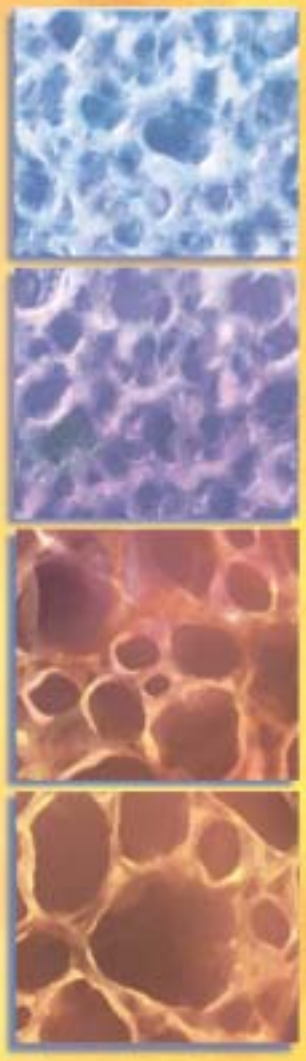
The State of the Art in the Management of Osteoporosis

Highlights From a Scientific Roundtable Held July 2003, Washington, DC



Presented by

The Office on Women's Health
of the
U.S. Department of Health and Human Services

Sponsored by

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College of Physicians and Surgeons

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This program is supported by an educational grant from The Alliance for Better Bone Health (Procter & Gamble Pharmaceuticals and Aventis Pharmaceuticals)

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* No Financial Interest or Affiliation; ** Other Financial Support From Abbott Immunology.

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Interdisciplinary Medicine®

JANUARY 2004 VOL. 5 NO. 5

The State of the Art in the Management of Osteoporosis

Publication date:
January 2004

Expiration date:
January 2005

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INTRODUCTION

More than 10 million Americans over the age of 50 years currently have osteoporosis, and more than 33 million have low bone mass.[1] These numbers are expected to rise significantly as the population ages. By 2020, approximately 14 million Americans will have osteoporosis, and more than 47 million will have low bone mass. Although persons of any race can develop osteoporosis, whites and Asians generally have lower bone mineral density (BMD) than do blacks or Hispanics (10% to 20% lower) and are at greater risk of developing osteoporosis.[2]

The association between osteoporosis and fractures makes osteoporosis a significant health concern. In fact, the number of people who experience fractures is higher than that of women who suffer from breast, ovarian, or uterine cancer (Figure 1, page 2).[3-5] These fractures lead to disability, increased nursing home admissions (hip), and increased mortality (vertebral and hip).[6-10] The economic burden of osteoporotic fractures ($20 billion annually) approaches that of congestive heart failure ($24.3 billion annually) and exceeds that associated with other common diseases such as asthma or breast cancer (Figure 2, page 2).[4,5,8,11]

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
- Identify the at-risk patient using modifiable and nonmodifiable risk factors
- Apply practical tools to decrease and mitigate patient risk for osteoporosis
- Discuss the diagnostic challenges of osteoporosis, including diagnostic testing and the role of bone markers and bone mineral density (BMD)
- Identify the strategies and benefits of therapeutic management through nonpharmacologic, pharmacologic, and evolving therapies
- Discuss the unique challenges of and strategies for treating/managing 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.

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 clinical synopsis summarizes the deliberations of that meeting.

DETERMINANTS OF BONE STRENGTH

Osteoporosis is characterized by compromised bone strength and increased risk of fracture.[12] Bone strength can be defined as bone density and other measures of bone quality. BMD is the gold standard by which the diagnosis of osteoporosis is made. This is largely because a major proportion of bone strength is determined by BMD and because it is the only index of bone strength that is easily measured clinically[13]; however, fracture risk is also determined by other measures of bone quality such as bone turnover, size and geometry, microarchitecture, mineralization, damage accumulation, and matrix quality.

Throughout life, bone undergoes a process of remodeling in which packets of old bone are removed and new bone is put in its place. A slow rate of turnover probably serves to keep bone healthy, but high bone turnover can compromise bone strength through a number of different mechanisms. In adults, bone remodels inefficiently, leaving less bone than there was at the beginning of the remodeling cycle. Increased bone-remodeling units lead to accelerated bone loss and to thinning of bone cortices and trabecular elements. As trabeculae are thinned and perforated, there is a preferential loss of the horizontal trabeculae that buttress and support the load-bearing vertical trabeculae. This loss of horizontal trabeculae is associated with reduced buckling load and translates into greater propensity for fracture with less force or trauma.[14-16]

The relative contribution of changes in bone architecture to bone strength was described in a study using ovariectomized minipigs.[15] Whereas true bone density (bone volume/tissue volume) explained an estimated 76% of variance in strength, there was a strong correlation between trabecular thickness and maximum load (R^2=0.63) in a simple linear regression model. Multiple linear regression revealed a strong correlation between bone volume/tissue volume, trabecular separation, and trabecular thickness and maximum load (R^2=0.91).[15]

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In addition to producing the abnormal bone microarchitecture that characterizes osteoporosis (Figure 3), the actual sites of bone remodeling are points of increased vulnerability to stress, defined in engineering terms as stress risers. These stress risers further weaken already vulnerable trabeculae, lead to even greater loss of strength, and heighten fracture risk.[16,17]

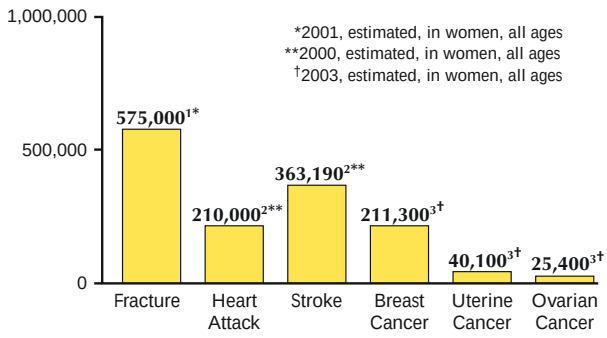
Increased bone turnover also leads to reduced mineralization, which may contribute to loss of bone strength. This most likely results from the shortened secondary mineralization period, which is associated with increased bone remodeling.[17]

Bone-compromising architectural changes have been described in postmenopausal women.[18] Ahlborg and colleagues reported that in postmenopausal women, reductions in bone strength associated with the loss of cortical bone on the inner surface are only partially negated by corresponding increases in periosteal diameter.[19] In their long-term observational study, postmenopausal women experienced mean annual reductions in BMD of 1.9% and reductions in bone strength of 0.7%. During the same time period, mean medullary diameter increased 1.1% and periosteal diameter increased 0.7%.[19]

Together, low BMD, increased bone turnover, and abnormal microarchitecture all contribute to reduced bone strength and an increased risk for osteoporotic fractures.

