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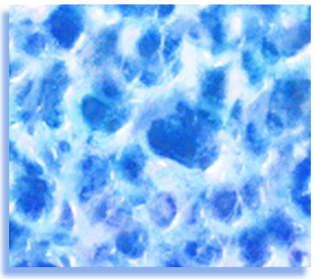
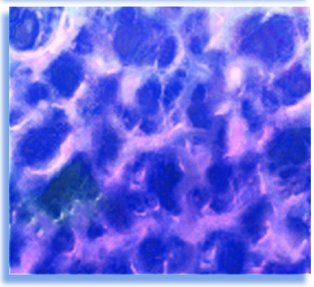
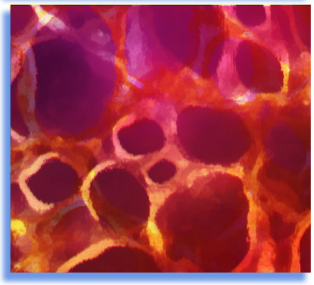
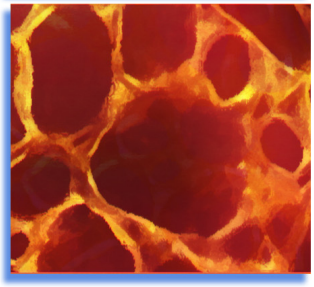
The State of the Art in the Management of Osteoporosis

Based in Part on the Proceedings of a Scientific Roundtable Held July 2003 in Washington, DC









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Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) by the College of Physicians & Surgeons of Columbia University. The College of Physicians & Surgeons of Columbia University is accredited by the ACCME to provide continuing medical education for physicians.

The College of Physicians & Surgeons designates this educational activity for a maximum of 2 Category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Statement of Need

Osteoporosis is a silent disease, progressing insidiously, often without symptoms, until a skeletal deformity or fracture occurs. The financial and personal costs are enormous, and they continue to grow as the U.S. population ages. One of the challenges that primary care practitioners face in detecting osteoporosis before complications occur is the limited office time they have for identifying patients and their risk factors. With recent advances in the treatment of osteoporosis, primary care physicians also need to keep up with the advantages and disadvantages of therapeutic options. These facts underscore the need for comprehensive contemporary educational activities for healthcare professionals in the diagnosis and management of osteoporosis. This mandate is supported by the opinions of many leading experts in metabolic bone diseases, a review of the current literature, and the results of surveys conducted at prior symposia.

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Expiration Date: June 2005

Educational Objectives

Upon completion of this CME program, participants will be able to:

- Describe the impact of osteoporosis on morbidity, mortality, economics, and patient quality of life
- Review the pathophysiology of osteoporosis and the role that bone microarchitecture plays in bone strength
- Discuss the diagnostic challenges of osteoporosis, including diagnostic testing and the role of bone markers and bone mineral density
- Identify the strategies and benefits of therapeutic management with nonpharmacologic, pharmacologic, and evolving therapies
- Discuss the unique challenges and strategies of treating patients with concomitant medical conditions
- Convey practical strategies for treating patients in a primary care/managed care setting

Target Audience

Primary care clinicians, obstetricians/gynecologists, endocrinologists, rheumatologists, orthopedic surgeons, and allied healthcare professionals who treat patients at risk for/with osteoporosis and/or who treat concomitant conditions that are associated with osteoporosis.

Educational Method

The State of the Art in the Management of Osteoporosis as published in this ***CLINICIAN®*** is based in part on the proceedings of a scientific roundtable held July 2003 in Washington, DC.

FACULTY DISCLOSURE INFORMATION

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The State of the Art in the Management of Osteoporosis

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Dear Colleague:

I'm pleased to welcome you to this important educational program, *The State of the Art in the Management of Osteoporosis*.

As we've learned over the past decade, osteoporosis can be an enormous threat to quality of life and ability to function. Also, it is not just a problem for postmenopausal women; it can affect younger women and men as well. People with osteoporotic fractures—or even just the fear of them—can end up dependent, isolated, frustrated, and unable to live the rest of their lives to the fullest. As the "baby boom" generation ages, there will be more and more people affected by conditions like osteoporosis and a greater burden on these individuals and society if we don't gain control of those conditions.

During the past couple of decades, we've made a great deal of progress in our understanding of the need to prevent, detect, and treat osteoporosis as early as possible. It's also become apparent how important it is to make sure that clinicians who treat patients with or at risk for osteoporosis recognize this need and have command of the information they need to achieve the goal of minimizing the impact of osteoporosis.

We at the Office on Women's Health are proud to present this program, which we believe will contribute substantially to clinicians' awareness of and ability to manage osteoporosis and its sequelae.

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Osteoporosis: Epidemiology and Impact

Osteoporosis is a common, progressive, skeletal disease characterized by low bone mass and microarchitectural deterioration. It is estimated that more than 7.8 million American women have osteoporosis and 21.8 million have low bone density at the hip. In the United States, osteoporosis is common among postmenopausal white women (20% have osteoporosis, and 52% have low bone density at the hip).[1] Osteoporosis also occurs in men; the prevalence of osteoporosis among men is approximately 4% to 6%, and that of osteopenia among men is 33% to 47%.[2] Although persons of any ethnicity can develop osteoporosis, data from the Third National Health and Nutrition Examination Survey (NHANES III) indicate that the risk is highest among non-Hispanic white women and lowest among non-Hispanic black women.[3] Data from the National Osteoporosis Risk Assessment (NORA) demonstrate a high osteoporosis risk for Asian women.[4] Data from NORA also demonstrate a high risk for osteoporosis and fractures in Hispanic women. Many diseases, such as type 1 diabetes, hypogonadism, hyperthyroidism, emphysema, and some gastrointestinal disorders, can increase the risk of osteoporosis and fractures. Further, individuals being treated with certain drugs, including glucocorticoids, anticonvulsants, and chemotherapeutics, are at higher risk as well.

Fractures are the most debilitating and costly consequence of osteoporosis. Approximately 1.5 million Americans experience osteoporotic fractures each year,[5] most commonly at the spine, hip, or wrist.[6] Osteoporotic fractures are associated with significant morbidity and mortality; the risk of dying following a clinical fracture is reportedly 2-fold higher than for persons without fractures.[7] Vertebral compression fractures are the most common type of osteoporotic fracture, with new vertebral fractures diagnosed in 700,000 Americans each year.[5] Vertebral fractures can be associated with significant pain (2- to 2.4-fold increased risk of back pain for women with vertebral fractures versus those with none) and disability: 47% to 53% of women with symptomatic vertebral fractures require bedrest, and 97% report limited activity.[8,9] Vertebral fractures were responsible for an estimated 70,000 U.S. hospital admissions in 1997 and are associated with significant increases in mortality.[10,11] The increase in mortality risk for women after spinal fracture is estimated at 23% over approximately 8 years.[12]

Nonvertebral fractures are also common. The annual incidence of hip fractures in the United States is approximately 300,000, and that of wrist fractures approximates 250,000.[5,6] In 1990, there were more than 1.6 million hip fractures among persons 35 years of age or older worldwide. This number is expected to increase to more than 3.9 million in 2025 and to 6.2 million in 2050.[13] The mortality risk associated with hip fractures is more immediate than that observed with vertebral fractures: Overall, elderly white women with hip, pelvis, or rib fractures have a 2- to 3-fold increase in mortality,[14] and the estimated increased 1-year mortality risk after hip fracture is approximately 20% to 24%.[15,16] In one large study, mortality rates after hip fracture were 17.2%/1000 person-months among white women and even higher among black women (22.9%), black men (33.5%), and white men (33.7%).[17] Hip fracture is also frequently associated with a need for admission to an assisted-care facility, at least temporarily; up to 25% of patients with hip fractures may require long-term care in nursing homes.[1] Approximately 25% of elderly persons who suffer from hip fractures are estimated to experience impairment in carrying out activities of daily living,[18] and only 40% of those who sustain fractures return to their prefracture level of independence.[1]

Osteoporotic fractures are associated with high healthcare resource utilization (4.1 million hospital days, 44.6 million nursing home days, and 3.4 million outpatient visits in 1995)[16] and the economic burden of osteoporotic fractures in the United States is approximately $20 billion annually.[19] Vertebral fractures are associated with costs of $8,000 to $10,000 per hospital admission.[10] Overall, medical expenditures for persons with fractures have been estimated to be 6 times higher than those for persons with no fractures.[20] It would seem obvious from these observations that the ultimate goal of treatment is to prevent osteoporotic fractures. Therapies that achieve this goal should not only improve the lives of millions of Americans but also reduce the associated burdens on the healthcare system and on society in general.

A multidisciplinary scientific roundtable was convened in Washington, DC, on July 28 and 29, 2003, to discuss osteoporosis, including current clinical diagnostic and management challenges. This monograph presents a synopsis of the presentations and discussions at that meeting as well as data from the current literature.

Osteoporosis Defined

Osteoporosis is a skeletal disease in which bone strength is compromised, resulting in increased risk for fracture.[21] A major proportion of bone strength is determined by bone mineral density (BMD), which explains why BMD measurements are effective tools for identifying patients at high risk for fractures; however, bone strength and fracture risk are also affected by other qualities of bone such as bone turnover, size and geometry, microarchitecture, mineralization, damage accumulation, and matrix quality.[21-23] (Table 1 provides definitions of key terms.)

Table 1

Osteoporosis Terms

Bone strength = bone density + bone quality
Bone density = grams of mineral per volume
Bone mineral density = grams of mineral per area
Bone quality = factors that influence bone strength, including microarchitecture, turnover, damage accumulation, and mineralization
Microarchitecture = general term that reflects trabecular thickness, number of trabeculae, spacing, etc

Throughout life, bone undergoes a process of remodeling in which packets of old bone are removed and replaced by new bone. A slow rate of remodeling probably serves to repair microdamage and keep bone healthy, but high bone turnover can compromise bone strength through a number of different mechanisms. In adults, bone remodels inefficiently so that less bone is formed than has resorbed when each remodeling unit had completed its cycle. If the number or activity of bone remodeling units is increased, a condition known as “high bone turnover” (accelerated bone loss and thinning of bone cortices) can ensue. As trabeculae are thinned and perforated, there is a preferential loss of the horizontal trabeculae that support the load-bearing vertical trabeculae.[24] This loss is associated with reduced buckling load, translating into greater risk for fracture with less force or trauma (Figures 1A & B). In addition, the

