ABSTRACT

OBJECTIVE: To describe the etiology, diagnosis, and nonprescription interventions for the prevention and treatment of postmenopausal osteoporosis.

BACKGROUND: Osteoporosis affects more than 20 million individuals in North America and is responsible for more than 1.5 million fractures in the United States. About 50% of white women in the United States will have an osteoporotic fracture during their lifetime.

SUMMARY: Postmenopausal osteoporosis is the result of estrogen deficiency, which results in up-regulation of several cytokines and excessive bone resorption. Various bone mineral density (BMD) testing methods are available, but the World Health Organization based the diagnosis of postmenopausal osteoporosis on the presence of a BMD T-score that is 2.5 standard deviations or greater below the mean for young women as assessed by dual-energy X-ray absorptiometry (DXA) at the hip, spine, and midradius. Ensuring adequate calcium and vitamin D intake is the cornerstone of any regimen aimed at preventing or treating postmenopausal osteoporosis. Other nonpharmacologic measures address modifiable risk factors for the disease and include exercise, smoking cessation, reducing consumption of caffeine and alcohol, and avoiding medications known to decrease bone mass.

CONCLUSIONS: Postmenopausal osteoporosis is the result of estrogen deficiency and excessive bone resorption. Ensuring intake combined with lifestyle changes to address modifiable risk factors for the disease may help in the prevention and treatment of this condition.

KEYWORDS: Postmenopausal osteoporosis, Bone, Estrogen, Calcium

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Until recently, osteoporosis was defined as a condition of generalized skeletal fragility in which bone strength is sufficiently weak that fractures occur with minimal trauma, often no more than is applied by routine daily activity.1 The diagnosis of osteoporosis was not made until a fracture occurred, when it was too late to intervene.

Osteoporosis currently is defined as a skeletal disorder characterized by compromised bone strength, predisposing to fractures.2 Bone strength reflects both bone density and bone quality. Bone density usually is assessed by noninvasive means using various measures of bone mineral density (BMD, i.e., the grams of mineral per area or volume). Bone quality reflects bone architecture (strength, connectivity), turnover (i.e., replacement), accumulated damage (e.g., microfractures), and mineralization.2 Bone quality usually is not assessed in clinical practice because it currently involves a bone biopsy, which is an invasive method. The incidence of fractures is an indirect measure of bone quality. The U.S. Food and Drug Administration (FDA) now requires data demonstrating a favorable impact on fracture incidence for approval of drugs to prevent or treat osteoporosis, although an impact on BMD sufficed for drug approval years ago.

Etiology

Bone undergoes a continuous remodeling process (i.e., replacement) involving resorption of old bone by osteoclasts and formation of new bone by osteoblasts.1 The activity of osteoclasts and osteoblasts ordinarily is balanced and regulated by physical factors and hormonal influences. Osteoporosis is characterized by an imbalance between osteoclast and osteoblast activity and a rate of bone resorption that exceeds the rate of bone formation, resulting in bone loss and skeletal fragility.

Osteoporosis may be primary or secondary to an identifiable cause (i.e., a drug, disease, or condition). Most cases of osteoporosis are primary, especially in the elderly. Approximately 20% of women and 40% of men with osteoporosis have a secondary cause (Table 1).1,4

Primary osteoporosis includes type I (postmenopausal) osteoporosis and type II (senile) osteoporosis. Postmenopausal osteoporosis is the result of estrogen deficiency, which results in up-regulation of several cytokines and excessive bone resorption.5 It affects women disproportionately, with a 6:1 female-to-male ratio, usually at an age of 51 to 75 years.1 Bone loss and fractures in postmenopausal osteoporosis primarily involve trabecular bone (i.e., interior porous bone) in the vertebrae and distal radius (i.e., forearm).1

Type II osteoporosis usually affects individuals older than 70 years and twice as many women as men.1 Bone loss typically involves both trabecular and cortical (i.e., outer) bone on the long bones, causing fractures of the femoral neck (i.e., hip), proximal

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Type II osteoporosis results from an age-related vitamin D deficiency, which leads to hypocalcemia, a compensatory increase in parathyroid hormone release, and bone resorption.

The risk factors for osteoporosis in postmenopausal women are listed in Table 2. An increased risk is associated with a thin build. Weight gain appears to protect against bone loss in elderly women.

Risk factors for hip fracture were determined in 9,516 white women aged 65 years or older who had no history of hip fracture and were followed for an average of 4.1 years. There were 192 hip fractures in this group, and many of the risk factors identified (e.g., a personal history of any fracture after the age of 50, a maternal history of hip fracture, poor health, a history of hyperthyroidism, tachycardia at rest, high caffeine consumption, low bone mass or BMD) are similar to those in Table 2. Some risk factors for hip fracture reflect a high risk for falls (e.g., a lack of exercise, the use of anticonvulsants or long-acting benzodiazepines, the inability to rise from a chair without using the arms, poor depth perception).

