



AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

A PRACTICE COMMITTEE REPORT

A Committee Opinion

PREVENTION AND MANAGEMENT OF OSTEOPOROSIS IN WOMEN

Definition and Background

This Committee Opinion focuses on postmenopausal osteoporosis (type I), as is commonly seen in women during the first 15-20 years after menopause. Osteoporosis is a systemic skeletal disease characterized by microarchitectural deterioration of bone tissue with a resultant increase in fragility.¹ This leads to an increased risk of fracture, which may occur even in the absence of significant trauma. Some 13-18% of U.S. women age 50 and older have osteoporosis while another 37-50% have low bone mass (osteopenia).² Both osteopenia and osteoporosis increase the risk of fracture. Although hip fracture has been properly emphasized as a source of significant morbidity and mortality (15-20%),³ the more common thoracic spine fracture accounts for significant morbidity, including pain, deformity, loss of independence and reduced cardiovascular, respiratory and even digestive function.

Pathophysiology and Diagnosis

The Bone Remodeling Cycle

The bone remodeling cycle, an intricate combination of bone breakdown (resorption) mediated by multinucleated giant cells

called osteoclasts and bone buildup (formation) mediated by osteoblasts remains in balance once peak bone mass is attained at skeletal maturity (typically age 25-35 years). From that time onward bone mass declines at a slow, but steady, rate of about 0.4% per year. The accelerated loss of bone begins in the perimenopausal years. After menopause this rate increases dramatically reaching 2 to 5% per annum for the first 5-10 years after the last menses.^{4,5}

WHO Criteria

Osteoporosis has been defined based on central bone mineral density (BMD) relative to a healthy young adult female population (T-score). The World Health Organization (WHO) defines osteopenia and osteoporosis using bone density measurements as follows.⁶

1. BMD > -1.0 SD below the young adult mean to < -2.5 SD is defined as osteopenia;
2. BMD \geq -2.5 SD below the young adult mean is defined as osteoporosis.

If a patient's bone density is > -2.5 SD below the young normal mean and a fracture(s) is present, then the patient is said to have severe osteoporosis.⁴ The Z-score is a value that

has been defined based on mean axial BMD distribution relative to the patient's chronologic age. If the Z-score is >1 SD, a more extensive evaluation for secondary causes of osteoporosis should be considered. Use of the T-score and Z-score for peripheral devices (i.e. ultrasound) may not be equally applicable unless established by independent investigation.

Risk Factor Assessment

Modifiable risk factors for osteoporosis include poor calcium and vitamin D nutrition, early menopause, limited physical activity especially immobilization or paralysis,^{7,8,9} difficulty seeing, poor health, tendency to fall, cigarette smoking⁷ and excessive alcohol consumption. Non-modifiable causes include a family history for osteoporosis or hip fractures.^{10,11} Secondary causes of bone loss include hyperthyroidism, hyperparathyroidism, hypercortisolism (including glucocorticoid use), multiple myeloma, osteogenesis imperfecta, and hypoestrogenism either with menopause or from the prolonged use of GnRH analogues or other agents.

Bone Densitometry

Ideally screening BMD measurements should be performed on all postmenopausal women not on HRT. The lumbar spine and hip bone densities as measured by dual energy xray absorptiometry (DEXA) remain the gold standard for both diagnosis and measuring response to treatment. In young, early menopausal women, the lumbar spine BMD responds rapidly to estrogen deficiency (with bone loss). These are the ideal body sites to test in this population. In older women, particularly those over age 65 years, osteophytes and spinal compression fractures often artificially elevate the lumbar spine BMD, which makes the total hip or femoral neck a

better site for analysis. Quantitative computerized tomography (QCT) has the advantage of assessing concomitant fractures and eliminating various artifacts during analysis, however, it generally is more costly, less precise and exposes the patient to greater levels of radiation. [See ¹¹ for review].

A variety of precise and accurate technologies can be used for screening of the peripheral skeleton at sites such as the finger, forearm, or calcaneus in addition to assessing the axial skeleton (i.e. spine and hip). In the absence of the ability to perform axial BMD screening, any screening is generally preferable to none at all. The preferred site for screening at the peripheral sites is the calcaneus. It is rich in trabecular bone, is weight bearing, and has excellent predictive value for hip fracture. This site, however, is less useful for monitoring response to therapy in individual subjects since it changes very slowly, and often imperceptibly. Follow-up scanning should usually be reserved for at least 2 years. Shorter intervals may be justified in certain clinical situations (i.e. corticosteroid therapy) where more rapid changes in BMD can occur.