FIGURE 1

Annual Incidence of Selected Diseases in Women in the United States



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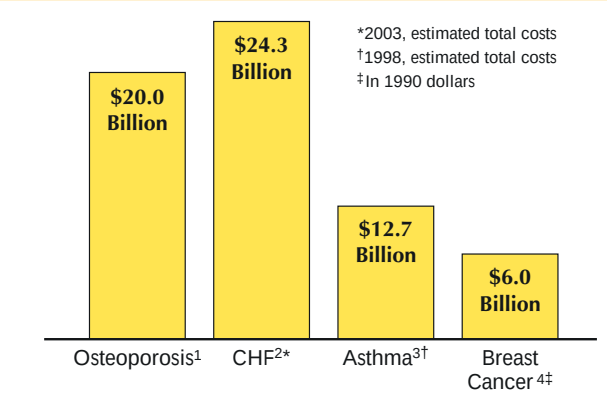
CAUSES OF OSTEOPOROSIS

Table 1 presents a list of risk factors for osteoporosis and related fractures identified by the National Osteoporosis Foundation (NOF). Osteoporosis is most commonly associated with menopause (postmenopausal osteoporosis), as changes in estrogen levels accelerate bone resorption and alter the balance between bone removal and bone replacement toward bone removal. However, a number of other conditions and medications can cause osteoporosis ("secondary" osteoporosis) (Table 2, page 4).[20] Data from the Canadian Database of Osteoporosis and Osteopenia demonstrated that approximately 51% of men and 41% of women with low bone density have known secondary causes of osteoporosis.[21] Among younger individuals, 44% to 73% of osteoporosis cases are reportedly attributable to secondary causes.[22-24] Like postmenopausal osteoporosis, osteoporosis due to these other causes is also associated with increased fracture risk.[25,26] Therefore, individuals with con-

FIGURE 2

Annual Economic Burden of Common Diseases in the United States



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2. American Heart Association. *Heart Disease and Stroke—Statistics 2003 Update*. Dallas, Tex; American Heart Association; 2002.
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ditions associated with osteoporosis or who are taking medications known to impair skeletal health should be evaluated for osteoporosis. This includes the growing population of patients with diabetes, who can be at increased risk for fractures. Type 1 diabetes has long been associated with increased risk for osteoporosis. Evaluation of fracture risk is also important for patients with type 2 diabetes, since recent studies have shown that they too may be at increased risk for fracture despite relatively high BMD.[27] Secondary causes should be considered for all patients diagnosed with osteoporosis, as treatment of contributing conditions or changes in drug therapy could affect outcomes.

Glucocorticoid-Induced Osteoporosis

Prolonged exposure to glucocorticoids has long been associated with osteoporosis and increased fracture risk. Several recent clinical studies have defined the scope of this problem, confirming that prolonged glucocorticoid use is an independent risk factor for fracture. In a study of 191 general-practice patients in Iceland who were taking glucocorticoids for 3 months or longer (mean dosage, 6 mg/day), 26% of patients were diagnosed with osteoporosis and 20% experienced fractures.[28]

Among patients with rheumatoid arthritis, a disease that has been directly associated with bone loss, glucocorticoid use has been demonstrated to be an independent risk factor for fracture. After adjustment for other variables (ie, body mass index, smoking, alcohol use, and functional impairment), the odds ratio for hip fracture associated with rheumatoid arthritis was 1.3. The odds ratio for hip fracture associated with use of corticosteroids, adjusted for the same confounding variables, was substantially higher, 2.1.[29]

Fracture risk among users of glucocorticoids appears to be dose related, starting at relatively low doses (relative risk [RR] of hip fracture, 0.99, 1.77, and 2.27 at dosages of <2.5 mg/day, 2.5 to 7.5 mg/day, and >7.5 mg/day [prednisone or its equivalent], respectively, and RR of vertebral fracture, 1.55, 2.59, and 5.18, respectively).[30] Therefore, even patients taking prolonged courses of relatively low doses of glucocorticoids should be considered at risk for osteoporosis and fractures. Baseline bone status may also help predict fractures. In a recent study, lower baseline lumbar spine BMD was associated with increased fracture risk.[31] Current guidelines set forth by the American College of Rheumatology recommend obtaining a baseline measurement of BMD for all patients initiating long-term (>6 months) glucocorticoid therapy.[32] Calcium and vitamin D are recommended for all patients receiving glucocorticoids, and bisphosphonates are approved for both prevention (risedronate) and treatment (alendronate and risedronate) of glucocorticoid-induced bone loss in patients at high risk for fractures.[33,34]

DIAGNOSIS

Osteoporosis remains largely underdiagnosed and undertreated. In 2001, only 12% (1.8 million) of the 15 million women aged 65 years or older who had osteoporosis or osteopenia had Medicare-reimbursed BMD tests.[35] Both patient perceptions and clinician practices likely contribute to this situation. Results of a telephone survey indicated that fewer than 1% of women 25 years of age or older perceive osteoporosis as a primary health concern or leading cause of death.[36] Unfortunately, very few women receive osteoporosis advice or counseling at routine office visits, a factor that likely contributes to women's lack of concern regarding the disease.[37] Several additional barriers to diagnosis exist in the primary care setting. These include a prolonged asymptomatic phase; competing demands on the physician's time; reduced time and reimbursement per visit; confusion regarding whom, how, and when to screen; confusion regarding how to interpret results; inconsistencies in insurance coverage for BMD testing; and provider attitudes regarding osteoporosis.

