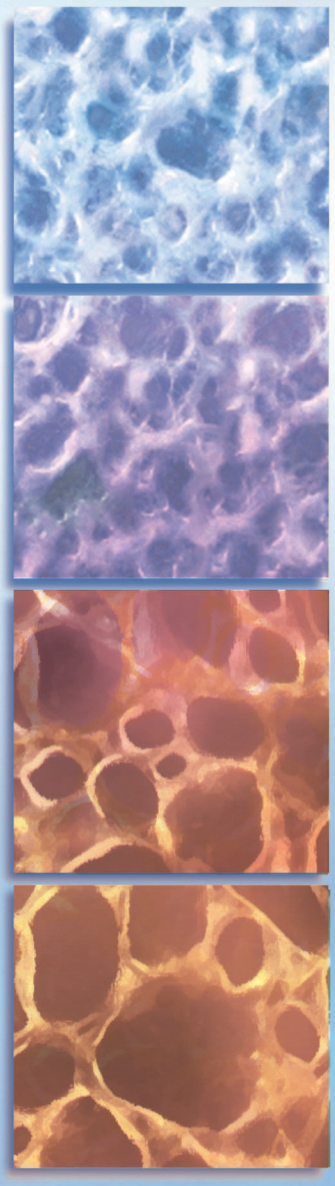
The State of the Art in the Management of Osteoporosis

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

A Case-Based CME Activity



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Program Co-Chairs

John P. Bilezikian, MD
Professor of Medicine and Pharmacology
Chief, Division of Endocrinology
Director, Metabolic Bone Diseases Program
Columbia University, College of Physicians & Surgeons
New York, New York

Marjorie Luckey, MD
Associate Professor, Obstetrics, Gynecology, and Reproductive Science
Mount Sinai Medical Center
New York, New York
Medical Director
Saint Barnabas Osteoporosis and Metabolic Bone Disease Center
Livingston, New Jersey

Program Steering Committee

John P. Bilezikian, MD
Professor of Medicine and Pharmacology
Chief, Division of Endocrinology
Director, Metabolic Bone Diseases Program
Columbia University, College of Physicians & Surgeons
New York, New York

Wanda K. Jones, DrPH
Deputy Assistant Secretary for Health
Office on Women's Health
U.S. Department of Health and Human Services
Washington, DC

Marjorie Luckey, MD
Associate Professor, Obstetrics, Gynecology, and Reproductive Science
Mount Sinai Medical Center
New York, New York
Medical Director
Saint Barnabas Osteoporosis and Metabolic Bone Disease Center
Livingston, New Jersey

Saralyn Mark, MD
Senior Medical Advisor to the Office on Women's Health
U.S. Department of Health and Human Services and the National Aeronautics and Space Administration (NASA)
Washington, DC
Assistant Clinical Professor
Internal Medicine, Obstetrics and Gynecology
Yale University School of Medicine
New Haven, Connecticut

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E. Canalis		Aventis, Eli Lilly, Merck, Procter & Gamble	Procter & Gamble
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M. Luckey	Aventis, Merck, Roche	Aventis, Eli Lilly, Merck, Procter & Gamble	Procter & Gamble, Roche
S. Mark*			
M. McClung	Aventis, Eli Lilly, Merck, Pfizer, Procter & Gamble, Roche		Aventis, Eli Lilly, Merck, Novartis, Procter & Gamble, Roche
P. Miller	Amgen, Aventis, Eli Lilly, GE Lunar, Merck, Novartis, Pfizer, Procter & Gamble, Roche, Upjohn & Pharmacia	Aventis, Eli Lilly, Merck, Procter & Gamble	
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B. Yawn			Eli Lilly

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* No Financial Interest or Affiliation; ** Other Financial Support From Abbott Immunology; †Direct Stock Shareholder for General Electric.

Faculty

Ernesto Canalis, MD
Professor of Medicine
University of Connecticut School of Medicine
Director of Research
St. Francis Hospital Medical Center
Hartford, Connecticut

Schumarry Chao, MD, MBA
Clinical Professor, School of Medicine
University of Southern California
Los Angeles, California
Senior Vice President
Strategic Development and Chief Medical Officer
MedImpact Healthcare Systems, Inc.
San Diego, California

Stanley Cohen, MD
Clinical Professor
University of Texas Southwestern Medical Center at Dallas
Medical Director, Radiant Research
Dallas, Texas

Bess Dawson-Hughes, MD
Professor of Medicine
Tufts University
Boston, Massachusetts

David W. Dempster, PhD
Professor of Clinical Pathology
Columbia University, New York
Director, Regional Bone Center
Helen Hayes Hospital
West Havenstraw, New York

Margery Gass, MD
Professor of Clinical Obstetrics and Gynecology
University of Cincinnati College of Medicine
Director, University Hospital Menopause and Osteoporosis Center
Cincinnati, Ohio

Susan Greenspan, MD
Professor of Medicine
Associate Program Director, General Clinical Research Center
Director, Osteoporosis Prevention and Treatment Center
University of Pittsburgh
Pittsburgh, Pennsylvania

Steven T. Harris, MD, FACP
Clinical Professor of Medicine and Radiology
Chief, Osteoporosis Clinic
University of California, San Francisco
San Francisco, California

Robert P. Heaney, MD
John A. Creighton University Professor
Creighton University
Omaha, Nebraska

Douglas P. Kiel, MD, MPH
Associate Professor of Medicine
Harvard Medical School
Director, Medical Research
Research and Training Institute
Hebrew Rehabilitation Center for Aged
Boston, Massachusetts

Cheryl L. Lambing, MD
Assistant Clinical Professor
University of California, Los Angeles
Director, Family Care Center
Associate Residency Director
Ventura County Medical Center
Family Practice Residency Program
Ventura, California

Andrew J. Laster, MD, FACR
Arthritis & Osteoporosis Consultants of the Carolinas
Charlotte, North Carolina
Assistant Consulting Professor of Medicine
Duke University Medical Center
Clinical Instructor in Medicine
University of North Carolina at Chapel Hill
Charlotte, North Carolina

Jeffrey P. Levine, MD, MPH
Assistant Professor
Director, Women's Health Programs
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School
New Brunswick, New Jersey

