Osteoporosis

Osteoporosis has a fivefold greater prevalence in women than in men. In the United States, although women only have twice the fracture rate of men, they sustain 80% of hip fractures because older women far outnumber older men. In 2005, the cost for direct care of the estimated 2 million osteoporosis-related fractures was projected to be $17 billion, with hip fractures accounting for approximately 72% of the cost (1). Morbidity and loss of function can occur with all fractures and consequently present a significant burden to the patient, the family, and society. Morbidity and mortality are especially high with hip fractures. Of women older than 80 years who have had a hip fracture, only 56% could walk independently after 1 year (2). Approximately 3–6% of women die of complications while hospitalized for hip fracture, an outcome often correlated with comorbidity and age (2, 3). Many aspects of gynecology and obstetrics can affect bone health. Obstetrician–gynecologists have the opportunity to play a key role in the prevention of osteoporosis and osteoporotic fractures. The purpose of this practice bulletin is to review the diagnosis, evaluation, and treatment of osteoporosis.

Background

Osteoporosis is a skeletal disorder characterized by loss of bone mass, deterioration of microarchitecture, and a decline in bone quality, all of which lead to an increased vulnerability to fracture. Changes in bone mass and microarchitecture have been well characterized. The other components that comprise bone quality are not as well understood. It is clear that age is one of the most important factors related to bone quality, but exactly how age affects bone quality is not entirely clear. Two women, one aged 50 years and one aged 80 years, with the same bone mineral density (BMD) will have dramatically different fracture risks because of their ages (Fig. 1).

The main determinants of peak bone mass and bone quality are thought to be genetic (4). Many gene polymorphisms that affect bone quality have been identified. Other genetically linked findings such as changes in the Wnt signaling pathway, lipoprotein receptor-related protein 5 pathway, nonenzymatic glycation of collagen, and homocysteine levels also appear to contribute to the complexity of bone quality (4).

Widely different age-adjusted hip fracture rates for women have been reported from around the world from 1 in 100,000 person-years among Nigerian black women to 421 in 100,000 person-years among Norwegian white women (5). Within the United States, there also is considerable variation in hip fracture rates, most notably between racial and ethnic groups. Caucasian women have the highest rates of hip fractures, African American women have the lowest rates, and Mexican American women have rates in between the other two groups (6). These racial and ethnic differences are important in counseling and management because fracture rates do not always correlate with BMD across ethnic groups. For example, Chinese American women typically have lower areal BMD than Caucasian American women, but lower rates of hip and forearm fracture (7). It is postulated that greater cortical density and thicker trabeculae compensate for less trabeculae in smaller bones. Thus, both
BMD and microarchitecture appear to play distinct roles in fracture vulnerability. However, apart from Chinese Americans, fracture rates correlated with BMD data collected in the National Health and Nutrition Examination Survey (NHANES) 2005–2006, which reported the highest BMD in African American women, lower BMD in Mexican American women, and the lowest BMD in Caucasian American women (8).

**Bone Physiology**

Bone is a dynamic tissue. The acquisition of bone that occurs during childhood and adolescence accounts for 90% of adult bone mass. A girl’s peak bone mass is largely influenced by heritable factors (60–80%) (9), but achievement of that potential can be thwarted by environmental, health, and lifestyle factors. Most bone growth and bone mineral content accrue in the 2–4 years before and after peak height velocity. Mean age of peak height velocity has been reported as 11.8 (plus or minus 1.0) years in females and 13.5 (plus or minus 1.0) years in males (10). A recent longitudinal multicohort study of middle-class Caucasian females and males found that final peak bone mass occurred around 19 years in women and 20.5 years in men. No significant increase in bone mineral content was noted after that time point (10). Other studies also reported an earlier peak bone mass in late adolescence (11–13). These findings underscore the importance of adolescence as an important time for bone health. They also provide strong support for an earlier achievement of peak bone mass than previously reported (14). It is believed that peak bone mass correlates with fracture risk later in life.

Remodeling and repair of bone during adulthood are accomplished through resorption and formation processes controlled by osteoclasts (resorption) and osteoblasts (formation). In the young adult years, net gain or loss of bone mineral content is minimal. In midlife, this bone turnover process shifts to greater resorption than formation in both women and men, resulting in a net loss of bone mineral content. The rate of bone loss with aging is controlled by genetic predisposition, endogenous estrogen levels, and other factors. The time of most rapid bone loss in women coincides with the marked decline in estrogen levels associated with menopause. This period of rapid bone loss begins 1 year before the final menses and lasts approximately 3 years, during which time there is a 6% and 7% bone loss at the femoral neck and lumbar spine, respectively (15).

All sex steroids play an important and complex role in adult bone development and maintenance. Hormonal activity at puberty appears to increase bone mineralization that leads to stronger bones and the reduction of the higher rate of fracture seen in prepubertal children. Estrogen is required by both males and females for optimal bone health, and the significant decline in estrogen levels at menopause triggers a time-limited rapid bone loss in women not seen in men. Although this menopausal loss in BMD is sometimes viewed as pathologic,
an another paradigm views it as physiologic. It has been documented by some investigators that girls gain more bone mineral content per lean body mass than boys at puberty (16). It is hypothesized that this mechanically excess bone serves as a reservoir for pregnancy and lactation.

A decline in adult estrogen levels has been associated with loss of BMD in a number of conditions: anorexia nervosa, lactation, menopause, hypogonadism, and prolonged use of medications such as depot medroxyprogesterone acetate (DMPA), gonadotropin-releasing hormone agonists, and aromatase inhibitors. The belief that decreased estrogen production causes bone loss has dominated the field of osteoporosis treatment and research for many years. Recently, it has been proposed that a decline in estrogen levels is only part of the pathophysiology of osteoporosis and an increase in reactive oxygen species with aging plays a key role in the increased rate of resorption and the decreased rate of osteoblastogenesis (17).

