Aging Bone and Osteoporosis

Strategies for Preventing Fractures in the Elderly

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As the older population increases, the incidence of osteoporotic fractures is expected to dramatically rise during the next few decades. Older patients are much more susceptible to fracture at any given bone mineral density (BMD) than are younger patients because of various factors, including the quality of aging bone, which involves more than BMD. Suppression of increased bone turnover by antiresorptive therapies, even with only small changes in BMD, can reduce fracture risk, especially in the lumbar spine. Bisphosphonate treatment can significantly reduce vertebral and nonvertebral fractures, including hip fractures, even in the very elderly. Prospective analyses show that risedronate therapy consistently and significantly reduces the risk of new morphometric vertebral fractures after 1 year in postmenopausal women. Post hoc analyses report significant reductions in the risk of 1 new clinical vertebral fracture after 6 months of risedronate therapy and after 1 year of alendronate therapy. Oral raloxifene therapy and salmon calcitonin nasal spray therapy have been shown to reduce the risk of vertebral fracture after 3 and 5 years, respectively, and post hoc data show a significant reduction in clinical vertebral fracture risk at 1 year with raloxifene use. However, neither raloxifene therapy nor calcitonin therapy reduce the risk of nonvertebral and hip fractures at currently approved doses. Bisphosphonates have been shown to be safe and efficacious with 7 years' risedronate sodium and 10 years' alendronate sodium data published, and bisphosphonates reduce bone turnover and increase BMD to a greater degree than raloxifene and calcitonin, which may partly account for their nonvertebral and hip fracture reduction effect. Therefore, bisphosphonate therapy with risedronate or alendronate should be considered in patients with low BMD at the hip and in older patients with osteoporosis and osteopenia, particularly those with an existing fracture.

Arch Intern Med. 2003;163:2237-2246

Osteoporosis is a common disorder that places a large medical and economic burden on the health care system. It is likely to become even more common and costly because of increasing longevity. Osteoporosis is characterized by low bone mass and microarchitectural deterioration, which lead to bones that are prone to fracture.[1] Patients with osteoporosis have a greatly increased incidence of fractures, and these events are associated with substantial morbidity and mortality. However, osteoporosis is all too often diagnosed or looked for only after low-trauma fractures occur.

Bone mass and bone turnover rates are major and measurable components of fracture risk. In the elderly, both sexes lose bone, and the rate of bone loss is initially higher in women than in men.[2] The elderly are at particularly high risk for osteoporotic fractures not only because of abnormalities in bone mass and architecture but also because of factors that affect the incidence of falls. Older patients are more susceptible to fracture than younger patients with the same

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Table 1. Predictors of Low Bone Mass and Clinical Risk Factors for Fractures*

Predictors of Low Bone Mass
Female sex
Advancing age
Gonadal hormone deficiency (estrogen or testosterone)
White race
Low body weight and body mass index
Family history of osteoporosis
Low calcium intake
Smoking or excessive alcohol intake
Low level of physical activity
Chronic glucocorticoid use
History of fracture
Clinical Risk Factors for Fractures
Low bone mass
History of falls
Impaired cognition (including medication adverse effects)
Low physical function such as slow gait or decreased quadriceps strength
Presence of environmental hazards (eg, throw rugs)
Long hip axis length
Chronic glucocorticoid use
Presence of an existing fracture
Chronic use of various seizure medications
Renal, hepatic, thyroid, parathyroid, and malabsorptive disorders; vitamin D deficiency; myeloma; and local neoplasia need to be ruled out

*Data from the National Osteoporosis Foundation.[7]

bone mineral density (BMD) T score.[3,4] The challenge for primary care physicians is to prevent bone loss, to diagnose and treat osteoporosis before fractures occur, and to treat patients who have already experienced an osteoporosis-related fracture (even if it is an asymptomatic vertebral deformity) to prevent recurrent fractures. This article reviews concepts about bone aging, fractures involved in age-related reduced bone quality, and fractures in the elderly and discusses osteoporosis diagnosis and antiresorptive treatment strategies to reduce fracture risk.

THE PREVALENCE OF OSTEOPOROSIS

Using World Health Organization criteria, 13% to 18% of women in the United States older than 50 years have osteoporosis and another 37% to 50% have osteopenia. This translates into 4 to 6 million women with osteoporosis and 13 to 17 million with osteopenia.[5] Of men in the same age group, 3% to 6% (1-2 million) are osteoporotic and 28% to 47% (8-13 million) are osteopenic. The prevalence of osteoporosis increases dramatically with age.[6]

Poor bone mass acquisition during adolescence and accelerated bone loss during the perimenopausal and postmenopausal periods are 2 of the major pathophysiologic processes responsible for osteoporosis in women, but other predictors and risk factors have been identified (**Table 1**). Secondary osteoporosis occurs as a result of various systemic disorders (eg, hyperparathyroidism, hyperthyroidism, and malabsorption) or drug therapies that contribute to accelerated bone loss, such as long-term glucocorticoid intake. Bone loss is observed even with the use of low doses of glucocorticoids, occurs early, and is most rapid and extensive at doses of 5 mg/d or greater of prednisone or its equivalent.[8-11] Glucocorticoids increase bone loss, reduce new bone formation, and accelerate osteocyte death, all of which weaken bone.

