Guidelines for the Diagnosis, Screening, and Treatment of Osteoporosis in Women

Michele L. Allen, MD, MS; Lacey E. Wyatt, MD, MPH

ABSTRACT

PURPOSE: To review the epidemiology, screening, diagnosis, and treatment of osteoporosis in women.

EPIDEMIOLOGY: Osteoporosis affects more than 8 million women in the United States, leading to 1.5 million fractures yearly.

REVIEW SUMMARY: The morbidity and mortality caused by osteoporosis have a significant impact on US healthcare costs. Effective diagnostic tools are available, including single x-ray absorptiometry, dual x-ray absorptiometry (DEXA), quantitative computed tomography, and ultrasound. Of these tools, DEXA is most commonly used. Laboratory screening is also recommended for premenopausal women without significant risk factors. Prevention of this disease is important because lifestyle changes, such as calcium supplementation, weight-bearing exercise, and cessation of smoking, all can have a significant effect on the risk of fracture. Available treatments include calcium, vitamin D, bisphosphonates, and low-dose estrogen. Each therapy has advantages and disadvantages, and treatment should be tailored to the needs of individual patients. Pharmacologic therapies under investigation include antiresorptive agents, statins, intravenous pamidronate, and zoledronic acid. Monitoring of treatment with DEXA and/or biochemical markers is important to ensure effective therapy.

TYPE OF AVAILABLE EVIDENCE: Randomized-controlled trials, electronic textbooks, and nationally recognized treatment guidelines.

GRADE OF AVAILABLE EVIDENCE: Fair.

CONCLUSION: Osteoporosis is a major cause of morbidity and mortality. Given current demographic trends, the burden of this disease will continue to increase. Increased screening, prevention, and treatment can mitigate the negative impact of this disease on individuals and on US healthcare costs.

See editorial on page 547.
of osteoporosis lead most often to vertebral and proximal femur fractures, which may result in chronic pain, inability to perform activities of daily living, loss of height, significant comorbidity, and death. The current estimated cost of treating osteoporotic fractures is $13.8 billion, with non-hip fractures accounting for 36.9% of this cost. With the aging of the US population, the impact of this disease will only increase—3 times the current number of fractures resulting from osteoporosis are predicted by the year 2040. These facts underscore the importance of appropriate prevention, diagnosis, and treatment of osteoporosis.

**Definitions**

Osteoporosis is a skeletal disorder characterized by compromised bone strength (microarchitectural deterioration of bone tissue), predisposing an individual to fracture. Clinically, the disease is diagnosed by either the presence of a fragility fracture (low-trauma fracture) or based on an axial skeleton measurement of bone mineral density (BMD). The difference between an individual’s BMD and the mean BMD for a reference population can be expressed in standard deviation units, referred to as a T-score. A score of 0 indicates a BMD equal to the mean for the reference population; 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, or more than 2.5 standard deviations below the mean peak BMD for white, young adult women. Osteopenia is defined as a T-score between -1 and -2.5. The Z-score, which also is reported on most BMD testing results, is used to compare an individual to others in the same age group and is more commonly used in children and adolescents. The T- and Z-score standards were developed by testing white women; because these diagnostic criteria are also used for men and for nonwhite individuals, more research is needed to assure that their application is appropriate for these groups.

**Diagnosis**

Low bone mass is most accurately determined by radiologic testing to assess BMD. The techniques available to measure BMD are single x-ray absorptiometry, dual x-ray absorptiometry (DEXA), quantitative computed tomography (CT), and ultrasound. The most widely accepted method, and the method used in guidelines for interpreting BMD and related diagnoses, is the DEXA, which can measure bone density accurately regardless of the amount of surrounding soft tissue. Measurement of BMD typically is taken at 2 locations: first in the spine because it is a sensitive indicator of bone loss in younger women, and second at the femoral neck owing to the serious consequences related to hip fractures. Other proposed screening tools that are less favored include quantitative CT and heel ultrasound. CT scanning has been used to evaluate the spine but is expensive and involves a higher dose of radiation compared with DEXA. Ultrasound holds the most promise as an alternative to DEXA because of its lower cost and good ability to predict fractures in men and women. However, criteria for diagnosis and treatment are not well established; thus, use of ultrasound is not common.

Laboratory testing to rule out secondary causes of osteoporosis is indicated in younger women with low BMD without risk factors or in women who do not respond to therapy. Initially, serum thyroid-stimulating hormone measurement, complete blood count, and a chemistry panel including calcium, phosphorus, and creatinine should be considered. In geographic areas—or in populations such as the housebound elderly—in which vitamin D deficiency is common, measuring 25-hydroxyvitamin D also may be useful. Measurement of serum parathyroid hormone concentration should be considered. Because screening for Cushing’s syndrome can be difficult and costly, it should be reserved for patients in whom the history and physical examination strongly suggest the possibility of this disorder. A targeted history should be obtained to screen for medications predisposing patients to low BMD, such as glucocorticoids, and signs and symptoms of primary cancers, such as multiple myeloma or metastatic cancers involving the bones.