Physical activity, adequate nutrition, and good health also are necessary for bone health (18, 19). Exercise during the growth phase of life has the added advantage of modulating bone geometry in a way that enhances bone strength beyond what an increase in BMD alone can provide and may have longer lasting benefit (20, 21). The most effective type of exercise to recommend has not yet been determined (22). However, a Cochrane analysis concludes that weight-bearing, resistance exercises and aerobics have a beneficial effect on spine BMD (no fracture data) and walking is beneficial for hip BMD (22).

Two nutritional components are especially important for bone quality: 1) vitamin D and 2) calcium. Vitamin D deficiency results in softer, poorly mineralized bone manifested as rickets in children and osteomalacia in adults. Prolonged calcium deficiency leads to osteoporosis.

**Diagnosing Osteoporosis**

The most widely recommended method of diagnosing osteoporosis in the United States is bone densitometry. Dual-energy X-ray absorptiometry (DXA) of the lumbar spine and hip is the preferred method. Although peripheral sites such as the wrist and heel are predictive of osteoporosis and fractures, they are not suitable for monitoring treatment effects. Because the rate of BMD loss varies from site to site in the body, measuring the sites of greatest concern (ie, the hip and spine) will provide the best prediction for fracture of that particular site.

The World Health Organization (WHO) provided criteria for diagnosing osteoporosis by DXA scan, and this is the only test that has been validated for osteoporosis diagnosis. The BMD measurement of the patient (preferably the femoral neck, total hip, and lumbar spine) is compared with the mean BMD of a young, healthy cohort of females to produce a T-score. The T-score categories are normal, low bone mass (formerly called osteopenia), and osteoporosis (Table 1). A T-score of less than or equal to –2.5 at any of the three previously mentioned sites establishes the diagnosis of osteoporosis. The Z-score, which is sometimes included in the report, compares the patient’s BMD to the mean BMD of women her age. Only the T-score is used for the purpose of diagnosing osteoporosis in postmenopausal women. The Z-score can be of value when it demonstrates that a woman’s BMD is significantly below that of her peer group.

Other bone densitometry technologies can be used for predicting fracture risk, but the WHO classification does not apply to these systems. Peripheral DXA can be used at the heel, finger, or wrist. Quantitative ultrasound densitometry has no radiation exposure because the technology involves the use of either broadband ultrasound attenuation or speed of sound to derive a quantitative measurement of the bone. Common sites for measurement are the heel, patella, and tibia. Peripheral sites cannot be used to monitor treatment. Quantitative computed tomography can measure volumetric BMD of trabecular and cortical bone, either centrally at the spine and hip or peripherally at the forearm or tibia. There are substantially greater amounts of radiation exposure with this modality.

Vertebral fracture assessment involves lateral spine imaging that can be performed by the lumbar spine DXA densitometer. The primary reason to order this test is to guide clinical management when the diagnosis of a vertebral fracture not previously detected would affect the treatment recommendation. A medical history of vertebral fracture or fragility fracture is a reason to treat an at-risk woman even in the absence of a T-score of less than –2.5.

A clinical diagnosis of osteoporosis can be established in the absence of imaging if there is a medical history of a low-trauma fracture in an at-risk woman (23). Low-trauma fractures are fractures that occur in a

**Table 1. Diagnosing Osteoporosis Using Bone Densitometry**

<table>
<thead>
<tr>
<th>Category</th>
<th>T Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Greater than or equal to –1.0</td>
</tr>
<tr>
<td>Low Bone Mass (osteopenia)</td>
<td>Less than –1.0 to greater than –2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Less than or equal to –2.5</td>
</tr>
</tbody>
</table>

*T-score is the number of standard deviations above or below the mean average bone density value for young adult women.
situation that would not be expected to cause fractures in most individuals (eg, a vertebral fracture from opening a window or a simple fall from a standing position). These examples are in contrast to a fracture caused by falling off a ladder or a fracture resulting from a car accident where higher trauma is present.

**Bone Turnover Markers**

Bone turnover markers are byproducts of bone resorption (deoxypyridinoline, N-telopeptides, and C-telopeptides from the breakdown of type I collagen) and bone formation (osteocalcin, bone-specific alkaline phosphatase, and procollagen type I N-terminal propeptide associated with bone matrix synthesis). They can be measured in urine or serum to determine a high bone turnover state or a low bone turnover state. High levels reflect a state of high bone turnover, which may indicate higher risk of fracture. Bone turnover markers have been used in clinical trials of osteoporosis therapies to demonstrate group response to treatment. Changes in bone turnover markers occur earlier than changes in BMD and can be used to ascertain the effect of treatment more promptly. Use of bone turnover markers in the management of individuals is more challenging because levels vary from day to day and throughout a single day. Bone turnover markers cannot be used to diagnose osteoporosis, and the usefulness of markers as an incentive for adherence has been questioned (24).

**Fracture Risk Assessment Tool**

The fracture risk assessment tool (FRAX) was developed in collaboration with the WHO to predict the risk of osteoporotic fracture for a person in the next 10 years (http://www.sheffield.ac.uk/FRAX/). It was validated in 11 different cohorts (25). The clinical risk factors used in FRAX include, age, sex, body mass index, previous fragility fracture, parental hip fracture, current smoking status, corticosteroid use (greater than or equal to 5 mg prednisolone per day for 3 months), alcohol intake greater than or equal to 3 units per day (approximately three drinks), rheumatoid arthritis, and other secondary causes of osteoporosis. Results are specific for gender and race for various countries where fracture data were available to incorporate into the tool. In the United States, FRAX has been most widely used as an aid in decision making regarding treatment initiation when the patient’s BMD score is in the low bone mass (osteopenia) range. It is recommended that DXA reports include a FRAX fracture risk score only when the patient’s BMD is in the osteopenia zone. Treatment should be considered when there is a 3% risk of hip fracture or a 20% risk of a major osteoporotic fracture (defined as a fracture of the forearm, hip, shoulder, or clinical spine) or both in the next 10 years. It is important to note that FRAX is valid with or without the incorporation of the femoral neck BMD score.