Figure 1A

Microarchitectural Changes in Osteoporosis—Loss of Horizontal Trabeculae

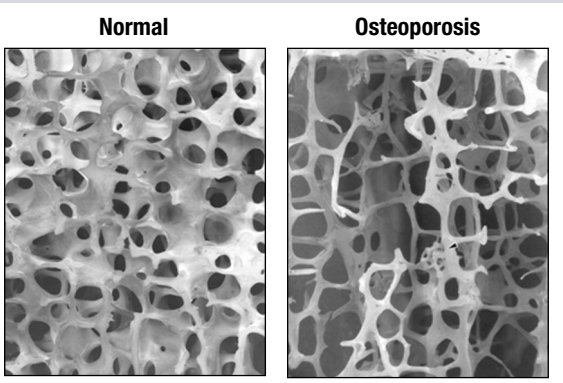
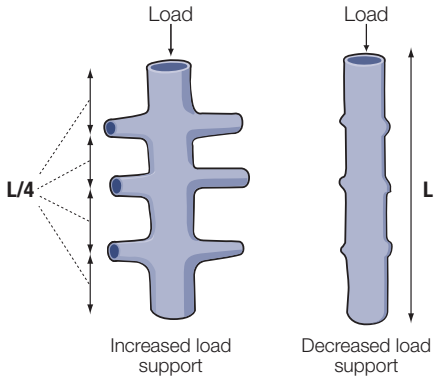


Figure 1B

Loss of Horizontal Trabeculae Effect on Bone Strength[208]



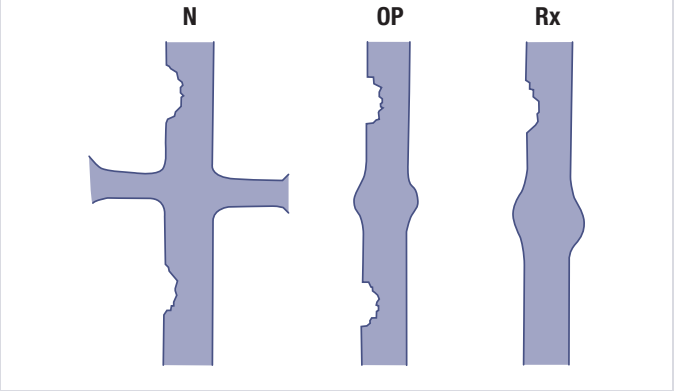
Load support is related to the length and number of horizontal struts. The shorter the length/the more horizontal struts, the more load can be borne. In osteoporosis, reduction in the diameter of the vertical trabeculae and loss of transverse ties result in increased unsupported trabecular length, leading to loss of strength.

actual sites of bone remodeling—the resorption cavities—are points of increased vulnerability to stress, defined in engineering terms as *stress risers* (Figure 2). A stress riser may be a notch, a crack, or any other irregularity in the surface that creates a starting point for generation or propagation of a fracture. These stress risers further weaken already vulnerable trabeculae, leading to even greater loss of strength and heightened fracture risk.[25,26]

Increased bone turnover is also associated with reduced mineralization. This likely results from the shortened duration of the secondary mineralization period that is associated with increased bone remodeling.[25] Although the optimal mineralization density is not known, it is likely that reduced mineralization contributes to reductions in bone strength and increases in fracture risk. Conversely, in states of reduced remodeling, mineralization can be increased, which helps explain the therapeutic efficacy of the antiresorptive therapies for osteoporosis. Increased mineralization is beneficial up to a point. Excessive mineralization, as seen in the pathological condition of osteopetrosis, can lead to more brittle material and can actually be detrimental to bone strength.

Figure 2

Resorption Cavities Are Weak Points



N: In a normal individual, a vertical trabecula is supported by horizontal trabeculae; 2 resorption cavities, each representing a focal weakness, are shown. **OP:** In a patient with osteoporosis, the supporting trabeculae have been lost and the resorption cavity depth is a higher proportion of the reduced trabecular thickness; thus, the unsupported length of the vertebral trabecula is increased, and each remodeling site has greater potential weakness. **Rx:** After treatment that reduces resorption depth and the frequency of remodeling activation, the unsupported length remains the same, but resorption cavities are fewer and shallower so that the liability to buckle is reduced.

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Bone size and shape also contribute to bone strength. These properties of bone are primarily determined by genetic, hormonal, and environmental factors during growth, but important changes in the size and distribution of bone also occur in adults. In a longitudinal study of postmenopausal women, Ahlborg et al showed that along with an annual 1.9% loss of BMD there was an increase in medullary and periosteal diameter, an effect that helps offset the loss in bone strength due to reduced bone density.[27] It is clear that compromised bone strength is due to a number of properties of bone, each of which may be more or less important depending on the etiology of the osteoporotic state.[28]

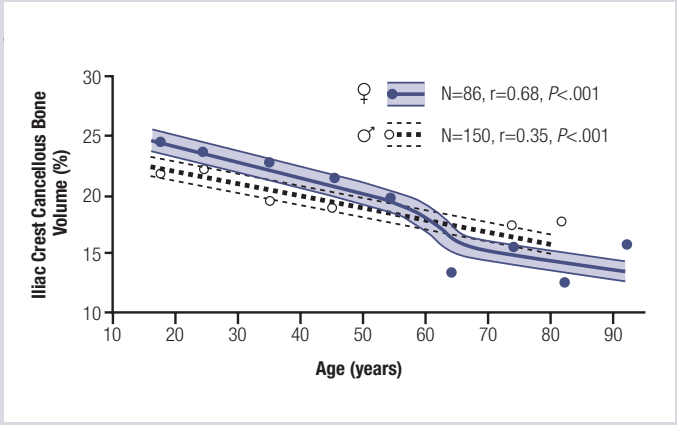
Primary Osteoporosis

Primary osteoporosis refers to bone loss associated with aging and menopausal estrogen deficiency.[29] Postmenopausal osteoporosis is the most common form of primary osteoporosis. When estrogen levels fall after menopause, bone turnover accelerates because of the loss of the regulatory effect of estrogen on bone resorption. Increased bone resorption at menopause is usually associated with accelerated bone loss (Figure 3, page 3), which is most rapid in the early postmenopausal years.[30-32]

Primary osteoporosis also occurs in men, but it usually develops somewhat later in life.[21] As in women, bone loss in men appears to be related both to age-related changes in bone turnover and to changes in levels of sex hormones. This

Figure 3

Bone Loss Accelerates After Menopause[209]



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change is more gradual in men, however, because men generally do not experience an abrupt period of sex hormone withdrawal as do postmenopausal women.[31] It is clear that the loss of bone density in men as a function of age is a result of declining androgen and estrogen levels. These 2 sex hormone classes are closely related, because in men androgens are the source of estrogens. Recent data suggest that declining estrogen levels may be more important in the process of age-related bone loss in men than are declining testosterone levels.[33]

Secondary Osteoporosis

When osteoporosis is caused, at least in part, by other diseases or medications, the term *secondary osteoporosis* is used.[21] A study using a Canadian database found a high prevalence of secondary osteoporosis among osteoporotic patients with or without a prior fragility fracture. Among patients with osteoporosis, secondary causes were identified in more than 41% of women and 51% of men.[34] The most important secondary causes of osteoporosis include endocrine/metabolic disorders, gastrointestinal/nutritional conditions, and drugs.[35] Table 2 presents these and other, less common causes of secondary osteoporosis. It is not uncommon for patients with these conditions to have more than one secondary cause of osteoporosis. For example, glucocorticoids, which are known to cause bone loss, are commonly prescribed for patients already at increased risk for osteoporosis because of rheumatoid arthritis,[36] chronic respiratory illnesses,[37] or organ transplantation.[35]

Glucocorticoid-Induced Osteoporosis

Glucocorticoid use has multiple adverse effects on skeletal health and bone strength that predispose patients to osteoporotic fractures. They reduce bone formation by inhibiting the number, lifespan, and function of osteoblasts and initially enhance bone resorption.[37-40] Glucocorticoid-induced reductions in sex-hormone production and in intestinal calcium and phosphate absorption further contribute to bone loss.[38-40] These effects often lead to rapid bone loss when glucocorticoids are initiated, particularly when they are given in high doses for more than 3 to 6 months.[38]

Glucocorticoid-induced changes in bone strength are related to dose and duration of therapy. A retrospective analysis of 244,235 glucocorticoid users and 244,235 age- and sex-matched controls demonstrated increased relative risk (RR) for vertebral fractures (2.60 [95% confidence interval (CI) 2.31-2.92]), nonvertebral fractures (1.33 [95% CI 1.29-1.38]), and hip fractures (1.61 [95% CI 1.47-1.76]) among long-term glucocorticoid users.[41] Importantly, the risk of fracture rises rapidly within 3 months of initiating glucocorticoid therapy. Reid and Heap reported significant reductions in vertebral BMD with 12-month, high-dose (average prednisone equivalent of 21 mg/day) glucocorticoid therapy versus long-term low-dose (8 mg/day) therapy (P=.009).[42] It is important to note that glucocorticoid users had sustained more fractures at every BMD level than did nonusers.[43]

Osteoporosis in Diabetes

Type 1 diabetes is a risk factor for fractures, with a reported RR for hip fracture among women ranging from 5.7 to 12.25.[44,45] Individuals with type 1 diabetes tend to have reduced BMD.[46-48]

Table 2

Common Causes of Secondary Osteoporosis

Endocrine/Metabolic	Nutritional	Drugs	Disorders of Collagen Metabolism	Other
Hypogonadism	Malabsorption syndromes	Glucocorticoids	Osteogenesis imperfecta	Rheumatoid arthritis
Hyperadrenocorticism	Malnutrition	Excessive thyroid hormone	Homocystinuria	Myeloma and some cancers
Thyrotoxicosis	Chronic liver disease	Heparin	Ehlers-Danlos syndrome	Immobilization
Anorexia nervosa	Gastric operations	GNRH* antagonists	Marfan syndrome	Renal tubular acidosis
Hyperprolactinemia	Vitamin D deficiency	Phenytoin		Hypercalciuria
Porphyria	Calcium deficiency	Phenobarbital		COPD†
Hypophosphatasia (adults)	Alcoholism	Vitamin D toxicity		Organ transplantation
Diabetes (type 1)				Mastocytosis
Pregnancy				Thalassemia
Hyperparathyroidism				
Acromegaly				

*GNRH = gonadotropin-releasing hormone; †COPD = chronic obstructive pulmonary disease.

Adapted with permission from the American College of Endocrinology & The American Association of Clinical Endocrinologists 2001 Medical Guidelines for Clinical Practice for the Prevention and Management of Postmenopausal Osteoporosis. Hodgson SF, Watts NB (Chairman). American Association of Clinical Endocrinologists. *Endocrine Practice*. 2001;7:293-312.

Reductions in bone mass associated with type 1 diabetes appear to be influenced by age and disease duration.[46] Factors contributing to bone loss in type 1 diabetes include decreased osteoblast function, altered calcium homeostasis, and collagen abnormalities.[49] Hypogonadism has been observed in men with type 1 diabetes,[50] and this may contribute to changes in bone strength that occur in these individuals.

