

## Position Statement

# Management of postmenopausal osteoporosis: position statement of The North American Menopause Society

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### ABSTRACT

**Objective:** The North American Menopause Society (NAMS) established a goal to create an evidence-based position statement regarding the management of postmenopausal osteoporosis.

**Design:** NAMS followed the general principles established for evidence-based guidelines to create this document. A MEDLINE search was conducted. Clinicians and researchers acknowledged to be experts in the field of osteoporosis were enlisted to review the evidence. The NAMS Board of Trustees reviewed and approved the final document.

**Results:** Osteoporosis, which has its highest rate of occurrence in postmenopausal women, increases the risk for fractures, including hip and spine fractures. These injuries are often associated with particularly high morbidity and mortality. Given the health implications of osteoporotic fractures, the primary goal of osteoporosis therapy is to prevent fractures by slowing or preventing bone loss, maintaining bone strength, and minimizing or eliminating factors that may contribute to falls. The evaluation of postmenopausal women for osteoporosis risk requires the recording of a medical history, a physical examination, and diagnostic tests. Major risk factors for osteoporosis are age, genetics, lifestyle (especially nutrition), and menopausal status. Management focuses first on non-pharmacologic measures, such as a balanced diet including adequate calcium and vitamin D intakes, appropriate exercise, smoking cessation, avoidance of excessive alcohol intake, and fall prevention. If pharmacologic therapy is indicated, FDA-approved options are estrogens (prevention only), bisphosphonates and selective estrogen-receptor modulators (prevention and treatment), and calcitonin (treatment only).

**Conclusions:** Management of postmenopausal osteoporosis involves identifying the potential risk for osteoporosis and osteoporotic fracture, followed by measures that focus on reducing modifiable risk factors through lifestyle changes and, if indicated, pharmacologic therapy.

**Key Words:** Menopause – Osteoporosis – Fractures – Bone mineral density – Estrogen replacement therapy – Bisphosphonates – Selective estrogen-receptor modulators – Calcitonin – Parathyroid hormone – Calcium – Vitamin D.

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The Board of Trustees of The North American Menopause Society (NAMS) developed this manuscript with assistance from an Editorial Board composed of J. Christopher Gallagher, MD (Chair); Bruce Ettinger, MD; Margery L. S. Gass, MD; Risa Kagan, MD; Betsy L. McClung, RN, MN; Michael R. McClung, MD; and James A. Simon, MD. It was edited, modified, and subsequently approved by the NAMS Board of Trustees in November 2001.

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Osteoporosis is a serious health threat for postmenopausal women that predisposes them to an increased risk of bone fracture. Osteoporotic bone fractures can be particularly devastating to elderly women, frequently confining them to long-term care and sometimes proving fatal. Given the consequences of osteoporosis in postmenopausal women, the most important goal of therapy is to prevent fractures by slowing or preventing

bone loss, maintaining bone strength, and minimizing or eliminating factors that contribute to the frequency of falls.

In response to the growing, and sometimes contradictory, body of clinical trial data, The North American Menopause Society (NAMS) has created this position statement on the management of postmenopausal osteoporosis. The objective is to define the current standards of clinical practice as they apply to diagnosis, prevention, and treatment of osteoporosis in the postmenopausal woman.

For this position statement, NAMS conducted a search of the medical literature on postmenopausal osteoporosis using the database MEDLINE, as well as a search of references in the published literature. Priority was given to evidence from randomized, controlled clinical trials and meta-analyses of such trials, followed by evidence from controlled observational studies, using criteria described elsewhere.<sup>1-3</sup> Conclusions from other evidence-based guidelines also were reviewed.

An editorial board composed of experts from both clinical practice and research institutions was enlisted to review the published data supporting statements and conclusions. If the evidence was contradictory or inadequate to form a conclusion, a consensus-based opinion was made. The NAMS consensus-building process was described in a previous issue.<sup>4</sup> The NAMS Board of Trustees was responsible for the final review and approval of this document. Additional updates to this position statement will be published as significant developments in scientific research occur that substantially alter the conclusions.

Because standards of care and available treatment options differ throughout the world, the focus is limited to therapies available in North America.