The fracture risk assessment tool is not without limitations. The fracture risk assessment tool is valid for women older than 40 years, and the National Osteoporosis Foundation recommends it be used in women who are postmenopausal, are not receiving osteoporosis treatment, have a T-score indicating low bone mass, and have no prior hip or vertebral fracture. Another limitation is the use of categorical variables where the effect is known to be related to the degree of exposure (eg, alcohol intake, corticosteroid use, smoking, and number of prior fractures). Spine BMD is not incorporated into the model, nor is a medical history of falls. Women affected by these factors may receive an underestimated fracture risk score. The fracture risk assessment tool is not considered valid for women who are taking prescription drugs for osteoporosis (26).

It may also be a useful tool for the concerned patient who does not meet criteria for a DXA scan. The fracture risk assessment tool can be performed by patients with minimal instructions, or a staff person can perform it while the patient is in the office. Reassurance of low risk, if confirmed, and information on prevention of osteoporosis, falls, and fractures can be provided.

**Treatment**

Before initiating treatment, it is important to consider the possibility of secondary causes of osteoporosis (Table 2). Fractures in a relatively young postmenopausal woman or a BMD lower than expected for age (eg, a Z-score below normal for her age group) suggests the need to check for secondary causes of osteoporosis. Discussing the many secondary causes of osteoporosis is beyond the scope of this bulletin. An initial approach to evaluating for secondary causes of osteoporosis can be found in Box 1. If the situation is unclear, referral to an osteoporosis specialist is the best option. Treatments have been broadly classified as antiresorptive or anabolic, depending on the primary mechanism of action. There are many options for treating osteoporosis (Table 3).

**Bisphosphonates**

Bisphosphonates are in the antiresorptive class and have been the leading treatment for osteoporosis since the alendronate was approved in 1995. The four bisphosphonates approved in the United States, alendronate, risedronate, ibandronate, and zoledronate, have been extensively studied in large randomized controlled trials that have demonstrated antifracture benefit (27–31).
Table 2. Conditions, Diseases, and Medications That Cause or Contribute to Osteoporosis and Fractures

<table>
<thead>
<tr>
<th>Condition/Disease/Condition</th>
<th>Condition/Disease/Condition</th>
<th>Condition/Disease/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic and autoimmune diseases</td>
<td>Rheumatic and autoimmune diseases</td>
<td>Rheumatic and autoimmune diseases</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Lupus</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Endocrine disorders</td>
<td>Endocrine disorders</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Diabetes mellitus</td>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Hyperparathyroidism</td>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Inflammatory bowel disease</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>Malabsorption</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>GI surgery</td>
<td>Pancreatic disease</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Lifestyle factors</td>
<td>Lifestyle factors</td>
<td>Lifestyle factors</td>
</tr>
<tr>
<td>Low calcium intake</td>
<td>Vitamin D insufficiency</td>
<td>Excess vitamin A</td>
</tr>
<tr>
<td>High caffeine intake</td>
<td>High salt intake</td>
<td>Aluminum (in antacids)</td>
</tr>
<tr>
<td>Alcohol (3 or more drinks/d)</td>
<td>Inadequate physical activity</td>
<td>Immobilization</td>
</tr>
<tr>
<td>Smoking (active or passive)</td>
<td>Falling</td>
<td>Thinness</td>
</tr>
<tr>
<td>Medications</td>
<td>Medications</td>
<td>Medications</td>
</tr>
<tr>
<td>Anticoagulants (heparin)</td>
<td>Cancer chemotherapeutic drugs</td>
<td>Gonadotropin releasing hormone agonists</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Cyclosporine A and tacrolimus</td>
<td>Lithium</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>Depo-medroxyprogesterone</td>
<td></td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Glucocorticoids (≥5 mg/d of prednisone or equivalent for ≥3 mo)</td>
<td></td>
</tr>
<tr>
<td>Genetic factors</td>
<td>Genetic factors</td>
<td>Genetic factors</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Homocystinuria</td>
<td>Osteogenesis imperfecta</td>
</tr>
<tr>
<td>Ehlers-Danlos</td>
<td>Hypophosphatasia</td>
<td>Parental history of hip fracture</td>
</tr>
<tr>
<td>Gaucher’s disease</td>
<td>Idiopathic hypercalcemia</td>
<td>Porphyria</td>
</tr>
<tr>
<td>Glycogen storage disease</td>
<td>Marfan syndrome</td>
<td>Riley-Day syndrome</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Menkes steely hair syndrome</td>
<td></td>
</tr>
<tr>
<td>Hypogonadal states</td>
<td>Hypogonadal states</td>
<td>Hypogonadal states</td>
</tr>
<tr>
<td>Androgen insensitivity</td>
<td>Hyperprolactinemia</td>
<td>Turner’s syndrome and Klinefelter’s syndrome</td>
</tr>
<tr>
<td>Anorexia nervosa and bulimia</td>
<td>Panhypopituitarism</td>
<td></td>
</tr>
<tr>
<td>Athletic amenorrhea</td>
<td>Premature ovarian failure</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous conditions and diseases</td>
<td>Miscellaneous conditions and diseases</td>
<td>Miscellaneous conditions and diseases</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Emphysema</td>
<td>Muscular dystrophy</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>End stage renal disease</td>
<td>Parenteral nutrition</td>
</tr>
<tr>
<td>Chronic metabolic acidosis</td>
<td>Epilepsy</td>
<td>Post-transplant bone disease</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Idiopathic scoliosis</td>
<td>Prior fracture as an adult</td>
</tr>
<tr>
<td>Depression</td>
<td>Multiple sclerosis</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Hematologic disorders</td>
<td>Hematologic disorders</td>
<td>Hematologic disorders</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Multiple myeloma</td>
<td>Systemic mastocytosis</td>
</tr>
<tr>
<td>Leukemia and lymphomas</td>
<td>Sickle cell disease</td>
<td>Thalassemia</td>
</tr>
</tbody>
</table>