Although no single action can ensure improved diagnosis, programs designed to teach clinicians and patients about osteoporosis could improve detection. A simple acronym may help trigger the performance of important routine osteoporosis activities in a busy primary care setting[38]:

FIGURE 3

Microarchitectural Changes in Osteoporosis

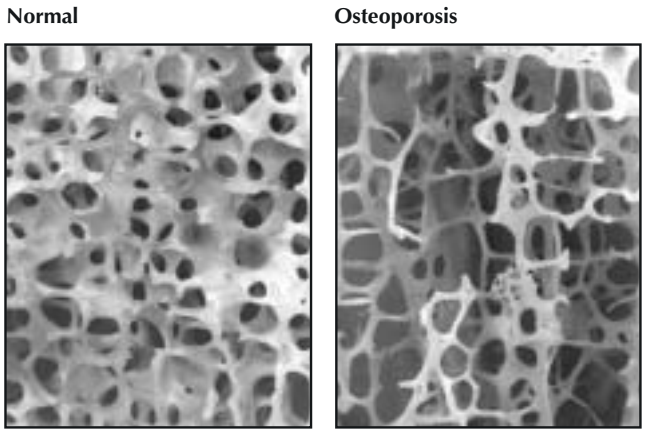


TABLE 1

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
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

Adapted from National Osteoporosis Foundation. Physician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2003. All rights reserved.

Preventive measures—for all patients

Risk assessment—perform routinely

Observe—for signs and symptoms of osteoporotic fractures

Test—all appropriate patients

Explain—test results and treatment options

Conservative measures—for all with abnormal BMD

Treat aggressively—with indicated therapies

Bone Mineral Density Measurement

BMD is commonly used to help assess fracture risk. Its predictive value for fractures appears to be as good as or better than that of tests for other silent diseases such as the measurement of cholesterol for predicting coronary artery disease or blood pressure for predicting stroke.[39]

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. Guidelines set forth by the NOF, the International Society for Clinical Densitometry, and the US Preventive Services Task Force, however, have not reached a clear consensus regarding when and how often to perform BMD measurements in younger women or in men.[34,40,41] The NOF advocates screening postmenopausal women under 65 who have 1 or more risk factors for osteoporosis or fractures (other than being white, postmenopausal, and female) or who have experienced 1 or more fractures (Table 3).[34] Bone density measurement in patients with conditions associated with osteoporosis is an aspect of disease management and does not fall under "screening guidelines."

The NOF has adopted the World Health Organization (WHO) criteria for the diagnosis of bone status based on BMD measurements by dual energy X-ray absorptiometry (DXA) of the hip and spine.[34] Currently, diagnostic criteria use T-scores, which indicate the number of standard deviations below or above the average peak bone mass in young adults of the same sex (Table 4). Interpretation of results derived from different technologies and bone sites remains difficult. The WHO criteria were designed to be applicable only to postmenopausal women and cannot be applied to measurements in premenopausal women or in children. Calculation of Z-scores, which indicate the number of standard deviations below or above the average bone mass in an age- and gender-matched population, may aid clinical decision making and prompt a search for secondary causes of osteoporosis by identifying patients with bone mass that is unusually low.

BMD Controversies

A number of different technologies are available to assess bone density at various skeletal sites. The gold standard is DXA measurement of the spine and hip; ultrasound of the heel or tibia; single or dual x-ray absorptiometry of heel, finger, or forearm; and quantitative computed tomography (QCT) of the spine or wrist are also available. Although bone densitometry remains the most clinically useful tool to predict fracture risk, a number of outstanding issues complicate the interpretation of BMD results.

Interpreting Results/T-Score Discrepancies

Although results of BMD testing are typically reported as T-scores, T-scores cannot be compared directly between the various technologies for 3 major reasons: (1) T-scores are derived from different and not necessarily similar reference population databases; (2) there are technical differences between measurement techniques; and (3) rates of bone loss are different at various skeletal sites.[42]

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 American Association of Clinical Endocrinologists 2001 Medical Guidelines for Clinical Practice for the Prevention and Management of Postmenopausal Osteoporosis. *Endocr Pract.* 2001;7:293-313.

Choosing the Right Technology/ Measurement Site

It is important for clinicians to bear in mind that the WHO criteria for diagnosis of bone status should be applied only to BMD measured by DXA of the hip and spine. T-score results are often higher when measured at peripheral sites than at central sites, and lower when measured by QCT, and the prevalence of osteoporosis or osteopenia can thus be underestimated or overestimated if these measurements are used.[43]

Peripheral technologies can, however, be used to predict fracture risk.[39,44] 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 (all fractures). Measurement of the specific site in question, however, is the best predictor of fracture risk at that site.[39]

Use for Evaluating Treatment Effects

Whereas BMD measurement has proven to be a useful clinical tool for diagnosis and assessment of treatment effects, it does not provide a complete explanation of changes induced by treatment. Meta-analyses, including BMD and fracture data from 12 clinical trials of antiresorptive therapy, demonstrated that changes in BMD did not account completely for fracture-risk reduction.[13,45] It is clear that antiresorptive agents are acting in ways to reduce fracture incidence that are not explained completely by changes in bone density (eg, slowing bone turnover and preserving bone microarchitecture) and that may contribute to reduced fracture risk. The application of new technologies such as those that evaluate bone size and microarchitecture may permit a more complete assessment of treatment effects in the future.

Biochemical Bone Markers

The measurement of biochemical bone markers can provide useful information about bone turnover and, when used in conjunction with BMD measurements, aid in clinical decision making regarding the initiation and maintenance of therapy. Proposed uses include identifying patients with high turnover who are at increased risk for fractures and monitoring the response to therapy.