### Diagnosis

The diagnosis of osteoporosis is based on assessment of BMD. Health Care Financing Administration (now called Centers for Medicare & Medicaid Services) regulations that became effective in 1998 provide for uniform coverage of BMD measurements in the Medicare population using any procedure approved by the FDA. Testing is indicated for estrogen-deficient women who are at clinical risk for osteoporosis, individuals with vertebral abnormalities, persons receiving long-term glucocorticoid therapy, patients with primary hyperparathyroidism, and patients receiving an osteoporosis drug therapy approved by the FDA. Testing may be performed once every 2 years, although more frequent testing is permitted if a physician considers it medically necessary.

Assessing BMD by dual energy X-ray absorptiometry (DXA) scans at the hip and spine, also known as central DXA, is the gold standard method for diagnosing osteoporosis. Central DXA scans involve low exposure to radiation and are easy to perform, even if the patient is bedridden or has problems with mobility. Patients need not undress for the procedure.

Portable instruments can be used to assess BMD at peripheral sites such as the forearm, finger, or heel. Examples of such devices include peripheral DXA scans, heel ultrasound, and single-energy X-ray absorptiometry (SXA) scans. While peripheral devices have the advantages of lower cost and portability over central DXA machines, they are less reliable because they can produce false negative results, and they cannot be used to follow BMD changes over time. Further, the WHO diagnostic criteria for osteoporosis by T-score were based on central DXA measurements, and the threshold was not validated for peripheral BMD measurements. Peripheral BMD measurement devices can be used for screening, but central DXA is required for a definitive diagnosis. BMD usually is reported as a T-score or a Z-score. The T-score is the difference between the individual's BMD and the expected BMD for a “young, normal” adult of the same sex, expressed as the number of standard deviations below the mean. The Z-score compares the individual's BMD with the average BMD for people of the same age and sex. A T-score of -1 or higher (i.e., a BMD within 1 standard deviation lower than that expected for a young, normal adult of the same sex) is considered normal. A T-score between -1 and -2.5 is considered osteopenia, and a T-score of -2.5 or lower (i.e., 2.5 or more standard deviations below the expected BMD) is considered osteoporosis. Patients with a T-score of -2.5 or lower and a history of one or more fragility fractures have what is referred to as established or severe osteoporosis.
The laboratory work-up for a patient with a diagnosis of osteoporosis includes a variety of assays to exclude secondary causes of the disease. These assays include thyroid function tests, 24-hour urinary calcium excretion, serum or urine protein electrophoresis to exclude multiple myeloma, and serum concentrations of calcium, phosphorus, alkaline phosphatase, parathyroid hormone, 25-hydroxycholecalciferol (a vitamin D precursor), and 1,25-dihydroxycholecalciferol (the active form of vitamin D). Free testosterone is often measured in men to check for hypogonadism.

### Nonprescription Interventions

Various nonprescription drug and nonpharmacologic interventions may be used to prevent and treat postmenopausal osteoporosis. Some of the risk factors for osteoporosis in postmenopausal women are modifiable with lifestyle modification (e.g., exercise, smoking cessation, reducing consumption of caffeine and alcohol). Efforts to improve lighting and remove physical hazards in the home that can cause falls and the use of undergarments with hip protectors are recommended for individuals with osteoporosis who are at risk for falls and fractures.

Ensuring adequate calcium and vitamin D intake is the cornerstone of any regimen to prevent or treat postmenopausal osteoporosis. Bone mass increases during the first 3 decades of life, reaching a peak at around the age of 30. Ensuring an adequate calcium and vitamin D intake at an early age can optimize the peak bone mass and reduce the risk for postmenopausal osteoporosis.

### Calcium

Epidemiologic studies have shown that calcium supplementation increases BMD and is linked to decreased risk for vertebral and hip fractures. Results from a recently completed 5-year, randomized controlled trial showed that supplementation with calcium carbonate 1,200 mg/day decreased clinical fractures in subjects who were compliant with their medications compared with placebo (10.2% vs. 15.4%; hazard ratio, 0.66; 95% confidence interval [CI], 0.45-0.97). The National Academy of Sciences dietary reference intakes for calcium and vitamin D may be used to make recommendations for the daily intake of calcium. These amounts are expressed as elemental calcium, and they reflect the increased nutritional needs of adolescents, persons aged 51 years and older, and pregnant and lactating women (Table 4). The National Institutes of Health recommends even larger amounts of elemental calcium (1,000-1,500 mg/day) than the National Academy of Sciences dietary reference intakes for older Americans.