Box 1. Evaluation of Secondary Causes of Osteoporosis

First Tier

- Complete blood count
- Metabolic profile
- 24-Hour urinary calcium level
- 25-Hydroxyvitamin D level
- Thyroid stimulating hormone level

Second Tier

- Celiac panel
- Serum protein electrophoresis

Table 3. Government-Approved Drugs for Postmenopausal Osteoporosis

<table>
<thead>
<tr>
<th>Generic (Brand name)</th>
<th>Dose and Route</th>
<th>Indication</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bisphosphonates (oral unless otherwise specified)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate (Fosamax)</td>
<td>5 mg/d or 35 mg/wk tablet or oral solution</td>
<td>Prevention</td>
<td>• Abnormalities of the esophagus</td>
</tr>
<tr>
<td></td>
<td>10 mg/d or 70 mg/wk tablet or oral solution</td>
<td>Treatment</td>
<td>• Inability to stand or sit upright for at least 30 minutes</td>
</tr>
<tr>
<td>Alendronate + vitamin D₃ (Fosamax Plus D², Fosavance³)</td>
<td>70 mg + 2,800 IU/wk; 70 mg + 5,600 IU/wk</td>
<td>Treatment</td>
<td>• Hypersensitivity to any component of this product</td>
</tr>
<tr>
<td>Risedronate (Actonel)</td>
<td>5 mg/d p.o.; 35 mg/wk; 75 mg in 2 consecutive d/mo; 150 mg/mo</td>
<td>Prevention + Treatment</td>
<td>• Hypocalcemia</td>
</tr>
<tr>
<td>Risedronate (Atelvia)</td>
<td>35 mg/wk (delayed release)</td>
<td>Treatment</td>
<td>• Patients at increased risk of aspiration should not receive Fosamax oral solution</td>
</tr>
<tr>
<td>Risedronate + calcium carbonate (Actonel with Calcium)</td>
<td>35 mg/wk (day 1) + 1,250 mg Ca for no-risedronate days (days 2–7 of 7-d treatment cycle)</td>
<td>Prevention + Treatment</td>
<td>• Hypocalcemia</td>
</tr>
<tr>
<td>Ibandronate (Boniva*)</td>
<td>150 mg/mo; 2.5 mg/d</td>
<td>Prevention + Treatment</td>
<td>• Creatinine clearance &lt; 35 mL/min and acute renal impairment</td>
</tr>
<tr>
<td></td>
<td>3 mg every 3 mo I.V.</td>
<td>Treatment</td>
<td>• Hypersensitivity to Zoledronic acid or any components of this product</td>
</tr>
<tr>
<td>Zoledronic acid (Reclast*)</td>
<td>5 mg/2 y I.V. 5 mg/y I.V.</td>
<td>Prevention</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Estrogen agonist/antagonist</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene (Evista)</td>
<td>60 mg/d</td>
<td>Prevention + Treatment</td>
<td>• Venous thromboembolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Pregnancy, women who may become pregnant, and nursing mothers</td>
</tr>
<tr>
<td><strong>Calcitonin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitonin-salmon (Fortical)</td>
<td>200 IU/d nasal spray</td>
<td>Treatment (&gt;5 y postmenopause)</td>
<td>• Allergy to calcitonin-salmon</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Allergy to synthetic calcitonin-salmon</td>
</tr>
<tr>
<td>Calcitonin-salmon (Miacalcin)</td>
<td>200 IU/d nasal spray</td>
<td>Treatment (&gt;5 y postmenopause)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 IU/every other day s.c. or i.m.</td>
<td>Treatment (&gt;5 y postmenopause)</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
Table 3. Government-Approved Drugs for Postmenopausal Osteoporosis (continued)