E. Michael Lewiecki, MD, FACP
President, International Society for Clinical Densitometry
Clinical Assistant Professor of Medicine
University of New Mexico School of Medicine
Osteoporosis Director
New Mexico Clinical Research & Osteoporosis Center
Albuquerque, New Mexico

Michael McClung, MD
Assistant Director, Department of Medical Education
Providence Portland Medical Center
Director, Oregon Osteoporosis Center
Portland, Oregon

Paul Miller, MD
Clinical Professor of Medicine
University of Colorado Health Sciences Center
Denver, Colorado
Medical Director
Colorado Center for Bone Research
Lakewood, Colorado

Arnold M. Moses, MD
Professor of Medicine
Director of Metabolic Bone Disease Center
Director of Clinical Research Unit
SUNY Upstate Medical University
Syracuse, New York

Graham Russell, MD, PhD
Norman Collison Professor of Musculoskeletal Sciences and Institute Director
The Botnar Research Centre and Oxford University Institute of Musculoskeletal Sciences
Nuffield Orthopaedic Centre
Oxford, England

Elizabeth Shane, MD
Professor of Clinical Medicine
Columbia University, College of Physicians & Surgeons
Attending Physician
New York Presbyterian Hospital
New York, New York

Ethel Siris, MD
Madeline C. Stabile Professor of Clinical Medicine
Columbia University, College of Physicians & Surgeons
Director, Toni Stabile Osteoporosis Center
New York Presbyterian Hospital
New York, New York

Nelson Watts, MD
Director, Bone Health and Osteoporosis Center
University of Cincinnati College of Medicine
Cincinnati, Ohio

Discussants

Cathy Kessenich, DSN, ARNP
Professor
University of Tampa
Nurse Practitioner
Private Practice, Internal Medicine
Tampa, Florida

Craig Langman, MD
Isaac A. Abt, MD Professor of Kidney Diseases
Feinberg School of Medicine
Northwestern University
Division Head, Kidney Diseases
Children's Memorial Hospital
Chicago, Illinois

Richard S. Pope, PA-C
Senior Rheumatology Physician Assistant
Arthritis Center of Connecticut
Adjunct Clinical Professor
Quinnipiac University
Founder and President, Society of Physician Assistants in Rheumatology
Waterbury Hospital
Waterbury, Connecticut

Barbara Yawn, MD, MSc
Associate Professor
University of Minnesota
Director of Research
Olmsted Medical Center
Rochester, Minnesota

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INTRODUCTION

Osteoporosis is a common disease and likely to become even more prevalent as the U.S. population continues to age. According to the National Osteoporosis Foundation (NOF), about 44 million Americans aged 50 years or older have either osteoporosis or low bone mass (osteopenia). This figure is projected to climb to 52 million in 2010 and to 61 million in 2020. The disease occurs in both sexes, but 80% of the U.S. population with osteoporosis are women.[1]

Because osteoporosis is a silent disease, it often goes undiagnosed and untreated until a patient suffers a fracture. Fractures carry significant personal and financial costs in terms of morbidity, mortality, functional decline, quality of life, and need for institutionalized care. Furthermore, a fracture markedly increases the likelihood of another fracture.

Recognizing the pervasive impact of osteoporosis, the National Committee for Quality Assurance (NCQA) has approved a new clinical measure for inclusion in its 2004 Health Plan Employer Data and Information Set, which evaluates the performance of health plans, hospitals, and other physician groups. This will measure the percentage of women aged 67 years or more who have had fractures and who received either bone mineral density (BMD) testing or medical treatment within 6 months of incurring the fracture.[2] This measure is only applicable to Medicare plans. This is a welcome development, since the majority of osteoporotic fractures in the United States are not followed with diagnostic or therapeutic approaches to the underlying disorder. Other managed care/insurance plans should take similar initiatives.

Clinicians now have several choices of therapy to prevent bone loss and protect against fractures, but there are still many challenges in identifying patients who are at risk and in selecting the proper prevention or treatment regimen for each individual. Time to response, duration of response, safety, and tolerability are among the many factors that must be weighed in clinical decision making.

These issues were the subject of a roundtable discussion held on July 28 and 29, 2003, in Washington, DC. The panelists included specialists in endocrinology, women's health, internal medicine, managed care, aging, and nutrition as well as allied health professionals. The cases discussed in this publication are a compilation of the data presented at the conference. The cases highlight several of the key points discussed and illustrate how they apply to daily clinical practice.

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.

CASE 1: MARGARET H.

History and Presentation

Margaret H. is a 60-year-old white woman who is employed, active in her community, and in general good health. She has been using hormone therapy (HT) for the past 10 years, but after reading news reports on the Women's Health Initiative (WHI), she asked her primary care physician to reevaluate her need for treatment. Margaret's current and past medical histories are significant for several osteoporosis risk factors: relatively low body weight (125 lb), current smoking (1 pack of cigarettes per day), and a sister and aunt with histories of fragility fractures of the forearm and hip. Margaret originally began taking HT for menopausal symptoms such as severe hot flashes and urogenital discomfort. Additional benefits of HT were believed to be protection against bone loss, cardiovascular disease, and age-related cognitive decline. Quality of life was also regarded to be improved by HT. The estrogen-plus-progestin arm of the WHI, which involved more than 16,000 postmenopausal women, showed that among those receiving combination HT, there were significant reductions in hip fracture, clinical vertebral fractures, and total osteoporotic fractures after 5 years of therapy. However, this arm of the WHI also showed that there were major risks, such as an increased incidence of coronary heart disease, stroke, venous thromboembolism, breast cancer, and dementia.[3,4] In addition, there were no clinically meaningful effects on quality of life in this older population, who were less likely

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Please direct all correspondence to:
Editor, *Interdisciplinary Medicine®*
IMED Communications
Dept.130, Suite 200
518 Route 513
PO Box 458
Califon, NJ 07830

to be experiencing severe vasomotor symptoms.[5] Another analysis, which considered a broad range of disease outcomes, confirmed that there was no net benefit of HT, even for women at high risk for fracture.[6] It is still not clear whether these results are applicable to women taking estrogen therapy alone to younger women (the average age of the study subjects was 63 years), or to women who have used HT previously. 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.[7] Nevertheless, the results of the WHI have led most authoritative bodies to discourage the use of HT for primary prevention or therapy of osteoporosis.