Bone Biomarkers

Bone biomarkers have been used in clinical studies to evaluate the effect of drug treatment on bone remodeling. Serum osteocalcin, bone specific alkaline phosphatase, and protein breakdown products of procollagen have been used to follow the process of bone formation. During resorption of the bone by osteoclasts, calcium and metabolites of the collagen matrix are released and can be measured in serum or urine. These markers of bone resorption include N-telopeptide, C-telopeptide, pyridinoline, and

(Continued on page 3)

deoxyridinoline. Unfortunately, serum and urinary concentrations of bone formation and bone resorption markers vary considerably throughout the day and from day to day. These large variations limit the clinical usefulness of biomarkers in screening for osteoporosis or following a patient's response to treatment.¹³

Pharmacologic Therapy for Prevention and Treatment of Osteoporosis

An increasing number of therapeutic agents have been approved for prevention and treatment of osteoporosis. In general, these compounds can be divided into drugs which inhibit bone resorption and also bone formation (i.e. antiresorptive agents) and those that can promote bone formation only (i.e. anabolic agents). At the present time, all drugs approved for osteoporosis demonstrate primarily antiresorptive action. Thus, once osteoporosis is established, antiresorptive treatment will prevent further bone loss but cannot appreciably increase bone mass, bone connectivity, or bone strength. Two bone anabolic agents, human parathyroid hormone 1-34 (hPTH 1-34)^{12,14} and fluoride^{15,16} show promise and are still in clinical trials.

Estrogens remain the most widely used agents for prevention and treatment of menopausal osteoporosis. Because of its antiresorptive action, estrogens administered through either oral, transdermal, or transvaginal routes are effective in prevention of bone loss. Current studies are focused on reducing the doses of estrogen required for its bone-conserving action. Table 1 provides recommended dosage guidelines for prevention of osteoporosis based on recent randomized clinical trial data. Although the concomitant use of a progestin is required in women who have a uterus, there is no clear

evidence that medroxyprogesterone acetate itself has significant effects on bone.¹⁸ By contrast, norethindrone, a less commonly utilized progestin, appears to have bone-sparing effects independent of estrogen.¹⁹

Table 1. Minimal established estrogen dose required for prevention of osteoporosis

Compound	Prevention Dose
Conjugated equine estrogen ²⁰	0.3 mg/day
Conjugated estrone ²¹	0.3 mg/day
Micronized estradiol	0.5 mg/day
Transdermal estradiol ²²	0.025 mg/day
Ethinyl estradiol ²³	5 ì g/day

Most recently, synthetic steroidal compounds called selective estrogen receptor modulators (SERMs) have been shown to have antiresorptive properties in bone. These compounds bind to the two types of estrogen receptor (á and â) with varying receptor affinities and appear to demonstrate estrogenic actions in some tissues (bone and liver) and antiestrogenic actions in other tissues (endometrium and breast). Clinical trials have demonstrated that raloxifene,^{24,25} and tibolone^{26,27} are effective in the treatment of osteoporosis (see Table 2).

Bisphosphonates are derivatives of pyrophosphate that specifically target the skeleton and are potent inhibitors of bone remodeling. Although these compounds are effective through oral administration, absorption is less than 1%, requiring that these agents be administered first in the morning with 6 to 8 ounces of water, one half hour before any food or drink. Currently, two bisphosphonates, alendronate^{28,29} and risedronate^{30,31} are marketed for osteoporosis indications (see Table 2).

(Continued on page 4)

(Continued from page 3)

Salmon calcitonin has been FDA-approved for treatment of osteoporosis. This hormone can be delivered by intranasal administration on a daily basis.^{33,34} Antibody formation in a significant proportion of patients has been found with long-term use and may be responsible for its reduced long-term efficacy (see Table 2).

Calcium supplementation at doses between 1000-1500 mg/day alone or in combination with vitamin D supplementation has been shown to be effective in preventing loss of bone mass in an elderly population.³⁵⁻³⁷ However this dose may be inadequate for prevention of osteoporosis during the early menopausal period, a time when estrogen-deficiency associated bone loss is accelerated.

Fluoride in the form of sodium fluoride or monofluorophosphate is not approved by the FDA for treatment of osteoporosis although it is used in other countries.³⁸ It is the only agent other than hPTH 1-34 which increases bone formation. Effective doses range from 20-30 mg of fluoride ion daily when given in a slow-release enteric-coated preparation.

Table 2. Effective doses of various bone-active agents based on randomized clinical trials.