## BACKGROUND

Osteoporosis is the most common bone disease affecting humans. It is characterized by reduced bone mass accompanied by architectural deterioration of the skeleton, which leads to an increased risk for fracture. The disease has no warning signs. Often, the first indication of osteoporosis is a fracture. Falls or other injuries can often break osteoporotic bones, but sometimes osteoporotic bones, such as vertebrae, become so fragile that they collapse without any obvious precipitating trauma.

Osteoporosis can be defined as either primary or secondary. Primary osteoporosis can occur in both sexes at all ages, but often follows menopause in women. Secondary osteoporosis is a result of medications (e.g.,

glucocorticoids), certain medical conditions (e.g., hypogonadism), or diseases (e.g., celiac disease).<sup>5</sup>

The primary clinical goal of osteoporosis therapy is to prevent fractures by slowing or stopping bone loss, maintaining bone strength, and minimizing or eliminating factors that may contribute to falls. Although the process of bone loss begins during a woman's 30s and declines to 70% of its maximum value by the age of 80, initiating preventive steps throughout life can lessen a woman's risk of osteoporosis and fracture. It is even possible to reverse some loss of bone mass in adults.

## Prevalence

Most cases of osteoporosis occur in postmenopausal women, and the incidence increases with age. In the United States, approximately 20% of white women aged 50 or older have osteoporosis, which is defined as femoral bone mineral density (BMD) greater than 2.5 standard deviations below the mean of young, healthy white women. Another 35-50% have low bone mass, defined as BMD between 1 and 2.5 standard deviations below the mean. Osteoporosis rates vary with ethnicity, with the highest rates in whites and those of Asian descent and the lowest rates in blacks. Age increases the rates, which rise from 4% in women 50 to 59 years old to 52% for women 80 and older.<sup>6</sup>

In the United States, it has been estimated that for white women older than age 50, the risk of developing an osteoporotic fracture is nearly 40% in their remaining lifetime, with two-thirds of the fractures occurring after age 75.<sup>7</sup> Up to 90% of all hip and spine fractures in white women aged 65 to 84 years can be attributed to osteoporosis.<sup>8</sup> The estimated lifetime risks of hip, vertebral, and forearm fracture for a 50-year-old white woman are 17.5%, 15.6%, and 16.0%, respectively.<sup>7</sup> Black women have about one-third the fracture rate of white women, a difference usually attributed to their higher bone mass.<sup>9,10</sup>

## Morbidity and mortality

Hip fractures have a particularly devastating toll, resulting in higher cost and greater disability and mortality than all other osteoporotic fracture types combined. Hip fractures cause up to a 20% increase in mortality within a year of the incident. Approximately 25% of women require long-term care after a hip fracture, and 50% will have some long-term loss of mobility.<sup>11</sup>

Fractures at other sites, however, can also result in serious morbidity. Vertebral fractures may cause substantial pain as well as loss of height and exaggerated thoracic kyphosis. The pain and deformity can greatly

restrict normal movement, including simple movements such as bending and reaching. An important consequence of vertebral fractures is that they greatly increase (5-fold to 7-fold) the risk of subsequent vertebral fracture.<sup>12,13</sup> Thoracic fractures can restrict lung function, and fractures of the lower back can cause non-vertebral disorders, especially digestive problems. Tooth loss is another potential complication of osteoporosis and low bone mass.<sup>14</sup>

Osteoporosis takes a psychological toll as well. Depression is common in women with osteoporosis.<sup>15</sup> Hip and vertebral fractures and the resultant pain, loss of mobility, and loss of independence can lead to depression and anxiety. The fear, anger, frustration, and loss of self-esteem that these women may experience can have significant effects on their personal relationships.

### PATHOPHYSIOLOGY

Bone remodeling is the process of bone resorption and bone formation. At the cellular level, osteoclasts promote bone resorption by stimulating the production of enzymes that dissolve bone mineral and proteins. Osteoblasts promote bone formation by creating a protein matrix consisting primarily of collagen, which is soon calcified, resulting in mineralized bone.

In normal bone remodeling, bone resorption is balanced by bone formation. Bone loss occurs when there is an imbalance between bone removal and bone replacement, resulting in a decrease in bone mass and an increase in the risk for bone fracture.