In some patients, genetically determined factors cause hereditary low bone mass, which reduces peak bone mass acquisition.[12] This means that their BMD at 1 or more major sites is lower than the reference range at skeletal maturity (age 25-30 years). Patients with hereditary low bone mass, therefore, have less bone to lose in later life before fracture risk further increases and have low BMD premenopausally. Genetic factors may also increase bone loss in later life. Thus, this group should be carefully monitored, and early preventive treatment should be considered.

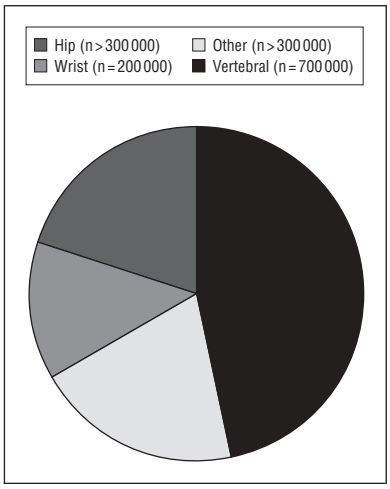

Figure 1. Annual incidence of osteoporotic fractures in the United States. Data compiled from the National Osteoporosis Foundation Web site (http://www.nof.org/osteoporosis/stats.htm).

FRACTURE RISK

Not every woman with osteoporosis will experience a fracture during her lifetime; however, the future risk of fracture for any given individual is greatly increased with osteoporosis. Future fracture risk can be reduced with antiresorptive therapy, even in the elderly. Approximately 1.5 million fractures are caused by osteoporosis each year in the United States (**Figure 1**).[13] The costs associated with osteoporotic fractures are considerable, especially for hip fracture,[14] and are expected to increase markedly as the population ages.[15]

The risk of osteoporotic fracture increases continuously as BMD declines, with approximately a 2-fold increase in fracture risk for each 1 SD decrease in BMD.[16] The estimated lifetime risk for a fragility fracture among 50-year-old women in North America is approximately 18% for hip fracture, 16% for clinically diagnosed vertebral fracture, and 16% for Colles fracture.[6,17] Overall, the National Osteoporosis Foundation estimates that 1 in 2 white women and 1 in 4 white men older than 50 years will sustain at least 1 osteoporosis-related fracture in their remaining lifetime.[13] At least 90% of hip and spine fractures among elderly women can be attributed to osteoporosis.[18] Previous fracture is an important predictor of future hip and other fractures.[19]

Fracture risk increases with age, but osteoporosis is underdiagnosed and undertreated,[20-22] even in patients discharged from the hospital after a hip fracture.[23-25] The challenge is to identify and treat asymptomatic at-risk women so that fracture risk can be reduced as rapidly as possible. Any low-trauma fracture in an older patient should trigger a workup for osteoporosis.

Postmenopausal women with risk factors should undergo a noninvasive peripheral or a central bone density test.[7,26] Peripheral tests of the calcaneus or radius, for example, can be quickly performed with ultrasound or x-ray absorptiometry. Patterns of bone loss may vary at different sites depending on age. In patients older than 65 to 70 years, peripheral BMD correlates better with spine and hip BMD than in younger patients, in whom discordance in BMD between peripheral and central anatomic sites is more commonly noted.[27] Low peripheral results should be followed up by central dual x-ray absorptiometry of the lumbar spine and hip if therapy is contemplated because this technique can better detect and monitor clinically significant changes in BMD.

Quantitative computed tomography and other techniques are less generally available. Because nearly three quarters of vertebral crush fractures are asymptomatic and unknown to patients,[28] a woman diagnosed as having osteoporosis could benefit from a lateral thoracic and lumbar spine radiograph to determine whether a vertebral deformity is present (some newer dual x-ray absorptiometry units are capable of providing lateral morphometric views for this purpose). If a deformity is present or if a low-trauma fracture has already occurred elsewhere in the presence of osteoporosis, the patient meets World Health Organization criteria for "severe osteoporosis."[1]

Vertebral Fracture

Vertebral fractures are a hallmark of osteoporosis and an important measured end point in clinical trials of osteoporosis treatment. Clinically, vertebral fracture can be suspected in patients with back pain, vertebral deformities by physical examination (kyphosis), or loss of height. Symptomatic vertebral fractures in patients with osteoporosis are associated with pain and disability, leading to loss of functional activity and quality of life.[29] In an observational study of 7223 white women 65 years and older (mean follow-up, 3.7 years), those with an acute clinical symptomatic vertebral fracture had approximately 10 additional limited-activity days and 1 to 2 days of bed rest per year compared with women without a vertebral fracture.[30] However, even women discovered to have asymptomatic vertebral deformities were significantly more likely to have had a history of increased back pain and back disability and had 7 days per year of limited activity and at least 1 day per year of bed rest owing to back pain.[30] These data underscore the negative impact that even asymptomatic vertebral deformities have on affected individuals.