There are 2 types of biochemical bone markers—markers of bone resorption and markers of bone formation (Table 5, page 6). The most commonly used clinically are the bone resorption markers: collagen cross-links (pyridinoline, deoxypyridinoline) and amino and carboxy terminal peptides of mature collagen (N-telopeptide and C-telopeptide), and the bone formation markers: bone-specific alkaline phosphatase and osteocalcin.[46]

The clinical use of biochemical bone markers is complicated by multiple sources of variability related both to biological factors and to the assay itself. Results are influenced by patient age, sex, ethnicity, physical activity, diet, drug therapy, and medical conditions such as pregnancy/lactation, active rheumatoid arthritis, kidney or liver disease, and acute fractures.[47] Assay variability 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 depending on when the sample is obtained. For these assays to be useful in the clinic, variables that can be controlled, such as specimen-collection criteria (eg, second-morning urine collection for resorption markers or a total 24-hour collection), must be standardized. In addition, one must know the laboratory precision to determine if serial changes in patient results are statistically significant. For this determination, the change in the patient's bone markers must exceed the least significant change of the measurement, which is defined, at the 95% confidence level, as 2.77 times the coefficient of variation (CV) of the measurement.[47,48]

A separate challenge regarding the clinical utility of biochemical bone markers is that of reimbursement. Medicare currently reimburses for the measurement of collagen cross-links in postmenopausal women on FDA-approved osteoporosis therapy (at baseline, 3 months after initiation of new therapy, and every 12 months thereafter).[49]

TABLE 3

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

Adapted with permission from National Osteoporosis Foundation. Physician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2003. All rights reserved.

TABLE 4

WHO Criteria for Diagnosis of Bone Status

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

National Osteoporosis Foundation. Physician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2003.

EARLY INTERVENTION

Despite the widespread availability and use of bone densitometry, it remains difficult to determine when to initiate preventive therapy for some individual patients. Although a clear relationship between BMD and fracture has been established, BMD does not provide insight into other properties of bone that contribute to fracture. Results of the Study of Osteoporotic Fractures demonstrated that fractures commonly occur in patients who have T-scores above –2.5. Of the hip and nonvertebral fractures that occurred within 5 years of baseline BMD measurement in this study, 54% and 74%, respectively, were in women with baseline BMD greater than –2.5.[50] Evidence from the National Osteoporosis Risk Assessment study further demonstrated that more people sustain fractures who have T-scores that are not in the osteoporotic range. From an epidemiologic viewpoint, these observations are not surprising, because there are many more individuals with T-scores higher than –2.5 than there are individuals whose T-scores are lower than –2.5. Even when a threshold value of T-score lower than –1.0 is used for peripheral sites, a significant proportion of individuals with fractures will be missed.[51] These observations do not discount the fact that individuals with T-scores lower than –2.5 are at greater risk for fragility fracture, but they do underscore the need for additional methods of determining fracture risk. Because osteopenia is considerably more prevalent than is osteoporosis,[52] identification of risk factors for fracture in this patient population would be expected to improve the efficient use of preventive therapies.

Identifying Patients With Increased Risk of Fracture

Since it is clear that fracture risk cannot be absolutely determined using any one measure, clinicians must integrate information from a variety of resources to evaluate risk for individual patients.

TABLE 5

Biochemical Bone Markers

Markers of Bone Formation	Osteoblast-derived enzymes • Total alkaline phosphatase • Bone-specific alkaline phosphatase Bone matrix formation products • Osteocalcin • Type 1 collagen propeptides
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

Adapted from Khosla S, Kleerekoper M. Biochemical markers of bone turnover. In: Favus M, ed *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 5th ed. Kelseyville, Ca: American Society for Bone and Mineral Research; 2003:166-171.

In addition to BMD measurement, the clinical approach to fracture risk assessment would use information easily gathered at any routine patient visit. Two of the most important independent predictors of future fracture risk are age and a 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 and/or because there are nonskeletal factors that become important over time, such as the risk of falling.[53]

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 osteoporotic fractures at the same or distant sites.[54] Patients experiencing vertebral fracture are at particularly high risk for additional spine fractures, with 4% to 24% experiencing new compression fractures within the next year.[55]

Other frequently identified independent risk factors for hip fracture include measures of frailty, a maternal history of hip fracture, factors associated with an increased risk of falls, and increased biochemical markers of bone turnover.[56-58] The FRACTURE Index, a simple, 7-question tool, synthesizes clinical and, if available, BMD to assess fracture risk (Table 6). Osteoporosis Education offers a calculator (http://www.osteoed.org/tools/tools_fracture.html) that clinicians can download to their computers or PDAs[59]; essentially, women with total scores of 6 or above (from a possible maximum of 15) should be considered for treatment. This index has a demonstrated predictive value of hip, vertebral, and nonvertebral fractures in women more than 65 years of age.[60] Although it may be a useful tool for predicting future fracture risk in the older postmenopausal population, the FRACTURE Index has not been validated in other populations (eg, younger women, older institutionalized persons, men, or persons with secondary osteoporosis). Therefore, it should not be relied on for these populations.[60]

TREATMENT AND PREVENTION

Nonpharmacologic Approaches

Nonpharmacologic approaches are important cornerstones of osteoporosis-prevention initiatives. They include dietary modifications, exercise programs, and fall-prevention strategies.

Nutrition

Both calcium and vitamin D supplementation have been associated with reduced bone loss and decreased risk for fractures in a number of prospective studies.[61-64] Supplementation must be continued long term for their efficacy to be maintained.[65] Deficiency in these nutrients is widespread. The majority of Americans (>90% of women and >50% of men) do not get enough calcium in their diet, to meet the intake recommendations put forth by the Food and Nutrition Board of the National Academy of Sciences. Although poor calcium intake is observed at all ages, it appears to be greatest among older individuals (<1% of women and <5% of men 71 years of age or older meet the recommendations).[66]

The prevalence of vitamin D deficiency is also high.[67-71] It leads to poor calcium absorption, secondary hyperparathyroidism, increased bone turnover,[65] increased rates of bone loss, and, if severe, impaired bone mineralization. In addition, vitamin D deficiency causes muscle weakness[72] and increases falls. Vitamin D supplementation can reverse many of these effects[64,65] and significantly reduce falls and hip fractures.[68]