The risk for osteoporotic fracture is less certain in type 2 diabetes, but some studies have noted an increase in RR of approximately 1.7.[44] Individuals with type 2 diabetes often have normal or increased BMD but also are at increased risk for fractures, particularly of the lower extremities.[51,52] The relationship between type 2 diabetes and fractures is not completely understood but could be related to the many complications of diabetes, such as retinopathy and neuropathy, which put these patients at increased risk for falls and consequent fractures.[53]

Identifying Persons at Risk for Fracture

Osteoporosis remains largely underdiagnosed and undertreated. In 2001, only 12% (1.8 million) of the 15 million women aged 65 years or older who were estimated to have osteoporosis or osteopenia had Medicare-reimbursed BMD tests.[54] Most women do not perceive osteoporosis as a primary health concern,[55] and they are therefore unlikely to seek testing without prompting from their clinicians. Unfortunately, very few women receive osteoporosis advice/counseling at routine office visits.[56] Furthermore, a very low proportion of persons who sustain fractures are subsequently recognized to have osteoporosis and then treated. Analysis of data from 2804 individuals with fractures who were members of a single health maintenance organization demonstrated that only 4.6% initiated pharmacologic treatment after their fractures.[57] This observation is further supported by other studies.[58,59]

Clinical Risk Assessment

Knowledge of accepted risk factors that predispose individuals to osteoporosis may improve diagnosis rates. Table 3 presents a list of risk factors for osteoporosis and related fractures summarized by the National Osteoporosis Foundation (NOF).

Two of the most important independent predictors of future fracture risk are age and history of prior fragility fractures. At any given bone density, the older the patient, the greater the risk of fracture. This may be due to age-related skeletal factors that are not being captured by bone mass measurement per se and/or because nonskeletal factors become important over time, such as the risk of falling.[60]

A history of fracture is one of the most important indicators of future fracture risk. Prior wrist, vertebral, or hip fractures significantly increase the risk of having other osteoporotic fractures in the same region (eg, another wrist, vertebral, or hip) or at other sites (eg, hip or wrist fracture following vertebral fracture).[61] Patients experiencing vertebral fracture are at particularly high risk for additional spine fractures, with 12% to 24% experiencing new vertebral compression fractures within the next year.[62]

Other frequently identified independent risk factors for hip fracture include measures of poor health/frailty, a maternal history of hip fracture, factors associated with an increased risk of falls, inability to rise from a chair without using one's arms, and increased biochemical markers of bone turnover.[63-65]

Table 3

Risk Factors for Osteoporosis and Related Fractures

Major	Additional
• Personal history of fracture in adulthood	• Estrogen deficiency <45 years of age
• History of fragility fracture in first-degree relative	• Dementia/cognitive impairment
• Current cigarette smoking	• Excessive alcohol use
• Low body weight (<127 lb)	• Lifelong low calcium intake
• >3 months of oral corticosteroid use	• Recent falls
	• Inadequate physical activity
	• Poor health/frailty
	• Impaired vision

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Bone Mineral Density Measurement

The predictive value of BMD is high, especially compared with that of tests for other silent diseases, such as cholesterol for coronary artery disease.[66] The World Health Organization (WHO) has developed criteria, also adopted by the NOF, that use BMD for assessment of bone status (Table 4). These criteria are based on bone mass measurements at the hip, wrist, and spine in postmenopausal white women.[1,67]

Table 4

WHO Criteria for Diagnosis of Bone Status[1,60]

T-Score	Classification
−1 or higher	Normal
−1 to −2.5	Osteopenia
−2.5 or lower	Osteoporosis
−2.5 or lower + fracture	Severe osteoporosis

Bone mineral density measurement should be performed on all patients at risk for osteoporosis and fracture. Guidelines for identifying these patients have been developed by a number of organizations, including the U.S. Preventive Services Task Force, the International Society for Clinical Densitometry, the American Association of Clinical Endocrinologists, and the NOF. All current national guidelines for BMD testing agree on the need for routine screening of women aged 65 and older and the evaluation and treatment of postmenopausal women with histories of fragility fractures.[1,68,69] The generally accepted age at which men should start being screened is 70 years,[70] but no national guidelines for screening men have yet been formulated. The NOF advocates screening postmenopausal women less than 65 years of age who have one or more risk factors for osteoporosis or fractures, such as early menopause,

a previous fracture, a family history of osteoporosis, or low body weight (Table 5).[1]

The Medicare Bone Mass Measurement Act defines the conditions under which Medicare will reimburse for bone densitometry. Medicare recently (in the Medicare Osteoporosis Measurement Act of 2003) proposed expanding its coverage of bone densitometry from estrogen-deficient women only to all individuals, including men, "at clinical risk for osteoporosis."[71]

Use for Diagnosis and Assessment of Fracture Risk

BMD measurement remains the best clinically available method of estimating bone strength and risk of fracture. It is the gold standard for diagnosis and provides important information about fracture risk.[66,72] Furthermore, knowing one's BMD can have desirable effects on a patient's bone-health behavior. Marci and colleagues demonstrated that knowledge of one's bone density influences decisions about pharmacologic treatment and about lifestyle modifications such as exercise, diet, and calcium/vitamin D supplementation.[73]

For diagnostic purposes, results of BMD testing should be reported as T-scores, a measure (in standard deviations [SDs]) of how different an individual's BMD is from what would be expected for a person of the same sex at peak bone mass (25 to 30 years old). A T-score of –2.0 in a woman, for example, means that her BMD is 2 SDs below the average peak bone mass for a young woman.[1] The current WHO definition of osteoporosis is a T-score of –2.5 or lower. Although this definition specifically refers to postmenopausal white women,[1] it has been adapted widely for other racial and ethnic groups and for men; however, it should not be applied to children and probably should not be used for premenopausal women or men less than 65 years old unless they have other fracture risk factors or known causes of secondary osteoporosis.[70]

Bone densitometry reports often provide Z-scores, which indicate the number of SDs below or above the average bone mass in an age- and sex-matched population. The Z-score is not used for the diagnosis of osteoporosis but can be helpful in raising the possibility of secondary causes of osteoporosis by identifying patients with bone mass that is unusually low.[74]

Although BMD can be measured at either the central or the peripheral skeleton, only measurements from a central site (hip or spine) should be used to diagnose bone status. T-scores are often higher when measured at peripheral sites (heel, finger) than at central sites (lumbar spine, hip), and the prevalence of osteoporosis or osteopenia can thus be underestimated if peripheral measurements are used. Furthermore, variability across peripheral measurement devices is high.[75]

Similar to central measurements of BMD, peripheral measurements can be used to predict fracture risk. Results of a meta-analysis comprising 11 studies and approximately 90,000 person-years of observation demonstrated that most measurement sites had similar ability to predict global fracture risk.[66] Results from the NORA trial confirm the predictive value of peripheral measurements for fracture risk.[72] In general, however, the specific site measured gives the best information about fracture risk at that site, which accounts, in part, for the importance of hip and spine measurements in clinical practice.

Table 5

NOF Guidelines for BMD Testing and Treatment Initiation

Patients should have BMD testing who are

- Women aged ≥65 years, regardless of risk factors
- Younger postmenopausal women with ≥1 risk factors (other than being white, postmenopausal, and female)
- Postmenopausal women with fractures

Therapy should be initiated for women who have

- T-scores below –2.0 by central hip DXA and no additional risk factors
- T-scores below –1.5 by central hip DXA with ≥1 additional risk factors
- Prior vertebral or hip fractures

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Use for Evaluating Treatment Effects

Whereas BMD measurement has proven to be the most useful clinical tool for diagnosis, its ability to account for fracture risk reduction after effective treatment is not as secure. In general, increases in bone density after treatment are associated with reductions in fracture incidence across a wide spectrum of antiresorptive therapies. Meta-analyses of 12 clinical trials of antiresorptive therapy, however, have confirmed that changes in BMD did not account completely for fracture-risk reduction.[76,77] It is clear that antiresorptive agents are acting in ways to reduce fracture incidence that are not explained completely by changes in bone density. The ability of the antiresorptives to reduce bone resorption, reflected by decreases in biochemical markers of bone turnover, for example,[78] may well be another key parameter of efficacy. Maintaining bone microarchitecture is undoubtedly also very important. In the future, newer technologies to quantitate these other properties of bone may permit more complete assessment of treatment effects.

When BMD is used for monitoring, serial measurements must be taken. To be considered significant, the difference in BMD over time must exceed the least significant change as determined by an in vivo precision study and established confidence limits. For 95% certainty that the change measured is a significant one rather than simply a result of technical variability, the measured change in BMD has to be greater than the precision value x 2.77. For example, if the precision of the instrument at a given site is 1%, the least significant change is 1% x 2.77, or 2.77%. A serial change in BMD less than 2.77% would not be significantly different from the previous measurement. If the serial change in BMD is greater than 2.77%, it would be considered to represent a true change in the patient's densitometric status.[70]

Role of Biochemical Bone Markers

Biochemical bone markers can provide useful information about bone turnover and aid clinical decision making regarding the initiation and maintenance of therapy.[79-81] Proposed uses include identifying patients with high turnover who are at increased risk for fractures and monitoring the response to therapy, as well as aiding in patient medication adherence.

There are 2 types of biochemical bone markers—markers of bone resorption and markers of bone formation (Table 6). The bone-resorption markers that are in clinical use are pyridinoline, deoxypyridinoline, N-telopeptide of type 1 collagen (NTX), and C-telopeptide of type 1 collagen (CTX). The currently available bone formation markers are bone-specific alkaline phosphatase and osteocalcin.[82]

The clinical use of biochemical bone markers is complicated by multiple sources of variability related both to biologic factors and to the assay itself. Results are influenced by patient age, sex, ethnicity, level of physical activity, drug therapy, and medical conditions such as pregnancy/lactation, kidney or liver disease,

and acute fractures.[83] Differences between assays can arise from variations in specimen processing, assay precision and accuracy, standardization, cross-reaction with other organ markers, nongaussian distribution, and interlaboratory variation. In addition, the bone markers display a circadian variability that can result in widely discrepant measurements in the same individual depending on when the sample is obtained.[83] For these assays to be useful clinically, variables that can be controlled, such as specimen-collection criteria (eg, second-morning urine collection or total 24-hour collection), must be standardized. In addition, one must know the laboratory's precision to determine if serial changes in patient results are statistically significant. Similar to the discussion for defining significant change in densitometry, the change in bone markers must exceed the least significant change. Since the precision of bone marker methodology does not come close to matching the precision of densitometry, the least significant change for most of the bone markers is 30% to 40% or even greater.[84]

A separate issue regarding biochemical bone markers is that of reimbursement. Medicare currently reimburses for the measurement of collagen crosslinks in postmenopausal women on FDA-approved osteoporosis therapy (at baseline, 3 months after initiation of new therapy, and every 12 months thereafter).[85] At this time, biochemical bone markers should be considered to complement, but not replace BMD measurement. It is recommended that clinicians become familiar with one bone-formation marker and one bone-resorption marker, as well as with the reference laboratory to improve the clinical utility of these measurements.

