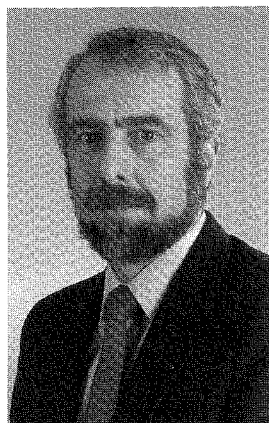
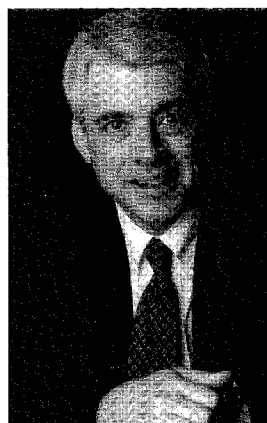


Current Approaches to Osteoporosis Prevention

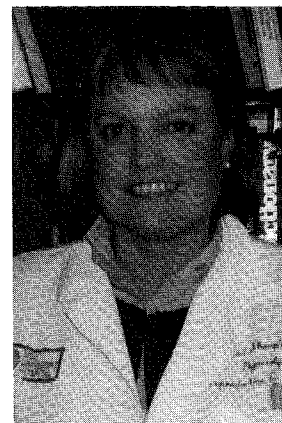
Based on presentations by Robert Lindsay, MD, PhD; Nelson B. Watts, MD; and Donna Shoupe, MD



Robert Lindsay, MD, PhD
Conference Chair



Nelson B. Watts, MD



Donna Shoupe, MD

Presentation Summary

As the US population ages, an increasing number of osteoporotic fractures will occur unless effective disease prevention strategies are initiated. Proper identification of risk factors and selection of appropriate candidates for therapeutic intervention during the early postmenopausal

years can help address this public health concern. Proactive recommendations for lifestyle changes, increased weight-bearing exercise, appropriate intake of calcium and vitamin D, and initiation of long-term preventive therapy in certain individuals will contribute to the overall goal of fracture reduction.

More than 1.5 million Americans experience osteoporotic fractures each year, with an annual cost of nearly \$14 billion to the US healthcare system (Table 1).¹ As the population ages and an increased number of fractures occur, these costs will more than double over the next 30 years.²

This trend is not inevitable, however. Successful prevention strategies have

been developed for other chronic diseases. For example, high blood pressure, which increases stroke risk, and high cholesterol levels, which can lead to cardiovascular disease, are conditions that can often be controlled with various medical treatments as well as through dietary and lifestyle modifications. Similarly, it is now possible to identify and to implement effective prevention strategies for osteoporosis. This is true now

more than ever as new therapies and diagnostic techniques become increasingly available.

Physical Evaluation and Risk Assessment

The link between estrogen depletion and bone loss has been well established. Assessment of each woman's risk of fracture is therefore an essential component of the menopause examination. These risk factors can be categorized as modifiable, treatable, and unmodifiable (Table 2). Modifiable risk factors include cigarette smoking, excessive alcohol intake, a sedentary lifestyle, and calcium deficiency. Treatable risk factors include estrogen deficiency, diseases or conditions that cause bone loss, such as hyperthyroidism, and use of certain medications, such as glucocorticoids, that accelerate bone loss. Unmodifiable risk factors include genetic traits, such as family history of osteoporosis or osteoporotic fracture, fair skin, and slender body build, as well as gender, age at menopause, and a personal history of fracture, kyphosis (dowager's hump), or nulliparity. Dramatic weight loss and low body weight are also risk factors for fracture.^{3,4}

In evaluating patients for possible preventive therapy, the healthcare provider should obtain a thorough family and personal history as well as a complete physical examination that includes pelvic and breast examinations, standard laboratory evaluations, and an accurate height measurement. During the initial evaluation, clinicians should also identify and treat other conditions that may contribute to the development of osteoporosis, such as endocrine and metabolic disorders, malignant diseases, and calcium or vitamin D deficiencies.

Preventive Regimens

Because currently available pharmacologic agents cannot replace lost bone with bone of equal quantity or quality, it is better to maintain bone health by preventing bone loss.⁵ Current therapies have an antiresorptive effect that slows

the process of bone collagen breakdown and results in increased bone mass that can be measured over time with bone densitometry. Therefore, osteoporosis prevention strategies should strive to optimize bone mass and to preserve skeletal integrity.⁴

Women with multiple risk factors for fracture are prime candidates for preventive therapy after menopause. Regardless of therapeutic intervention, clinicians should recommend regular weight-bearing exercise, adequate calcium and vitamin D intake, minimal alcohol consumption, and smoking cessation for all patients. Although these

Table 1. Scope of Osteoporosis

| |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> ■ 28 million Americans are affected or have low bone mass* ■ 4 of 5 affected are women* ■ Risk of hip fracture is equal to a woman's combined risk of developing breast, uterine, and ovarian cancer* ■ 1.5 million fractures annually* ■ Cost to society of \$14 billion per year† |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

*Stand Up to Osteoporosis: Your Guide to Staying Healthy and Independent Through Prevention and Treatment. Washington, DC: National Osteoporosis Foundation; 1997:10.