<table>
<thead>
<tr>
<th>Generic (Brand name)</th>
<th>Dose and Route</th>
<th>Indication</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parathyroid hormone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Teriparatide (recombinant human PTH 1-34) (Forteo) | 20 µg/d s.c. | Treatment (high Fx risk) | • Hypersensitivity to teriparatide or to any of its excipients  
• Reactions have included angioedema and anaphylaxis |
| **RANK ligand inhibitor** |                |            |                   |
| Denosumab (Prolia) | 60 mg every 6 months s.c. | Treatment | • Hypocalcemia |
| **Estrogen prescription drugs approved for prevention of postmenopausal osteoporosis** | | | |
| Conjugated estrogens (Premarin) | 0.3, 0.45, 0.625, 0.9, 1.25 mg/d | Prevention | • Undiagnosed abnormal genital bleeding  
• Known, suspected, or history of cancer of the breast except in appropriately selected patients being treated for metastatic disease  
• Known or suspected estrogen-dependent neoplasia  
• Active deep vein thrombosis, pulmonary embolism or a history of these conditions  
• Active or recent (within the past year) arterial thromboembolic disease (for example, stroke, myocardial infarction)  
• Known or suspected pregnancy |
| Estropipate (Ogen) | 0.625 (0.75 estropipate, calculated as sodium estrone sulfate 0.625), 1.25 (1.5), 2.5 (3.0) mg/d (in Canada, only approved for treatment) | Prevention | |
| 17β-estradiol (Alora*) | 0.025, 0.05, 0.075, 0.1 mg/d matrix patch (twice weekly) | Prevention | |
| 17β-estradiol (Climara) | 0.025, 0.0375, 0.05, 0.075, 0.1 mg/d (0.025 dose not approved in Canada) matrix patch (once weekly) | Prevention | |
| 17β-estradiol (Estrace) | 0.5, 1.0, 2.0 mg/d | Prevention | |
| 17β-estradiol (Menostar*) | 0.014 mg/d matrix patch (once weekly) | Prevention | |
| 17β-estradiol (Vivelle*) | 0.025, 0.0375, 0.05, 0.075, 0.1 mg/d matrix patch (twice weekly) | Prevention | |
| 17β-estradiol (Vivelle-Dot*, Estradot†) | 0.025, 0.0375, 0.05, 0.075, 0.1 mg/d matrix patch (twice weekly) | Prevention | |
| 17β-estradiol (Estraderm) | 0.05, 0.1 mg/d reservoir patch (twice weekly) | Prevention | |
| **Estrogen-progestin prescription drugs approved for prevention of postmenopausal osteoporosis** | | | |
| Conjugated estrogens + medroxyprogesterone acetate (continuous-cyclic) (Premphase*) | 0.625 mg E + 5.0 mg P/d (2 tablets: E and E+P) | Prevention | |
| Conjugated estrogens + medroxyprogesterone acetate (continuous-combined) (Prempro*) | 0.3 or 0.45 mg E + 1.5 mg P/d (1 tablet); 0.625 mg E + 2.5 or 3.0 mg P/d (1 tablet) | Prevention | |
| Ethinyl estradiol + norethindrone acetate (femhrt*, femHRT†) | 2.5 µg E + 0.5 mg P/d (1 tablet); 5 µg E + 1 mg P/d (1 tablet) | Prevention | |
| 17β-estradiol + norethindrone acetate (Activella*) | 0.5 mg E + 0.1 mg P/d (1 tablet); 1 mg E + 0.5 mg P/d (1 tablet) | Prevention | |
| 17β-estradiol + norgestimate (interrupted-combined) (Prefest*) | 1 mg E + 0.09 mg P (2 tablets: E and E+P) 1 E tablet/d for 3 d followed by 1 E+P tablet/d for 3 d continuously | Prevention | |
| 17β-estradiol + levonorgestrel (continuous-combined) (Climara Pro*) | 0.045 mg E + 0.015 mg P (22 cm² patch, once/wk) | Prevention | |

*Available in the United States but not Canada. †Available in Canada but not the United States. Products not marked are available in both the United States and Canada. Abbreviations: p.o., by mouth; I.V., intravenous; s.c., subcutaneous; i.m., intramuscular.

All bisphosphonates significantly reduce vertebral fractures by 35–65%. Risedronate reduces nonvertebral fractures, and both alendronate and zoledronate significantly reduce hip fractures specifically. These drugs are classified as antiresorptive agents because the mechanism of action is inhibition of osteoclast resorption of bone. Inhibition of osteoclasts leads to a lesser decrease in bone formation by osteoblasts, but the net result is an increase in BMD and a decrease in bone turnover.

The bisphosphonates differ in binding affinity, dose frequency, and route of administration (see Table 3). To facilitate absorption and to prevent esophageal trauma, most oral bisphosphonates are taken on an empty stomach with a full glass of water. Patients are instructed to remain in a sitting or standing position for 30–60 minutes in order to avoid reflux that could irritate the esophagus. One delayed-release formulation of alendronate can be taken without attention to posture.

Duration of effect after discontinuation may vary. Discontinuation of alendronate after 5 years of treatment resulted in maintenance of bone turnover markers below baseline for 5 years while BMD remained stable or decreased slowly (32–34). Discontinuing risedronate after 2 years of treatment resulted in a significant loss of BMD during the first year (35).

Zoledronate is contraindicated in patients with acute renal failure or creatinine clearance of less than or equal to 35 mL/min. Patients should be screened for renal disease before zoledronate infusion because renal failure has occurred after infusion in patients with compromised renal function. Caution with regard to renal function should be exercised with other drugs in this class as noted in the product information sheets. Hypocalcemia should be corrected before the use of these drugs.

Other adverse effects of bisphosphonates include musculoskeletal aches and pains, gastrointestinal irritation, and esophageal ulceration. Potential risks reported after marketing include osteonecrosis of the jaw, seizures, atypical fractures of the femoral shaft, and esophageal cancer. A precise understanding of the true risk of these events has been difficult to determine because of the lack of data on the incidence of these problems in the general population. Although rare cases of osteonecrosis of the jaw have been reported in patients using bisphosphonates for osteoporosis (36), it has been seen most commonly after dental extractions in those being treated with large intravenous doses of bisphosphonates in association with supportive cancer therapy (37). There is no requirement to discontinue bisphosphonates for dental procedures. However, there is likely to be no harm in discontinuing a bisphosphonate temporarily for a dental procedure, if the patient so desires, given the long duration of action of bisphosphonates.

**Partial Estrogen Agonists and Antagonists**

Raloxifene was the first drug in the class of partial estrogen agonists and antagonists (also known as selective estrogen receptor modulators) approved for the prevention and treatment of osteoporosis. These compounds are antiresorptive. Raloxifene has been demonstrated to reduce vertebral fractures. It has also been shown to reduce the risk of invasive breast cancer in postmenopausal women with osteoporosis as well as reduce the risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer.