Bone markers may be useful in improving patient adherence to osteoporosis treatment. The IMPACT study was designed to evaluate the effect of clinician counseling using bone-marker response on adherence to therapy among women taking risedronate. It was found that those who received reinforcement messages on the basis of favorable bone-marker measurements at routine follow-up visits had higher medication adherence rates (P=.02), whereas those whose bone-marker measurements were nonresponsive had lower adherence rates (P=.005).[86]

Treatment Thresholds for Patients With Low BMD

Postmenopausal women who have experienced fragility fractures and those with osteoporosis (T-score equal to or less than –2.5) are at high risk for future fractures and are generally agreed to be candidates for therapy.[67] Taking a somewhat proactive position, the NOF advocates initiation of treatment to reduce fracture risk at a T-score of –2.0 or below by central DXA or at a T-score of –1.5 in postmenopausal women with other risk factors for fracture.[1]

Because osteopenia is considerably more prevalent than is osteoporosis,[3] the majority of fractures occur in women with osteopenia.[87,88] Thus, it remains a challenge to determine when to initiate preventive therapy for these individuals.[89] Another issue relates to uncertainty about what thresholds to use for patients whose BMD measurements have been made with peripheral instruments. Evidence from the NORA study involving more than 200,000 postmenopausal women has demonstrated that using a peripheral-site T-score cutpoint of –2.5 for treatment intervention would miss 82% of women in NORA who actually experienced fractures during the year following bone density measurement. The current NOF intervention T-score thresholds of –2.0 or less or –1.5 or less plus at least one additional risk factor would have led to treating about one quarter of the population in NORA and would have captured about one half of those women who actually fractured. Using a threshold of –1.0 or less at distal limb sites was associated with increased sensitivity but still missed up to 30% of patients who experienced fractures.[87] There are important practical implications of these findings. For fracture risk to be reduced maximally in the population, treatment thresholds would have to include individuals who may even be close to the normal range. Such extrapolations become impractical from many points of view, particularly with regard to cost-effectiveness of treatment.

It is clear from the data that fracture risk cannot be determined absolutely using any one measure alone. To identify which patients with osteopenia should be treated, clinicians must integrate information from a variety of sources to evaluate risk for each individual. In addition to BMD measurement, clinical fracture risk assessment should incorporate information easily gathered during a routine patient visit, such as age, personal and family fracture history, risk factors for falling, and the presence of medical conditions known to affect bone health.

The Fracture Index, one potential tool to improve the identification of older high-risk individuals, is a simple, 7-question formula that synthesizes clinical information and, if available, BMD to assess fracture risk.[90] Osteoporosis Education offers a calculator (http://www.osteoed.org/tools/tools_fracture.html) that clinicians can download to their computers or PDAs. Although the Fracture Index can be a useful tool for predicting future fracture risk in postmenopausal women and identifying those for whom further assessment and/or preventive measures may be useful, it has not been validated in other populations (eg, younger women, older institutionalized persons, men, or persons with secondary osteoporosis). Therefore, it cannot be relied on for these populations.[90]

Nonpharmacologic Factors

Nonpharmacologic interventions are important cornerstones of osteoporosis prevention. They include dietary modifications,

Table 6

Biochemical Bone Markers

Markers of bone resorption	Osteoclast-derived enzymes • Acid phosphatase • Tartrate-resistant acid phosphatase Bone matrix degradation products • Collagen cross-links (pyridinoline, deoxypyridinoline, N-telopeptide, C-telopeptide) • Hydroxyproline
Markers of bone formation	Osteoblast-derived enzymes • Total alkaline phosphatase • Bone-specific alkaline phosphatase Osteoblast products • Osteocalcin—this comes from the osteoblast • Type 1 collagen propeptides

Adapted from Khosla S, Kleerekoper M. 2003. Biochemical Markers of Bone Turnover. In: Favus M (ed.) *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 5th ed. American Society for Bone and Mineral Research, Washington DC, USA, pp.166-171 with permission of the American Society for Bone and Mineral Research.

exercise programs, fall prevention strategies, and education. Table 7 describes key nonpharmacologic interventions.

Table 7

Nonpharmacologic Approaches to Osteoporosis Prevention[204,205]

Treatment	Effects on BMD	Effects on Fracture Risk
Exercise	Preserved BMD in short-term studies	No direct evidence of risk reduction
Fall prevention	N/A	Hip protectors reduce fractures; Tai Chi may prevent falls
Supplements		
Calcium	Preserves BMD, especially in older women	Likely reduces risk by ≥10%
Vitamin D	With calcium, provides modest protection	With calcium, reduces risk >15% for vitamin D-deficient patients

Calcium and Vitamin D

Both calcium and vitamin D supplementation have been associated with reduced bone loss and decreased risk for fractures in a number of prospective studies.[91-95] Supplementation must be continued long term for efficacy to be maintained.[96] Deficiency in these nutrients is widespread. The majority of Americans (more than 90% of women and more than 50% of men) do not get enough calcium in their diets to meet the intake recommendations put forth by the Food and Nutrition Board of the National Academy of Sciences.[97] Although poor calcium intake is observed at all ages, it appears to be most common among older individuals (less than 1% of women and less than 5% of men 71 years of age or older meet the recommendations).[97]

The prevalence of vitamin D deficiency is also high.[98-102] It leads to poor calcium absorption, secondary hyperparathyroidism, increased bone turnover,[96] increased rates of bone loss, and, if severe, impaired bone mineralization. In addition, vitamin D deficiency causes muscle weakness and increases falls.[103] Vitamin D supplementation can reverse many of these effects and significantly reduce falls and hip fractures.[95,96,99] Although a large study of patients 70 years of age and older (N=2578) failed to demonstrate a decrease in hip fractures using 400 IU/day of vitamin D for 3 years,[101] other studies using approximately 800 IU/day of vitamin D have demonstrated fracture protection.[93,94] These findings suggest that doses higher than the current RDA for vitamin D may be necessary for antifracture efficacy.

The NOF currently recommends that all individuals maintain adequate calcium and vitamin D intake as set forth by the National Academy of Sciences (Table 8).[1,104] The NOF further recommends that a higher intake of vitamin D be maintained by all individuals at risk for deficiency, not just the elderly (eg, chronically ill, housebound, or institutionalized individuals).

Protein

A relationship between protein intake and BMD has been reported, but a relationship with fractures has not been described. Using data from the NHANES III, Kerstetter and colleagues demonstrated a significant association between protein intake and total femur BMD among non-Hispanic white women aged 50 years and older. Women in the lowest or second lowest quartile of protein intake (0 to 43 g/day or 44 to 58 g/day, respectively) had significantly lower BMD than did those in the highest quartile (more than 75 g/day) (P=.003 and P=.03, respectively). The results remained the same when adjusted for calcium intake.[105] A similar relationship between lower protein intake and increased loss of BMD at the femoral neck, Ward's area, and spine was observed in the Framingham Osteoporosis Study, which included both elderly men and women.[106] Protein supplementation (20 g/day) 5 times weekly for 6 months following hip fracture was associated with a 50% reduction in femoral bone loss versus placebo at 1 year.[107] An interrelationship between the effects of protein, calcium, and vitamin D intake on BMD was demonstrated recently. In an analysis of data from a calcium and vitamin D supplementation study with 342 healthy subjects at least 65 years of age, a 20% higher mean protein intake was associated with increased BMD among patients taking calcium and vitamin D but not among those not taking supplements.[108] Whereas no specific recommendations regarding protein intake can be made based on the limited data available, it would be prudent for clinicians to ensure that their patients eat healthy diets that provide the recommended dietary allowance of protein as put forth by the Institute of Medicine of the National Academy of Sciences (at least 46 g/day and 56 g/day for women and men, respectively).[109] There may be upper limits for desirable protein intake as well. Excess urinary calcium excretion has been observed in association with the large acid loads delivered by very-high-protein diets. Although it is not yet proven, there is concern that these calcium losses may jeopardize bone strength.[110]

Vitamin K

Dietary vitamin K intake may also affect bone health. Vitamin K is required for the formation of osteocalcin, the most abundant noncollagenous protein in bone and a regulator of bone mineralization. Analysis of data from the Framingham Heart Study demonstrated a relationship between higher dietary vitamin K intake and reduced risk of hip fracture (RR 0.35 for highest quartile [median intake 254 µg/day] versus lowest quartile [median intake 56 µg/day]).[111] Prospective vitamin K intervention studies are ongoing. At this time, clinicians should encourage their patients to maintain adequate vitamin K intake. Adequate intake as defined by the Institute of Medicine is 90 µg/day for women and 120 µg/day for men. Dietary sources of vitamin K include leafy green vegetables, cruciferous vegetables (eg, cabbage, broccoli, Brussels sprouts), and plant oils.[109]

Nutritional Supplements

In a recent study designed to investigate the effects of nutritional improvement on bone metabolism in elderly community-dwelling women, women who were given 1 or 2 cartons of a

Table 8

National Academy of Sciences Recommendations for Calcium and Vitamin D Intake[104]

Age (years)	Calcium (mg/d)	Vitamin D (IU/d)
30-50	1000	200
51-70	1200	400
71+	1200	600

nutritional supplement drink per day, in addition to calcium/vitamin D and dietary advice, had a significant reduction (P<.01) in serum CTX, a marker of bone resorption, which led to a small but positive effect on bone formation, indicated by modest increases in osteoprotegerin and bone-specific alkaline phosphatase. The study supports a role for improving nutrition in the elderly population.[112]

Caffeine

Caffeine consumption does not appear to influence bone health in healthy postmenopausal women who maintain adequate intake of calcium and vitamin D, but a longitudinal study showed that even moderate amounts of caffeine (2 to 3 servings of coffee per day) may lead to bone loss in women with low calcium intake (less than 800 mg/day).[113] Additional studies are needed to define the relationship between caffeine and bone health.

Sodium

Because calcium reabsorption is directly proportional to sodium reabsorption in the renal tubule, increases in dietary sodium have been observed to cause increases in urinary calcium excretion, with corresponding increases in biochemical markers of bone turnover.[114,115] A relationship between high sodium intake (more than 1768 mg/day) and lower bone density also has been described. This effect appears to be independent of calcium intake and activity levels.[116] Additional studies are needed to confirm this finding. As with caffeine, it would be considered practical for all women to moderate sodium intake as a precautionary measure until this relationship is fully understood.

Exercise

Small but statistically significant increases in BMD have been observed in postmenopausal women participating in exercise programs, including aerobic exercise and resistance training (heavy weight, low repetitions).[117-120] A recent meta-analysis of 18 randomized, controlled trials concluded that aerobic, weight-bearing, and resistance exercise were all effective in increasing BMD of the spine; walking was observed to benefit BMD of both the spine (weighted mean difference 1.31) and the hip (weighted mean difference 0.92), and aerobic exercise also increased wrist BMD.[121]

Although an increase in bone density may occur, especially at the sites at which the exercise is directed, it is important to note that the benefits of exercise are likely to be due to factors other than changes in BMD. For example, an association between exercise and reduced falls has been reported.[122,123] Improvements in balance, stronger muscles, better muscle tone, and stronger bones all undoubtedly contribute to fracture reduction.

Fall-Prevention Strategies

Falls are responsible for more than 90% of hip fractures.[124] Sideways falls appear to be the most detrimental and were independently associated with hip fracture in one recent study (adjusted odds ratio, 5.7; P=.004).[125] Therefore, fall prevention is important for women with osteoporosis. It is important for patients to optimize their living conditions in this regard by using nonslip tile, rugs with nonskid backing, and night lights and reducing clutter as much as possible.