Bone mass increases rapidly throughout childhood. After a slowing of bone mineral accumulation in the late teens, bone mass continues to increase during the 20s, the time of peak bone mass. Adequate nutrition and exercise in childhood are essential to reach one's optimal bone mass.

As women move toward midlife and menopause, bone loss begins to accelerate. The decline in circulating levels of 17 $\beta$ -estradiol is the predominant factor influencing the increased bone loss associated with menopause.<sup>16</sup> Bone loss at the spine begins about 1.5 years before the last menstrual period and totals approximately 10.5% over 8 years. Bone mass at the hip has an age-related rate of decline of about 0.5% per year before and after menopause, and it sustains an additional estrogen-related loss of approximately 5–7% across the menopause transition, defined as 2 to 3 years before and 3 to 4 years after menopause.<sup>17</sup> Bone mass continues to decline in women older than age 70. This effect may be accelerated by secondary hyperparathyroidism caused by an age-related drop in calcium

absorption. Overall, women lose about one-third of their BMD between menopause and age 80.

### RISK FACTORS

In addition to age, the major factors that influence bone mass are genetics, lifestyle (including nutrition), and menopausal status.

#### Genetics

The greatest influence on a woman's maximal bone mass is heredity. Studies have suggested that up to 80% of the variability in peak bone mass might be attributable to genetic factors.<sup>18,19</sup> Female children of women who have osteoporotic fractures have less bone mass than would be expected for their age.<sup>20,21</sup> First-degree relatives of women with osteoporosis also tend to have lower bone mass than those with no family history of osteoporosis.<sup>22</sup> Black women have higher BMD than white women,<sup>6</sup> a difference that further suggests a genetic influence.

#### Lifestyle

Several lifestyle factors affect the risk of developing osteoporosis. These include nutrition, physical activity, cigarette smoking, and heavy alcohol consumption.

#### Nutrition

A balanced diet plays a crucial role in bone development and maintenance of bone health throughout life. Adequate intakes of calcium are required for a woman to achieve her genetically determined peak bone mass.<sup>23</sup> After peak bone mass is attained, proper nutrition remains important for maintaining optimal bone mass and strength.

Both calcium and vitamin D have well-known roles in bone metabolism. During and after menopause, several factors increase women's calcium requirements. By age 65, intestinal calcium absorption has typically declined to less than 50% of that in adolescents.<sup>24</sup> In addition, the renal enzymatic activity that produces vitamin D metabolites (which control calcium absorption) decreases.<sup>25</sup> A more comprehensive overview of the role of calcium in perimenopausal and postmenopausal women is the subject of a previously published NAMS consensus opinion.<sup>26</sup>

#### Physical activity

Regular exercise has been associated with reduced fracture risk, although few studies have evaluated the effects of exercise on BMD.<sup>5</sup> There is general agree-

ment that weight-bearing exercise confers a positive effect on the skeleton and that high-impact exercises (e.g., running, step aerobics, gymnastics) provide the greatest osteogenic stimulus.<sup>27-29</sup> Extreme opposites to intensive physical training, such as prolonged bed rest, extended space travel, or hemiplegia, are associated with rapid and significant bone loss.<sup>30,31</sup> The effects of exercise on bone mass are attributed to a stimulation of osteoblast activity.<sup>32</sup> Exercise also appears to reduce the risk of falls, although it is unclear if exercise affects the risk for fracture from falls that do occur.<sup>5</sup>

#### *Cigarette smoking*

Compared with nonsmokers, women smokers tend to lose bone more rapidly, have lower bone mass, and reach menopause up to 2 years earlier.<sup>33-35</sup> In addition, some data show that postmenopausal women who smoke have significantly higher fracture rates than nonsmokers.<sup>36</sup> The mechanisms by which smoking might adversely affect bone mass are not known, although evidence suggests that cigarette smoke interferes with calcium absorption<sup>34,37</sup> and lowers endogenous 17 $\beta$ -estradiol levels.<sup>38</sup>

#### *Alcohol consumption*

Heavy alcohol consumption (defined in the Framingham Study as 7 oz or more per week)<sup>39</sup> has been shown to increase the risk for falls and hip fracture. Excessive alcohol consumption also has detrimental effects on BMD. However, moderate alcohol consumption in women 65 years of age and older seems to increase BMD<sup>40</sup> and lower the risk for hip fracture.<sup>39</sup>

#### **Hormonal status**

The increased rate of bone resorption after menopause clearly indicates a hormonal influence on bone mass in women. The most likely explanation for the increased resorption in women versus men after the age of 50 is the drop in estrogen production that accompanies menopause. Women experiencing early menopause (i.e., before age 40)—either naturally or induced (e.g., through surgery, chemotherapy, or pelvic radiation therapy)—are at greater risk of osteoporosis because they spend more years without the protective effect of endogenous estrogen. However, there is no evidence that these women have an increased risk of osteoporotic fracture.