Adverse effects of raloxifene include venous thromboembolism (VTE), leg cramps, and death from stroke (not increased risk of stroke). A medical history of stroke should be carefully weighed when considering use of this drug. Women close to menopause may experience vasomotor symptoms for a while after initiating therapy.

The risk–benefit profile of this drug (vertebral fracture benefit; breast cancer benefit; but no documented hip fracture benefit, risk of thrombosis, or risk of death from stroke) make it better suited to the younger postmenopausal woman with osteoporosis who is at low risk of hip fracture and stroke by virtue of her age and who is often concerned about breast cancer and osteoporosis. Other drugs in this category (bazedoxifene, lasofoxifene, ospemifene) have been under investigation. Tamoxifen has demonstrated some BMD benefit in postmenopausal women but is not approved for this indication.

**Denosumab**

Denosumab, an antiresorptive treatment, is a human monoclonal antibody to the receptor activator of nuclear factor-κB ligand. The receptor activator of nuclear factor-κB ligand binds to the receptor activator of nuclear factor-κB on the surface of osteoclasts and promotes proliferation and differentiation of these osteoclasts. The antibody blocks this interaction therein decreasing bone resorption and increasing BMD as a result (38, 39). Denosumab was approved in 2010 for treatment of postmenopausal women with osteoporosis who are at high risk of fracture. Studies revealed a vertebral and hip fracture reduction of 68% and 40%, respectively (39). Denosumab is administered subcutaneously every 6 months. A higher rate of infections that required hospitalization was seen in the clinical trials. However, concerns about suppression of the immune system leading to increased rates of cancer were not substantiated.

**Calcitonin**

Salmon calcitonin, an antiresorptive treatment, is available as a nasal spray and a subcutaneous injection. It has been shown to reduce vertebral fractures and to reduce
bone pain associated with vertebral fractures (40, 41). Fracture reduction is less robust than with other agents and was not seen in early postmenopausal women. It should not be used until women are 5 years from menopause. Adverse effects include flushing and nausea with subcutaneous injection and local irritation with nasal spray.

**Parathyroid Hormone**

Recombinant human parathyroid hormone (PTH) 1-34 (teriparatide) and PTH 1-84 are anabolic bone treatment agents that stimulate osteoblastic activity. The latter is approved in Europe, but not in the United States. Parathyroid hormone increases trabecular size and connectivity, thereby improving bone microarchitecture and geometry. Route of administration is daily subcutaneous injection. Treatment is restricted to 2 years because of research in laboratory rats that found an increased incidence of osteosarcoma with high-dose treatment. Because of this finding, it is recommended that teriparatide not be used in women with bone metastases or Paget disease of the bone or women who have had skeletal irradiation.

Adverse effects include nausea, dizziness, muscle cramps, and infrequent hypercalcemia. Fracture reduction was demonstrated in vertebral and nonvertebral categories (42). Bone mineral content is lost quickly after discontinuation of PTH. Studies have demonstrated the importance of adding an antiresorptive agent after discontinuation of PTH (43, 44).

**Clinical Considerations and Recommendations**

**When should bone health be addressed?**

Bone health should be addressed in all age groups, including during puberty and adolescence, because of the effect of nutrition and lifestyle on bone health. Poor nutrition (including anorexia nervosa), inactive lifestyle, and smoking may prevent girls from reaching their peak genetic bone mass potential. Moderate alcohol intake has not been associated with detrimental bone effects, but an intake of greater than or equal to 3 units of alcohol per day conveys a dose-related increase on the risk of fracture (23).

**Are lifestyle changes beneficial?**

Vitamin D deficiency can lead to osteomalacia in adults or rickets in children, and a calcium-deficient diet results in lower bone mineral content. Population studies suggest that geographic areas with higher calcium intake have fewer fractures than areas with low calcium intake (45, 46). A retrospective study using the third NHANES found that women who had higher milk intake in childhood had higher BMD and fewer fractures as adults (47). However, prospective lifestyle modifications generally have yielded modest benefits. Calcium supplementation studies in normal adolescents have yielded small increases in BMD that may not persist when supplementation is discontinued. One meta-analysis of calcium supplementation in a pediatric population reported an estimated 1.7% increase in BMD found only in the arm (48). Protein also is essential for bone health. Protein supplements have been reported to reduce fractures and promote fracture healing in older adults (49, 50).

Similar to the effect of poor nutrition on BMD, immobilization and total lack of exercise results in loss of bone mineral content. Exercise may lead to site-specific gain in BMD depending on the type of exercise. Partial or complete loss of this bone benefit can occur when the exercise is discontinued. A Cochrane review reported that in terms of adherence, brisk walking might be the best regimen to recommend to the public. Long-term follow-up and fracture data are lacking (22).

**What are the current calcium and vitamin D guidelines?**

The 2011 report by the Institute of Medicine (IOM) lowered some of the recommendations from their earlier report. The recommended dietary allowance for calcium now ranges from 1,000 mg per day to 1,300 mg per day depending on age, and the vitamin D recommended dietary allowance now ranges from 600 international units per day for most of life to 800 international units per day after age 70 years (Table 4) (51). The IOM recommends a serum vitamin D level of 20 ng/mL (50 nmol/L) for good bone health because that level covers the requirements of

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Calcium Recommended Dietary Allowance (mg/day)</th>
<th>Vitamin D Recommended Dietary Allowance (international units/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9–18</td>
<td>1,300</td>
<td>600</td>
</tr>
<tr>
<td>19–50</td>
<td>1,000</td>
<td>600</td>
</tr>
<tr>
<td>51–70</td>
<td>1,200</td>
<td>600</td>
</tr>
<tr>
<td>71 and older</td>
<td>1,200</td>
<td>800</td>
</tr>
</tbody>
</table>

concluded that soy supplements were not likely to have a significant effect on BMD (60, 61).