Dietary intake of adequate protein is also important to bone health and has been associated with lower rates of bone loss and lower incidence of fractures in elderly women if accompanied by adequate calcium intake.[73-75] Intake of vitamin K, caffeine, and sodium may also affect bone health; however, their relationship to osteoporosis has not been as well established.[76-78]

Exercise

The benefits of exercise are 2-fold. Several intervention trials indicate small but consistent improvement in BMD from weight-bearing exercise,[79] but these changes are modest, at best, in the adult skeleton. Exercise is more importantly associated with reduced risk of falling.[79] Proposed exercise regimens vary and may include stretching, walking, running, and weight training. Even Tai Chi has been reported to be beneficial.[80]

Fall Prevention

Falls are responsible for 90% of hip fractures,[81] with sideways falls (the type of fall that typically occurs in an older individual) increasing the risk of fracture nearly 6-fold.[82] Hip protectors can be used by at-risk patients, as they have been shown to reduce the risk of hip fractures among nursing home residents[83] and ambulatory elderly persons with at least 1 risk for falling[84]; however, compliance with hip-protector use is poor.[83]

Bone-Health Awareness

Recently, the Office on Women's Health of the U.S. Department of Health and Human Services, the Centers for Disease Control and Prevention, and the NOF partnered to raise public awareness of osteoporosis and promote 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 for osteoporosis. Unfortunately, a large proportion of teenagers do not participate in these bone-promoting activities. Only one half and three fourths of female and male high school students, respectively, regularly participate in vigorous exercise (Figure 4, page 8),[85] and most children and adolescents do not consume adequate calcium (Figure 4).[86] The campaign uses multiple vehicles, including a Web site (www.cdc.gov/powerfulbones), advertising and promotion, and partnerships with key organizations (eg, Girl Scouts® of America).

Pharmacologic Approaches

The NOF recommends the initiation of treatment to reduce fracture risk for women with T-scores below –2.0 by central DXA with no risk factors, those with low bone mass (T-score below –1.5 by central DXA and other risk factors for fracture), and those who have experienced prior vertebral or hip fractures (Table 3, page 5).[34]

Antiresorptive Therapy

Most of the bone-active agents currently available in the United States act by inhibiting bone resorption. Estrogens, selective estrogen receptor modulators (SERMs), bisphosphonates, calcitonin, calcium, and vitamin D all have antiresorptive properties. The SERM raloxifene (60 mg/day)[87] and the bisphosphonates alendronate (10 mg/day or 70 mg/week)[88] and risedronate (5 mg/day or 35 mg/week)[89] are all approved for the prevention and treatment of postmenopausal osteoporosis. Weekly doses of both bisphosphonates were found to be equally effective in increasing bone density and decreasing biochemical markers of bone turnover as daily doses.[90,91] Alendronate and risedronate are also approved for treating glucocorticoid-induced osteoporosis, and risedronate is approved for prevention of this condition as well.[34]

The mechanisms by which these agents reduce fractures are not completely understood but are believed to include their ability to reduce bone turnover (which, in turn, reduces stress risers and preserves bone architecture), increase or preserve bone mass, and increase secondary mineralization. The antiresorptive mechanisms of these agents, however, differ by drug. 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. In contrast, calcitonin appears to inhibit osteoclast activity directly (interaction with specific osteoclast receptors).

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

Table 6

The FRACTURE Index*

Question	Point Value
What is your current age? <65 – ≥85	0 – 5
Have you broken any bones after age 50? Yes	1
Has your mother had a hip fracture after age 50? Yes	1
Do you weigh ≤125 pounds? Yes	1
Are you currently a smoker? Yes	1
Do you usually need to use your arms when standing up from a chair? Yes	2
BMD (total hip T-score) ≤-1 – <-2.5	0 – 4

*Women with total scores of ≥6 (from a possible maximum of 15) should be considered for treatment.

Adapted with permission from Black DM et al. *Osteoporosis Int*. 2001;12:519-528.

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). The differing pharmacologic properties of the bisphosphonates may account for subtle but important differences between these drugs.[92]

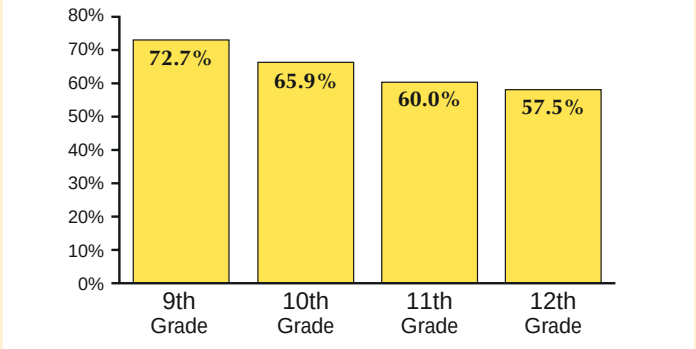
In a study using ovariectomized minipigs, Borah and colleagues described the relative contribution of changes in bone architecture to bone strength.[15] In this study, suppression of bone turnover with the antiresorptive agent risedronate was associated with increased bone mass and the preservation of trabecular architecture, including trabecular number, thickness, and separation.

Studies examining the effects of alendronate have demonstrated a significant role of increased bone mineralization in overall increases of BMD and a relationship between reduced activation frequency and prolongation of the secondary mineralization period.[93,94]

FIGURE 4

Current Behavior

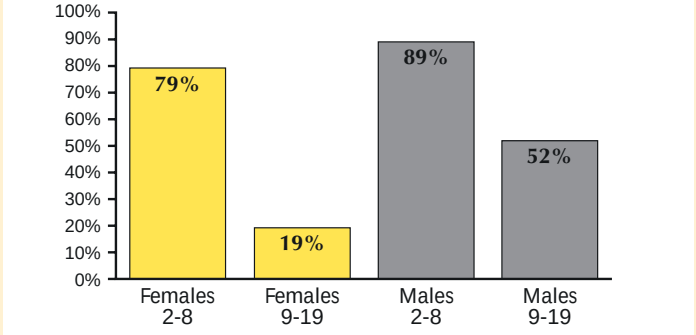
Percentage of High School Students Who Participated in Vigorous Sports or Physical Activity,* by Grade



*Activities that caused sweating and hard breathing for at least 20 minutes on 3 or more of the 7 days preceding the survey.