**Screening Guidelines and Risk Factors**

Current screening guidelines for osteoporosis differ

<table>
<thead>
<tr>
<th>Table 1. Risk Factors for the Development of Osteoporotic Fractures</th>
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<tbody>
<tr>
<td>- Personal history of fracture as an adult</td>
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<td>- History of fracture in a first-degree relative</td>
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<tr>
<td>- Current cigarette smoking</td>
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<tr>
<td>- Low body weight (&lt;58 kg [127 lbs])</td>
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<tr>
<td>- Female sex</td>
</tr>
<tr>
<td>- Estrogen deficiency</td>
</tr>
<tr>
<td>- White race</td>
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<tr>
<td>- Advanced age</td>
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<tr>
<td>- Lifelong low calcium intake</td>
</tr>
<tr>
<td>- Alcoholism</td>
</tr>
<tr>
<td>- Inadequate physical activity</td>
</tr>
<tr>
<td>- Recurrent falls</td>
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<tr>
<td>- Poor health/frailty</td>
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by organization. In general, screening by DEXA at least once is recommended for all postmenopausal women aged 65 years or older. For women younger than 65 years, routine screening is recommended only in the presence of risk factors, such as smoking, low body weight, maternal or personal history of fracture, low calcium intake, or loss of height (Table 1). Several quantitative risk factor-based assessment tools are under development that may produce a more individualized approach to diagnosis and treatment of osteoporosis. At this time, these tools are limited by lack of studies evaluating risk factors across both sexes and all genders, ages, and ethnic groups. Other indications for screening include long-term steroid use, hyperthyroidism, hyperparathyroidism, vitamin D deficiency, and rheumatoid arthritis.

PREVENTION AND TREATMENT

All women should be counseled about beginning prevention of osteoporosis at a young age. Although decline in bone mass begins at age 35 years, most recommendations suggest a lifelong prevention strategy, including early adequate calcium intake and weight-bearing exercise. Specific modifiable risk factors that clinicians should address with those who are at increased risk for or have received a diagnosis of osteoporosis include smoking cessation, increase in weight-bearing activities, gait and balance training, and environmental modifications for fall prevention. The risks versus benefits of all medications that could contribute to an increased likelihood of falls should be considered. For a summary of dosing recommendations see Table 2.

WHO SHOULD BE TREATED?
The National Osteoporosis Foundation recommends initiating therapy in women with a T-score of -2.0 or lower by hip DEXA and no risk factors or those with a history of a low-trauma hip or spine fracture. Women with one or more risk factors should be treated if they have a T-score below -1.5.

CALCIUM AND VITAMIN D SUPPLEMENTATION

Calcium. Calcium intake increases spinal BMD and reduces vertebral and nonvertebral fractures; thus, it is considered important for prevention and as an adjuvant to other pharmacologic therapy. The Institute of Medicine recommends 1000 mg of elemental calcium per day in women aged 19-50 years, and 1200 mg per day in those aged 51 years or older. The National Institutes of Health recommends 1500 mg per day in all women older than 65 years. Calcium may be obtained either through diet or supplements. Three 8-oz glasses of milk in addition to the calcium in the rest of a normal diet should provide sufficient calcium for most adults. Those with lactose intolerance should consume foods with lower lactose content, such as yogurt, hard cheeses, or lactose-reduced products. Recommendations for calcium supplementation relate to elemental calcium, which varies by source and chemical composition; patients should therefore be advised to read labels closely. All forms of calcium are equally well absorbed when taken with meals but should be consumed in small doses (no more than 500-600 mg) spread throughout the day.

Vitamin D. Vitamin D is important for reducing risk of fractures through its role in calcium homeostasis and its association with increased strength and balance mediated through receptors in muscle tissue. Despite the availability of vitamin D from exposure to sunlight, vitamin D insufficiency has been documented worldwide. Concerns regarding the increased risk of skin cancer associated with exposure to ultraviolet radiation have caused most experts to recommend oral vitamin D supplementation over exposure to sunlight. Daily intake of 400 U is recommended for all adults older than 50 years; 800 U is recommended for those at increased risk for deficiency, such as older adults or malnourished individuals and those receiving long-term glucocorticoid therapy. Dietary sources of vitamin D include fortified milk and cereals, fish oil, egg yolks, and liver.