When should bone density screening be initiated?

All major guidelines state that DXA screening should begin at age 65 years for women (23, 62–66). Most guidelines also agree that DXA screening can be used selectively for women younger than 65 years if they are postmenopausal and have other risk factors for fracture (Box 2). Alternatively, FRAX can be used in women younger than 65 years to determine which women should have a DXA scan (65). Those women with a FRAX 10-year risk of major osteoporotic fracture of 9.3% could justifiably be referred for DXA because that is the risk of fracture found in a 65-year-old Caucasian woman with no risk factors. Routine screening of newly menopausal women is not recommended nor is a “baseline” screen recommended (see Fig. 2).

After treatment initiation, one DXA scan 1 year or 2 years later can be used to assess the effect of treatment. If the BMD is improved or stable (no significant change), the DXA does not usually need to be repeated in the absence of new risk factors (67). Testing generally should not be undertaken before 2 years after initiation of treatment because it often takes 18–24 months to document a clinically meaningful change.

Although the use of DMPA is associated with loss of BMD, current evidence suggests that partial or full recovery of BMD occurs at the spine and at least partial recovery occurs at the hip after discontinuation of DMPA. Practitioners should not perform BMD monitoring solely in response to DMPA use because any observed short-term loss in BMD associated with DMPA use may be...
Recommendations include performing weight-bearing exercises and muscle-strengthening exercises to reduce the risk of fractures and falls, taking the appropriate amount of vitamin D and calcium, stopping smoking and avoiding secondhand smoke, reducing alcohol intake, and adopting fall-prevention strategies.

Preventing falls requires a combination of maximizing the physical capability of the individual along with maximizing the safety of the environment. For the individual, attention should be given to improving or maintaining muscle strength, balance, and vision. Medications should be scrutinized for potential adverse effects of hypotension, dizziness, or confusion. Shoes and clothing should not pose a risk of tripping or stumbling. Where disabilities exist, canes or walkers should be strongly recommended. A checklist of ways to improve safety around the house can be helpful (Box 3).

*Fragility fracture is an indication for treatment despite lack of osteoporosis on DXA.

**Fig. 2.** Screening and treating postmenopausal women for fracture prevention. (Screening and treating premenopausal women is generally restricted to women who have diseases, conditions, or medication use known to increase risk of fractures). Abbreviations: FRAX, fracture risk assessment tool; DXA, dual-energy X-ray absorptiometry.

**When should treatment for osteoporosis be recommended?**

All major guidelines state that treatment should be recommended for women who have a BMD T-score of less than or equal to –2.5. For women in the low bone mass category (T-score between –1 and –2.5), the FRAX calculator can be used to make an informed treatment decision. Women who are found to have a 10-year risk of major osteoporotic fracture greater than or equal to 20% or a risk of hip fracture greater than or equal to 3% using the FRAX calculator are candidates for medical pharmacologic therapy. Women who have had a low-trauma fracture (especially of the vertebra or hip) also are candidates for treatment even in the absence of osteoporosis on the DXA report (see Fig. 2).

**What lifestyle and environmental modifications can be undertaken to reduce fracture risk?**

Women with osteoporosis or who are at risk of osteoporosis should be counseled about lifestyle changes to reduce the risk of bone loss and osteoporotic factors.

Recommendations include performing weight-bearing exercises and muscle-strengthening exercises to reduce the risk of fractures and falls, taking the appropriate amount of vitamin D and calcium, stopping smoking and avoiding secondhand smoke, reducing alcohol intake, and adopting fall-prevention strategies.

Preventing falls requires a combination of maximizing the physical capability of the individual along with maximizing the safety of the environment. For the individual, attention should be given to improving or maintaining muscle strength, balance, and vision. Medications should be scrutinized for potential adverse effects of hypotension, dizziness, or confusion. Shoes and clothing should not pose a risk of tripping or stumbling. Where disabilities exist, canes or walkers should be strongly recommended. A checklist of ways to improve safety around the house can be helpful (Box 3).

**Are there reasons for selecting one treatment over another?**

Bisphosphonates are generally considered first-line therapy, but raloxifene can be a good first choice in younger postmenopausal women for the previously described reasons. A woman using raloxifene can be transitioned to another therapy, such as a bisphosphonate, in her recovered and is unlikely to place an adolescent or adult woman at risk of fracture during use or in later years.
drug. The previously mentioned drugs provide many options for patients and physicians.

> **Is there a maximum duration for bisphosphonate therapy?**

It is not yet known if there should be a limit to the duration of use of bisphosphonates. An advisory panel to the U.S. Food and Drug Administration (FDA) reviewed the issue of treatment interruption (drug holidays) and duration of therapy and recommended that labeling be more specific with regard to duration of use. In practice, despite lack of evidence or labeling guidance, there seems to be a trend toward offering treatment interruption after 5–10 years of use. One way to minimize long-term exposure to bisphosphonates is to use an estrogen agonist/antagonist for women in their 50s who require treatment and have no contraindications to this drug, and then use a bisphosphonate for women in their 60s when the risks of hip fracture and venous thrombosis begin to increase. Alternatively, if a bisphosphonate is used first, the patient could switch after 5–10 years of use to a completely different class of drug like denosumab, although atypical fractures and osteonecrosis of the jaw also have been reported with use of this drug.