Kann L, et al. *MMWR CDC Surveillance Summaries*. 1998;(55-3)47:1-89.

Percentage of Children Meeting Recommendations for Daily Calcium Intake



Source: National Health and Nutrition Examination Survey (NHANES)

Antiresorptives and Vertebral Fractures

Vertebral fractures are often silent and not recognized clinically; however, they can have a significant impact on patient health and overall well-being. When patients do present with symptoms, they are commonly associated with acute or chronic back pain, height loss, gastrointestinal (GI) and respiratory difficulties, depression, loss of self-esteem, loss of ability to perform the activities of daily living,[34] and increased mortality (5% to 10%).[95] Therefore, reduction in vertebral fracture risk is a primary treatment goal and one of the beneficial effects of antiresorptive therapy.

Reduced vertebral fracture rates have been observed in randomized, double-blind, placebo-controlled trials with postmenopausal women with osteoporosis following treatment with raloxifene, alendronate 5 to 10 mg/day, risedronate 5 mg/day, and calcitonin 200 IU/day. These reductions, ranging from 30% to 50% (Figure 5), were generally apparent among women with and without preexisting vertebral fractures and were similar with all therapies despite significant differences in their effects on BMD.[96-101] This discordance in bone density after effective therapy with antiresorptive agents underscores the point that the antiresorptive drugs are improving bone quality by means that cannot be measured completely with bone densitometry.

Reduction in bone turnover, with its associated preservation of bone architecture, reduced stress risers, and increased mineralization, is thought to be the primary means by which this improvement in bone quality is accomplished. The benefits of antiresorptive therapy in preserving bone architecture were recently demonstrated in a bone-biopsy study with 26 postmenopausal women treated with either risedronate or placebo. After 1 year, those treated with risedronate 5 mg daily had higher bone volume, trabecular thickness, and trabecular number; and lower percent plate perforation, trabecular separation, and connectivity as measured by marrow star volume than did placebo-treated patients.[18]

The benefits of antiresorptive therapy occur rapidly. In separate trials, the administration of raloxifene (post hoc analysis), risedronate (morphometric vertebral fracture reduction as part of predetermined outcome), and alendronate (post hoc analysis) to postmenopausal women with osteoporosis reduced the risk of vertebral fracture at 1 year by 59% to 68%.[100,102,103] Analysis of combined data from 2 large risedronate trials showed that significant reductions in clinical vertebral fractures are evident even after just 6 months of therapy.[104]

The effectiveness of bisphosphonates is also sustained over time. Data are available to support maintenance of vertebral fracture risk reduction for 3 years with alendronate,[105] 4 years with raloxifene,[106] and 5 years with risedronate.[107] Furthermore, bone density continued to increase, and the low incidence of fractures was maintained at 7 years in the risedronate trial.[108] Extension studies with alendronate have shown continued increases in BMD for up to 10 years,[109] but fracture risk during this period remains to be determined.[110] Overall, long-term use of these agents is generally well tolerated.

The comparative long-term effects of antiresorptive therapy remain to be established, since head-to-head trials comparing fracture reduction have not been performed and differences in designs of completed studies prevent direct comparison.

Antiresorptives and Nonvertebral Fractures

Nonvertebral fractures also have a significant impact on healthcare, because they are the most common consequences of osteoporosis.[111] Only the bisphosphonates alendronate and risedronate have demonstrated efficacy in reducing the risk of nonvertebral fractures; however, the evidence is not as robust as that for vertebral fractures. In most studies, nonvertebral fractures were examined only as secondary outcomes.

Bisphosphonates reduce nonvertebral fracture risk for women with osteoporosis, but their effects in postmenopausal women without osteoporosis or in men are not known. In the Fracture Intervention Trial, alendronate 5 or 10 mg daily was associated with RRs for nonvertebral fracture of 0.74 (*P*=.002) and 0.88 (95% confidence interval [CI] 0.74-1.04) at 3 and 4 years, respectively.[98,103] RRs were also reduced with risedronate 5 mg/day in the Vertebral Efficacy with Risedronate Therapy and Risedronate Multinational studies (RR at 3 years, 0.6 [95% CI 0.39-0.94] and 0.67 [95% CI 0.44-1.04], respectively).[99,100] The incidence of hip fracture was found to be significantly reduced by alendronate in a study whose primary endpoint was vertebral fractures,[103] but only risedronate has demonstrated efficacy in reducing hip fractures in a primary endpoint trial. In the Hip Intervention Program study, women taking risedronate 2.5 mg/day or 5 mg/day for a mean of 2.3 years experienced fewer hip fractures than did women taking placebo (2.8% vs 3.9%; RR, 0.7 [95% CI 0.6-0.9]; *P*=.02). Among women aged 70 to 79 years with established osteoporosis, fracture risk was reduced 40%. Fracture risk was reduced 60% among those with osteoporosis and prevalent fractures.[112]

Neither raloxifene nor calcitonin use has been associated with significant reductions in nonvertebral fracture risk. With nasal calcitonin, the only change in nonvertebral fracture risk that achieved statistical significance vs placebo was that associated with 100 IU/day (RR 0.64 [95% CI 0.41-0.99], *P*<.05), but no reduction was seen with the currently approved dosage of 200 IU/day or with 400 IU/day.[101]

Head-to-head comparative trials have not been conducted, and data from these placebo-controlled trials cannot be compared directly, because patient populations, use of calcium/vitamin D, and fracture definitions varied between studies. As nonvertebral fractures constitute the majority of fragility fractures and account for a substantial portion of osteoporosis-related costs, additional data regarding the efficacy of these agents for reducing the risk of nonvertebral fractures are needed.