According to recent Food and Drug Administration (FDA) guidelines, alternative agents should be strongly considered as first-line therapy if the prevention of postmenopausal osteoporosis is the sole reason for considering HT. After weighing the benefits against the risks, Margaret and her physician elect to discontinue HT.

Bone loss may be rapid after HT withdrawal. In one study of postmenopausal women 65 to 77 years of age who used combination HT for 3 years, virtually all the gains they achieved in lumbar spine, femoral neck, trochanter, total-hip, and total-body BMD were lost within 2 years of discontinuation, with no significant differences from pretreatment levels noted (Figure 1).[8] In another study, somewhat younger postmenopausal women lost 6% of spine BMD within 1 year after estrogen withdrawal.[9] Unfortunately, these rapid declines after HT withdrawal are not widely appreciated.

Diagnostic Considerations

Based on guidelines of the NOF (Table 1),[1] the International Society for Clinical Densitometry, the American Academy of Clinical Endocrinology, and the U.S. Preventive Services Task Force,[10] Margaret is a candidate for osteoporosis screening because of her low body weight, current smoking, withdrawal from HT, and her family history of fractures.[1] A central dual-energy X-ray absorptiometry (DXA) study of the hip and spine is ordered because this test identifies women at high risk for fractures and can be used to diagnose osteoporosis before fractures occur.

Margaret's densitometry findings reveal that she has low bone mass (osteopenia) at the lumbar spine (T-score = −1.8) and the femoral neck (T-score −1.9). The T-score compares the patient's BMD with the mean value of normal young individuals of the same sex and expresses the difference as a standard deviation score. In contrast, the Z-score compares the patient's BMD to the mean value of a population matched for age and sex.

For each standard deviation lower than the age-adjusted mean BMD, fracture risk approximately doubles.[11] A T-score of 2.5 or less is categorized as osteoporosis, and a T-score between −1.0 and −2.5 is considered indicative of low bone mass, or osteopenia. Values higher than −1.0 are considered normal.[1]

According to NOF guidelines, women with T-scores between −1.5 and −2.0 may be eligible for drug treatment if they have other risk factors for fractures such as prior fracture, low body weight (<127 lb), or a first-degree family history of a fragility fracture.[1] Older age is also a major risk factor for fractures and should be considered in making treatment decisions. Risk factors for osteoporosis and fracture are shown in Table 2.

STATEMENT OF NEED

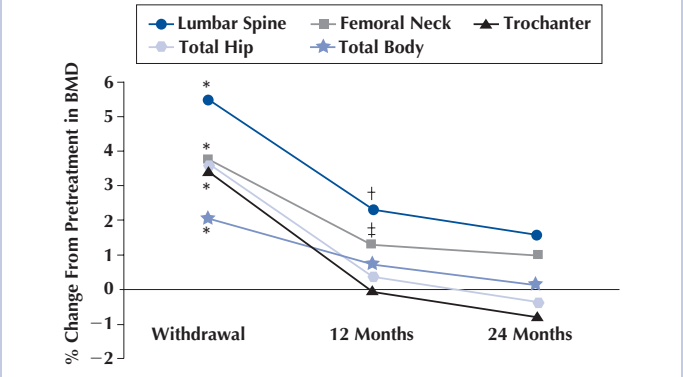
Osteoporosis is a silent disease, progressing insidiously, often without symptoms until a skeletal deformity or fracture occurs. The financial and personal costs are enormous, and they continue to grow as the U.S. population ages. One of the challenges that primary care practitioners face in detecting 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.

Initiating Therapy

Despite the widespread availability and use of bone densitometry, it remains a challenge to determine when to initiate preventive therapy for 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. The Study of Osteoporotic Fractures demonstrated that fractures commonly occur in women over age 65 who have T-scores that are not in the osteoporotic range, namely 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 T-scores above −2.5.[12] Correctly identifying patients before fractures occur using peripheral bone density measurements is even more challenging, because there

FIGURE 1

Change in BMD After Discontinuation of Combination HT[8]



*Significantly different from pretreatment ($P<.0001$)
†Significantly different from pretreatment ($P<.005$)
‡Significantly different from pretreatment ($P<.05$)

currently are no national guidelines regarding diagnostic or treatment thresholds for BMD at peripheral sites. Evidence from the National Osteoporosis Risk Assessment study involving more than 200,000 postmenopausal women has demonstrated that using a T-score cutpoint of −2.5 for treatment intervention would miss 82% of women in NORA who actually fractured 1 year after the bone density measurement. The current NOF intervention threshold 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.[13] In both of these studies, women with osteoporosis were at the highest risk for fracture. However, because osteopenia is considerably more prevalent than is osteoporosis,[14] a large proportion of fractures occur in women with osteopenia.[15] These findings clearly indicate the need to develop new tools to identify other factors which influence fracture risk (eg, bone quality, architecture) in this patient population to improve the efficient use of preventive therapies.

Additional Considerations for Assessing Risk

Although BMD is a key measurement for diagnosing osteoporosis and estimating fracture risk, it is not the only relevant measure. Other qualities of bone health, including architecture, turnover, mineralization, and damage such as microfractures,[16] are known to contribute to bone strength as well. Because the goal of osteoporosis therapy is to reduce fracture risk, not just to increase BMD, clinicians should consider other risk factors for fracture that may reflect or influence bone strength when making therapeutic decisions.