> **What is the role of hormone therapy?**

Hormone therapy (HT), either estrogen therapy (ET) or combined estrogen and progestogen therapy, has a beneficial effect on bone health as discussed earlier. The WHI provided randomized controlled trial data that demonstrated a statistically significant reduction of 33–36% in hip and vertebral fractures with either ET or combined estrogen and progestogen therapy (68, 69). These data were not sufficient to apply for an osteoporosis treatment indication because the guidance from the FDA specifies that osteoporosis must be diagnosed in the study population by means of DXA or the study population must have a medical history of osteoporotic fractures, neither of which were enrollment criteria for the WHI cohort.

Hormone therapy is approved for the prevention of osteoporosis in women at an increased risk of osteoporosis and fracture. A number of HT products have been approved by the FDA for the prevention of osteoporosis from standard dose to very low-dose estradiol transdermal patches (Table 3). The benefit of HT for bone health is dose-related. The lower doses recommended today may not be as effective for fracture prevention as the higher doses used in the past.

Deciding on the duration of HT is a challenge because recent HT guidelines specify using the lowest dose for the shortest amount of time, especially when using...
combined estrogen and progestogen therapy (70, 71). Current data suggest that combined estrogen and progestogen therapy can be used for 3–5 years before encountering an increased risk of breast cancer (72). Estrogen therapy can be used for a longer period of time (70), in the absence of other risk factors because of the delayed risk of breast cancer seen with ET (approximately 15 years according to the Nurses' Health Study) (73). Thus, the clinician must work closely with the patient to determine what is in her best interest because risks of HT are smallest in the younger postmenopausal woman and increase with age.

Bone mineral density and fracture benefit from HT is lost within 1–2 years of discontinuing treatment (74, 75). To maintain the benefit obtained with HT use, it may be necessary to switch to a different osteoporosis therapy when discontinuing HT. Bisphosphonates have been shown to preserve BMD after discontinuation of HT in postmenopausal women (74, 76).

**How often should a DXA scan be repeated in a woman older than 65 years who does not have osteoporosis?**

If the initial BMD report indicates low bone mass, FRAX should be used to determine if the woman has a high risk of fracture. If she does, treatment should be recommended. If FRAX does not indicate a high risk of fracture, data from the Study of Osteoporotic Fractures suggest a screening interval of 15 years for a woman older than 65 years with a normal BMD or mild bone loss (T-score greater than or equal to −1.5), a 5-year screening interval for a T-score from −1.5 to −1.99, and a 1-year screening interval for a T-score between −2.0 and −2.49 (77). The fracture risk assessment tool should continue to be used on an annual basis to monitor the important effect of age on fracture risk.

**What approach should be undertaken if a patient loses bone density during treatment?**

The initial assessment should determine whether there has been a significant decrease in BMD. Every DXA center should periodically test the equipment and the technicians who perform the test to determine the margin of error for that DXA center. The information should be specified in the DXA report or the report should state that there is a significant change in BMD so that the clinician will know if the patient’s loss is greater than the margin of error for that office. It also is important to determine if the patient was taking the medication correctly and consistently. Next, a thorough evaluation for secondary causes of osteoporosis (Box 1 and Table 2), or referral to a specialist are appropriate. One common cause of bone loss during treatment was found to be insufficient vitamin D levels (78). Other secondary causes of osteoporosis that are not uncommon are idiopathic hypercalciuria and celiac disease.

**Summary of Recommendations and Conclusions**

*The following recommendations and are based on good and consistent scientific evidence (Level A):*

- Treatment should be recommended for:
  - Women with a T-score of −2.5 or less
  - Women who have had low-trauma fracture
  - Women who have a T-score from −1 to −2.5 and a FRAX score greater than or equal to 3% for risk of hip fracture or a FRAX score greater than or equal to 20% for risk of a major osteoporotic fracture (defined as forearm, hip, shoulder, or clinical spine fracture) or both in the next 10 years
- FDA-approved therapies should be used for medical treatment: raloxifene, bisphosphonates, PTH, denosumab, calcitonin.
- Bone density screening for women should begin at age 65 years. Dual-energy X-ray absorptiometry screening can be used selectively for women younger than 65 years if they are postmenopausal and have other significant risk factors for osteoporosis or fracture.

*The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B):*

- In the absence of new risk factors, DXA screening should not be performed more frequently than every 2 years.
- In the absence of new risk factors, DXA monitoring of therapy should not be repeated once BMD has been determined to be stable or improved.
- Women should be counseled about lifestyle factors that may affect BMD and fracture risk: smoking, poor nutrition and excessive weight loss, weight-bearing and muscle-strengthening exercise, and fall-prevention measures.
- Women should be advised of current IOM calcium and vitamin D recommendations.
The following conclusion is based primarily on consensus and expert opinion (Level C):

- The effect of lifestyle on bone health should be considered for girls and women of all ages and they should be counseled accordingly.

Proposed Performance Measure

Percentage of women aged 65 years and older who have been screened for osteoporosis by DXA

References


5. Bouxsein ML. Bone structure and fracture risk: do they go arm in arm? J Bone Miner Res 2011;26:1389–91. (Level III) [PubMed] [Full Text]


54. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial [published erratum appears in JAMA 2010;303:2357]. JAMA 2010;303:1815–22. (Level I) [PubMed] [Full Text]
57. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women’s Health Initiative limited access dataset and meta-analysis. BMJ 2011;342:d2040. (Level III) [PubMed] [Full Text]
58. Lewis JR, Calver J, Zhu K, Flicker L, Prince RL. Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up. J Bone Miner Res 2011;26:35–41. (Level I) [PubMed] [Full Text]


75. LaCroix AZ, Chlebowski RT, Manson JE, Aragaki AK, Johnson KC, Martin L, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. WHI Investigators. JAMA 2011;305:1305–14. (Level I) [PubMed] [Full Text]  


The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists’ own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1990 and March 2012. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.