Hormone Therapy and Fracture

Results of the Women's Health Initiative (WHI) demonstrated a reduced risk of vertebral and nonvertebral fracture with hormone therapy (HT) for postmenopausal women without diagnosed osteoporosis. In this study, administration of conjugated equine estrogen plus medroxyprogesterone acetate for a mean of 5.2 years reduced the risk of vertebral and hip fractures by one third and the risk of all fractures by almost one fourth.[113] Despite the efficacy of HT in preventing fracture shown in this study, significant risks were also revealed (see "Risks Associated With Antiresorptive Therapy"). A more recent report on the WHI concluded that in consideration of the adverse risk-to-benefit ratio, therapy with estrogen plus progestin should not be recommended for prevention or treatment of osteoporosis for women without vasomotor symptoms.[114] Further, the effects of HT on fractures in women with osteoporosis have not been evaluated.

Risks Associated With Antiresorptive Therapy

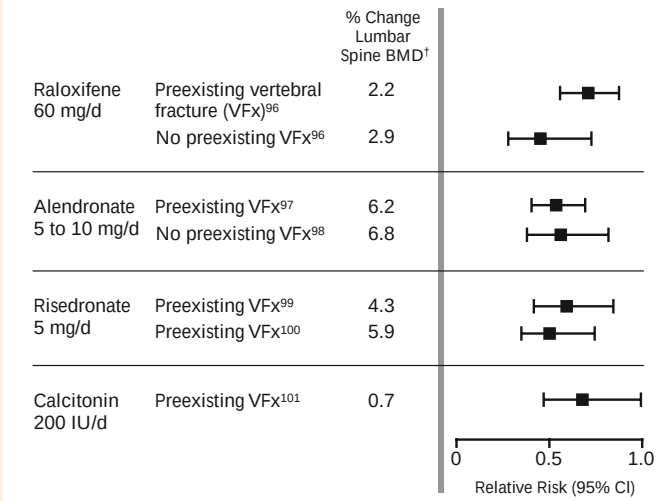
The WHI revealed significant risks associated with long-term HT. In this study, use for an average of 5.2 years was associated with increased risk of coronary heart disease (HR 1.29; adjusted 95% CI 0.85-1.97) and death (HR 1.18; adjusted 95% CI 0.47-2.98), stroke (HR 1.41; adjusted 95% CI 0.86-2.31), venous thromboembolic disease (HR 2.11; adjusted 95% CI 1.26-3.55), invasive breast cancer (HR 1.26; adjusted 95% CI 0.83-1.92), and probable dementia (HR 2.05; 95% CI 1.21-3.48).[113,115] These studies examined risks associated with a single HT regimen; therefore, it remains to be determined if the risk-benefit profile can be improved with the use of lower doses, a different estrogen formulation, a different progestin, or unopposed estrogen (which is only prescribed for women who have had hysterectomies).

This evidence prompted the US Preventive Services Task Force to recommend that estrogen and progestin not be used by postmenopausal women to prevent chronic conditions (including osteoporosis).[41] Prempro®, the product tested, maintains its indication for osteoporosis prevention; however, this is now tempered by a recommendation that it "only be considered for women at significant risk" and that "non-estrogen medications should be carefully considered."[116] Furthermore, a black box warning has been added to emphasize the associated cardiovascular risks revealed by the WHI. In this light, current data do not support prescribing HT for long-term prevention of osteoporosis after menopause.

The SERM raloxifene has been associated with hot flashes during the first 6 months of use and with increased risk of thromboembolic events.[96,106,117] No significant health risks were associated with the bisphosphonates or with salmon calcitonin in clinical trials.[97-101,105,107,109,110,112]

FIGURE 5

Risk of Vertebral Fractures Among Women With Postmenopausal Osteoporosis Taking Antiresorptives*



*Not head-to-head comparisons. †vs placebo.
Note: All pivotal trials included showed significant reduction in risk of vertebral fracture but confidence intervals were broad.

Overall, both bisphosphonates are well tolerated, although both have the potential for GI complications. Pivotal placebo-controlled clinical trials of each drug have not demonstrated an increased risk of GI adverse events with either alendronate or risedronate, and no head-to-head trials have been performed. More prospective studies would be needed to confirm an advantage of one over the other. It is important to note that because the bisphosphonates vary pharmacologically and structurally, the results of studies with one cannot be extrapolated to other bisphosphonates. Further studies with other bisphosphonates are under way.

With any of these agents, clinicians must weigh the risks and benefits carefully to determine the best regimen for each patient.

Anabolic Therapy

A number of agents that have a clear ability to increase bone formation, and are therefore anabolic agents, are currently being studied for use in the treatment of osteoporosis and prevention of fractures. One agent, the 1-34 fragment of parathyroid hormone [recombinant human PTH(1-34)] (teriparatide), has been approved for the treatment of women and men with established osteoporosis at high risk for fracture. Full-length PTH(1-84) is currently under active investigation. Other agents with anabolic potential include fluoride, growth hormone, insulinlike growth factor-1, androgens, tibolone, strontium, and statins. Recombinant human PTH(1-34) appears to increase bone mass by increasing osteoblast numbers and activity.[118] Exogenously administered PTH (teriparatide) also provides benefits to bone through effects on osteoblasts (increased function) and other regulatory factors (eg, insulinlike growth factor).[119,120] At low daily dosing of teriparatide, the anabolic effects of PTH predominate. This is in contrast to the catabolic effects generally associated with long-term, higher-dose exposure to PTH.[121] Clinical studies suggest that teriparatide increases bone density, turnover, size, and geometry.[122-126] Furthermore, impressive improvements in microarchitectural elements are evident at both cancellous and cortical regions.[127]

For postmenopausal women, 20 µg/day of teriparatide (the approved dosage), along with calcium and vitamin D supplementation, significantly increased bone density at the lumbar spine and femoral neck (P<.001) and reduced vertebral and nonvertebral fracture risk (65% and 35%, respectively).[122] The beneficial effects of teriparatide on BMD have also been observed in men; however, effects on fracture risk have not been evaluated.[123,124]

Use of concomitant antiresorptive and anabolic therapy with teriparatide is under study at this time. Recent data suggest that there are no overt advantages to be gained by combining teriparatide with alendronate and that there may be disadvantages.[128,129] Some studies have shown a brisk response to PTH in patients on estrogen therapy, but comparison with the response to PTH alone has not been done.[125,130] On the other hand, Ettinger et al demonstrated that among individuals who were previously treated with raloxifene or alendronate, only those receiving raloxifene showed robust early gains in BMD when subsequently treated with PTH.[131] The gains in BMD after teriparatide treatment for patients who had previously been treated with alendronate were delayed but eventually were seen.[132]

Though teriparatide appeared to be generally well tolerated in these short-term studies, long-term safety data are needed. Toxicity studies with rats have shown an increased risk of osteosarcoma,[133] 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, and use of teriparatide should be avoided by patients at increased risk for skeletal malignancy.

