected for either their baseline bone density or their risk factors for osteoporosis. In addition, their average body mass index (BMI 28.5 kg/m²) bordered on obesity and, in fact, 34% of WHI participants were obese (BMI >30 kg/m²) (23). Given the very strong antiosteoporosis and fracture effects of obesity, the marked fracture

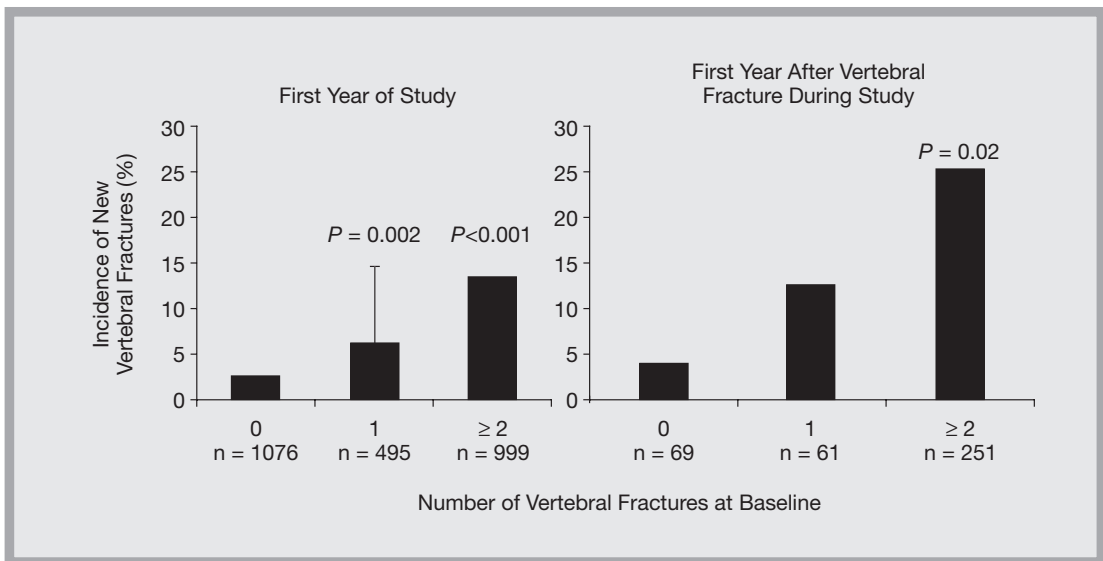


Figure 1. Preventing the first fracture is critical. Reprinted with permission from Lindsay et al (15).

reduction in the WHI becomes even more impressive (Figure 2). However, other findings from the study regarding the absence of benefits for cardiovascular events and the increased risk of breast cancer limit the indications for the use of HT. The evidence suggests that HT should be limited to menopausal or postmenopausal women who are at highest risk for the prevention of osteoporosis and should not be considered as a form of treatment for osteoporosis.

Selective Estrogen Receptor Modulators

Raloxifene is a SERM that has estrogen agonistic effects on bone and estrogen antagonistic effects on breast and endometrial tissue. This selective action appears to provide the benefits of estrogen therapy on BMD without the increased risks for breast or endometrial cancers. Results of the Multiple Outcomes of Raloxifene Evaluation (MORE) Study showed that raloxifene treatment in older women reduced the incidence of new vertebral fractures to half of those experienced in the placebo group. However, there was no effect seen in the reduction of nonvertebral fractures (24).

Parathyroid Hormone

Parathyroid hormone is a new approach to osteoporosis therapy. PTH increases bone formation, an effect reflected as an increase in markers of bone turnover such as osteocalcin and bone resorption markers such as N-telopeptide cross-links. Early studies of PTH effects have shown a 65% decrease

in vertebral fractures and a 53% decrease in non-vertebral fractures. Additionally, a marked increase in bone mass was evident in <2 years after treatment was initiated (25).

KEY POINT

After initial analysis of the data, the NORA study made clear that physicians are not adequately identifying women who have low bone mass and thus a higher risk of fractures.