Hip Protectors

Until recently, hip protectors were thought to reduce hip fractures dramatically in nursing home residents and frail elderly adults; however, a recent analysis of the Cochrane database indicates that the effectiveness of hip protectors may be less certain—and compliance remains low.[126] Fractures often occur at night, when women are likely to have taken off their hip protectors. This may be due to the fact that hip protectors are bulky and uncomfortable to wear while sleeping.[127]

Importance of Diet and Exercise for Bone Health During Adolescence

Diet and exercise are important long before most people begin thinking about osteoporosis and bone health. Most women achieve peak bone mass in their 20s; therefore, these activities are important even in adolescence. Research shows that only one half and three fourths of female and male high school students, respectively, regularly participate in vigorous exercise,[128] and most do not consume adequate calcium.[129] Only 18% of girls aged 9 to 19 years meet the dietary calcium recommendations.[130] Low milk intake—less than 1 serving per day—during adolescence has been associated with reduced bone mass. Early milk intake also appears to influence bone mineral content and BMD in adulthood. In one study, there was a significant nonlinear association between milk intake in childhood and adolescence and bone mineral content and BMD in adulthood (P<.04 among women at least 50 years of age). Adults reporting low milk intake during childhood had a 2-fold greater fracture risk (P<.05).[131]

Recently, the U.S. Department of Health and Human Services' Office on Women's Health, the Centers for Disease Control and Prevention, and the NOF partnered to raise public awareness of osteoporosis and promoted strategies to improve and maintain bone health starting early in life. The program, titled "Powerful Bones. Powerful Girls. The National Bone Health Campaign™," was designed to promote optimal bone health in girls 9 to 18 years of age and reduce their risk of osteoporosis later in life. The initial target audience is girls aged 9 through 12 years, with outreach programs directed to parents and other adults who influence them. The initiative is based on the premise that girls who consume sufficient calcium and participate regularly in weight-bearing physical activity can develop stronger, denser bones and reduce their subsequent risk of osteoporosis. The campaign uses multiple vehicles, including a Web site (www.cdc.gov/powerfulbones), advertising and promotion, and partnerships with key organizations such as the Girl Scouts® of America.

Pharmacologic Approaches

Currently, there are 2 main types of pharmacologic agents: those that primarily act by inhibiting resorption (antiresorptives) and those that act by increasing bone formation (anabolic agents).

Antiresorptive Agents

Most of the bone-active agents currently available in the United States inhibit bone resorption. Estrogen, selective estrogen receptor modulators (SERMs), bisphosphonates, calcitonin, calcium, and vitamin D all have antiresorptive properties. The SERM raloxifene and the bisphosphonates alendronate and risedronate are all approved for the prevention and treatment of postmenopausal osteoporosis.[1,132] The bisphosphonate ibandronate has also been approved for the treatment and

prevention of osteoporosis in postmenopausal women,[133] but it is not yet marketed in the United States. Intranasal calcitonin is indicated for the treatment of postmenopausal osteoporosis in women who are more than 5 years postmenopause.[134]

The mechanisms by which these agents reduce fractures are not completely understood but are believed to include their ability to increase bone mass and to reduce bone turnover, which, in turn, decreases fracture risk by preserving bone microarchitecture and reducing the number of stress risers, allowing time for increased mineralization. The antiresorptive mechanisms of these agents differ between drugs. Most of the activities of estrogens and SERMs are probably mediated via estrogen receptors (α and β) and estrogen-responsive genes throughout the body. They include physiologic and endocrine effects, reduced activity of bone-resorbing cytokines, effects on apoptosis, and possible nongenomic effects.

The clinical pharmacology of calcitonin is not completely understood; however, calcitonin receptors have been discovered in osteoblasts and osteoclasts. In vitro studies show that calcitonin inhibits osteoclast function with loss of the ruffled osteoclast border that is necessary for bone resorption.[134]

The bisphosphonates inhibit bone resorption through uptake by osteoclasts. Potency and clinical effects vary between the bisphosphonates and appear to be related to differences in uptake, retention in bone, and subsequent biochemical activities. Two major subclasses have been identified: (1) those that are incorporated into nonhydrolyzable analogues of adenosine triphosphate and inhibit adenosine triphosphate-dependent intracellular processes (eg, clodronate, etidronate) and (2) those that inhibit enzymes of the mevalonate pathway, thereby preventing biosynthesis of isoprenoid compounds that are essential for the posttranslational modification of small guanosine triphosphatases (eg, the amino-substituted bisphosphonates pamidronate, alendronate, risedronate, zoledronate, ibandronate). Within each class, differing pharmacologic properties of the bisphosphonates may account for subtle but important differences between these drugs.[135]

Effects of Antiresorptives on BMD

All antiresorptives have been shown to halt bone loss, and most also increase BMD. Substantial increases in BMD are seen with risedronate, alendronate, and hormone therapy (HT), and the effects of the bisphosphonates on BMD increase with longer durations of treatment.[136] Weekly doses of the bisphosphonates alendronate and risedronate were found to be as effective as daily doses in increasing bone density and decreasing biochemical markers of bone turnover.[137-139]

Effects on Bone Properties

Effects on other bone properties such as the degree and uniformity of mineralization and microarchitectural structure may also contribute to the antifracture efficacy of antiresorptive therapies. No studies have systematically examined the effects of estrogen, raloxifene, or calcitonin on these properties; however, there are early observations with the bisphosphonates. Prolonged administration (2 or 3 years) of alendronate has been shown to increase the degree and uniformity of mineralization and decrease the porosity of bone in postmenopausal women with osteoporosis.[140,141] Recently, Ritman and colleagues reported that microcomputed tomography scanning revealed significant reductions in percentages of low-density bone and increases in higher-density bone (P=.0001) in transiliac bone biopsies treated with risedronate versus placebo.[142] In ovariectomized minipigs, the administration of risedronate 2.5 mg/kg/day for 18 months preserved trabecular architecture and increased bone strength.[143] In a bone-biopsy study of 26 recently postmenopausal women treated with either risedronate or placebo (Figure 4A-C), microarchitectural integrity deteriorated significantly in patients on placebo, whereas patients on risedronate maintained bone mass and microarchitecture.[144] Other technologies, such as infrared spectroscopy, have been used to study mineralization and crystal properties of bone.[145] These studies, in the aggregate, demonstrate that the bisphosphonates have the ability to influence multiple bone properties, other than BMD, thought to contribute to bone strength.

Antifracture Efficacy of Antiresorptives: Vertebral Fractures

Vertebral fractures can be associated with significant pain, limitation of activities, and increases in mortality.[8,9,146] Therefore, prevention of vertebral fractures is a primary goal of antiresorptive therapy. A majority of vertebral fractures are asymptomatic, but they may be suspected if a patient has experienced a loss of 1.5 inches or more from peak adult height. This extent of height loss is probably an indication for spinal X-ray studies.[147] Although all the approved antiresorptive drugs have been documented to reduce vertebral fracture incidence, they have not been examined in head-to-head comparative trials. Direct comparison of the results of existing studies also cannot be made because patient populations, calcium/vitamin D use, and fracture definitions varied significantly among the studies.

Hormone Therapy

HT with estrogen alone or estrogen in combination with progestin has been found in several studies to be effective in the prevention of postmenopausal bone loss. Most recently, the Women's Health Initiative (WHI) demonstrated that therapy with estrogen plus progesterone prevents vertebral fractures in postmenopausal women not known to have osteoporosis. Administration of conjugated equine estrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg daily (n=8506) for a mean of 5.2 years was associated with a 34% reduction in vertebral fractures. Estrogen alone (n=5310) reduced the risk of vertebral fracture by 38%.[148] Unfortunately, significant health risks with the administration of conjugated equine estrogen alone or in combination have been documented in the WHI. The discovery of these risks has led to substantial reduction in the use of HT by postmenopausal women, who will now have to explore alternative treatments (see Safety/Tolerability section, page 13).[149]

Raloxifene

Raloxifene prevented vertebral fractures in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, which enrolled 7705 postmenopausal women with osteoporosis. The beneficial effects of raloxifene appeared rapidly—clinical vertebral fracture risk was reduced by 68% the first year of therapy (60 mg/day).[150] This effect was sustained over time, with 30% and 50% reductions with 60 mg/day and 120 mg/day, respectively, at 3 years and 36% and 43% reductions at 4 years.[151,152]

Calcitonin

Salmon calcitonin nasal spray has also been associated with a reduction in vertebral fracture risk among postmenopausal women with osteoporosis. In the Prevent Recurrence of Osteoporotic Fractures (PROOF) study (N=1255), salmon calcitonin nasal spray 200 IU/day for up to 5 years reduced the risk of vertebral fractures by 33% (P<.05 versus placebo). Vertebral fracture reduction was not seen at the lower (100-IU/day) or higher (400-IU/day) dosage.[153]

Bisphosphonates

Alendronate

Alendronate has been shown to reduce the risk of vertebral fractures in postmenopausal women with low bone mass or osteoporosis either with or without existing vertebral fractures.[154] Vertebral fracture data from 881 postmenopausal women with osteoporosis who participated in multicenter dose-ranging studies demonstrated a 48% reduction in vertebral fracture risk (radiographic) following 3 years of alendronate therapy (5 or 10 mg/day for 3 years or 20 mg/day for 2 years followed by 5 mg/day for 1 year).[155] The Fracture Intervention Trial, which enrolled postmenopausal women with femoral neck T-scores of –1.6 or less, comprised 2 groups: Group 1 consisted of 2027 women with prevalent vertebral fractures at baseline, and Group 2 consisted of 4432 women without prior vertebral fractures.[156] Among all of the women in Group 1 and 1631 women from Group 2 with T-scores below –2.5, alendronate therapy reduced the risk of radiologic (P<.001) and clinical vertebral (P=.003) fractures significantly.[154] In Group 2, alendronate therapy for a mean of 4.2 years reduced the risk of radiographic vertebral fractures by 44% (P=.001).[157] An extension study with alendronate showed continued increases in BMD for up to 10 years. Fracture risk was not an efficacy endpoint, there was no placebo group after the first 3 years of the study and fracture rates were not compared directly. Information on fractures was collected for safety assessment and the authors reported that they observed no significant differences in the proportion of new vertebral fractures among women who took 5 or 10 mg of alendronate for 10 years, and those who discontinued therapy after 5 years of treatment. Thus, no increase in vertebral fracture risk was observed with long-term alendronate use.[158]