ROLE OF MANAGED CARE

Managed care plays a major role in preventive programs and currently faces a challenge in balancing costs and quality of care related to osteoporosis prevention. Historically, adherence to preventive programs, such as smoking cessation, mammograms, Pap smears, and prenatal care, has been greater in the managed care setting than in the fee-for-service setting.[134-136] However, in all settings, BMD testing for at-risk individuals remains low.[35] Appropriate prescribing of osteoporosis medications following vertebral fractures also remains low.[137] Current estimates indicate that only one fourth of patients receive either diagnostic evaluation or prescriptions for approved therapies for osteoporosis following distal radial fracture,[138] and even fewer are treated after hip fracture.[139]

The National Committee for Quality Assurance (NCQA) has added a new Health Plan Employer Data and Information Set (HEDIS) measure for 2004 that tracks women who have had fractures, which may improve diagnosis and treatment rates.[140] Although the measure only applies to Medicare, it may also improve rates in commercial health plans.

Numerous cost considerations must be incorporated into managed care programs for the prevention of osteoporosis. These include medication costs (acquisition and monitoring), costs associated with fractures (short-term care, rehabilitation, ongoing care for patients with long-term disability), and costs associated with medication side effects (eg, deep vein thrombosis with HT and SERMs).[141]

Several studies have examined the cost-effectiveness of osteoporosis interventions over the past 10 years; however, interpretation is complicated by inconsistent methodologies and outcomes. Reported costs per quality-adjusted life-year gained ranged from $1,073 to $17,694 with risedronate to $28,510 to $37,031 with calcitonin. Even greater ranges have been reported for costs per hip fracture avoided ($1,111 to $44,700 for parenteral vitamin D and $2,977,297 for calcitonin).[141] Although these 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 quality contribute to the development of osteoporosis and increased fracture risk. At this time, BMD measurement remains the primary tool for diagnosis; however, as tools for measuring other bone characteristics become more widely available, diagnostic capabilities should continue to improve. Clinicians must recognize that many factors affect the risk of fracture and may influence treatment decisions. Synthesis of individual BMD and other risk factor data should provide clinicians with adequate information to assess fracture risk and the need for therapy.

The primary goal of osteoporosis therapy is to prevent fractures. Current therapies have been shown to improve bone mass and reduce fracture risk. Careful consideration of the risks and benefits (including fracture reduction) of these treatments should help guide clinicians in choosing therapies for individual patients.

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THE STATE OF THE ART IN THE MANAGEMENT OF OSTEOPOROSIS

PM #Med 946A

CME CREDIT INFORMATION AND POSTTEST ASSESSMENT

Publication date: January 2004 **Expiration date: January 2005**

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 and Surgeons of Columbia University. The College of Physicians & Surgeons of Columbia University is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians.

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

Instructions:
To apply for category 1 credit, you must

- Complete the posttest.
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POSTTEST ASSESSMENT (*Please record your answers below in the space provided*)

1. Which of the following contribute(s) to delayed diagnosis of osteoporosis?
   a. Prolonged asymptomatic phase
   b. Confusion regarding whom, how, and when to screen
   c. Lack of understanding of the gravity of associated risk
   d. All of the above

2. Increased bone turnover is associated with which of the following?
   a. Destruction of trabecular architecture
   b. Decreased bone mineralization
   c. Reduced bone strength (or increased number of stress risers)
   d. All of the above

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. Patients can take relatively low doses of glucocorticoids (2.5 to 7.5 mg/day of prednisone or its equivalent) without increasing their risk for hip fracture.
   a. True
   b. False

5. Which of the following BMD measurements can be used to assess bone status based on the WHO criteria?
   a. Central DXA
   b. Peripheral DXA
   c. Central quantitative computed tomography
   d. Any of the above

6. Which of the following is a biochemical marker of bone resorption?
   a. Alkaline phosphatase
   b. N-telopeptide
   c. Osteocalcin
   d. Type 1 collagen propeptides

7. Which bisphosphonates are approved for treating osteoporosis?
   a. Alendronate and pamidronate
   b. Etidronate and risedronate
   c. Alendronate and risedronate
   d. Etidronate and pamidronate

8. The WHI revealed which of the following risks associated with HT?
   a. Invasive breast cancer
   b. Coronary heart disease
   c. Probable dementia
   d. All of the above

9. Teriparatide does which of the following at low doses?
   a. Increases bone density
   b. Increases risk of vertebral fractures
   c. Decreases bone turnover
   d. Decreases bone size

10. A meta-analysis including BMD and fracture data from 12 clinical trials of antiresorptive therapy demonstrated that changes in BMD did not account completely for changes in fracture risk.
    a. True
    b. False

POSTTEST ANSWERS PM #Med 946A Expiration date: January 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. ____

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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: (please ✔)

	Excellent	Good	Fair	Poor
a. Value of the topic	❑	❑	❑	❑
b. Relevance to your practice	❑	❑	❑	❑
c. Organization of newsletter	❑	❑	❑	❑
d. Publication 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 newsletter 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 newsletter 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
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7. Would you recommend this newsletter to a colleague? ❑ Yes ❑ No

8. Additional comments and/or suggested topics for future CME activities: _____

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

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Interdisciplinary Medicine®
January 2004 Vol.5, No.5

Produced by IMED Communications
for The Office on Women's Health of the
U.S. Department of Health and Human Services

and
COLUMBIA UNIVERSITY
College of Physicians and Surgeons

This program is supported by an educational grant from The Alliance for Better Bone Health (Procter & Gamble Pharmaceuticals and Aventis Pharmaceuticals)