ESTROGEN WITH OR WITHOUT PROGESTIN

Since the 2002 results of the Women’s Health Initiative (WHI), a prospective, randomized, placebo-

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Table 2. Dosing Guidelines

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
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<tr>
<td>Estrogen/progestin</td>
<td>Lowest possible dose for shortest duration</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td></td>
</tr>
<tr>
<td>Alendronate prevention</td>
<td>5-mg tablet daily/35-mg tablet once weekly</td>
</tr>
<tr>
<td>Treatment</td>
<td>10-mg tablet daily/70-mg tablet once weekly</td>
</tr>
<tr>
<td>Risedronate prevention</td>
<td>5-mg tablet daily/35-mg tablet once weekly</td>
</tr>
<tr>
<td>Treatment</td>
<td>2.5-mg tablet daily/150-mg tablet once monthly</td>
</tr>
<tr>
<td>Ibandronate prevention</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Raloxifene prevention</td>
<td>60-mg tablet daily</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Calcitonin treatment</td>
<td>200 U (1 puff) intranasal spray daily</td>
</tr>
<tr>
<td>Teriparatide treatment</td>
<td>20 µg injected subcutaneously daily</td>
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controlled, double-blind trial, the use of estrogen to prevent osteoporosis has been controversial. The US Preventive Services Task Force (USPSTF) states that there is good evidence that estrogen plus progesterin therapy increases BMD and fair to good evidence that it reduces fractures. Given the risk profile, particularly based on results from the WHI, the USPSTF and the American Association of Clinical Endocrinologists recommend against the routine use of estrogen and progesterin in postmenopausal women with an intact uterus for the prevention of chronic conditions, including osteoporosis. The USPSTF found the evidence insufficient to recommend for or against the use of unopposed estrogen in women who have had a hysterectomy. The absolute increase in risk from hormone therapy is modest, however, and the American College of Obstetricians and Gynecologists recommends that the use of this therapy should be evaluated given an individual woman’s risk profile and history, including the need for treatment of vasomotor symptoms. A shared decision-making approach between clinicians and patients should be used to arrive at treatment decisions, and patients should be given alternative treatment options. Because of the associated risks, the US Food and Drug Administration (FDA) recommends that hormone therapy be used at the lowest possible dose for the shortest possible duration.

The FDA has recently approved an ultra-low dose of estrogen without progesterin (Menostar®) for prevention of osteoporosis in postmenopausal women. Ultra-low-dose 17-β estradiol released at a rate of 0.014 mg per day—about one quarter the standard dose—via a transdermal patch has been found to improve BMD at the hip and spine and is relatively safe in older postmenopausal women. To reduce the chance of endometrial hyperplasia, the manufacturer recommends that women with an intact uterus take progesterin for 14 days every 6 to 12 months and have an endometrial biopsy annually. Though promising, the safety and efficacy of this treatment have been established for only up to 2 years; importantly, it has not been shown that the improvement in BMD correlates with decreased fracture risk.

**Bisphosphonates (Alendronate, Risedronate, Ibandronate)**

Bisphosphonates are FDA approved for prevention of bone loss in recently menopausal women and for treatment of established postmenopausal osteoporosis. These medications inhibit osteoclast activity and thus reduce bone resorption and bone loss. They have been shown to increase BMD at the spine and hip and to reduce the risk of fractures of the spine, hip, and other nonvertebral sites by 30% to 50%. Bisphosphonates have poor absorption and therefore should be taken first thing in the morning on an empty stomach with 8 oz of plain water, one half hour before eating or taking other oral medications. The patient should remain upright during this 30-minute period. Clinical trials show that the incidence of upper gastrointestinal side effects with bisphosphonates is comparable to that with placebo, but clinical experience suggests some patients may experience dysphagia, esophagitis, and esophageal or gastric ulcers. Some groups therefore recommend against bisphosphonate use in individuals with gastroesophageal reflux disease or esophageal abnormalities, such as achalasia or stricture. Other contraindications include hypocalcemia.

**Selective Estrogen Receptor Modulators (Raloxifene)**

Selective estrogen receptor modulators are designed to provide the benefits of estrogen on BMD with lower risk of breast cancer, endometrial cancer, and cardiovascular disease. Raloxifene is approved by the FDA for prevention and treatment of osteoporosis and has been shown to increase BMD and reduce the risk of vertebral fracture by 30% to 50%. There is no evidence that raloxifene reduces nonvertebral fractures. The adverse effects associated with raloxifene include venous thromboembolic disease, pulmonary embolism, and hot flashes.

**Calcitonin**

Nasal salmon calcitonin is approved for treatment of osteoporosis in women 5 or more years after menopause. The nasal spray increases BMD and reduces lumbar spine fractures by 36% but has not been shown to reduce hip fractures. Adverse effects associated with nasal calcitonin include rhinitis and occasional epistaxis.