Asymptomatic vertebral deformities are often noted on routine chest radiographs, and this should be a "red flag" to physicians to perform a workup on these patients for osteoporosis. Nearly three fourths of all vertebral deformities are asymptomatic[28]; therefore, imaging is necessary to diagnose prevalent vertebral deformities. Standard spine radiographs or new techniques of thoracic and lumbar spine lateral morphometry using new software (such as the IVA Hologic system or the LVA GE-Lunar system) for x-ray absorptiometry units can identify the presence of vertebral fractures at the time a bone density test is performed.[31,32]

Hip Fracture

Hip fractures are the most serious consequence of osteoporosis because of the associated morbidity, mortality, and financial cost of treatment and rehabilitation. Femoral neck bone strength declines with age, and this decrease occurs earlier in women than in men.[33] Accordingly, hip fracture rates increase exponentially with age, and hip fractures are 4 times more frequent in women than in men, although by age 80 years the incidence of hip fractures and the associated mortality rate greatly increase in men.[34]

Following a hip fracture, nearly 1 in 6 patients aged 50 to 55 years and more than half of those older than 90 years are discharged from the hospital to a nursing home.[34] One year after a hip fracture, only approximately 40% of suviving patients regain their previous level of mobility, and only approximately 25% regain their former functional status.[35] In the United States, hip fractures result in approximately 31 000 excess deaths within 6 months of the event.[36] Mortality rates after a hip fracture are higher in men than in women.[37,38]

Why Fractures Are a Red Flag

The presence of a low-trauma fracture, such as that caused by falling from standing height or a vertebral crush fracture caused by picking up the vacuum cleaner, should be a red flag for physicians to consider a diagnosis of osteoporosis and to proceed with a workup to rule out neoplasia in bone and secondary causes of bone loss. The first fracture indicates poor bone strength, and recurrent fractures serve to further confirm this fact. Once patients experience a vertebral fracture, their risk of sustaining another vertebral fracture increases markedly. Patients with an existing vertebral deformity have a more than 12-fold risk during a 10-year period of sustaining another vertebral fracture compared with controls (those without prevalent vertebral deformity).[39] Moreover, 1 in 5 women with an existing symptomatic or asymptomatic vertebral deformity will experience a fracture again within a year.[28] This highlights the need for treatment, which can rapidly reduce fracture risk.

Vertebral fractures also represent an important risk factor for all fractures in general. A symptomatic or an asymptomatic vertebral fracture increases the risk of subsequent hip fracture by 2.3-fold and of distal forearm (Colles) fracture by 1.6-fold during a 10-year period.[39] An increased mortality rate is also observed after diagnosis of vertebral fracture.[34,40]

PATHOGENESIS OF AGING BONE

"Younger" vs "Older" Bone

The typical perimenopausal woman will usually start to lose bone when

estrogen levels decline and bone remodeling turnover rates and osteoclast activity increase owing to a lack of the suppressive effects of estrogen on bone receptors.[41] This can occur at natural menopause or at an earlier age after complete oophorectomy. Men also lose bone with advancing age because of loss of hormones.[42,43] In this setting, osteoclasts cause more bone to be lost than osteoblasts can restore, and the normal balance of bone turnover and repair/replacement is lost.

Nutritional factors also contribute to bone loss, including low calcium and vitamin D intake, malnutrition, smoking, decreased absorption of calcium through the gastrointestinal tract (occurs with increasing age), and impaired renal conversion of vitamin D.[44] Older patients are also more likely to have decreased balance, vision, and muscle mass relative to younger patients, and they may be taking medications that can affect balance and cognition. All of these factors further increase the fracture risk of elderly patients compared with that of younger patients with the same BMD.

Although low BMD in the lumbar spine or hip,[45] especially with an existing vertebral fracture (even if asymptomatic),[28] is a powerful predictor of future low-trauma fractures, recent concepts suggest that osteoporosis fracture risk also is based on other aspects of bone quality, not just BMD alone. For this section, assume that patients have undergone workup for systemic disorders that can cause bone loss (ie, hyperparathyroidism; hyperthyroidism; underlying systemic, renal, or hepatic diseases; alcoholism; malabsorption; vitamin D deficiency; developmental disorders; and neoplasia such as myeloma or local bone lesions).

BMD, High Bone Turnover, and Fracture Risk

In addition to low BMD, fracture risk increases if bone turnover rates are high (here, risk increases independently of BMD).[46] Despite success in increasing BMD, one research medication failed to adequately suppress bone turnover and did not reduce fractures compared with the calcium control group in one clinical study[47]; however, the same agent using different doses, routes of administration, and dose schedules suppressed bone turnover, increased BMD, and reduced fractures in a subsequent clinical trial.[48,49] High rates of bone loss typically occur first in the lumbar spine and other areas of high trabecular bone content, where there are many metabolically active surfaces.[50] Beginning with estrogen deficiency, this period of high bone turnover and of accelerated bone loss may last a decade, then continue at different rates of bone loss for the remainder of a woman's life.[51-53] During the early postmenopausal decades, the incidence of vertebral fracture greatly increases with the onset of high bone turnover rates and bone loss. Many elderly women have elevated bone turnover rates, which seems to adversely affect BMD and fracture risk.[54,55] Other women and men may have long, slow, cumulative bone losses, with increasing fracture risk as age increases.

