

Osteoporosis

Milisa K Rizer, MD, MPH

*Department of Family Medicine, The Ohio State University, 2231 North High Street,
Columbus, OH 43201, USA*

Osteoporosis, as defined by the National Osteoporosis Foundation, is a disease that is characterized by low bone mass and structural deterioration of bone tissue, which leads to bone fragility and an increased susceptibility to fractures [1]. Aging is only one factor that contributes to the development of osteoporosis. Genetics, suboptimal nutrition, deficiency of calcium and vitamin D, lifestyle, smoking, decrease in sex hormone production, and medications also contribute to skeletal fragility.

In the United States, more than 10 million individuals have osteoporosis and more than 34 million have low bone mass or osteopenia of the hip [2]. It has been estimated that 1.5 million individuals suffer a bone disease–related fracture each year [3]. Osteoporosis is responsible for more than 700,000 vertebral fractures and more than 300,000 hip fractures every year [3,4]. Women who are older than the age of 50 years have a 50% chance of suffering a fracture; men of the same age have a 25% risk. Those who have a hip fracture have a 10% to 20% mortality in the first year, and less than 50% regain their prefracture level of mobility and independence [2]. Mortality within 90 days of osteoporotic fractures in individuals who are older than 65 years is substantially higher than predicted; for some fractures, the risk for early death increases by nearly sevenfold [5]. Osteoporotic fractures are a frequent and important cause of disability and medical costs worldwide. Fortunately, osteoporotic fractures are preventable.

Guidelines for the prevention, screening, diagnosis, and management of osteoporosis have been established by the US Preventive Services Task Force (USPSTF), the National Osteoporosis Foundation, Surgeon General, American College of Obstetrician and Gynecologists, American Association of Clinical Endocrinologists, and the Osteoporosis Society of Canada. Although some are consistent and similar, others are not.

E-mail address: rizer.8@osu.edu

Prevention

Exercise is an important component of any osteoporosis prevention program. All types of physical activity can contribute to bone health. Activities that are weight bearing or involve impact are most useful for increasing or maintaining bone mass [2]. Recent small studies found that the use of vibrating platforms increased bone mineral density (BMD) and slowed bone loss [2]. A systematic review of randomized trials shows that impact and nonimpact exercises have a positive effect at the lumbar spine in pre- and postmenopausal women. Impact exercise probably has a positive effect at the femoral neck. More studies are required to determine the optimal intensity and type of exercise [6]. Throughout life, men and women should be encouraged to participate in exercise, particularly in weight-bearing exercises, which include impact as a component. A review of eight trials found that exercise programs showed a trend toward prevention of bone loss in the lumbar spine with impact and nonimpact exercise [6].

Calcium

Calcium supplementation has a small, positive effect on bone density. The data show a trend toward reduction in vertebral fractures, but do not address, in a meaningful way, the possible effect of calcium on reducing the incidence of nonvertebral fractures [7]. Hip fractures are related strongly to low BMD, cost more to repair, and cause more disability than does any other type of osteoporotic fracture [8]. A study by Dawson-Hughes and colleagues [9] concluded that healthy older postmenopausal women with a daily calcium intake of less than 400 mg can reduce bone loss significantly by increasing their calcium intake to 800 mg per day. They also showed that supplementation with calcium citrate maleate was more effective than was supplementation with calcium carbonate at the doses used in the study.

Vitamin D

Vitamin D decreases vertebral fractures and may decrease nonvertebral fractures. A meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women showed that it reduced the incidence of vertebral fractures [relative risk (RR), 0.63; 95% CI, 0.45–0.88; $P < .01$], and showed a trend toward reduced incidence of nonvertebral fractures [RR, 0.77; 95% CI, 0.57–1.04; $P = .09$] [10]. The use of standard or hydroxylated vitamin D has not been studied well. In a study of 3270 healthy ambulatory women with a mean age of 84 ± 6 years, 1634 received 800 IU/d of vitamin D3 along with 1200 mg of elemental calcium, and 1632 received double placebo. The bone density of the proximal femur increased 2.7% in the group that received vitamin D and decreased 4.6% in the group

that received placebo ($P < .001$). The number of hip fractures was 43% lower ($P < .043$) and the total number of nonvertebral fractures was 32% lower ($P < .015$) in the group that took vitamin D plus calcium [11].