**Recombinant Human Parathyroid Hormone (Teriparatide)**

Teriparatide is a subcutaneously administered anabolic agent that stimulates new bone formation, in contrast to bisphosphonates, which reduce bone loss. It is approved for treatment of osteoporosis in postmenopausal women who are at high risk for fracture or for whom other therapies have failed. One study showed an increase in BMD and a 65% and 54% decrease in the risk of vertebral and nonvertebral fractures, respectively, over a 19-month period. Therapy with bisphosphonates should be discontinued when initiating treatment with teriparatide because these agents may blunt the anabolic effects of parathyroid hormone. No evidence shows that combining teriparatide with estrogen or raloxifene confers any clinical advantage. The safety and efficacy of teriparatide has not been demonstrated past 2 years of therapy.
Because of the risk of hypercalcemia, total daily calcium intake from supplements and dietary sources should be limited to 1500 mg, with up to 1000 U vitamin D per day; measurement of baseline and 1-month posttreatment levels of serum calcium should be considered. Baseline evaluation of serum levels of parathyroid hormone, 25-hydroxyvitamin D, creatinine, and phosphorous also may be considered. Teriparatide was shown to increase incidence of osteosarcomas in rats and is therefore contraindicated in patients with Paget’s disease, open epiphyses, history of irradiation involving the skeleton, or undefined elevation in alkaline phosphatase of skeletal origin.

**OTHER TREATMENTS**

Several additional agents are either under investigation for treatment of osteoporosis or are not currently approved by the FDA for treatment of osteoporosis but are used off-label for this purpose. Intravenous pamidronate, a bisphosphonate used to treat hypercalcemia and Paget’s disease, has been used off-label to treat severe osteoporosis. Small studies have shown that it increases BMD. Zoledronic acid, used in the treatment of metastatic breast cancer and myeloma, has been shown to increase bone mass when administered intravenously once annually and is under investigation to determine if it reduces fractures. A new class of antiresorptive agents called integrin inhibitors has been shown to prevent osteoclasts from absorbing bone, but further research is needed to determine if fracture risk is decreased. Another therapy using the element strontium ranelate, which has mixed antiresorptive and anabolic action, has been shown to improve spine BMD and decrease spine fracture in early studies. Also under early investigation is AMG 162, a monoclonal antibody that targets, binds to, and inhibits a ligand responsible for osteoclast-mediated bone loss. Statins, commonly used for treatment of hypercholesterolemia, have been shown to stimulate bone formation, though results from observational studies have been mixed regarding their role in fracture reduction.

**TREATMENT EVALUATION**

Serial DEXA scanning should be conducted on all patients receiving treatment, but decisions regarding timing of testing are difficult owing to slow changes in BMD and therapy-specific response rates. Guidelines for when to initiate treatment evaluation vary between 1 and 3 years depending on the issuing group, but most suggest waiting until 2 years after the start of therapy, a time period that allows for bone mass response to bisphosphonates. Medicare will pay for screening every 2 years. The definition of treatment failure is complex and relies on the precision error of the testing device and on the varying skill levels of the technologists performing the test. Whereas precision of densitometric measures at the best centers is within 2% to 3%, the average measurement is far less precise. It therefore is important to avoid overinterpretation of small changes in BMD. Assessment of patient adherence to therapy and understanding of dosing instructions, as well as evaluation for secondary causes of osteoporosis, should be considered if a patient’s BMD has decreased by more than 4% to 5% when measured by DEXA 2 years after initiation of treatment. More data regarding treatment outcomes are needed to produce evidence-based guidelines for treatment, monitoring, and modifications in therapy.

Biochemical markers of bone turnover may hold a future role for optimal selection of patients for specific therapies and for monitoring response to these therapies, and may even predict fracture risk and rate of bone loss. Current limitations include the considerable variability within individuals, low sensitivity and specificity, and wide-ranging rates of false-positive and false-negative results among the markers. Though biochemical markers hold great promise, their use is not widespread and is not considered standard care.

**CONCLUSION**

Osteoporosis affects millions of patients in the United States and is a source of significant healthcare expenditures. Physicians can affect the morbidity and mortality rates associated with osteoporotic fractures by engaging in risk assessment of all women, followed by appropriate diagnostic screening with DEXA. Preventive counseling is essential—lifestyle changes, such as diet, calcium supplementation, weight-bearing exercise, and smoking cessation all have a significant effect on fracture risk. Treatment is recommended, with close monitoring to evaluate effectiveness. More research is needed to determine if the diagnostic standards for white women are applicable to other ethnic groups and to better tailor screening and treatment protocols. In addition, more research is needed to produce guidelines defining treatment failure and recommendations for treatment modification.