†Ray NF, Chan JK, Thamer M, Melton LJ III. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: Report from the National Osteoporosis Foundation. *Bone Miner Res* 1997;12:24-35.

Table 2. Osteoporosis Risk Factors*

| Modifiable | Treatable | Unmodifiable |
|--------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> ■ Smoking ■ Sedentary lifestyle ■ Excessive alcohol intake | <ul style="list-style-type: none"> ■ Estrogen depletion ■ Comorbid conditions ■ Corticosteroid use ■ Certain pharmacologic agents | <ul style="list-style-type: none"> ■ Gender ■ Age at natural menopause ■ Race/ethnicity ■ Small, thin frame ■ Family or personal history |

*Stand Up to Osteoporosis: Your Guide to Staying Healthy and Independent Through Prevention and Treatment. Washington, DC: National Osteoporosis Foundation; 1997:10.

recommendations are important to overall bone health, they do not necessarily eliminate osteoporotic risk. Therapeutic options should be thoroughly explained to women who may benefit from pharmacologic intervention. In addition to preventive therapy, vitamin D and calcium supplementation should be recommended for patients with deficiencies.

The following section describes each component of the osteoporosis prevention regimen in detail. Although these components comprise a successful approach to osteoporosis prevention, clinicians should adapt the regimen to individual patient needs.

Therapeutic options should be thoroughly explained to women who may benefit from pharmacologic intervention. In addition to preventive therapy, vitamin D and calcium supplementation should be recommended for patients with deficiencies.

Diet and Lifestyle Issues

Calcium and Vitamin D. Adequate calcium intake is important in maintaining bone mass after menopause. Current recommendations from the National Institutes of Health suggest that postmenopausal women who are not taking estrogen should receive 1500 mg of calcium per day, and those on hormone replacement therapy (HRT) should receive 1000 mg of calcium per day.⁶ While adequate calcium intake is important, it should not be considered a substitute for therapeutic intervention.

Vitamin D enhances calcium absorption. Deficiencies in vitamin D, which are caused most often by inadequate dietary intake or insufficient exposure to sunlight, reduce calcium absorption. For patients with vitamin D deficiency, exposure to sunlight, intake of vitamin D-

fortified dairy products, or vitamin supplements should be recommended.⁶

Exercise. Weight-bearing exercise helps build bone and muscle mass. It also contributes to overall well-being and quality of life. Maintaining physical activity after menopause can reduce age- and menopause-related bone loss and decrease the incidence of falls by improving strength and coordination.⁷ In a 12-month study on the effect of aerobic training on postmenopausal women, participants either maintained or slightly increased their bone mineral density (BMD). Those who entered menopause within 6 years demonstrated reduction in lumbar BMD loss, suggesting that exercise may have a more beneficial effect on BMD when initiated close to the onset of menopause.⁸

Smoking Cessation. Cigarette smoking has been implicated as a risk factor for osteoporosis, but the mechanisms of its effect on BMD are unknown. Results from a 2-year calcium supplementation study of 320 women with low to moderate calcium intake suggest that smoking is associated with decreased calcium absorption.⁹ Another study of 41 pairs of female twins ages 27 to 73 years demonstrated that women who smoke one pack of cigarettes per day throughout adulthood will have a 5% to 10% deficit in BMD by the time they reach menopause.¹⁰

Use of Bone Densitometry

The utility of screening with bone densitometry at menopause remains controversial. This is due, in part, to concerns about cost in relation to the clinical value of densitometry as a screening tool. Questions also have been raised regarding the clinical utility of measuring BMD at a time when women are perceived to be at or near their peak bone density. These issues, as well as recommendations for the optimal timing of bone density measurement, will be explored in the final segment of this supplement.