An analogy to high bone turnover in trabecular bone is a roof supported by wooden trusses riddled with multiple small termite holes and tunnels—the trusses may still contain a large amount of the original wood but are very weakened structurally. If many termite pits (bone turnover pits) are present, the roof may fall (like bone may fracture) if the pits occur in a critical spot, regardless of how much of the average amount of wood is still present in the trusses, although the greater the wood loss, the higher the risk of mechanical failure. Left untreated, high bone turnover from unsuppressed osteoclasts will erode or transect bone-supporting trabecular struts and perforate cancellous bone plates, thereby changing the geometry of the bone and greatly weakening it (**Figure 2**).[56] Untreated osteoclast-mediated high bone turnover can cause the trabecular bone struts to undergo progressive erosion that renders them weakened and, in some cases, disconnected (Figure 2). This underscores the importance of early identification and treatment of osteoporosis (ie, before struts break).

It is intuitive that bone fragility is affected by bone size, shape, architecture, and "quality."[57] In the early postmenopausal years, the lack of estrogen can lead to particularly rapid trabecular bone turnover in areas such as the lumbar spine. This is believed to contribute to the higher incidence of vertebral fractures seen in the early postmenopausal decades. Later in life, cortical bone loss is increased in the hip and other nonvertebral areas. This is believed to contribute to hip and other nonvertebral fractures.

Bone Turnover Markers

Patients with low BMD and high turnover are at greatest risk for fractures.[54,55,58-60] Clinically, bone turnover rates can be measured by "bone turnover markers," which are tests that can measure bone breakdown products in serum or urine (pyridinoline, deoxypyridinoline, and N- or C-terminal cross-linked peptides).[61] Owing to individual patient test variability, a 30% or greater reduction in bone turnover is desirable to confirm a response to therapy. Because of testing sensitivity and cost-related issues, these tests need to be used selectively.

THERAPEUTIC IMPLICATIONS OF AGING BONE

Bone loss continues throughout life for older men and women.[42,62] Later in life, ongoing cumulative cortical bone loss will increase in the hip and other nonvertebral areas of bone. However, because fracture risk increases in the elderly to a greater extent than one would expect simply from BMD,[3] the term *bone quality* is believed to encompass more than just BMD. In addition to higher risks of falling, this suggests that there are other important factors in the aging process that affect bone quality and ultimately fracture risk.

Current concepts now suggest that as women age, additional factors further weaken older bone compared with younger bone. Whereas trabecular bone loss in the lumbar spine is rapid in the early menopausal years, cortical bone loss at the hip, radius, and other nonvertebral sites is an additional important risk factor for fracture in older age.[50] Cumulative age-related loss of cortical bone thickness, increased cortical bone porosity from erosion and re-