Osteoporosis is characterized by compromised bone strength and increased risk of fracture.[16] Bone strength can be defined as bone density and other measures of bone quality. Bone continually undergoes a process of remodeling in which old bone is resorbed and new bone replaces it. Whereas normal rates of turnover can help maintain bone health, high bone turnover can compromise bone strength via several different mechanisms. Adult bone remodels inefficiently, leaving less bone than there was at the beginning of the remodeling cycle. This can lead to thinning of bone cortices and trabecular elements. As trabeculae become thinner and are perforated, the horizontal trabeculae that support the load-bearing vertical trabeculae are decreased. This loss of horizontal trabeculae is associated with reduced buckling load and translates into a greater propensity for fracture with less force or trauma.[17-20]

In addition to producing the abnormal bone microarchitecture that characterizes osteoporosis, 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 bone strength, and increase fracture risk.[19,21]

Increased bone turnover also causes 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.[21]

Other skeletal properties besides microarchitecture and mineralization (eg, bone size and shape) also contribute to bone strength. In a longitudinal study, loss of BMD (−1.9% annually) in postmenopausal women was associated with an increase in medullary diameter, reflecting endosteal resorption and decreased bone strength. Interestingly, the authors also reported an increase in periosteal diameter, suggesting that in postmenopausal women, periosteal apposition partially preserves bone strength.[22]

Treatment Considerations

The decision to treat Margaret is based on the combination of her low bone density, personal and family history, and her discontinuation of HT. Antiresorptive agents suppress bone remodeling and resorption, thereby slowing or arresting bone loss and helping prevent fracture (Figure 2). They also produce bone gain proportional to the degree of remodeling suppression. Interestingly, antiresorptive agents reduce fracture risk far more than the degree that would be expected based on their effects on BMD. In a recent meta-analysis of 12 trials of antiresorptive agents with postmenopausal women, the treatments that were expected to reduce vertebral fracture risk by slightly more than 15% based on BMD actually reduced the risk by more than 45%.[23] This reinforces the fact that properties of bone affected by therapy other than increases in BMD are working to strengthen bone and decrease fracture risk.

Calcitonin

Although calcitonin has been shown to be effective in halting bone loss in women at least 5 years postmenopause, it has not demonstrated efficacy for women less than 5 years postmenopause,[24] and it is not approved by the FDA for use by this patient population.[25]

Although calcitonin has not been studied in women who are discontinuing HT, this clinical situation is physiologically comparable to early menopause, and calcitonin would not be expected to be

TABLE 1

NOF Criteria for BMD Testing[1]

All Women

- Aged ≥65 regardless of risk factors
- Younger postmenopausal with risk factors
  - Personal history of fracture in adulthood
  - History of fragility fracture in a first-degree relative
  - Low body weight (<127 lb)
  - Current smoking
  - Use of oral corticosteroid therapy for >3 months

TABLE 2

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

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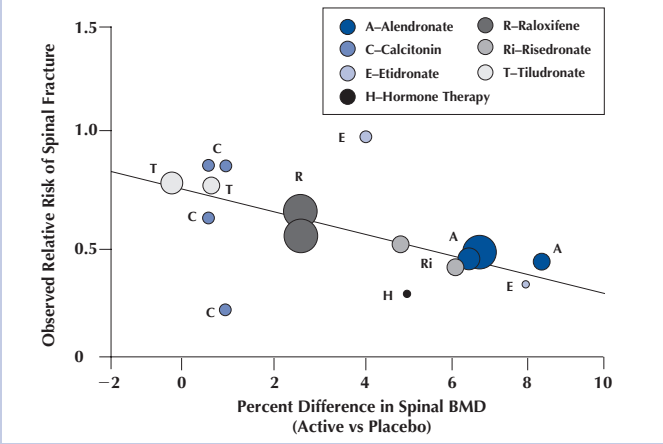
FIGURE 2

Relative Risk of Fracture and Change in BMD: Treatment vs Placebo



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effective. In women more than 5 years postmenopause, calcitonin reduces the risk of vertebral fractures, but clinical trials have not demonstrated efficacy in preventing nonvertebral fracture.[26,27]

Raloxifene

In studies with healthy postmenopausal women, raloxifene treatment (relative to placebo) significantly suppressed bone turnover markers, preserved BMD at the hip, and increased lumbar spine BMD at 3 and 5 years. It also reduced the likelihood of developing osteoporosis or osteopenia at those sites.[29,30] Among women with postmenopausal osteoporosis (PMO), raloxifene reduces the risk of new vertebral fractures in patients with or without preexisting vertebral fractures.[26] For these reasons, raloxifene would be a reasonable therapeutic option for this patient. Raloxifene, however, is known to increase the risk of hot flashes, which may limit its use for some women transitioning from HT.[1] Although raloxifene has been observed to lower the risk of clinical vertebral fractures after 1 year of use,[30] there is currently no strong evidence that it prevents nonvertebral fractures, of which Margaret has a family history. In addition, an increased risk of deep vein thrombosis with raloxifene may be a factor in clinical decisions.

Effects of Bisphosphonates on Bone Parameters and Fracture Risk

Risedronate and alendronate are potent antiresorptive bisphosphonates that are indicated for the treatment and prevention of osteoporosis. They decrease bone turnover, preserve bone structure, increase BMD, and reduce the risk of spinal and nonspinal fractures for patients with osteoporosis. For these reasons, they are often considered first-line agents for the treatment of this disease.

The bisphosphonates have been shown to reduce fracture risk more than would be expected from their effects on BMD alone. Recent analyses of data from risedronate clinical trials indicate that increases in BMD account for only a part of the observed protection against nonvertebral fractures,[31] whereas reductions in bone turnover as monitored by bone resorption markers account for a greater percentage of the reduction in vertebral and nonvertebral fracture risk.[32]

Studies examining the effects of alendronate and risedronate[33,34] 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. This is another feature of bone affected by the bisphosphonates that helps explain the observed contributions of bisphosphonates to improvements in bone strength.