Randomized controlled trials indicate that supplemental calcium and vitamin D reduce the risk for hip fractures and other nonvertebral fractures in elderly women [4]. Table 1 outlines the current recommended amounts of calcium and vitamin D in the diet.

Screening

Risk factors

The USPSTF recommends that women aged 65 years and older be screened routinely for osteoporosis, although the USPSTF does not define "routinely." This screening should begin at age 60 years for women who are at increased risk for osteoporotic fractures [2]. To estimate the benefits of routine screening for women in different age groups, the USPSTF used estimates from recent studies to project the number of fractures that would be prevented over 5 years from a hypothetical cohort of 10,000 postmenopausal women [12]. For women 65 to 69 years of age, the numbers needed to screen were 731 to prevent one hip fracture and 248 to prevent one vertebral fracture in 5 years [13]. For women with low bone density, the number needed to screen was 88 to prevent one hip fracture and 30 to prevent one vertebral fracture. The number needed to screen became more favorable as age advanced [14]. In addition, it found three clinical risk factors that consistently predicted increased risk for fracture: advanced age, low weight or body mass index, and nonuse of hormone replacement therapy (HRT). The presence of any of the three risk factors increased the risk for fracture by 70% (RR, 1.7) [13,14].

The USPSTF makes no recommendation for or against routine osteoporosis screening in postmenopausal women who are younger than 60 years or

Table 1
Recommended daily dosages of calcium and vitamin D

Age group	Calcium		Vitamin D	
	(mg/d)	[SOR]	(IU/d)	[SOR]
Prepubertal children (ages 4–8 y)	800	[B]	No data	
Adolescents (ages 9–18 y)	1300	[B]	No data	
Women (ages 19–50 y)	1000	[A]	400	[D]
Women over 50 y	1500	[A]	800	[A]
Pregnant or lactating women (≥ 18 y)	1000	[A]	400	[D]
Men (ages 19–50 y)	1000	[C]	400	[D]
Men over 50 y	1500	[C]	800	[A]

Abbreviation: SOR, strength of recommendation.

Data from Whiting SJ, Calvo MS. Dietary recommendations for vitamin D: a critical need for functional end points to establish an estimated average requirement. *J Nutr* 2005;135:304–9.

in women who are aged 60 to 64 years who are not at increased risk for osteoporotic fractures [2]. No study has evaluated the effect of screening in reducing fractures in this younger population [4,13]. Although several studies have tested screening tools, the Osteoporosis Society of Canada recommends targeted case finding strategies for those at increased risk, using at least one major or two minor risk factors (Box 1), along with BMD measurement with central dual-energy x-ray absorptiometry (DEXA) at age 65 years [13].

Low bone BMD along with the major risk factors of previous fragility fracture, age, and family history of osteoporosis stand out as predictors of fracture related to osteoporosis. Clinically, a fragility fracture may be defined as one that occurs as a result of minimal trauma, such as a fall from a standing height or less, or no identifiable trauma [15]. These risk factors

Box 1. Risk factors for osteoporosis

Major risk factors

- Age older than 65 years
- Vertebral compression fracture
- Fragility fracture after age 40
- Family history of osteoporotic fracture
- Systemic glucocorticoid therapy of longer than 3 months
- Malabsorption syndrome
- Primary hyperparathyroidism
- Propensity to fall
- Osteopenia apparent on radiograph
- Hypogonadism
- Early menopause before age 45

Minor risk factors

- Rheumatoid arthritis
- Low dietary calcium intake
- Chronic anticonvulsant therapy
- History of clinical hyperthyroidism
- Smoking
- Excessive alcohol intake
- Excessive caffeine intake
- Weight less than 57 kg
- Chronic heparin therapy
- Weight loss greater than 10% of weight at age 25

Data from Brown JP, Josse RG. 2002 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 2002;167:S1-34.

have a cumulative effect such that, for example, if a person has a low BMD in addition to a fragility fracture or is older than 65 years of age and has a BMD in the range associated with osteoporosis, he or she should be considered to be at high risk for fracture and a candidate for therapy.