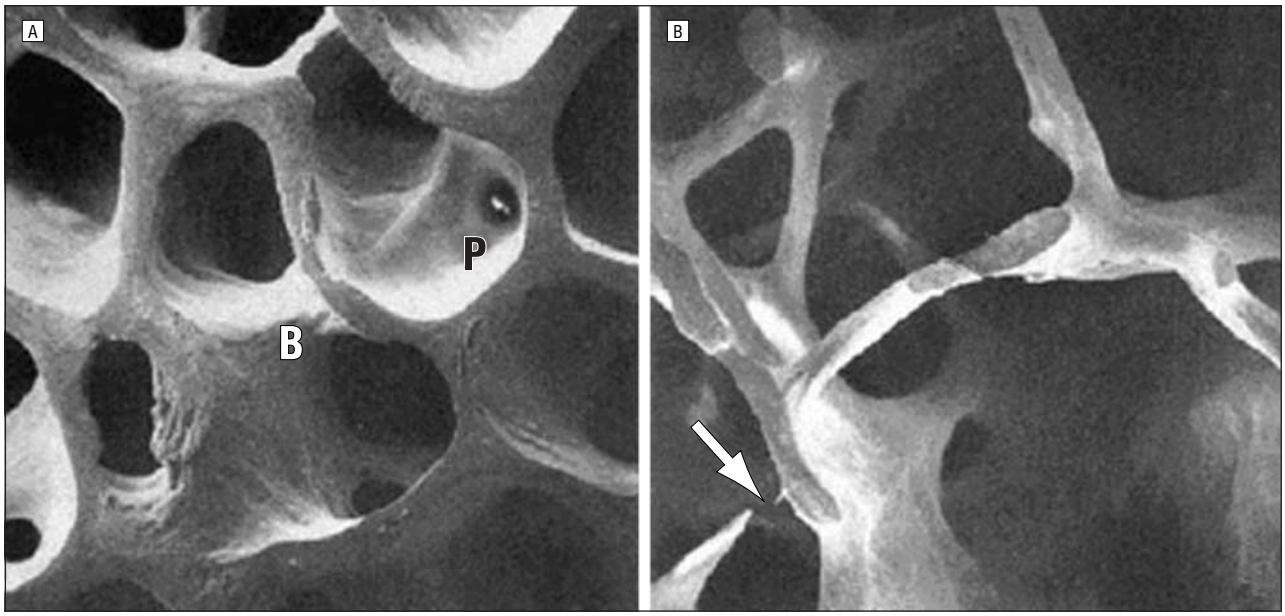

Figure 2. Scanning electron microscopic images of trabecular bone. A, Note the amount and thickness of the normal trabecular bone and that the trabecular network is confluently connected. In normal bone, bone turnover and subsequent replacement are in balance. B indicates a thick, normal trabecular bar; P, a trabecular plate. B, In the osteoporotic bone, increased bone resorption by osteoclasts has reduced the total amount of bone and transected trabecular struts (arrow). The strut above and to the right of the arrow shows how resorption pitting has partially eroded a bone strut but not yet cut through it. Transection of struts, erosion, and loss of bone associated with increased bone turnover greatly increase fracture risk. Reprinted from the *Journal of Bone Mineral Research*[56] with permission from the American Society for Bone and Mineral Research.

sorption in areas such as the hip,[63] and endosteal bone loss are all believed to greatly weaken the breaking strength of bone. In addition, it is believed that aged bone has accumulated fragility and may have mechanically weakened areas of microdamage from microcracks due to the wear and tear of repetitive mechanical loading—the cyclic loading from activities of daily living for many years—and that these microcracks may accumulate even more rapidly in women with low bone density.[64] This microdamage in older bone may affect the material properties of bone by changing the elasticity, bone toughness, stiffness, and bone strength, although not all of these may affect fracture risk equally. These factors may affect energy-related resistance to fracture.[65,66] The strength, fracture risk, and overall quality of aging bone involves many factors in bone microstructure, trabecular thickness, connectivity, spacing, orientation, quantity, and microhealing. Bone density by itself is not the same as bone quality, nor is it the same as bone strength, although it is an important contributor to both. Of the many factors involved in bone quality, only BMD and bone turnover rates can be easily measured clinically.

Older bone may also lose its ability to remodel and add bone in critical weightbearing or stress-bearing microscopic sites (a proposed loss of mechanostat or biomechanical repair responses).[67] Patients with osteoporosis may have several variables of femoral neck geometry (hip axis length, neck-shaft angle, and mean femoral neck width) that increase hip fracture risk in addition to the quality of their bone.[68-71] Add the cumulative weakening effect of bone resorption pits and perforated bone plates, and that older patients may have more cortical bone porosity and endosteal bone resorption and possible effects from microfatigue, and all of these factors may partly explain why older bone has lower quality and is at higher risk for fracture at any given BMD than is younger bone (**Figure 3**).[72] All of these factors relate to reduced bone quality. Fracture risk increases if bone quality and structure are poor.[57]

TREATMENT TO REDUCE FRACTURE RISK

Recent data[46,73] suggest that if trabecular bone turnover (in areas such as the lumbar spine) is reduced with antiresorptive treatment (reducing bone turnover), fractures will be reduced. These therapies also can increase BMD. Conceptually, if bone turnover micropitting is reduced and osteoblasts are allowed to restore bone into some of these small pits, especially if restored in structurally critical areas, this combination could increase the mechanical strength and the quality of bone and reduce fracture risk. Even small increases in BMD, if achieved in critical areas, are believed to increase mechanical strength, especially in trabecular bone. In the lumbar spine, reduction of fractures may be more a function of reducing bone turnover rates than increasing BMD.[46,73,74] Treatment with antiresorptive agents will suppress this bone turnover and loss, and a net increase in BMD can occur because restorative osteoblast function continues.

Effective antiresorptive treatments induce a decrease in bone turnover that reaches plateau within 1 to 3 months for oral bisphosphonates and usually up to 6 months for various types of estrogen, raloxifene, and nasal calcitonin, depending on the potency and route of administration of the drug and on the marker.[75] Changes in bone turnover markers produced by raloxifene and calcitonin are generally smaller than those produced by the

bisphosphonates and hormone therapy (HT).[75]

The studies summarized in **Table 2** generally recruited women who were at least 5 years postmenopausal. Although not specifically designed to assess the effects of antiresorptive therapy in a geriatric population, the mean age of the women in most of these trials was close to or greater than 70 years (Table 2).