Architectural benefits in bone after antiresorptive therapy were demonstrated recently in a bone-biopsy study with 26 postmenopausal women treated with either risedronate or placebo. Microarchitectural integrity deteriorated significantly in patients on placebo, whereas patients on risedronate maintained bone mass and microarchitecture. At the end of 1 year, those treated with risedronate 5 mg daily had higher bone volume, trabecular thickness, and trabecular number; lower percentage plate perforation and trabecular separation; and better connectivity as indicated by marrow star volume than did placebo-treated patients.[20] It is now believed that control of remodeling and maintenance of bone microarchitecture, along with increases in bone density, explain much of the ability of bisphosphonates to prevent fractures.[31,32]

Several large, placebo-controlled studies have demonstrated the antifracture efficacy of both risedronate and alendronate for women with PMO. Risedronate significantly decreased 1- and 3-year vertebral fracture rates as well as 3-year nonvertebral fracture rates in women with preexisting vertebral fractures.[35,36] In women with PMO but no preexisting vertebral fractures, the risk of first morphometric vertebral fracture was reduced by 75%.[37] Results from the Fracture Intervention Trial-1 demonstrated 47% and 51% reductions with alendronate in vertebral fracture and hip fractures, respectively, in women with prior vertebral fractures. In addition, 4 years of treatment with alendronate increased BMD and decreased the risk of vertebral fractures among women with low BMD.[38]

The effects of bisphosphonates are also sustained over time. Data are available to support maintenance of vertebral fracture risk reduction for 3 years with alendronate[39] and 5 years with risedronate.[40] Furthermore, bone density continued to increase, and the low incidence of fractures was maintained at 7 years in the risedronate trial.[40] Extension studies with alendronate have shown continued increases in BMD for up to 10 years,[41] but fracture risk during this period remains to be determined. Overall, long-term use of these agents is generally well tolerated.

Given the evidence above and Margaret's preference for once-weekly dosing (available only with bisphosphonates), Margaret and her physician make the decision to initiate bisphosphonate therapy.

Other Components of Therapy

Other components of treatment for Margaret include adequate intake of vitamin D (400 to 600 IU/d) and calcium (1000 to 1500 mg/d),[17] weight-bearing and muscle-strengthening exercise, and counseling on smoking cessation and moderate alcohol intake.

TABLE 3

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* agonists	Marfan syndrome	Renal tubular acidosis
Hyperprolactinemia	Vitamin D deficiency	Phenytoin		COPD†
Porphyria	Calcium deficiency	Phenobarbital		Organ transplantation
Hypophosphatasia (in adults)	Alcoholism	Vitamin D toxicity		Mastocytosis
Diabetes mellitus (Type 1)				Thalassemia
Pregnancy				
Hyperthyroidism				
Hyperparathyroidism				
Acromegaly				
Hypercalciuria				
Hypogonadism				

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

Adapted with permission from the American College of Endocrinology & The American Association of Clinical Endocrinologists. Hodgson SF, Watts NB, Bilezikian JP, et al. American Association of Clinical Endocrinologists 2001 Medical Guidelines for Clinical Practice for the Prevention and Management of Postmenopausal Osteoporosis. *Endocr Pract*. 2001;7:293-312.

CASE 2: MAYA L.

History and Presentation

Maya L. is a 55-year-old Asian-American woman who presents with a complaint of sudden-onset lower back pain. Her medical history shows that her bone density was first measured 5 years ago (2 years postmenopause) because of a strong family history of osteoporosis (her mother, maternal grandmother, and 2 aunts). At that time, her lumbar spine T-score was −1.8 and Z-score was −1.3; her total hip T-score was −2.5 and Z-score was −1.8. She had no history of earlier fractures or medical conditions that might contribute to osteoporosis (except past smoking, about 1 to 2 packs per day in her early adulthood).

Her physician's initial recommendations were estrogen plus progestin, calcium and multivitamin supplements, and regular exercise. Her lumbar spine bone loss continued over the next 2 years, however, exceeding the diagnostic center's least significant change (defined, at the 95% confidence level, as more than 2.77 times the precision error, or coefficient of variation.)[42]

Calcitonin was added to Maya's regimen, but her lumbar spine BMD continued to decrease over the subsequent 2 years. At that point, alendronate was added to her regimen, but her BMD continued to decline over the next year. By the time of her current visit, she had been on osteoporosis medication for a total of 5 years, and her cumulative BMD decline over this period was 11.6%.

Maya's acute back pain prompts a referral for spine X-ray studies, which show a vertebral compression fracture at L2, a finding with ominous implications. Each such fracture greatly increases the risk of future fractures of the vertebrae, hip, and wrist,[43] and 4% to 24% of patients with an acute fracture will experience a new compression fracture within the next year.[44] Additionally, 5-year survival after vertebral fractures is significantly reduced.[45] The financial costs of such fractures are tremendous. According to a recent estimate, almost 70,000 patients are hospitalized each year for osteoporotic vertebral fractures, at a cost of more than $500 million.[46]

Vertebral fractures also take an immeasurable toll on quality of life for both the patient and his or her family and friends. Physical limitations and dependence can cause depression, anxiety, loss of self-esteem, and strained interpersonal relationships.[1]

Diagnostic Considerations

Before initiating or changing treatment for any patient with osteoporosis, it is essential to seek out underlying medical conditions that can cause or exacerbate bone loss or interfere with therapy. This is especially important if response to therapy has been unsatisfactory. Osteoporosis that is caused or contributed to by specific diseases or medications is referred to as secondary osteoporosis. 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.[47] Metabolic disorders associated with secondary osteoporosis double the risk of hip fractures.[48] Secondary osteoporosis can be caused by many drugs and medical conditions, as listed in Table 3.

Many of these disorders can be present without significant signs or symptoms. Occult causes of secondary osteoporosis have been found in more than 40% of otherwise healthy women who initially appear to have primary osteoporosis. (Personal communication with Marjorie Luckey, MD, March 5, 2004). The most common abnormalities found were vitamin D deficiency, hypercalciuria, calcium malabsorption, and overreplacement of thyroid hormone. All patients should therefore have minimum laboratory evaluations, including serum calcium, complete blood count, 24-hour urine calcium, and 25-hydroxyvitamin D (25-OH-D). (Thyroid-stimulating hormone should be measured if patients are on thyroid supplementation or if there are symptoms of excess thyroid hormone.) These tests should be done before any specific pharmacologic therapy for osteoporosis is begun or if patients are losing bone on therapy.