A meta-analysis of 29 published cross-sectional studies of smoking and bone density indicated that postmenopausal bone loss was greater in current smokers than in nonsmokers [4]. Other studies found that the risk for hip fracture was higher for thinner smokers than for normal or overweight smokers [4]. Alcohol use is an inconsistent predictor of bone mass and fractures [4]. Caffeine intake is associated inconsistently with low bone density and fractures [4]. Another reasonable recommendation is to screen postmenopausal women who are younger than 65 years who have low weight (or body mass index) or who have never used HRT [16].

People who receive 7.5 mg of prednisone daily for more than 3 months should be assessed for initiation of a bone-sparing therapy. People who receive more than 2.5 mg of prednisone daily should be regarded as being at increased risk for fragility fracture and require further assessment, with at least BMD measurement [15].

Dual-energy x-ray absorptiometry scanning

DEXA is the technical standard for measuring BMD because it measures at important sites of osteopathic fractures, has high precision and accuracy, is inexpensive, and has modest radiation exposure [17]. Typically, measurement of BMD is taken at two locations, spine and hip, and reported as a T-score and a Z-score. The T-score is the difference between an individual's BMD and the mean BMD for a reference population. It is expressed in standard deviation units. A score of 0 indicates a BMD equal to the mean, a score of +1 indicates one standard deviation above the mean, and a score of -1 is one standard deviation below the mean. Osteoporosis is defined as a T score that is less than -2.5 [16]. The Z-score is used to compare an individual with others in the same age group [16]. Measuring BMD remains the single best predictor of fracture risk available [2]. Central (hip and spine) DEXA is the most accurate tool for evaluating BMD in clinical settings [15]. Access to BMD measurement should not be limited by decision tools based on clinical risk factors [15].

Screening frequency

Optimal screening frequency has not been studied, but the USPSTF suggests a frequency of not more than every 2 years for older women or every 5 years for younger postmenopausal women [14]. For younger individuals who initially were screened based upon risk factors but who have normal BMD values, repeat testing every 5 to 10 years may be helpful [14]. Those who have a borderline low BMD or may lose bone rapidly (eg, exposure

to high doses of glucocorticoids) require repeat screening in 2 to 3 years [15]. DEXA is useful in monitoring patients who are on medical therapy for osteoporosis [15]. Patients should be rescanned using central DEXA scanning 2 years after initiating medication therapy.

Ultrasound

Quantitative ultrasound may assist in the diagnosis of osteoporosis, but is not useful for monitoring. Sound waves that are used to assess bone mass do not emit radiation. It can measure bone density in a variety of peripheral sites. Most devices use a formula to calculate a bone density equivalent and are not sufficiently precise for follow-up or monitoring [15].

Treatment

The National Osteoporosis Foundation recommends starting pharmacologic intervention for those patients who are determined to be at increased risk for an osteoporotic-related fracture: patients with a T-score of -2.0 or lower by hip DEXA with no risk factors, those with a T-score of -1.5 or lower and one or more risk factors, or those with a previous hip or vertebral fracture [1]. Antiresorptives or anabolic agents can be used. Antiresorptives include HRT, bisphosphonates, calcitonin, and selective estrogen receptor modulator. The only anabolic agent available is teriparatide. There is convincing, patient-oriented evidence for nonvertebral fracture reduction for only two agents: risedronate (Actonel) and alendronate (Fosamax) [18].

Bisphosphonates

The bisphosphonates are a first-line preventive therapy in postmenopausal women with low bone density, and first-line treatment for postmenopausal women who have osteoporosis, especially those with pre-existing vertebral fractures [15]. For weekly dosing regimens, once-weekly alendronate is slightly better than is once-weekly risedronate in increasing the bone density in the trochanter and spine [19]. Bisphosphonates also are the first-line therapy for prevention of glucocorticoid-induced osteoporosis and for the treatment of glucocorticoid-induced osteoporosis in patients who require prolonged glucocorticoid therapy [15]. Bisphosphonates also are indicated as first-line treatment for men who have low bone mass or osteoporosis [15].