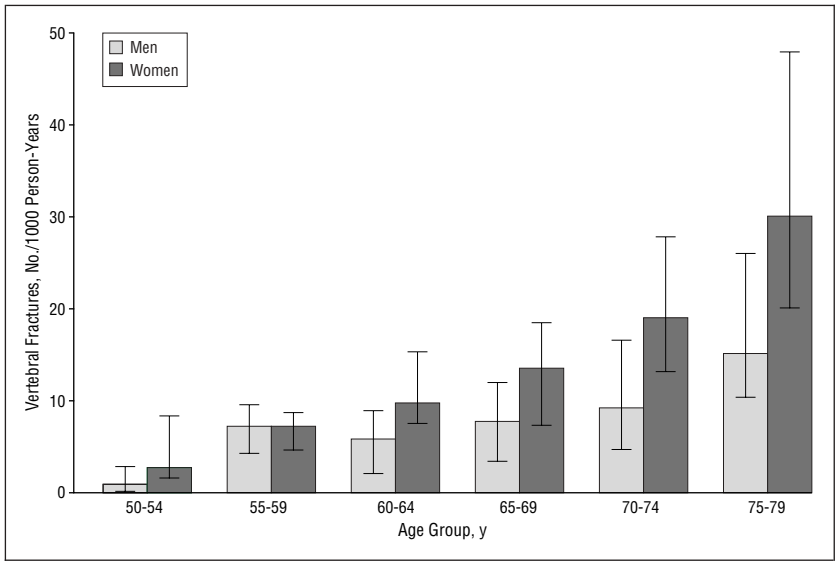

Figure 3. Incidence of morphometric vertebral fracture by age and sex. Error bars represent 95% confidence intervals. Reprinted from the *Journal of Bone Mineral Research*[72] with permission from the American Society for Bone and Mineral Research.

Clinicians must be cautious in comparing statistics from one clinical trial to another when different agents are used for the same disease process because each study has a different population of patients and results can vary from one patient group to another. Nonetheless, statistically significant results in clinical trials are very important, particularly if results are consistent in several different studies.

Bisphosphonates

Several large, placebo-controlled, randomized clinical trials have been conducted to assess the antifracture efficacy of risedronate sodium and alendronate sodium in postmenopausal women (Table 2). In these studies, all of the patients received oral elemental calcium supplementation,

Table 2. Summary of Antifracture Results From Clinical Trials in Women With Postmenopausal Osteoporosis

Source	Patients, No.	Age, Mean, y	Patients With Vertebral Fracture at Baseline, %	Treatment Duration, y	Fracture Risk Reduction vs Placebo, % (*P* Value)		
					Vertebral	Nonvertebral	
						Total Fractures	Hip Fractures
Risedronate							
VERT-NA study[76]	2458	69	80	1	65 (<.001)	NA	NA
				3	41 (.003)	39 (.02)	NA
VERT-MN study[77]	1226	71	100	1	61 (.001)	NA	NA
				3	49 (<.001)	33 (.06)	NA
VERT-MN study[78]	265	NA	100	5	50 (<.001)	37 (.02)	NA
HIP[79]							
Women aged 70-79 y with osteoporosis	5445	74	31	3	NA	20 (.03)	40 (.009)
	1703*			3	NA	30 (.01)	60 (.003)
Women aged ≥80 y with ≥1 clinical risk factor for hip fracture	3886	83	29	3	NA	9 (.43)	20 (.35)
Alendronate							
FIT[80]	2027	71	69	3	47 (<.001)	20 (.06)	51 (.047)
FIT[81]	4432	68	0	4	44 (.002)	12 (.13)	21 (.44)
FOSIT[82]	1908	63	NA	1	NA	47 (.02)	NA
Alendronate Phase III Osteoporosis Treatment study[83]	994	64	21	3	48 (.03)	21†	NA
Calcitonin							
PROOF study[84]‡	1255	68	75	5	33 (.03)	12†	50†
Raloxifene							
MORE[85]§	7705	NA	37	3	30 (<.01)	10 (.24)	10 (.71)

Abbreviations: FDA, Food and Drug Administration; FIT, Fracture Intervention Trial; FOSIT, Fosamax International Trial; HIP, Hip Intervention Program; MORE, Multiple Outcomes of Raloxifene Evaluation; NA, not available; NS, not significant; PROOF, Prevent Recurrence of Osteoporotic Fractures; VERT-MN, Vertebral Efficacy With Risedronate Therapy Multinational; VERT-NA, Vertebral Efficacy With Risedronate Therapy North America.

*Women with preexisting vertebral fractures at baseline.

†Not statistically significant (exact *P* value not provided).

‡Data are for the 200-IU/d group (FDA-approved dose).