MANAGING MEDICAL TREATMENT

Regardless of BMD, all patients should be following the guidelines for nonmedical prevention techniques, such as taking calcium and vitamin D supplements, eating healthy diets, exercising regularly, eliminating smoking, and drinking alcohol in moderation. However, determining a cost-effective approach for the prevention and treatment of osteoporosis and fracture and establishing guidelines for initiating medical treatments are much more difficult tasks that need to include more than BMD measurement. In theory, calculating a patient's risk should involve entering a person's age and the BMD and multiplying this by a person's other risk factors, including lifestyle, risk of falls, and the

	HRT	Placebo	% Risk Δ	Fractures
Hip*	44 (0.10)	62 (0.15)	-34	-5
Vertebral	41 (0.09)	60 (0.15)	-34	-6
Others \dagger	579 (1.31)	701 (0.70)	-23	-39
Total	650 (1.47)	788 (1.91)	-24	-44

*Excess number of cases/10,000 patient years. \dagger Others = other osteoporotic fractures, excluding fractures of the chest/sternum, skull/face, fingers, toes, and cervical vertebra.

Figure 2. Women's Health Initiative: fracture outcomes. HRT = hormone replacement therapy. Reprinted with permission from Rossouw et al (23).

direction of a fall, to get a global number that would determine whether a particular patient would benefit from medical intervention. However, at the current time an accurate model that takes each of these factors into account does not exist. In addition, data on risks for vertebral fractures differ from that for hip and other nonvertebral fractures. Also, little information exists for men and non-white women.

In an effort to gain information on women at risk for osteoporosis and fracture, a nationwide study, the National Osteoporosis Risk Assessment (NORA) Program, was initiated. The study enrolled >200,000 women into a comprehensive osteoporosis education and risk-assessment program. This initiative created a longitudinal, observational database of postmenopausal women without prior diagnosis of low bone mass who were recruited from practices of primary care physicians. Data on the women recorded the incidence of osteopenia, osteoporosis, and fractures and provided information on risk factors. After initial analysis of the data, one fact that the NORA study made clear was that physicians and other health care providers are not adequately identifying women who have low bone mass and thus a higher risk of future fractures. The study found that almost half of the postmenopausal women enrolled had low bone mass; 7% of the participants were found to have osteoporosis and nearly 40% had osteopenia. During the 1-year follow-up period, the rate of bone fracture was 4 times higher for women with osteoporosis and twice as high for women with low bone mass compared to women with normal bone density (26).

The NORA study reinforces the need to initiate medical treatment for those women who already have established osteoporosis. However, it is less clear as to what the recommendations should be for women who have decreased bone mass (osteopenia) but who are not yet osteoporotic. If recommendations were made that all the patients in this group should begin treatment, many women who are at risk for fracture would be captured. At the same time, many women would also receive treatment unnecessarily as the NORA data suggest that nearly half the total population of women have

either osteoporosis or osteopenia. The cost of treating this many patients is simply too high a price for the economy to support and is unnecessary as many patients will never fracture. Still this group of women cannot go untreated. In the NORA study, the fact that such a large number of participants, 40%, were osteopenic, meant that more than 50% of all fractures occurred in this group even though they were at a lower risk than women in the osteoporosis group.

In an effort to establish more specific guidelines for treatment, research has focused on finding other clinical risk factors, independent of BMD, that contribute to fracture risk. The National Osteoporosis Foundation has created a list of clinical factors considered to be of primary importance for risk: personal history of fracture after age 40; history of fracture of hip, wrist, or spine in a first-degree relative; body weight = 127 lb (57.8 kg); current cigarette smoking (27). Other risk factors that have been identified by large prospective studies include white or Asian race, older age, female sex, frequent falls, impaired eyesight, frailty, estrogen deficiency, inadequate calcium intake, alcoholism, cognitive impairment, and inadequate physical activity/exercise (14, 28–30). This list of “other” factors is long and imprecise and helps demonstrate the need for the development of risk stratification algorithms that can better predict risk of future fractures in women with osteopenia.

Taken together, the BMD and clinical risk factors can be used to approximate a treatment action threshold for a patient. There are no absolute guidelines that establish when treatment would be appropriate and the clinician must use discretion in determining which patients would benefit from treatment.