Risedronate

Risedronate has demonstrated sustained antifracture efficacy in postmenopausal women with osteoporosis. In the Vertebral Efficacy with Risedronate Therapy (VERT) multinational study (N=1226), in which osteoporosis was defined by the presence of at least 2 confirmed vertebral fractures, risedronate 5 mg/day reduced the risk of new vertebral fractures by 61% (P=.001) at 1 year and by 49% (P<.001) at 3 years.[159] In a VERT study in North America (N=2458), postmenopausal women with osteoporosis (defined as at least 1 confirmed radiographic vertebral fracture) who took 5 mg/day risedronate for 3 years experienced a 41% reduction in new radiographic vertebral fractures (P=.003 versus placebo). A significant 65% reduction (P<.001) was evident at 1 year.[160] Analysis of combined data from the VERT studies demonstrated significant reductions in vertebral fractures as early as 6 months after initiation of risedronate therapy (P<.05).[161] Two extensions of these trials have provided evidence of sustained efficacy. The continuation of risedronate therapy for 2 additional years (5 years total) in the multinational VERT study was associated with a 59% reduction in new vertebral fractures over the 2-year extension period (P=.01 versus placebo).[162] The incidence of vertebral fractures among risedronate-treated patients remained at the same low level during years 6 to 7 as was observed during years 0 to 3 and 4 to 5. Furthermore, women who began taking risedronate after receiving placebo for 5 years demonstrated a rapid reduction in vertebral fracture risk. Within 2 years, the annualized incidence of new vertebral fractures was similar to that for women who had received risedronate continuously for 7 years.[163]

Figure 4A

Risedronate-Treated Early Postmenopausal Women

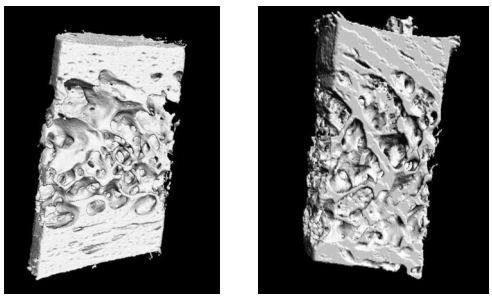

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Figure 4B

Placebo-Treated Postmenopausal Women Rapidly Lose Microarchitectural Elements

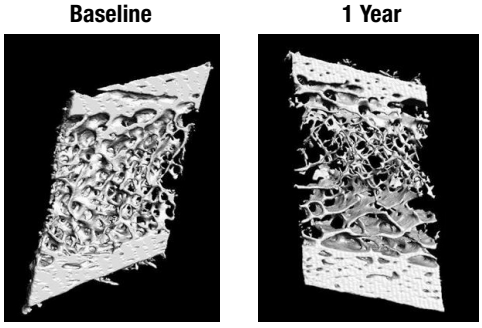

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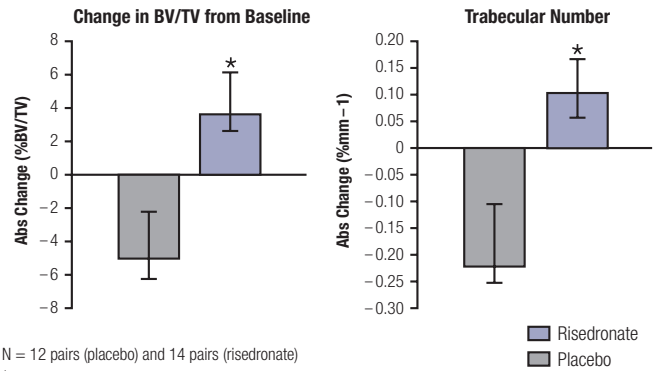
Figure 4C

Bone Volume and Trabecular Number Maintained With Risedronate[144]



N = 12 pairs (placebo) and 14 pairs (risedronate)
*P<.05 (risedronate vs placebo)
BV/TV = bone volume/trabecular volume.

Women with osteoporosis and no prevalent vertebral fractures also benefit from risedronate therapy. Using data from such women who participated in phase III risedronate clinical studies of 1.5 to 3 years' duration (N=640), Zizic and colleagues demonstrated a 75% reduction in the risk of first vertebral fracture (*P*=.002) with risedronate 5 mg daily. A significant effect was observed as early as 1 year and was sustained for the duration of the studies (*P*=.02).[164]

The efficacy of risedronate in reducing vertebral fractures also extends to elderly women. Using data from the VERT studies and the Hip Intervention Program (HIP), Boonen and colleagues demonstrated a 65% reduction in 1-year vertebral fracture risk among women 75 years of age or older. The antifracture efficacy of risedronate in this population was maintained for at least 3 years.[165]

Antifracture Efficacy: Nonvertebral Fractures

Nonvertebral fractures are the most common consequence of osteoporosis.[166] Hip fractures are of particular concern; like vertebral fractures, they are associated with significant morbidity and mortality.[15,18]

As with vertebral fractures, the effects of antiresorptive therapies on nonvertebral fractures have not been examined in head-to-head comparative trials. The studies described here and summarized in Table 9 involved different patient populations, calcium/vitamin D supplementation protocols, and fracture definitions; therefore, data from these trials cannot be compared directly.

Hormone Therapy

Combined estrogen/progestin therapy for a mean of 5.6 years reduced the risk of nonvertebral fractures by 25% in the WHI (HR 0.85; nominal 95% CI 0.70-1.03). Hip fractures were reduced by 33% (HR 0.67; 95% CI 0.47-0.96). This is the first study to show that an antiresorptive given to women without osteoporosis (the average T-score in the small cohort of women whose BMD was measured was approximately –1.3) can reduce the incidence of hip fracture. Estrogen alone also reduced the risk of hip fracture, by 39%.[148] However, significant risks were associated with long-term administration (see Safety/Tolerability, page 13).[167] It has also been shown that the antifracture efficacy of HT may be lost rapidly following discontinuation of therapy[168] (Figure 3, page 3). Women participating in the NORA trial who had discontinued estrogen therapy within the 5 years preceding the study demonstrated a significantly higher hip fracture risk than did women who had never received estrogen therapy (odds ratio 1.69; 95% CI 1.08-2.66).

Raloxifene

In the MORE trial, raloxifene therapy was not associated with significant reductions in nonvertebral fracture risk (RR versus placebo at 3 and 4 years, respectively, 0.9 [95% CI 0.8-1.1] and 0.93 [95% CI 0.81-1.06]).[151]

Calcitonin

Calcitonin has not demonstrated consistent significant reductions in nonvertebral fracture risk (RR versus placebo at 5 years 0.64 [95% CI 0.41-0.99], 0.88 [95% CI 0.59-1.32], and 0.81 [95% CI 0.53-1.23] with salmon calcitonin 100, 200, and 400 IU/day, respectively).[153]

Bisphosphonates

Alendronate

Alendronate reduces nonvertebral fracture risk in women with osteoporosis. In the Alendronate Phase III Osteoporosis Treatment Study, alendronate (5 or 10 mg/day for 3 years or 20 mg/day for 2 years followed by 5 mg/day for 1 year) reduced the risk of nonvertebral fractures by 21%.[155] Among women with osteoporosis (baseline vertebral fractures or femoral neck T-scores ≤–2.5) who participated in the Fracture Intervention Trial, the risk of nonvertebral fractures was significantly reduced by month 24. Alendronate 5/10 mg/day for up to 4 years reduced the risk of nonvertebral fractures by 27% (*P*<.001) and that of hip fractures by 53% (*P*=.002).[154] The effects of alendronate on nonvertebral fracture rates in postmenopausal women without osteoporosis and in men are not known.

Risedronate

Risedronate also reduces nonvertebral fracture risk for women with osteoporosis, with significant reductions observed as early as 6 months after the start of risedronate therapy.[169] In the VERT studies, risedronate 5 mg/day for 3 years reduced the risk of nonvertebral fracture by 33% (*P*=.06) to 39% (*P*=.02).[159,160] The effect was sustained in extension trials for up to 7 years.[163] HIP, the only study in which hip fracture was a primary endpoint, enrolled women between 70 and 79 years of age with femoral neck T-scores below –4 or below –3 plus at least 1 nonskeletal risk factor for hip fracture and women 80 years old or older with at least 1 nonskeletal risk factor for hip fracture or femoral neck T-scores below –4 or below –3 plus hip-axis length of at least 11.1 cm. Overall, those who took risedronate 2.5 or 5 mg/day for a mean of 2.3 years experienced fewer hip fractures than did women taking placebo (2.8% versus 3.9%; *P*=.02).[170] Relative risk for hip fracture was reduced by 40% (*P*=.009) among those aged 70 to 79 years with osteoporosis and by 60% (*P*=.003) among those aged 70 to 79 years with osteoporosis and prevalent vertebral fractures.[170] A significant benefit was not seen for women more than 80 years old, most of whom did not have BMD measurements but were eligible for the study because of risk factors for falls.[170] The explanation for these observations in the older cohort may be related to the increasing importance of nonskeletal factors, such as risk of falling, with age. The lack of BMD data in this cohort is a serious limitation to interpretation of the finding, because fracture data from the placebo arm raised the possibility that many of the patients may not have had osteoporosis. In a separate analysis of data from this study, risedronate therapy was associated with reduced risk of both intertrochanteric and femoral neck fractures among older women with osteoporosis.[171] Antifracture effects in postmenopausal women without osteoporosis or in men are not known.

Antifracture Efficacy: Glucocorticoid-Induced Osteoporosis

Only risedronate and alendronate are approved for the treatment of glucocorticoid-induced osteoporosis. Risedronate is approved for prevention as well. The effects of antiresorptive therapies on patients with glucocorticoid-induced osteoporosis are described in Table 10, page 13.

Both alendronate and risedronate have been shown to preserve BMD in men and women requiring prolonged courses of glucocorticoid therapy for a variety of disorders.[172,173] Although these studies were not powered to detect meaningful differences in fracture rates, the data suggest that both agents reduce fracture risk. In one 48-week study, the administration of alendronate 5 or 10 mg daily was associated with a small reduction in radiographically proven vertebral fractures versus placebo (2.3% versus 3.7%; RR, 0.6; 95% CI 0.1-4.4).[172] In a 1-year extension of this trial (N=208), alendronate therapy was associated with a significant reduction in the risk of new vertebral

Table 9

Antifracture Efficacy of Antiresorptive Therapies in Major Clinical Trials With Postmenopausal Women (NOTE: Data from these placebo-controlled trials cannot be directly compared)