§Vertebral fracture data are for the 60-mg/d group (FDA-approved dose); nonvertebral fracture data are for the pooled 60- and 120-mg/d groups.

and some protocols allowed for cholecalciferol supplementation if baseline levels were low. Bisphosphonates must be taken on an empty stomach and only with water. No food may be ingested for a minimum of 30 minutes because any food or beverage (other than water) will block the absorption of bisphosphonates.[86,87]

Risedronate. The Vertebral Efficacy With Risedronate Therapy North American (VERT-NA)[76] and Multinational (VERT-MN)[77] studies evaluated the effect of risedronate therapy on fracture risk in postmenopausal women with osteoporosis and existing symptomatic or asymptomatic vertebral deformities. In prospective analyses, the use of risedronate sodium, 5 mg/d, reduced the risk of new vertebral fractures diagnosed radiographically by 65% ($P<.001$) and 61% ($P=.001$) after 1 year of treatment in the VERT-NA and VERT-MN studies, respectively (Table 2). A post hoc analysis[88] of combined VERT study data showed a statistically significant reduction in the risk of new first recurrences of a painful acute clinical vertebral fracture after 6 months of treatment ($P<.01$). These risk reductions were maintained after 3 years by 41% and 49% of patients in the VERT-NA and VERT-MN studies, respectively (Table 2), and after 5 years by 50% of patients in a 2-year extension of the VERT-MN study.[78]

Risedronate therapy has also been shown to significantly reduce the risk of nonvertebral fractures in postmenopausal women: the risk of confirmed nonvertebral fractures was reduced by 39% ($P=.02$) and 33% ($P=.06$) after 3 years in the VERT-NA and VERT-MN studies, respectively, and by 37% after 5 years in a 2-year extension of the VERT-MN study (Table 2).[76-78] In a post hoc analysis of combined data from 4 clinical trials (n=4845), risedronate therapy reduced the risk of nonvertebral fractures, collected as adverse events, by 74% after 1 year of therapy ($P=.001$).[89]

The Hip Intervention Program study[79] assessed the effect of risedronate therapy on 3-year hip fracture risk in 2 groups of elderly women—1 in women aged 70 to 79 years with established osteoporosis (n=5445; mean age, 74 years) and those 80 years and older with at least 1 clinical risk factor for hip fracture or low femoral neck BMD (n=3886; mean age, 83 years). Treatment with risedronate significantly reduced the 3-year risk of hip fracture by 40% ($P=.009$) in women with established osteoporosis and by 60% ($P=.003$) in women with osteoporosis and at least 1 vertebral fracture (Table 2).[79] Overall, nonvertebral fracture risk was significantly reduced in these populations (Table 2). The nonsignificant reduction in hip and nonvertebral fracture risk in the group of women 80 years and older may be accounted for by the fact that they were selected largely on the basis of clinical risk factors, and most of the patients likely did not have osteoporosis, as was assumed during protocol development.[79] In a post hoc analysis of Hip Intervention Program study data, risedronate therapy also significantly reduced vertebral fracture risk by 55% after 1 year ($P<.001$).[90] Data have been published showing safety and consistent effects with the use of risedronate sodium use for a duration of 7 years.[91]

Alendronate. Multiple long-term studies have shown fracture reduction with alendronate therapy (Table 2). In 994 postmenopausal women with osteoporosis, treatment with alendronate sodium (5 mg/d for 2 years and 10 mg/d in year 3 or 20 mg/d for 2 years and then 5 mg/d in the third year) reduced the risk of any new vertebral fracture by 48% (Table 2).[83] The Fracture Intervention Trial (FIT) evaluated the effect of alendronate therapy on vertebral and nonvertebral fractures in postmenopausal women with osteoporosis or low bone mass.[80,81] In the 3-year FIT arm,[80] alendronate sodium, 5 mg/d for 2 years and then 10 mg/d in the third year, significantly reduced the 3-year risk of any new vertebral fracture by 47% ($P<.001$) (Table 2). In the 4-year FIT arm,[81] alendronate sodium, 5 mg/d for 2 years and then 10 mg/d for 2 years, significantly reduced the 4-year risk of new vertebral fracture by 44% ($P=.002$).

In clinical trials, alendronate therapy has produced reductions in the risk of nonvertebral fractures (Table 2). The risk of clinical nonvertebral fractures, captured during adverse event reporting, was significantly reduced by 47% ($P=.02$) at 1 year in another alendronate study.[82] Three-year hip fracture risk was significantly reduced by 51% ($P=.047$) with alendronate therapy in the 3-year FIT study in women with prevalent vertebral fracture.[80] As with risedronate therapy, alendronate therapy has been shown to have an additive effect with HRT in increasing BMD, although fracture data are not available for these short-term studies.[92-94] Data have been published showing safety and consistent effects with the use of alendronate sodium for a duration of 7 and 10 years.[95-97]

Post hoc analysis[98] of combined FIT data showed that alendronate use significantly reduced the 3-year risk of radiologic vertebral fractures (48%; $P<.001$), clinical vertebral fractures (45%; $P=.003$), hip fractures (53%; $P=.005$), and any nonvertebral fractures (27%; $P<.001$) in women with existing vertebral deformity plus those with osteoporosis without vertebral deformity. This analysis[98] also reported a 59% reduction in clinical vertebral fracture risk after 12 months of alendronate therapy ($P<.001$). Another post hoc analysis[99] of FIT data reported a significant reduction in the risk of multiple clinical vertebral fractures after 6 months of alendronate therapy. This analysis showed a reduction not in the first recurrence of acute symptomatic fractures after randomization but rather a statistically significant reduction after the patients had experienced at least 2 additional acute symptomatic clinical deformities.