Compound	Class	Mode of Action	Prevention Dose	Treatment Dose
Raloxifene	SERM	Antiresorption	60 mg/day	60 mg/day
Tibione	SERM	Antiresorption	2.5 mg/day	2.5 mg/day
Alendronate	Bisphosphonate	Antiresorption inhibit osteoclasts	5 mg/day	10 mg/day 70 mg/week
Risedronate	Bisphosphonate	Antiresorption inhibit osteoclasts	2.5 mg/day	5 mg/day
Salmon Calcitonin	Calcium regulation	Antiresorption	Not approved	200 IU/day
Calcitriol	Vitamin D analog	Antiresorption	1 µg/day	—
Calcium Carbonate	Calcium	Antiresorption	1000 mg/day	—

Compliance, Adherence, and Conclusions

Despite evidence indicating that estrogens are effective in prevention of bone loss, less than 20% of women remain on estrogen for more than five years.^{39,40} Current surveys suggest that aside from physician input, other influences such as media sources, and close friends may significantly alter patient motivations to remain on estrogen replacement therapy. With the introduction, documented efficacy, and promotion of other non-estrogen agents such as SERMs and bisphosphonates, there is optimism that consistent long-term use of bone-conserving agents will become widespread during the postmenopausal years.

References

1. Consensus development conference: diagnosis, prophylaxis and treatment of osteoporosis. *Am J Med.* 1993;94:646-650.
2. Looker AC, Orwoll ES, Johnston CC Jr, et al. Prevalence of low femoral bone density in older US adults from NHANES III. *J Bone Miner Res.* 1997;12:11:1761-1768.
3. National Osteoporosis Foundation. *Physician's Guide to Prevention and Treatment of Osteoporosis.* Belle Mead, NJ: Excerpta Medica, Inc;1998.
4. Meunier PJ, Delmas PD, Eastell R, et al. Diagnosis and management of osteoporosis in postmenopausal women: clinical guidelines. *Clin Ther.* 1999;21:1025-1044.
5. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med.* 1995; 332:767-773.
6. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Report of a WHO Study Group. (Technical report series 843.) Geneva, Switzerland: World Health Organization;1994.
7. Slemenda CW, Johnston CC Jr. High intensity activities in young women: site specific bone mass effects among female figure skaters. *Bone Miner.* 1993;20:125-132.
8. Globus RK, Bikle DD, Morey-Holton E. The temporal response

(Continued on page 5)

(Continued from page 4)

- of bone to unloading. *Endocrinology*. 1986;118:733-742.
9. Seeman E, Hopper JL, Bach LA, et al. Reduced bone mass in daughters of women with osteoporosis. *N Engl J Med*. 1989; 320:554-558.
 10. Evans RA, Marel GM, Lancaster EK, et al. Bone mass is low in relatives of osteoporotic patients. *Ann Intern Med*. 1988;109: 870-873.
 11. Jergas M, Genant HK. Current methods and recent advances in the diagnosis of osteoporosis. *Arthritis Rheum*. 1993;36:1649-1662.
 12. Fujita T, Inoue T, Morii H, et al. Effect of an intermittent weekly dose of human parathyroid hormone (1-34) on osteoporosis: a randomized double-masked prospective study using three dose levels. *Osteoporos Int*. 1999; 9(4):296-306.
 13. Jensen JE, Kollerup G, Sorensen HA, Sorenson OH. Intraindividual variability in bone markers in the urine. *Scand J Clin Lab Invest*. 1997;57(suppl 227)29-34.
 14. Finkelstein JS, Klibanski A, Arnold AL, Toth TL, Hornstein MD, Neer RM: Prevention of estrogen deficiency-related bone loss with human parathyroid hormone-(1-34): a randomized controlled trial. *JAMA*. 1998;280(12):1067-1073.
 15. Alexandersen P, Riis BJ, Christiansen C: Monofluorophosphate combined with hormone replacement therapy induces a synergistic effect on bone mass by dissociating bone formation and resorption in postmenopausal women: a randomized study. *J Clin Endocrinol Metab*. 1999;84(9):3013-3020.
 16. Ringe JD, Kipshoven C, Coster A, Umbach R: Therapy of established postmenopausal osteoporosis with monofluorophosphate plus calcium: dose-related effects on bone density and fracture rate. *Osteoporos Int*. 1999;9(2):171-178.
 17. Pak CY, Zerwekh JE, Antich PP, Bell NH, Singer FR: Slow-release sodium fluoride in osteoporosis. *J Bone Miner Res*. 1996;11(5):561-564.
 18. The Writing Group for the PEPI Trial: Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. *JAMA*. 1996;276:1389-1396.
 19. Surrey ES, Fournet N, Voigt B, Judd HL: Effects of sodium etidronate in combination with low-dose norethindrone in patients administered a long-acting GnRH agonist: a preliminary report. *Obstet Gynecol*. 1993; 81:581-586.
 20. Recker RR, Davies KM, Dowd RM, Heaney RP: The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. A randomized, controlled trial. *Ann Intern Med*. 1999;130(11): 897-904.
 21. Ettinger B, Genant HK, Cann CE: Postmenopausal bone loss is prevented by treatment with low-dosage estrogen with calcium. *Ann Intern Med*. 1987;106:40-45.
 22. Weiss SR, Ellman H, Dolker M: A randomized controlled trial of four doses of transdermal estradiol for preventing postmenopausal bone loss. Transdermal Estradiol Investigator Group. *Obstet Gynecol*. 1999;94(3):330-336.
 23. Speroff L, Rowan J, Symons J, Genant H, Wilborn W: The comparative effect on bone density, endometrium, and lipids of continuous hormones as replacement therapy (CHART study). A randomized controlled trial. *JAMA*. 1996;276:1397-1403.
 24. Ettinger B, Black DM, Mitlak BH, et al: Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators *JAMA*. 1999;282(7):637-645.
 25. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med*. 1997;337:1641-1647.
 26. Beardsworth SA, Kearney CE, Purdie DW. Prevention of postmenopausal bone loss at lumbar spine and upper femur with tibolone: a two-year randomized controlled trial. *Br J Obstet Gynaecol*. 1999;106(7):678-683.
 27. Studd J, Arnala I, Kicovic PM, Zamblera D, Kroger H, Holland N. A randomized study of tibolone on bone mineral density in osteoporotic postmenopausal women with previous fractures. *Obstet Gynecol*. 1998;92(4 pt 1):574-579.
 28. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med*. 1995;333:1437-1443.
 29. Karpf DB, Shapiro DR, Seeman E, et al. Prevention of nonvertebral fractures by alendronate. *JAMA*. 1997;277:1159-1164.