CONCLUSIONS

Patients with low bone mass, which include those with osteoporosis or osteopenia, are at increased risk of fracture. For older patients, sustaining a fracture can have substantial consequences on the individual's quality of life and health. Medications capable of preventing bone loss and preserving bone integrity are available and have been shown to effectively reduce the risk of fracture. While exer-

cise, calcium, and vitamin D can help keep bones healthy, these therapies alone may not be enough to prevent fracture if bone density is already reduced. BMD measurements provide the best diagnostic tool for predicting fracture risk. However, despite the availability of this testing, patients are not receiving adequate screening. Proper assessment of bone density along with assessment of other personal risk factors is essential for determining those patients who would benefit from prevention and treatment strategies. Most important, however, is that physicians should treat the patient and not the T-score.

REFERENCES

1. National Osteoporosis Foundation. America's bone health: The state of osteoporosis and low bone mass. Available at: www.nof.org/advocacy/prevalence/index.htm. Accessed January 7, 2003.
2. Melton LJ III, Thamer M, Ray NF, et al. Fractures attributable to osteoporosis: Report from the National Osteoporosis Foundation. *J Bone Miner Res.* 1997;12:16–23.
3. US Congress Office of Technology Assessment. Effectiveness and Costs of Osteoporosis Screening and Hormone Replacement Therapy, Volume II: Evidence on Benefits, Risks and Costs, OTA-BP-H-144. Washington, DC: US Government Printing Office; August 1995.
4. Barrett-Connor E. The economic and human costs of osteoporotic fracture. *Am J Med.* 1995;98:3S–8S.
5. 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.
6. Ray NF, Chan JK, Thamer M, et al. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995. Report from the NOF. *J Bone Miner Res.* 1997;12:24–35.
7. National Osteoporosis Foundation. America's bone health: The state of osteoporosis and low bone mass. Available at: www.nof.org/osteoporosis/stats.htm. Accessed January 7, 2003.
8. Consensus Development Conference. Diagnosis, prophylaxis and treatment of osteoporosis. *Am J Med.* 1993;94:646–650.
9. Miller PD, Bonnick SL, Rosen CJ. Consensus of an international panel on the clinical utility of bone mass measurements in the detection of low bone mass in the adult population. *Calcif Tissue Int.* 1996;58:207–214.
10. National Osteoporosis Foundation. Osteoporosis: Review of the evidence for prevention, diagnosis, and treatment and cost-effective analysis. *Osteoporosis Int.* 1998;8:S1–S88.
11. Teegarden D, Proulx WR, Martin BR, et al. Peak bone mass in young women. *J Bone Miner Res.* 1995;10:711–715.
12. Prince RL, Smith M, Dick IM, et al. Prevention of postmenopausal osteoporosis. A comparative study of exercise, calcium supplementation, and hormone-replacement therapy. *N Engl J Med.* 1991;325:1189–1195.
13. World Health Organization: Assessment of Fracture Risk and Application to Screening for Postmenopausal Osteoporosis. Geneva, Switzerland: WHO Technical Report Series; 1994.
14. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med.* 1995;332:767–773.
15. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA.* 2001;285:320–323.
16. Cummings SR, Duong T, Kenyon E, et al. Serum estradiol level and risk of breast cancer during treatment with raloxifene. *JAMA.* 2002;287:216–220.
17. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: Results from the Fracture Intervention Trial. *JAMA.* 1998;280:2077–2082.
18. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med.* 1995;333:1437–1443.
19. 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;282:1344–1352.
20. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on hip fracture risk in elderly women. Hip Intervention Program Study Group. *N Engl J Med.* 2001;344:333–340.
21. Chesnut CH III, 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;109:267–276.
22. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;109:267–276.
23. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321–333.
24. 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;282:637–645.
25. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001;344:1434–1441.
26. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: Results from the National Osteoporosis Risk Assessment. *JAMA*. 2001;286:2815–2822.
27. National Osteoporosis Foundation. *Physician's Guide to Prevention and Treatment of Osteoporosis*. National Osteoporosis Foundation: Washington, DC; 2000.
28. Seeley DG, Kelsey J, Jergas M, et al. Predictors of ankle and foot fractures in older women. *J Bone Miner Res*. 1996;11:1347–1355.
29. Dargent-Molina P, Favier F, Grandjean H, et al. Fall-related factors and risk of hip fracture: The EPIDOS prospective study. *Lancet*. 1996;348:145–149.
30. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *Lancet*. 2002;359:1929–1936.
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