Maya's routine chemistry panel test results are normal, but her 25-OH-D level is slightly low (18 ng/mL), and her 24-hour urine calcium level is significantly below normal (40 mg), despite her daily intake of more than 1500 mg of calcium. Additional testing reveals positive transglutaminase antibodies, slightly low hematocrit, slightly low serum iron and ferritin levels, and normal levels of vitamin B_{12}, folate, and carotene. A small-bowel biopsy shows flattened villi consistent with celiac disease. Celiac disease is characterized by inflammation of the small intestinal mucosa in response to gluten, which results in malabsorption of calcium and phosphorus. Gastrointestinal symptoms may or may not be present.[49] About one third of patients with celiac disease have osteoporosis at the lumbar spine, femoral neck, or radius, and another third have osteopenia at these sites.[50] The fracture rate is more than tripled among patients with celiac disease compared with age– and gender-matched controls (Figure 3).[51]

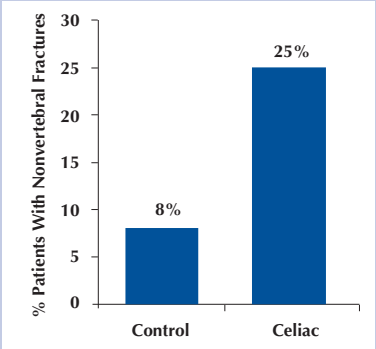
Treatment Recommendations

Maya is advised to begin a strict gluten-free diet and to maintain her calcium and add vitamin D supplementation. She also elects to continue her HT. One year later, follow-up densitometry reveals a 15% increase in spinal BMD. Based on information from the Women's Health Initiative, her physician advises her to discontinue HT. Alternative antiresorptive therapy is reasonable now that her calcium absorption has been normalized.

FIGURE 3

Fractures and Celiac Disease[51]

- 165 patients with celiac disease
- 350 times more likely to have had fractures than control subjects
- Related to late diagnosis of celiac disease
- Only 7% of patients had fractures after beginning a gluten-free diet



CASE 3: SELMA D.

History and Presentation

The staff of a local nursing home requests an evaluation of Selma D., an 82-year-old black woman with hip and back pain following several falls. Selma is small and thin and walks unsteadily with a cane, but her overall health and functioning are reasonably good for her age. Her medical history is significant for a wrist fracture 4 years ago and an estimated height loss of 3 to 4 inches since young adulthood. In general, a loss of 1.5 inches or more from a patient's adult height is an indication for spinal X-ray studies.[52]

Selma's current medical status is significant for mild hypertension, which is managed with propranolol. Her family history is significant for a hip fracture in her mother and low bone mass in her daughter. She reports that she has always avoided dairy foods because she is lactose intolerant.

Diagnostic Considerations

Osteoporosis is an extremely common problem in nursing and extended care facilities. Both the prevalence of osteoporosis and the rate of hip fractures are far higher among nursing home patients than among community residents of the same age.[53] Of black women of Selma's age who live in nursing homes, more than half have osteoporosis and another third have osteopenia.[53] Although prevalence of osteoporosis in nursing homes is high, very few patients receive treatment.

FIGURE 4

Calcium and Vitamin D Supplementation and Hip Fracture[60]

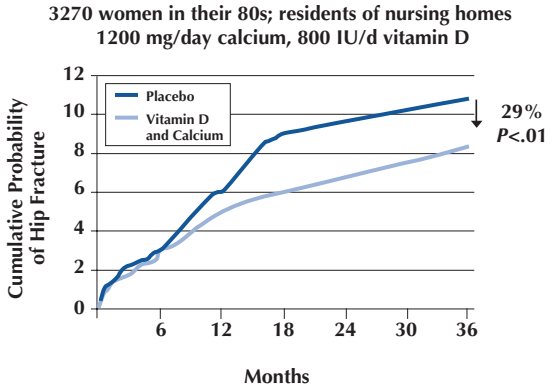
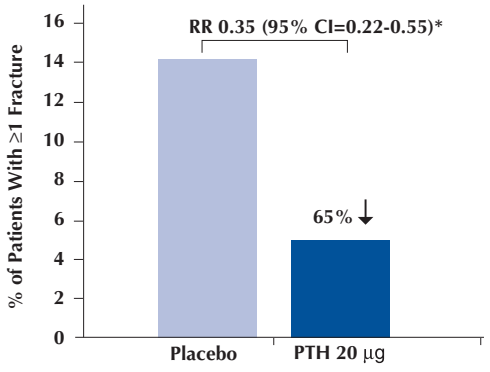


FIGURE 5A

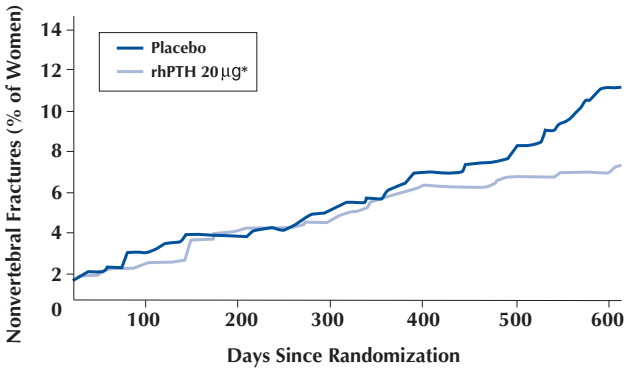
Effect of PTH (1-34) on Risk of Vertebral Fractures in Postmenopausal Women[78]



*P<.001 vs placebo

FIGURE 5B

Effect of PTH (1-34) on Risk of Nonvertebral Fractures in Postmenopausal Women[78]



*P<.005 vs placebo

Selma's advanced age, low body weight, and previous fracture put her at high risk for osteoporosis, and her loss of height may be a surrogate marker for asymptomatic compression fractures. The most helpful diagnostic test for this type of patient is a spinal X-ray study.[52] If compression fractures are noted, osteoporosis can be diagnosed without a BMD measurement, although BMD can be useful baseline information. Selma's lateral spine X-ray films do in fact show 3 compression fractures, which probably account for her pain complaints and loss of height.

The morbidity and mortality associated with spine and hip fractures in the elderly highlight the importance of aggressive prevention and treatment. In general, elderly individuals with hip fractures have a mortality risk of 20% in the first year (almost twice the risk for sex- and age-matched controls); for those residing in nursing homes when they experience fractures, the mortality risk is 20% in the first 3 months after the fracture versus 7% for nursing home residents without fractures.[54] These mortality figures are even higher among black women. Patients who do survive hip or vertebral fractures usually face repeated hospitalizations, diminished mobility, and increased disability and dependence.[55,56]

A history of past fractures is a major indicator of future fracture risk. Previous wrist, vertebral, or hip fractures significantly increase the risk of having osteoporotic fractures at the same or distant sites. Patients who have had vertebral fractures are at 4-fold higher risk for additional vertebral fractures and have more than double the risk for hip fractures.[43] This woman, who is clearly at great risk for further osteoporotic fractures, should be treated without delay.