In premenopausal women who have osteopenia or osteoporosis, the use of bisphosphonates has not been examined, and is not recommended in the absence of an identified secondary cause of osteoporosis [15]. Table 2 outlines the important uses of the bisphosphonates in the treatment of osteoporosis.

Table 2
Bisphosphonates in the treatment of osteoporosis

Condition	Strength of recommendation		
	Alendronate	Risedronate	Etidronate
Preventive therapy in postmenopausal women with low bone density	A	A	No data
Treatment of postmenopausal women who have osteoporosis	A	A	B
Preventive therapy for glucocorticoid-induced osteoporosis	A	A	B
Treatment of glucocorticoid-induced osteoporosis	A	A	B
Treatment for men with low bone mass	A	No data	B

Data from Brown JP, Josse RG. 2002 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 2002;167:S1–34.

Calcitonin

Nasal or parenteral calcitonin is a first-line treatment for pain associated with acute vertebral fractures [15]. It is considered as a second-line treatment for postmenopausal women who have osteoporosis [15]. Nasal calcitonin was shown to increase BMD and reduce lumbar spine fractures by 36%, but has not been shown to reduce hip fractures [20].

Hormone replacement therapy

HRT is a first-line preventive therapy in postmenopausal women with low bone density [15]; however, when used only for the prevention of postmenopausal osteoporosis, the risks of HRT may outweigh the benefits. HRT is a first-line preventive therapy for women who experience menopause before age 45 [15]. It is a second-line treatment for postmenopausal women who have osteoporosis [15]. With prolonged use of HRT taken only for the treatment of postmenopausal osteoporosis, the substantial risks for cardiovascular disease, stroke, and invasive breast cancer may lead to an unfavorable risk-benefit ratio [17]. It should be administered for the shortest period at the lowest possible dose.

Raloxifene

Raloxifene (Evista) is a selective estrogen receptor modulator that is designed to provide the benefits of estrogen on BMD with a lower risk for breast cancer, endometrial cancer, and cardiovascular disease [20]. Raloxifene is a first-line therapy in the prevention of further bone loss in postmenopausal women with low bone density, and a first-line treatment for osteoporosis in postmenopausal women [15]. Raloxifene was shown to increase BMD and reduce the risk for vertebral fractures, but there is no evidence that it reduces nonvertebral fractures [20]. The adverse effects that are

associated with raloxifene include venous thromboembolic disease, pulmonary embolism, and hot flashes [20].

Teriparatide

Teriparatide (Forteo) is a once-daily, subcutaneously administered anabolic agent that stimulates osteoblastic bone formation at trabecular and cortical sites [16]. It is approved for treatment of osteoporosis in postmenopausal women who are at high risk for fracture or for whom other therapies have failed. In conjunction with adequate calcium and vitamin D, it produces increases in bone mass of 10% to 15% per year [5,16]. It also reduces all vertebral fractures by approximately 67% and nonvertebral fracture rates by approximately 50%.

Parathyroid hormone

Parathyroid hormone (PTH) is tolerated well, although some patients experience leg cramps and dizziness. Because PTH caused an increase in the incidence of osteosarcoma in rats, patients with an increased risk for osteosarcoma (eg, patients who have Paget's disease of bone, previous radiation therapy of the skeleton, bone metastases, hypercalcemia, or a history of skeletal malignancy) should not receive PTH therapy. The safety and efficacy of PTH have not been demonstrated beyond 2 years of treatment [20,21].

Table 3 summarizes the options for the screening, prevention, and treatment of osteoporosis.