Diet is a good source of calcium (Table 5). However, many patients (especially the elderly and patients with lactose intolerance) have difficulty consuming enough food to obtain adequate amounts of calcium. Moreover, dietary sources of calcium may provide excessive amounts of calories, fat, or both. Oral calcium supplements are recommended for patients who are

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**Biochemical markers of bone turnover (i.e., the rate of resorption and formation) in serum and urine (Table 3) are not used for diagnosis.** However, they may be useful for assessing the response and adherence to treatment. The most commonly used marker in the United States is urinary and serum collagen type I cross-linked N-telopeptide, a marker of bone resorption.
unable to obtain adequate amounts of calcium from the diet.7

Most oral calcium supplements should be taken with meals to optimize absorption, which requires an acidic environment (calcium citrate is an exception because it does not need an acidic environment for absorption and may be taken without food).5,19 The gut cannot absorb calcium doses greater than 600 mg; thus, calcium supplements should be taken in divided doses.5 The elemental calcium content and cost of various calcium supplements vary. Calcium carbonate, which contains about 400 mg (40%) elemental calcium per gram of calcium carbonate, is preferred because it is the least expensive salt and requires the least number of tablets to reach dietary goals.5 Because calcium carbonate requires an acidic environment for absorption, it may not be suitable for individuals who receive proton pump inhibitors or histamine H2-receptor antagonists.5 Although it is more costly, calcium citrate may be used instead because absorption of calcium from this salt does not depend on the presence of acid.5 It contains about 21% elemental calcium.5 Adequate vitamin D is required for calcium absorption from all calcium salts.

**Vitamin D**

Exposure of the skin to ultraviolet light leads to the formation of cholecalciferol (vitamin D3). Cholecalciferol is converted to 25-hydroxycholecalciferol in the liver and then to the active form, 1,25-dihydroxycholecalciferol, in the kidneys. The active form of vitamin D plays a vital role in promoting intestinal calcium absorption. Parathyroid hormone activates vitamin D in the kidneys in response to low calcium concentrations. Excessive calcium concentrations inhibit parathyroid hormone through a negative feedback mechanism.

Age-related vitamin D deficiency is common because of limited exposure to ultraviolet light (especially in northern latitudes in the United States). In addition, advanced age is associated with diminished renal and hepatic conversion of vitamin D precursors, decreased renal response to parathyroid hormone, and increased resistance of intestinal mucosal cells to the active form of vitamin D.5

The National Academy of Sciences dietary reference intakes for vitamin D, are listed in Table 4. Although these figures reflect an increase in needs in older persons (aged 51 years and older), they are inadequate to meet requirements. Many clinicians recommend 800-1,000 units/day.5

Serum 25-hydroxycholecalciferol levels of 30-60 ng/mL are considered optimal.20,21 Levels less than 30 ng/mL are insufficient, and concentrations less than 20 ng/mL are deficient. Levels of 60-90 ng/mL are high and those above 90 ng/mL are toxic. Diet (e.g., fatty fish, eggs) is a source of cholecalciferol and ergocalciferol (vitamin D2, which is obtained from plant sources and metabolized in the body in a manner similar to vitamin D3), although the diet is not a particularly good source. Milk and certain other foods (e.g., orange juice, breakfast cereals) are often fortified with cholecalciferol or ergocalciferol in the United States.

**TABLE 5 Examples of Dietary Sources of Calcium**

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving Size</th>
<th>Amount of Elemental Calcium (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yogurt (plain, low-fat)</td>
<td>8 oz</td>
<td>415</td>
</tr>
<tr>
<td>Ricotta cheese (part skim milk)</td>
<td>1/2 cup</td>
<td>335</td>
</tr>
<tr>
<td>Skim or fat-free milk</td>
<td>1 cup</td>
<td>306</td>
</tr>
<tr>
<td>Swiss cheese</td>
<td>1 oz</td>
<td>224</td>
</tr>
<tr>
<td>Fortified orange juice</td>
<td>1 cup</td>
<td>350</td>
</tr>
<tr>
<td>Provolone cheese</td>
<td>1 oz</td>
<td>214</td>
</tr>
<tr>
<td>Cheddar cheese</td>
<td>1 oz</td>
<td>204</td>
</tr>
<tr>
<td>Salmon (canned with bones)</td>
<td>3 oz</td>
<td>181</td>
</tr>
<tr>
<td>American cheese food (pasteurized processed)</td>
<td>1 oz</td>
<td>162</td>
</tr>
<tr>
<td>Low-fat (1%) cottage cheese</td>
<td>1 cup</td>
<td>138</td>
</tr>
<tr>
<td>Macaroni and cheese (canned)</td>
<td>1 cup</td>
<td>88</td>
</tr>
<tr>
<td>Almonds</td>
<td>1/2 cup</td>
<td>200</td>
</tr>
<tr>
<td>Tofu</td>
<td>1/3 cup</td>
<td>150</td>
</tr>
</tbody>
</table>

* Adapted from reference 18.