Other Drugs

Estrogen. The Women's Health Initiative study[100] showed that HRT plus progesterone therapy reduced fractures, but it was associated with increased incidences of cardiovascular morbidity and breast cancer. Much evidence for the antifracture efficacy of HRT has previously been based on observational studies. A recent meta-analysis[101] determined that HRT was responsible for an overall 27% reduction in nonvertebral fracture risk, an effect that was greater and statistically significant only among women younger than 60 years. Hip or wrist fracture risk was not reduced among women 60 years

or older.[101] The bone protective effects of HRT seem to occur only during and not long after therapy, with bone turnover rates rapidly increasing after the cessation of HRT.[102] With rising concern over the risks of breast cancer with HRT,[103] data that question the ability of standard or reduced doses of HRT to protect against hip fractures,[104] and new questions raised about whether additional cardiovascular benefits with HRT are real in older women with existing cardiovascular disease,[105,106] HRT plus progesterone therapy in particular is now being used selectively in women for treatment of menopausal symptoms. Hormone replacement therapy and progesterone are no longer recommended as a primary therapy for the sole indication of treatment or prevention of osteoporosis until further data become available.

Salmon Calcitonin. In 1255 postmenopausal women with established osteoporosis, the use of salmon calcitonin nasal spray, 200 IU/d (but not 100 IU/d or 400 IU/d), significantly decreased 5-year vertebral fracture risk by 33% relative to placebo ($P=.03$) (Table 2).[84] Vertebral fracture risk was not reduced after 1 year of therapy with calcitonin. Insufficient patient numbers (n=305-315 in each treatment group for 5 years) precluded meaningful analysis of nonvertebral and hip fracture risk.

Raloxifene. Three years' therapy with raloxifene, 60 mg/d, reduced new vertebral fracture risk by 30% relative to placebo in 7705 postmenopausal women with osteoporosis ($P<.001$) (Table 2).[85] This benefit was sustained during the fourth year.[107] A post hoc analysis reported that use of raloxifene hydrochloride, 60 mg/d, reduced the risk of new clinical vertebral fractures in the first year in the total population (relative risk, 0.32) and in women with prevalent vertebral fracture (relative risk, 0.34). The 3-year risk of hip and overall nonvertebral fractures was not significantly reduced with raloxifene therapy.

CONCLUSIONS

Osteoporosis is often recognized in the clinical setting by the occurrence of a low-trauma fracture, an event that usually results in morbidity, has a negative impact on quality of life, and increases mortality rates. Physiologic and anatomic patterns suggest that younger bone and older bone have several differences that make bone in older patients more susceptible to fractures, including cumulative cortical bone loss, thinning, and increased porosity in the hip and other nonvertebral areas, plus areas of bone weakened from microdamage from repetitive loading. These are some of the factors that lead to diminished bone quality and increased fracture risk.

Antiresorptive agents such as raloxifene and nasal calcitonin that suppress bone turnover and yield modest increases in BMD reduce vertebral fracture risk almost as much as, but not as rapidly as, more powerful antiresorptive agents such as the bisphosphonates risedronate and alendronate.[76,77,81,84,85,98] Nasal calcitonin and raloxifene therapies have not demonstrated nonvertebral or hip fracture risk reduction in clinical trials, suggesting that prevention of nonspine fractures requires larger reductions in bone turnover and larger increases in bone mass than can be achieved by using these agents. Reduction in the risk of nonvertebral and hip fractures can be achieved by treatment with risedronate or alendronate.[46,74,76,77,79,80]

Bisphosphonates have a long track record of safety and efficacy in preventing vertebral and nonvertebral fractures in postmenopausal women with osteoporosis. Whereas nasal calcitonin, HRT, and raloxifene seem to protect against fracture with current use only, bisphosphonates continue to reduce bone turnover and maintain bone mass after discontinuation of use.[108-112] When 35 and 70 mg are taken once a week, risedronate sodium and alendronate sodium, respectively, each produce equivalent improvements in BMD and bone turnover markers compared with daily administration.[113,114]

Although the exact physiologic mechanisms involved in fracture reduction are not fully understood, the bisphosphonates risedronate and alendronate provide the most potent clinical benefit of the available antiresorptive drugs in terms of fracture risk reduction in postmenopausal women with osteoporosis, including elderly patients. Published prospective trial results and current concepts about aging bone, therefore, suggest that patients with low BMD at the hip and older patients with osteoporosis or osteopenia particularly with risk factors such as an existing fracture, should be considered for bisphosphonate therapy with risedronate or alendronate.

Accepted for publication December 3, 2002.

I thank Rick Davis, MS, RPh, for his editorial and research contributions; David Dempster, PhD, Department of Clinical Pathology, Columbia University, and Regional Bone Center at Helen Hayes Hospital, West Haverstraw, NY, for stimulating my interest in bone microarchitecture; and Darrell Fiske, MD, Radiant Research and Rheumatology Associates, Stuart, Fla, and John Houri, MD, Rheumatology Associates, Stuart, for their many contributions to our osteoporosis research programs and for their comments and support.

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