Therapy	Study	Population Studied	Dose	Effect on Vertebral Fractures	Effect on Nonvertebral Fractures
HT	WHI[149,167]	Postmenopausal women (N=16,608)	Conjugated equine estrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg daily	34% reduction in vertebral fractures (hazard ratio 0.66, adjusted 95% CI 0.32-1.34) after ~5 years	Reduced the risk of nonvertebral fractures Reduced the risk of hip fractures 33% Hip (hazard ratio 0.66, adjusted 95% CI 0.33-1.33) Other osteoporotic fracture (hazard ratio 0.77, adjusted 95% CI 0.63-0.94) 25% after ~5.5 years
Raloxifene	MORE[150-152]	Postmenopausal women with osteoporosis (N=7705)	60 or 120 mg daily	68%, 30%, and 36% reductions with 60 mg daily following 1, 3, and 4 years of therapy, respectively 50% and 43% reductions with 120 mg daily following 3 and 4 years of therapy, respectively	No significant reductions in nonvertebral fracture risk
Calcitonin	PROOF[153]	Postmenopausal women with osteoporosis (N=1255)	100, 200, or 400 IU daily	200 IU daily for 5 years reduced the risk of vertebral fractures 33% ($P<.05$ versus placebo) 100 IU daily and 400 IU daily reduced the risk of vertebral fractures 15% and 16%, respectively (P=NS)	No consistent reductions in nonvertebral fracture risk 36% reduction in nonvertebral fracture risk was observed with 100 IU/day ($P<.05$)
Alendronate	Alendronate Phase III Osteoporosis Treatment Studies[155]	Postmenopausal women with osteoporosis (N=881)	5 or 10 mg daily for 3 years or 20 mg daily for 2 years followed by 5 mg daily for 1 year	48% reduction in vertebral fracture (radiographic) risk following 3 years of alendronate therapy (P=.03)	A trend toward reduced nonvertebral fracture risk (estimated risk 0.79, 95% CI 0.52-1.22)
	FIT[154,156,157,206] (pooled analyses)	Postmenopausal women with low bone mass (N=6459)	5 mg daily for 2 years followed by 10 mg daily for the remainder of the study	Administration for ~4 years to women with no vertebral fractures at baseline reduced the risk of clinical vertebral fractures 44% (P=.002 versus placebo) and radiographic vertebral fractures 44% (P=.001 versus placebo) Administration for ~3 years to women with prevalent vertebral fractures at baseline reduced the risk of clinical vertebral fractures 55% ($P<.001$ versus placebo) and radiographic vertebral fractures 47% ($P<.001$ versus placebo) Administration for 3 or 4 years to women who met the WHO criteria for osteoporosis reduced clinical and radiologic vertebral fractures 45% (P=.003) and 48% ($P<.001$), respectively Administration for 3 or 4 years to women who met the WHO criteria for osteoporosis reduced multiple symptomatic vertebral fractures 84% ($P<.001$ versus placebo)	Administration for up to 4 years in women with osteoporosis resulted in 27% ($P<.001$) reduction in nonvertebral fractures and 53% (P=.005) reduction in hip fractures
Risedronate	VERT-MN[159,162,163]	Postmenopausal women with osteoporosis (N=1226)	5 mg daily	Reduced the risk of new vertebral fractures 61% (P=.001) at 1 year and 49% ($P<.001$) at 3 years Reduced the risk of new vertebral fractures 59% (P=.01) during a 2-year extension study Low incidence of fractures was maintained for 7 years	33% (P=.06) reduction in nonvertebral fracture risk
	VERT-NA[160]	Postmenopausal women with osteoporosis (N=2458)	5 mg daily	41% reduction in new vertebral fractures (radiographic) over the 3-year treatment period (P=.003 versus placebo) Significant reductions in vertebral fracture risk were evident at 1 year ($P<.001$)	39% (P=.02) reduction in nonvertebral fracture risk
	VERT studies combined[161]	Postmenopausal women with osteoporosis (N=2442)		Significant reductions in vertebral fracture risk were evident at 6 months ($P<.05$)	
	HIP[170]	Postmenopausal women (N=9331) at risk for hip fracture • Women 70-79 with osteoporosis (n=5455) • Women ≥80 with at least 1 nonskeletal risk factor for hip fracture with osteoporosis (n=3886)	2.5 mg daily or 5 mg daily		Administration for ~2 years resulted in fewer hip fractures versus placebo (2.8% versus 3.9%; RR 0.7 [0.6-0.9]; P=.02) Administration for ~2 years reduced the risk of hip fracture 60% (P=.003) among women with osteoporosis and prevalent vertebral fractures No significant effect on women ≥80

CI = confidence interval.

fractures at 2 years (0.7% versus 6.8%; *P*=.026).[174] In separate small studies, risedronate reduced the 12-month risk of vertebral fracture versus placebo by approximately 70% in patients on long-term high-dose glucocorticoid therapy (*P*=.042)[173] and in those initiating steroid therapy (*P*=.072).[175] When data from these studies were analyzed together (pooled analysis), risedronate 2.5 and 5 mg/day were associated with significant reductions in 12-month vertebral fracture risk versus placebo of 58% (*P*=.01) and 70% (*P*=.08), respectively.[176]

Safety and Tolerability of Antiresorptive Therapies

When making decisions regarding treatment options, clinicians should always consider safety as well as efficacy. The following issues have been identified with specific therapies and should be considered in the selection of therapy for an individual patient.

The WHI has provided important information about risks associated with estrogen-plus-progestin therapy and most recently about estrogen therapy alone. Both arms of this large, prospective study were halted when risks were considered to outweigh the benefits of predetermined endpoints. Use of combined estrogen/progestin therapy for an average of 5.2 years increased the risk of coronary heart disease (HR 1.29; adjusted 95% CI 0.85-1.97) and death from coronary heart disease (HR 1.18; adjusted 95% CI 0.47-2.98), stroke (HR 1.41; adjusted 95% CI 0.86-2.31), venous thromboembolic disease (HR 2.11; adjusted 95% CI 1.26-3.55), and invasive breast cancer (HR 1.26; adjusted 95% CI 0.83-1.92).[149,177] The results of the Women's Health Initiative Memory Study prompted a recent labeling change by the Food and Drug Administration (FDA). Manufacturers of HT products are now required to include a warning indicating that increased dementia was seen in women 65 and older and that estrogen plus progestin failed to prevent mild cognitive impairment.[167,178] Recently, the estrogen-only arm of the WHI was stopped as well, because preliminary results indicated that estrogen alone also increased the risk of stroke and dementia while offering no cardioprotection.[179] The prescribing information for the product used in the WHI also now carries a black box warning that describes the health risks associated with its use.[180]

In view of the results of the WHI, many authoritative bodies now do not recommend the use of estrogen for primary prevention or treatment of osteoporosis. It is recommended at this time primarily for those who are symptomatic of estrogen deficiency.[69]

Raloxifene therapy can cause hot flashes, although the incidence is low.[181] Furthermore, raloxifene 60 mg/day for 4 years has been associated with an increased risk of thromboembolic events (RR 1.78, 95% CI 0.99-3.19); in one study, the RR associated with any dosage of raloxifene was 2.76 (95% CI 1.30-5.86) for deep vein thrombosis, 2.76 (95% CI 0.95-8.01) for pulmonary embolism, and 0.50 (95% CI 0.15-1.73) for retinal vein thrombosis.[152] On the other hand, observational studies based on various clinical trials of raloxifene suggest that the drug may protect against breast cancer and may not have the same increased cardiovascular risk profile as does estrogen. These potential benefits of raloxifene are being addressed in 2 large, ongoing clinical trials, Raloxifene Use for the Heart and the Study of Tamoxifen and Raloxifene.[182,183]

Calcitonin appears to be relatively safe and well tolerated. No significant health risks were associated with salmon calcitonin in one 5-year clinical trial.[153] The intranasal route of administration can be associated with some rhinitis.[134]

No significant health risks were associated with bisphosphonate therapy in clinical trials.[157,158,163,165,170,175,184] Overall, both

Table 10

Antifracture Efficacy of Antiresorptive Therapies in Patients With Glucocorticoid-Induced Osteoporosis*

Therapy	Study	Population	Dosage	Vertebral	Nonvertebral
Alendronate (ALN)	2 combined 48-wk, multicenter, multinational studies[172]	477 patients, mean age 55 y, on GC <4 to >12 mo	5 mg/d ALN (n=161), 10 mg/d ALN (n=157), placebo (n=159)	Nonsignificant reduction with ALN (2.3%) vs PLB (3.7%); borderline significant difference in postmenopausal women (3.7% vs 7.6%, *P*=.05)	4.4% incidence in both ALN and PLB groups
Alendronate	12-mo double-blind extension of above study[174]	208 patients still on GC at end of 1 year	5 mg/d ALN (n=63), 10 mg/d ALN (n=84), PLB (n=61)	Significantly fewer (*P*=.026) fractures with ALN (0.7%) than with PLB (6.8%)	Nonsignificant reduction with ALN (5.4%) vs PLB (9.8%)
Risedronate (RSD)	12-mo multicenter study [175]	228 patients on GC ≤3 mo, expected to continue 12 mo	2.5 mg/d RSD (n=75), 5 mg/d RSD (n=76), PLB (n=77)	71% reduction with 5 mg RSD (5.7%) vs PLB (17.3%); 11.1% with 2.5 mg RSD	5.2% incidence with PLB, 4.0% with 2.5 mg RSD, 3.9% with 5 mg RSD
Risedronate	12-mo European multicenter study[173]	290 patients, mean age 59 y, on GC ≥6 mo	RSD 2.5 mg/d (n=94), RSD 5 mg/d (n=100), PLB (n=96)	70% reduction with RSD (5% each) vs PLB (15%); significant (*P*=.042) when RSD groups combined	Not reported
Risedronate	Analysis of men from 2 above studies[173,175,207]	184 men from Cohen (n=77) and Reid 2000 (n=107) studies	2.5 mg/d RSD (n=61), 5 mg/d RSD (n=63), PLB (n=60)	24% incidence with PLB, 0% with RSD 2.5 mg, 9% with RSD 5 mg; significant 82.4% reduction (*P*=.008) when RSD groups combined	Not reported
Risedronate	Pooled analysis of Cohen and Reid 2000[176]	509 patients on GC who took ≥1 dose of study drug	2.5 mg/d RSD (n=165), 5 mg/d RSD (n=174), PLB (n=170)	Reductions of 70% (*P*=.01) and 58% (*P*=.08) with RSD 5 mg and 2.5 mg, respectively, vs PLB	6% incidence with PLB and 5 mg RSD; 7% with 2.5 mg RSD

*In all studies, glucocorticoid (GC) therapy was ≥7.5 mg/d prednisone or equivalent; PLB = placebo.

bisphosphonates are well tolerated, although both have the potential for gastrointestinal (GI) complications.[185,186] In alendronate postmarketing surveillance, the following GI adverse reactions were reported: esophagitis, esophageal erosion/ulcer, rare esophageal stricture or perforation, and oropharyngeal ulceration. This potential, however, appears low. It was found that many patients were not following dosing instructions, which underscores the importance of advising patients to review package inserts carefully.[187] As is the case for any therapy, potential risks must always be considered in connection with potential benefits.

Anabolic Therapies

A number of agents that build bone (anabolic) have been or are currently being studied for use in the treatment of osteoporosis. These include exogenous PTH, fluoride, growth hormone, insulin-like growth factor-1, androgens, tibolone, strontium, and statins.

One agent, recombinant human PTH (1-34), known as teriparatide and given by subcutaneous injection, has been approved by the FDA for the treatment of postmenopausal women and men with established osteoporosis at high risk for fracture.[188] Full-length PTH (PTH1-84) is currently under investigation.