Table 3
Summary of recommendations for the screening, prevention and treatment of osteoporosis

Recommendation	Strength of recommendation
Treatment should be initiated to reduce fracture risk in postmenopausal women who have experienced a fragility or low-impact fracture. [1,15]	A
Treatment should be instituted in those postmenopausal women with BMD T scores less than -2 by central DEXA in the absence of risk factors and in women with T scores less than -1.5 in the presence of one or more risk factors. [1,15]	A
First-line pharmacologic options determined by the FDA to be safe and effective for osteoporosis prevention should be used. [1,15]	A
First-line pharmacologic options determined by the FDA to be safe and effective for osteoporosis treatment should be used. [1,14]	A
Women should be counseled about the following preventive measures: adequate calcium, vitamin D, exercise, smoking cessation, moderate alcohol intake, and fall prevention strategies. [1,15]	B
BMD testing should be recommended to all postmenopausal women 65 y Lears of age or older. [1,2,12]	B
BMD testing should be recommended for postmenopausal women younger than 65 years of age who have one or more risk factors for osteoporosis. [1,2,12]	B

References

- [1] National Osteoporosis Foundation. Fast facts about osteoporosis. Available at: www.nof.org/osteoporosis/diseasefacts.htm. Accessed January 23, 2006.
- [2] US Department of Health and Human Services. Bone health and osteoporosis: a report of the Surgeon General. Available at: www.surgeongeneral.gov/library/bonehealth. Accessed January 22, 2006.
- [3] Riggs BL, Melton LJ III. The worldwide problem of osteoporosis: insights afforded by epidemiology. *Bone* 1995;17(5 Suppl):505S–11S.
- [4] HSTAT. Guide to clinical preventive services. 3rd edition: recommendations and systematic evidence reviews, guide to community preventive services. Available at: www.ncbi.nlm.nih.gov. Accessed January 29, 2006.
- [5] Heaney RP. Advances in therapy for osteoporosis. *Clin Med Res* 2003;1(2):93–9.
- [6] Wallace BA, Cumming RG. Systematic review of randomized trials of the effect of exercise on bone mass in pre- and postmenopausal women. *Calcif Tissue Int* 2000;67(1):10–8.
- [7] Shea B, Wells G, Cranney A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. *Endocr Rev* 2002;23(4):552–9.
- [8] Cummings S, Melton LJ III. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002;359:1761–67.
- [9] Dawson-Hughes B, Dallal GE, Krall EA, et al. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med* 1990;323(13):878–83.
- [10] Papadimitropoulos E, Wells G, Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. *Endocr Rev* 2002;23(4):560–9.
- [11] Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med* 1992;327(23):1637–42.
- [12] The US Preventive Services Task Force. Screening for osteoporosis in postmenopausal women: recommendations and rationale. Available at: www.ahrq.gov/clinic/3rddupstf/osteoporosis/osteorr.htm. Accessed December 27, 2005.
- [13] Nelson H, Helfand M, Woolf S, et al. Screening for postmenopausal osteoporosis: a review of the evidence for the US Preventive Services Task Force. *Ann Intern Med* 2002;137:529–41.
- [14] Cronholm P. Densitometry identifies women in whom treatment will reduce fracture risk. *J Fam Pract* 2003;52(2).
- [15] Brown J, Josse R. 2002 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *CMAJ* 2002;167(Suppl 10):S1–34.
- [16] South-Paul JE. Osteoporosis: Part 1. Evaluation and assessment. *Am Fam Physician* 2001;63:897–904, 908.
- [17] Neff M. Practice guidelines: ACOG releases guidelines for clinical management of osteoporosis. Available at: www.aafp.org/afp/20040315/practice.html. Accessed February 5, 2006.
- [18] Cranney A, Guyatt G, Griffith L, et al. Meta-analysis of osteoporosis therapies for postmenopausal osteoporosis. *Endocr Rev* 2002;23(4):570–8.
- [19] Allen ML, Watt L. Guidelines for the diagnosis, screening and treatment of osteoporosis in women. *Adv Stud Med* 2005;5(10):518–23.
- [20] National Osteoporosis Foundation. Pharmacologic options for drug treatment of osteoporosis. Accessed at www.nof.org/physguide/pharmacologic.htm on 1/29/2006.
- [21] Rosen CJ, Hochberg MC, Bonnick SL, et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. *J Bone Miner Res* 2005;20(1):141–51.