Nevertheless, dietary vitamin D intake often is inadequate and supplementation is needed, especially for older Americans. Increasing skin exposure to ultraviolet light is not advised because of the risk of skin cancer. Furthermore, sunscreen prevents the necessary ultraviolet wave lengths from converting skin cholecalciferol to vitamin D. Cod liver oil is a source of vitamin D but it also contains vitamin A, which is associated with bone toxicity.5

Vitamin D supplementation alone does not appear to reduce the incidence of hip or vertebral fractures, but use of vitamin D in combination with calcium has been shown to be effective in reducing the risk of vertebral and nonvertebral fractures, including hip fractures.22 In a randomized, placebo-controlled study of 3,270 healthy, elderly ambulatory women who were followed for 18 months, 1,200 mg/day of elemental calcium and 800 units/day of cholecalciferol provided a 43% reduction in the number of hip fractures (P = 0.043) and a 32% reduction in the number of nonvertebral fractures (P = 0.015).23 A reduction in nonvertebral fractures was observed over a 3-year period from the use of calcium 500 mg/day and vitamin D 700 units/day in a randomized, placebo-controlled study of 389 elderly, noninstitutionalized men and women.24 Of the 37 subjects who had nonvertebral fractures, 26 were in the placebo group and 11 were in the calcium plus vitamin D group (P = 0.02). Recently published data from the Women's Health Initiative, a randomized, placebo-controlled study in 36,282 healthy, postmenopausal women aged 50 to 79 years, demonstrated that the use of elemental calcium 1,000 mg/day and vitamin D3 400 units/day over an average of 7 years resulted in a 1.06% increase in hip BMD compared with the placebo group (P <0.01). Calcium plus vitamin D3 supplementation did not significantly reduce the incidence of hip fractures.
fractures, and it increased the risk of kidney stones. However, when the analysis was limited to adherent patients, the reduction in risk for hip fracture was significant.  

Vitamin D supplementation appears to reduce the risk of falls in ambulatory older individuals. Data from 5 randomized controlled trials involving 1,237 subjects showed that vitamin D reduced the corrected odds ratio (OR) of falling by 22% (corrected OR, 0.78; 95% CI, 0.64-0.92). Research in elderly patients with a history of falls suggests that the reduction in falls associated with vitamin D supplementation might be mediated by improvements in neuromuscular function.

Serum half-life for vitamin D supplements is long and weekly doses may suffice, although daily administration in combination with calcium is convenient. A combination product containing the osteoporosis drug alendronate and cholecalciferol 2,800 units that is taken weekly was recently introduced. Vitamin D supplements include cholecalciferol and ergocalciferol. Cholecalciferol is often preferred because it has greater potency than vitamin D2. In addition, intake recommendations for vitamin D are based on vitamin D3 not D2, which makes it easier with vitamin D3 to decide what dose to take. Calcitriol is the active form of vitamin D (i.e., 1,25-dihydroxycholecalciferol). Calcitriol may stimulate bone formation by osteoblasts, but it has a narrow therapeutic index.

Calcitriol is a prescription medication and is often reserved for patients with renal impairment who cannot create the active moiety. Alfacalcidol is a safer analogue that recently became available as a prescription medication in the United States.

Exercise
Prolonged physical inactivity results in bone loss. Weight-bearing (e.g., walking a mile) and resistance exercises are recommended for postmenopausal women because they help preserve BMD. Exercise reduces the risk of falls in the elderly by improving strength, balance, and coordination.

Smoking Cessation
Smoking cessation should be advocated for patients with or at risk for postmenopausal osteoporosis. Cigarette smoking reduces BMD, increases estrogen metabolism, and leads to early menopause and malnutrition in addition to causing harm to the lungs.

Caffeine
Caffeine has a diuretic effect that leads to the loss of calcium in the urine when 2 to 5 cups of caffeinated beverages are consumed daily. Therefore, limiting caffeine intake and increasing consumption of calcium-rich beverages, foods, or supplements (e.g., fat-free or skim milk) can be beneficial for postmenopausal women.

Alcohol
Postmenopausal women should be advised to limit their weekly intake of alcoholic beverages to 7 drinks. One 12-ounce beer, 4 ounces of wine, or 1 ounces of liquor is considered 1 drink. Excessive alcohol consumption causes liver toxicity; has a diuretic effect that can lead to calcium loss, and has been linked with low BMD, falls, and fractures.

Conclusion
Postmenopausal osteoporosis is the result of estrogen deficiency and excessive bone resorption. Lifestyle changes to address modifiable risk factors for the disease, particularly ensuring an adequate calcium and vitamin D intake, are beneficial for the prevention and treatment of the disease.

DISCLOSURES
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