Teriparatide

Among a host of possible mechanisms, teriparatide increases osteoblast numbers and activity by both recruiting new cells and reducing apoptosis of differentiated osteoblasts.[189,190] At low daily doses of teriparatide, the anabolic effects of PTH predominate. This is in contrast to the catabolic effects generally associated with long-term, higher-dose, and chronic exposure to PTH. Clinical studies indicate that teriparatide increases bone quality by increasing bone density, turnover, and size.[191-194] Furthermore, improvements in microarchitectural elements are evident at both cancellous and cortical regions.[195]

Effects on Bone Mass

Teriparatide significantly increases bone density in postmenopausal women with osteoporosis and men with osteoporosis. Neer and colleagues demonstrated significant dose-dependent increases in total-body BMD ($P<.0001$) as well as in BMD at the lumbar spine, femoral neck, trochanter, intratrochanter, and total hip ($P<.001$ versus placebo) in women with postmenopausal osteoporosis and at least one vertebral fracture (N=1637) with teriparatide 20 or 40 mcg/day for approximately 18 months. Increases in lumbar spine BMD were 9.7% and 13.7%, and those in femoral neck BMD were 2.8% and 5.1% with 20 and 40 mcg/day, respectively.[196] Similar findings were reported in a study of 52 women treated with concomitant teriparatide (400 IU/day) and HT versus HT alone. In this study, increases in spine, total hip, and total body BMD were 13.4%, 4.4%, and 3.7%, respectively, at the end of 3 years.[197] The addition of alendronate to teriparatide does not appear to enhance effects on BMD.[198] The effects of combination use of teriparatide with other bisphosphonates are not known.

In men with idiopathic osteoporosis (N=23), 400 IU/day teriparatide increased lumbar spine BMD 4.8%, 9.6%, and 13.5% at 6, 12, and 18 months, respectively ($P<.001$ versus placebo).[191] In a larger study (N=437), the administration of teriparatide 20 or 40 mcg/day to men with idiopathic osteoporosis resulted in dose-dependent increases in lumbar spine BMD of 5.87% and 9.03%, respectively, and in femoral neck BMD of 1.53% and 2.93%, respectively ($P<.001$ versus placebo for all).[192]

Effects on Bone Microarchitecture

Microarchitectural effects have been demonstrated in men and women with osteoporosis treated with 400 IU/day of teriparatide for 18 and 36 months, respectively. Cancellous bone area was maintained in both groups; cortical width was maintained in men and significantly increased in women ($P<.01$). A trend toward increased trabecular connectivity was also reported (Figure 5).[194] In a subset of patients from the Fracture Prevention Trial, analysis of bone biopsies indicated that teriparatide improves both cancellous and cortical bone structure.[195]

Antifracture Efficacy

In women with postmenopausal osteoporosis (N=1637), teriparatide 20 or 40 mcg/day for approximately 21 months was associated with 65% and 69% reductions in vertebral fractures and 35% and 40% reductions in nonvertebral fractures, respectively.[196] (Figure 2, page 2)

Use for Patients With Glucocorticoid-Induced Osteoporosis

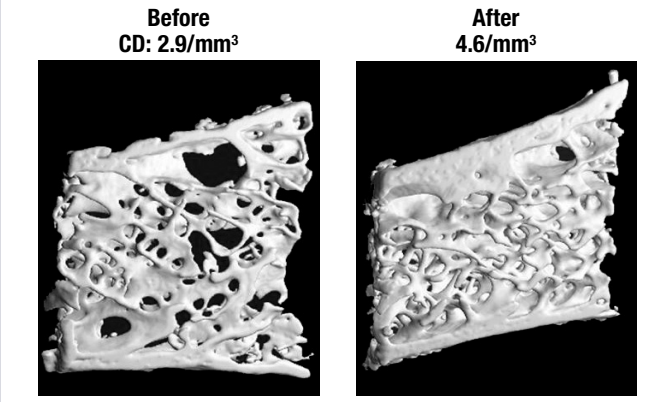
In women with glucocorticoid-induced osteoporosis (N=51) already taking HT, 12 months of 40 mcg/day teriparatide with HT was associated with a 35% increase in vertebral BMD, as measured by quantitative computed tomography, and a 4.8% increase in vertebral cross-sectional area ($P<.001$ versus continued HT alone). These changes led to more than a 200% increase in estimated compressive strength.[199]

Safety/Tolerability

PTH appears to be generally safe and well tolerated, although additional data from long-term studies are needed. Use for more than 2 years is not recommended. Toxicity studies with rats have shown an increased risk of osteosarcoma,[200] but there are significant differences in bone metabolism between rats and humans that make it unlikely that the rat data are applicable to humans. However, a black box warning has been included on the product labeling in the United States, and use of teriparatide should be avoided by patients at increased risk for skeletal malignancy.

Figure 5

Improved Trabecular Connectivity After hPTH (1-34) Therapy



CD = cortical density.

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Prescribing Osteoporosis Therapies: Cost Considerations

Numerous costs are associated with osteoporosis and osteoporosis therapies. These include the costs of acquiring and monitoring the effects of medication; costs associated with short-term care, rehabilitation, and ongoing care for patients with long-term disability resulting from fractures; costs associated with medication side effects such as deep vein thrombosis and thromboembolism with HT and SERMs[201]; and costs associated with evaluating and treating upper-GI complaints of patients on bisphosphonates.[202] Despite the costs associated with drug therapy, treatment likely reduces overall healthcare costs. In a recent analysis of costs at a single mixed-model health plan in the Midwestern United States, women who received drug therapy for osteoporosis incurred lower total direct healthcare costs (average, $7070 per patient per year) than did women who had untreated osteoporosis (average, $11,628 per patient per year).[203]

Several studies have examined the cost-effectiveness of osteoporosis interventions over the past 10 years; however, interpretation is complicated by inconsistent methodologies and varying patient populations. It is extremely difficult to gather consistent data directly comparing the costs of various treatments.[201] Although existing analyses cannot yet be used to drive clinical decision making, they clearly indicate a need for cost-effective osteoporosis interventions.

Summary

Osteoporosis is a disease of compromised bone strength. Changes in bone density and other bone qualities contribute to the development of osteoporosis and increased fracture risk. Ideally, diagnosis should be based on examination of all aspects of bone strength. At this time, BMD measurement remains the primary tool for diagnosis; as tools for measuring other bone characteristics become more widely available, diagnostic capabilities should continue to improve. Until then, clinicians must rely on information gathered from each patient's history (risk factors for osteoporosis and fracture) and BMD testing to make clinical decisions regarding the initiation of measures to prevent and treat this insidious disease.

The primary goal of osteoporosis therapy is to prevent fractures. Current therapies have been shown to improve BMD and reduce fracture risk. For maximal benefits to be achieved, interventions should be implemented early. Careful consideration of the risks and benefits of available treatments should help guide clinicians in choosing appropriate therapies for individual patients.

Clinicians should remain cognizant of bone health in patients of all ages. It is hoped that education about the benefits of a healthy diet and adequate exercise will encourage younger patients to participate in activities that should help prevent the development of osteoporosis later in life.

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continued on inside back cover

The State of the Art in the Management of Osteoporosis

PM #Med 946C

Publication Date: June 2004 Expiration Date: June 30, 2005

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This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) by the College of Physicians & Surgeons of Columbia University. The College of Physicians & Surgeons of Columbia University is accredited by ACCME to sponsor continuing medical education for physicians.

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Posttest Assessment (Please record your answers below in the space provided)

1. What is the estimated number of women with osteoporosis in the United States?
   a. More than 7.8 million
   b. 10 million
   c. 12 million
   d. 14 million
2. What are the approximate annual medical costs associated with osteoporotic fractures?
   a. $5 billion
   b. $8 billion
   c. $14 billion
   d. $20 billion
3. Individuals with type 2 diabetes typically have which of the following?
   a. Decreased bone density
   b. Increased fracture risk
   c. Decreased collagen synthesis
   d. a and b
4. What score is used by the WHO to define osteoporosis?
   a. T-score ≤ –1
   b. T-score –1 to 2.5
   c. T-score ≤ –2.5
   d. Z-score ≤ –2.5
5. Which of the following is a biochemical marker of bone resorption?
   a. Alkaline phosphatase
   b. N-telopeptide of type 1 collagen
   c. Osteocalcin
   d. Type 1 collagen propeptide
6. Risk factors for osteoporosis-related fractures include:
   a. More than 3 months of oral corticosteroid use, distant relatives with fracture histories, and excessive alcohol use
   b. More than 3 months of oral corticosteroid use, first-degree relatives with fracture histories, and impaired vision
   c. Distant relatives with fracture histories, excessive alcohol use, and impaired vision
   d. 1 to 2 months of oral corticosteroid use, first-degree relatives with fracture histories, and low calcium intake
7. Which of the following factors likely influences the effects of caffeine on bone?
   a. Concomitant calcium and vitamin D intake
   b. Concomitant protein intake
   c. Age
   d. Gender
8. The WHI revealed which of the following risks associated with HT?
   a. Invasive breast cancer
   b. Coronary heart disease
   c. Dementia
   d. All of the above
9. Which of the following therapies have not demonstrated reductions in nonvertebral fractures?
   a. Alendronate
   b. HT
   c. Raloxifene
   d. Risedronate
10. In patients with rheumatoid arthritis, glucocorticoid use is associated with a risk for hip fracture that is double that of age- and sex-matched controls.
    a. True
    b. False

POSTTEST ANSWERS PM #Med 946C Expiration Date: June 30, 2005

To receive CME credit, please record your posttest answers and return this page to the College of Physicians & Surgeons of Columbia University prior to the expiration date.

1. ___ 2. ___ 3. ___ 4. ___ 5. ___ 6. ___ 7. ___ 8. ___ 9. ___ 10. ___

Participants are eligible for up to 2 category 1 credits; however the number of credit hours awarded is based on the time actually spent reviewing the material and taking the test. Please indicate the total time you spent on this educational activity.

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EVALUATION FORM

We would appreciate your answers to the following questions in order to help us plan for future activities of this type.

1. How would you rate:

	Excellent	Good	Fair	Poor
a. Value of the topic	❑	❑	❑	❑
b. Relevance to your practice	❑	❑	❑	❑
c. Organization of monograph	❑	❑	❑	❑
d. Monograph length	❑	❑	❑	❑
e. Quality of information	❑	❑	❑	❑

2. Were the goals and objectives clearly stated and achieved? ❑ Yes ❑ No
3. Do you feel the content in this monograph was objective, balanced, and free of commercialization? ❑ Yes ❑ No ❑ Maybe
   If no or maybe, please comment: _____
4. Were alternate treatments presented in a fair and balanced manner? ❑ Yes ❑ No
5. Will reading this monograph change the way in which you manage patients? ❑ Yes ❑ No
   Please be as specific as possible: _____
6. How do you prefer to receive continuing medical education information? (On a scale of 5 to 1, please score each of the following: 5=very useful; 3=somewhat useful; 1=don't use.)
   a. Newsletter ___ d. Symposium/Conference ___ g. Teleconference ___
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   c. Monograph ___ f. Journal Articles/Supplements ___ i. Internet ___
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8. Additional comments and/or suggested topics for future CME activities:

_____

Answer Key
1.a; 2.d; 3.b; 4.c; 5.b; 6.b; 7.a; 8.d; 9.c; 10.a

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