Treatment Recommendations

Treatment plans for Selma begin with supplementation of calcium and vitamin D. Vitamin D deficiency is common in aging patients,[16] occurring in up to 60% of nursing home residents.[57,58] In addition to reducing calcium absorption and accelerating bone loss, vitamin D deficiency leads to muscle weakness and increased risk of falls. It is important to measure vitamin D and correct deficiency (any level <20 ng/mL). For an octogenarian, the currently recommended daily intake of vitamin D (400 to 600 IU) is probably inadequate to correct a deficiency.[59] A study of 3270 elderly women (mean age, 84 years) showed that 1200 mg/d of calcium plus 800 IU/d of vitamin D reduced hip fractures by 29% and total nonvertebral fractures by 24% after just 36 months (Figure 4).[60] Another recent study showed that elderly women treated with calcium (1200 mg/d) and vitamin D (800 IU/d) experienced a 49% reduction in the risk of falling, which suggests that one of the antifracture effects of vitamin D may be improving musculoskeletal function.[61]

Because more than 90% of hip fractures are due to falls,[62] comprehensive management should include strategies for reducing falls (eg, slip-proof rugs, low-heeled shoes, grab bars in the bathroom, good lighting) and their impact. Another strategy is the use of hip protectors, which are padded plastic disks sewn into special undergarments so that they reside over the greater trochanter. Until recently, these devices were considered to reduce hip fractures dramatically in nursing home residents and frail elderly adults. A recent study appearing in the Cochran Database of Systematic Reviews indicated that the effectiveness of hip protectors may be less certain – and compliance remains low.[63]

Selma's propranolol dose is adjusted to minimize postural hypotension, which can contribute to falls. Her eyesight is checked and she is fitted with glasses for distance vision. Also, Selma is referred to a physiotherapist for a modest physical activity program. A simple set of in-home strength and balance exercises has been shown to reduce the total number of falls and injuries significantly among women 80 years of age and older.[64]

Antiresorptive Therapy

Antiresorptive therapy may offer considerable benefits for elderly patients, though relatively few trials have been conducted. In a study of elderly women in nursing homes, alendronate increased BMD at the posterior-anterior spine (4.4%) and femoral neck (3.4%) after 2 years, but the study was too small to evaluate an effect on fractures. Alendronate has also been shown to reduce the rate of hip fractures in postmenopausal women with osteoporosis, but its

antifracture efficacy has not been evaluated specifically in women over 80.[65] A study of risedronate with women aged 70 to 79 years showed a decrease of 30% in hip fractures overall and 40% for women with confirmed osteoporosis, although a significant benefit was not seen for women more than 80 years old. The explanation for these observations is probably related to the increasing importance of nonskeletal factors, such as risk of falling, with age. A limitation of this study is that the majority of these subjects did not have BMD measurement, and the fracture data from the placebo arm in the study raised the possibility that many of the subjects may not have had osteoporosis.[66] Raloxifene has not been shown to have significant nonvertebral fracture-prevention efficacy among postmenopausal women.[26]

Statistics show that because of Selma's fracture history, she is at high risk for a new fracture in the next year. Therefore, it is important to provide Selma with protection against fracture risk as quickly as possible. The protective effects of bisphosphonates are evident soon after treatment is initiated. The risk of vertebral and nonvertebral fractures has been reduced significantly as early as 6 months after the start of therapy with risedronate.[67,68] The risk of vertebral and nonvertebral fractures has been significantly reduced by month 12 and 24, respectively, after the start of alendronate therapy.[69]

Selma is prescribed a bisphosphonate to help prevent future fractures. Since once-weekly dosing is as effective as daily dosing,[70,71] a once-weekly regimen is used by most patients and would most likely be appropriate for Selma.

CASE 4: DOROTHY R.

History and Presentation

Dorothy R. is a retired 67-year-old white woman with severe osteoporosis (T-scores of −3.5 at the lumbar spine and −2.8 at the hip), 2 prior vertebral fractures, at T1 and L4, and a recent wrist fracture. She is 20 years postmenopause and has never taken HT. Her previous physician initiated treatment with raloxifene 18 months ago. After 18 months, Dorothy's physician decided to discontinue raloxifene therapy, because Dorothy had now suffered a nonvertebral fracture. Her physician is aware of the fact that there is no substantial evidence to date that raloxifene reduces the risk of this type of fracture. Because Dorothy has severe osteoporosis, she needs treatment to prevent future fractures.

Treatment Recommendations

The impact of fracture in terms of morbidity, mortality, and quality of life is significant; therefore, preventing more fractures is imperative in Dorothy's case. The first step is to evaluate Dorothy for other causes of bone loss. The results of all laboratory tests are within normal ranges, so the next step may be referral to an osteoporosis specialist. Referrals may be advisable in several circumstances, such as for idiopathic osteoporosis in premenopausal women and young men, patients who are losing bone while on therapy, and patients with complicated secondary or severe osteoporosis.[72]

In addition to adequate calcium and vitamin D intake and an individualized exercise program, reasonable therapeutic options for Dorothy would be either a bisphosphonate or the new anabolic agent, teriparatide (recombinant human parathyroid hormone, or rhPTH 1−34). Both of these alternatives have been shown to significantly reduce the incidence of both vertebral and nonvertebral fractures for patients with severe osteoporosis.