(Continued on page 6)

(Continued from page 5)

30. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA*. 1999;282(14):1344-1352.
31. Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston CC Jr. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. *J Clin Endocrinol Metab*. 1998;83(2):396-402.
32. Bone HG, Greenspan SL, McKeever C, et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. *J Clin Endocrinol Metab*. 2000;85(2):720-726.
33. Reginster JY, Deroisy R, Lecart MP, 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.
34. Peichl P, Rintelen B, Kumpan W, Broll H. Increase of axial and appendicular trabecular and cortical bone density in established osteoporosis with intermittent nasal salmon calcitonin therapy. *Gynecol Endocrinol*. 1999;13(1):7-14.
35. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. *N Engl J Med*. 1992;337:1637-1642.
36. Storm D, Eslin R, Porter ES, et al. Calcium supplementation prevents seasonal bone loss and changes in biochemical markers of bone turnover in elderly New England women: a randomized placebo-controlled trial. *J Clin Endocrinol Metab*. 1998;83(11):3817-3825.
37. Aerssens J, Declerck K, Maeyaert B, Boonen S, Dequeker J. The effect of modifying dietary calcium intake pattern on the circadian rhythm of bone resorption. *Calcif Tissue Int*. 1999;65(1):34-40.
38. Pak CY, Sakhaee K, Zerwekh JE, Parcel C, Peterson R, Johnson K. Safe and effective treatment of osteoporosis with intermittent slow release sodium fluoride: augmentation of vertebral bone mass and inhibition of fractures. *J Clin Endocrinol Metab*. 1989;68:150-159.
39. Torgerson DJ, Donaldson C, Russell I, Reid DM. Hormone replacement therapy: compliance and cost after screening for osteoporosis. *Eur J of Obstet Gynecol Reprod Biol*. 1995;59:57-60.
40. Brett KM, Madans JH. Use of postmenopausal hormone replacement therapy: estimates from a nationally representative cohort study. *Am J Epidemiol*. 1997;145:536-545.

This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. While this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources and institutional or clinical practice limitations. This Committee Opinion was approved by the Practice Committee of the American Society for Reproductive Medicine May, 2000, the Board of Directors of the American Society for Reproductive Medicine July, 2000 and reviewed by the ASRM Practice Committee January, 2001.



COPYRIGHT 2001 AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

1209 Montgomery Highway, Birmingham, Alabama 35216-2809 • phone 205/978-5000 • fax 205/978-5005
E-mail asrm@asrm.org • URL <http://www.asrm.org>