In addition, studies have demonstrated that BMD measurement may be

helpful for women who are undecided about the use of long-term HRT after menopause.^{11,12} A study of 140 women who had recently entered menopause and were undecided about estrogen use indicated that results of bone densitometry can greatly influence a woman's willingness to initiate therapy for osteoporosis prevention. Subjects were randomized to receive either educational information about osteoporosis and a voucher for a BMD measurement after 1 year or the same educational information and a bone densitometry voucher for immediate use. Both groups were offered an HRT prescription. Twenty percent of the women who did not have an immediate BMD measurement filled their estrogen prescription, compared with 64% of those who received an immediate BMD measurement (Figure 1).¹¹

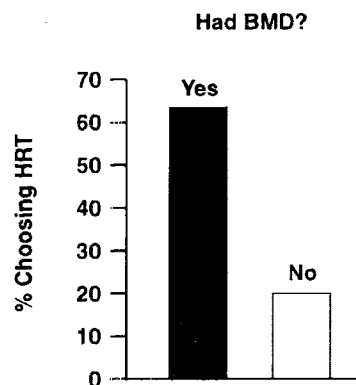
Several techniques for measuring BMD are available. All are based on the preferential attenuation of X rays by bone in comparison with fat and soft tissue.¹³ Currently, dual-energy X ray absorptiometry (DEXA) is most commonly used because its results are highly reproducible. Quantitative measurement of a patient's BMD is reported in relation to a reference population of age-matched or young normal subjects.

Biochemical Markers

Biochemical markers of bone turnover may represent a promising new category of diagnostic tests. These analytes, released from bone into the bloodstream, are measured by a laboratory test performed on a serum or urine sample. They can be categorized as markers for bone resorption (bone collagen breakdown) or markers for bone formation. The lab test quantifies an analyte in the specimen and generates a numerical test result that is compared with values from a reference population for clinical interpretation. To date, markers of bone resorption have been more widely used than markers of bone formation because available therapies have an antiresorptive effect on bone.

Currently, these tests are used in some clinical practices to monitor response to therapy. Because antiresorptive therapy has a positive effect on bone by decreasing bone resorption, a marker of bone resorption at initiation of therapy and then several months later should show a decline in bone resorption levels in response to therapy.

Figure 1. Effect of Having a Bone Density Test on Estrogen Use



BMD = bone mineral density.
Data from reference 11.

In the future, biochemical markers may be used to identify patients who need therapeutic intervention, either by independently assessing fracture risk or in combination with bone densitometry. Markers may also aid in selecting pharmacotherapy and are already being used in specific cases when an assessment of therapeutic response is needed between BMD measurements. Biochemical markers should demonstrate therapeutic response within 3 to 6 months after initiation of therapy.¹⁴

The use of biochemical markers is still in its infancy. Broad use among large

postmenopausal populations will depend on results from ongoing research and the cost per test. The last article in this supplement includes specific recommendations on the use of these diagnostic measurements.

Therapeutic Interventions

Several therapies are indicated for osteoporosis prevention. They include HRT and alendronate sodium. Other compounds, such as raloxifene and salmon calcitonin, are under investigation for similar use. At press time, raloxifene had been approved in the United States for prevention of osteoporosis. These therapies will be addressed in greater detail in another article.

Hormone Replacement Therapy. In the United States, HRT is first-line therapy for prevention and treatment of osteoporosis.⁴ For maximum skeletal protection, therapy should begin at menopause and continue indefinitely, although medication can be initiated at any time after menopause.⁴ Epidemiological studies show that women exposed to estrogen for 7 to 10 years or longer may have a 50% or greater reduction in the incidence of osteoporotic fractures of the hip and wrist¹⁵ and a 75% reduction in incidence of vertebral fractures.¹⁶

Long-term HRT also has several drawbacks. Hormonal therapy has been linked to increased risk and incidence of certain cancers. For example, HRT has been shown to stimulate breast and endometrial tissue. In particular, unopposed estrogen has been linked with increased risk and incidence of endometrial cancer.^{17,18} However, risk of endometrial cancer is substantially reduced with concomitant administration of a progestin.¹⁹

Adherence to long-term HRT is poor in the United States, with only 30% of women filling their first prescription.²⁰ Many women discontinue estrogen therapy because menopausal symptoms cease, vaginal bleeding persists, or they are concerned about the risk of breast or

uterine cancer.^{21,22} Adherence issues will be discussed in detail in the next article.

Bisphosphonates. Bisphosphonates comprise a class of potent antiresorptive compounds. One of these agents, alendronate sodium, is indicated for the prevention and treatment of osteoporosis. Among patients with osteoporosis, alendronate has been shown to progressively increase bone mass in the spine, hip, and total body and reduce the incidence of hip²³ and vertebral fractures.²⁴

Calcitonin. Salmon calcitonin is indicated for treatment of established osteoporosis. When administered nasally, calcitonin is generally well tolerated and has an analgesic effect for some patients. Currently, it is most frequently used among patients with osteoporosis who are unable to take HRT or alendronate. Use of calcitonin for osteoporosis prevention is under investigation and has shown positive effect at the lumbar spine,²⁵ but has not yet been well established clinically for this use.

Developing Therapies. The potential market for appropriate and effective therapies to prevent osteoporosis is enormous. Of particular interest will be the emergence of selective estrogens that retain the attributes of traditional hormonal therapy without the drawbacks. As new compounds become available, clinicians need to identify appropriate candidates for therapeutic intervention and guide women in the selection and utilization of appropriate therapy.