Appropriate candidates for teriparatide therapy are postmenopausal women and men with established osteoporosis who are at high risk for fracture. Examples of individuals at high risk are those with very low bone mass, advanced age, and previous fragility fractures. Other indications include loss of BMD or persistently low T-scores after other osteoporosis therapies (if no secondary cause can be identified), inability to tolerate bisphosphonates, and contraindications to other therapies.[73,74]

Challenges associated with teriparatide treatment include the high cost, the need for daily subcutaneous injections, and potential toxicity concerns.[74] Studies with rats have shown an increased risk of osteosarcoma, which has prompted the FDA to require a "black box" warning in the drug's labeling in the U.S., but the relevance of this finding to humans is unknown. Whereas antiresorptive agents such as bisphosphonates improve bone density and maintain microarchitecture by reducing bone turnover, teriparatide stimulates bone turnover and thus affects bone quality differently than do antiresorptives. There appears to be an "anabolic window" in which bone-formation markers peak several months before bone-resorption markers do.[75] Teriparatide improves bone size and geometry as well as bone microarchitecture.[76,77] In men with idiopathic osteoporosis, it substantially increases BMD at the hip and lumbar spine,[75] and in postmenopausal women with preexisting vertebral fractures, it raises vertebral, femoral, and total-body BMD and greatly reduces the risk of vertebral and nonvertebral fractures after 21 months of treatment (Figures 5A and B).[78] The recommended duration of treatment with teriparatide is 18 to 24 months. Safety and efficacy beyond 2 years of use have not been evaluated.[73,74]

SUMMARY AND CONCLUSIONS

Osteoporosis is an insidious and disabling disease that exerts a tremendous toll on older Americans in terms of mortality, impaired function, and lost mobility. Therefore, efforts to prevent, identify, and treat this disease should be priorities for all clinicians treating patients at risk.

Although BMD is a major tool for diagnosis, other aspects of bone quality and strength should be considered as well; when fracture risk is estimated, variables such as family and personal medical history, comorbidities, and personal habits must be taken into account.

The primary goal of osteoporosis therapy is to prevent fractures. Several agents are available that improve bone mass and strength and reduce fracture risk (Table 4).[75,78,79] In selecting therapies for individual patients, clinicians should weigh the risks and benefits of therapies in the context of each patient. With appropriate treatment, the consequences of low bone strength can be greatly minimized. Pharmacologic and dietary therapy, along with appropriate physical activity, offer important benefits for both treatment and prevention, helping older women and men enjoy longer and more productive lives.

TABLE 4

Osteoporosis Treatment Options[3,75,78,79]

Treatment	Effects on BMD	Effects on Fracture Risk
Nonpharmacologic		
Exercise	Preserved BMD in short-term studies	No direct evidence of risk reduction
Fall prevention	N/A	Hip pads reduce fractures; other methods controversial
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
Pharmacologic		
Bisphosphonates (alendronate, risedronate)	Preserve or increase BMD	Reduce risk of vertebral and nonvertebral by ~50%
Calcitonin	Preserves BMD in spine but not proven at other sites	Probably reduces vertebral risk – controversial
HT	Preserves BMD, but bone loss may accelerate when HT is stopped	Decreases both hip and vertebral fracture risk by 30%
Selective estrogen receptor modulators	Preserve or increase BMD	Raloxifene lowers vertebral risk 30% - 50%; not yet shown to reduce nonvertebral risk
Teriparatide (PTH 1-34)	Stimulates bone turnover, increases BMD	Reduces vertebral and nonvertebral risk

Key Summary Points

- The prevalence of osteoporosis is high and growing; about 80% of Americans with osteoporosis are female, and most are older, but no one is immune.
- Osteoporosis is quite common among nursing home residents.
- Osteoporosis – and even fractures – can often go unrecognized and untreated; a fracture is a risk factor for subsequent fractures and can diminish health, survival, and quality of life.
- BMD is just one of several factors in diagnosing osteoporosis and estimating fracture risk.
- Secondary causes of osteoporosis should be considered and ruled out or treated if found.
- Bisphosphonates and selective estrogen receptor modulators are effective alternatives to HT for preventing osteoporosis and its sequelae.
- Adequate calcium, vitamin D, and exercise are essential in preventing osteoporotic fractures.
- Anabolic therapy, such as teriparatide, shows promise for treating patients with severe osteoporosis.
- Antiresorptive therapy includes calcitonin, raloxifene, and bisphosphonates such as alendronate and risedronate.

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THE STATE OF THE ART IN THE MANAGEMENT OF OSTEOPOROSIS

PM #Med 946B

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Publication date: March 2004 **Expiration date: March 31, 2005**

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POSTTEST ASSESSMENT (*Please record your answers below in the space provided*)

1. In the WHI, HT was found to
   a. reduce fracture risk and reduce breast cancer risk
   b. increase fracture risk and increase risk of heart disease and breast cancer
   c. reduce fracture risk but increase breast cancer and heart disease risk
   d. increase fracture risk but reduce breast cancer risk

2. In the study of women 65 to 77 years of age, by Gallagher et al (2002), the BMD benefits of HT were lost within ___ of discontinuation.
   a. 6 months
   b. 1 year
   c. 1.5 years
   d. 2 years
   e. 3 years

3. Peripheral BMD measurement predicts fracture as accurately as does central BMD measurement.
   a. True
   b. False

4. A patient with a T-score of –1.8 is considered to have
   a. normal bone mass
   b. osteopenia
   c. osteoporosis
   d. none of the above

5. Risk factors for fracture include
   a. low body weight
   b. prior fracture
   c. family history of fracture
   d. low BMD
   e. all of the above

6. Rates of fracture have been reduced with antiresorptive therapy by larger percentages than can be explained by changes in BMD alone.
   a. True
   b. False

7. Teriparatide stimulates bone turnover and improves bone size, geometry, and microarchitecture.
   a. True
   b. False

8. Celiac disease is a result of allergy to
   a. gluten
   b. rice
   c. wheat
   d. lactose

9. Causes of secondary osteoporosis include
   a. type 1 diabetes
   b. malnutrition
   c. glucocorticoid use
   d. vitamin D deficiency
   e. all of the above

10. Results of the Study of Osteoporotic Fractures demonstrated that fractures occur _____ in patients who have T-scores higher than –2.5.
    a. rarely
    b. commonly

POSTTEST ANSWERS **PM #Med 946B** **Expiration date: March 31, 2005**

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	Excellent	Good	Fair	Poor
a. Value of the topic	❑	❑	❑	❑
b. Relevance to your practice	❑	❑	❑	❑
c. Organization of publication	❑	❑	❑	❑
d. Publication length	❑	❑	❑	❑
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