Conclusion

Osteoporosis is a preventable disease that can adversely affect postmenopausal women's health. The physical and socioeconomic costs of the disease can be reduced by proactive intervention during the early postmenopausal years. Patients should be evaluated for osteoporosis risk factors at the time of menopause. They also should be educated about the magnitude of the disease, given appropriate diet and

lifestyle recommendations, and offered therapeutic intervention when appropriate.

... REFERENCES ...

1. Ray NF, Chan JK, Thamer M, Melton LJ III. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: Report from the National Osteoporosis Foundation. *J Bone Miner Res* 1997;12:24-35.
2. Riggs BL, Melton LJ III. The prevention and treatment of osteoporosis. *N Engl J Med* 1992;327:620-627.
3. Col NF, Eckman MH, Karas RH, et al. Patient-specific decisions about hormone replacement therapy in postmenopausal women. *JAMA* 1997;277:1140-1147.
4. AACE clinical practice guidelines for the prevention and treatment of postmenopausal osteoporosis. *Endocrine Practice* 1996;2:155-171.
5. Lindsay R, Marcus R, Recker R. Osteoporosis: What's new in prevention and treatment. *Patient Care* August 15, 1996;8:24-53.
6. *NIH Consensus Statement: Optimal Calcium Intake*. Bethesda, Md: National Institutes of Health 1994;12(4):1-31.
7. Prince RL, Smith M, Dick IM, et al. Prevention of postmenopausal osteoporosis. A comparative study of exercise, calcium supplementation, and hormone-replacement therapy. *N Engl J Med* 1991;325:1189-1195.
8. Martin D, Notelovitz M. Effects of aerobic training on bone mineral density of postmenopausal women. *J Bone Miner Res* 1993;8:931-936.
9. Krall EA, Dawson-Hughes B. Smoking and bone loss among postmenopausal women. *J Bone Miner Res* 1991;6:331-338.
10. Hopper JL, Seeman E. The bone density of female twins discordant for tobacco use. *N Engl J Med* 1994;330:387-392.
11. Silverman SL, Greenwald M, Klein R, Drinkwater BL. Effect of bone density information on decisions about hormone replacement therapy: A randomized trial. *Obstet Gynecol* 1997;89:321-325.
12. Rubin SM, Cummings SR. Results of bone densitometry affect women's decisions about taking measures to prevent fractures. *Ann Intern Med* 1992;116:990-995.
13. Johnston CC, Melton LJ III, Lindsay R, Eddy DM. Clinical indications for bone mass measurement. *J Bone Miner Res* 1989;4(suppl 2):1-28.
14. Delmas PD, Garnero P. Utility of biochemical markers of bone turnover in osteoporosis. In: Marcus R, Feldman D, Kelsey J, eds. *Osteoporosis*. San Diego, Calif: Academic Press. 1996:1075-1088.
15. World Health Organization. *Assessment of Fracture Risk and Its Application to Screening for Postmenopausal Osteoporosis: Report of a WHO Study Group*. Geneva, Switzerland: World Health Organization, 1994. Technical report series 843.
16. Lindsay R, Hart DM, Forrest C, Baird C. Prevention of spinal osteoporosis in oophorectomized women. *Lancet* 1980;2:1151-1154.
17. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997;350:1047-1059.
18. Brinton LA, Hoover RN, The Endometrial Cancer Collaborative Group. Estrogen replacement therapy and endometrial cancer risk: Unresolved issues. *Obstet Gynecol* 1993;81:265-271.
19. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestins Interventions (PEPI) Trial. *JAMA* 1995;273:199-208.
20. Ravnikaar VA. Compliance with hormone therapy. *Am J Obstet Gynecol* 1987;156:1332-1334.
21. Ferguson KJ, Hoegh C, Johnson S. Estrogen replacement therapy: A survey of women's knowledge and attitudes. *Arch Intern Med* 1989;149:133-136.
22. Dupont WD, Page DL. Menopausal estrogen replacement therapy and breast cancer. *Arch Intern Med* 1991;151:67-72.
23. Karpf DB, Shapiro DR, Seeman E, et al. Prevention of nonvertebral fractures by alendronate. A meta-analysis. Alendronate Osteoporosis Treatment Study Groups. *JAMA* 1997;277:1159-1164.
24. Liberman UA, Weiss SR, Bröll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med* 1995;333:1437-1443.
25. Reginster JY, Deroisy R, Lecart MP, Sarlet N, et al. A double-blind, placebo-controlled, dose-finding trial of intermittent nasal salmon calcitonin for prevention of postmenopausal lumbar spine bone loss. *Am J Med* 1995;98:452-458.