#### **Secondary causes of bone loss**

Various medical conditions and medications are associated with bone loss. The most common secondary

causes of osteoporosis in younger women include hypoestrogenicity, excessive thyroxine dosages for hypothyroidism, and anticonvulsant therapy. Oral glucocorticoid use causes the most common form of drug-related osteoporosis (evidence is sparse on the effect of inhaled glucocorticoid use). The long-term administration of oral glucocorticoids for disorders such as rheumatoid arthritis and chronic obstructive pulmonary disease is associated with a high rate of fracture. Gonadotropin-releasing hormone therapy (agonist or analogue) and intramuscular medroxyprogesterone (150 mg/3 months) also contribute to bone loss, so women who have used these drugs could be at risk.

Excess urinary calcium excretion, which may be caused by a renal calcium leak or a thyroid disorder, can lead to osteoporosis. Vitamin D deficiency, an especially common condition in the elderly, is a correctable cause of accelerated bone loss. Other conditions that can have a detrimental effect on bone include multiple myeloma, endocrine disorders such as hyperparathyroidism and Cushing's syndrome, and disorders of collagen structures (Table 1).

### **EVALUATION**

All postmenopausal women should be assessed for risk factors associated with osteoporosis. This assessment requires a history, physical examination, and diagnostic tests. The goals of this evaluation are to identify the woman's risk of fracture, establish whether the woman has osteoporosis, assess the severity of the woman's osteoporosis, rule out secondary causes in a woman with osteoporosis, and identify modifiable risk factors for falls and injuries.

The history-taking and physical examination for a postmenopausal woman should focus on the detection of risk factors for osteoporosis and fractures. Most of these risks can be uncovered with a simple questionnaire along with the standard physical measurements. Potentially modifiable risk factors should be noted. Risk factors may help explain contributing causes of osteoporosis or help guide therapeutic recommendations, but they cannot be used to diagnose osteoporosis.

#### **Physical signs of osteoporosis**

Loss of height may be a sign of vertebral fracture in postmenopausal women. After achieving maximum height, most midlife women (and men) will lose 1.0 to 1.5 inches of height as part of their normal aging process, primarily as a result of shrinkage of intervertebral disks. In otherwise asymptomatic women, height loss greater than 1.5 inches may be associated with verte-

**TABLE 1.** *Common secondary causes of bone loss*

Medications
Glucocorticoids (e.g., prednisone) for >6 mo
Excessive thyroxine doses
Long-term use of certain anticonvulsants (e.g., phenytoin)
Anticoagulants (e.g., heparin, warfarin)
Cytotoxic agents
Gonadotropin-releasing hormone agonists or analogues
Intramuscular medroxyprogesterone contraceptive
Immunosuppressives (e.g., cyclosporine)
Genetic disorders
Hemophilia
Thalassemia
Hypophosphatasia
Hemochromatosis
Disorders of calcium balance
Hypercalciuria
Vitamin D deficiency
Endocrinopathies
Cortisol excess
Cushing's syndrome
Gonadal insufficiency (primary and secondary)
Hyperthyroidism
Type I diabetes mellitus
Primary hyperparathyroidism
Gastrointestinal diseases
Chronic liver disease (e.g., primary biliary cirrhosis)
Malabsorption syndromes (e.g., celiac disease, Crohn's disease)
Total gastrectomy
Billroth I gastroenterostomy
Other disorders and conditions
Multiple myeloma
Lymphoma and leukemia
Systemic mastocytosis
Nutritional disorders (e.g., anorexia nervosa)
Rheumatoid arthritis
Chronic renal disease

bral compression fractures that are indicative of osteoporosis. Height should be measured using an accurate and precise method, such as a stadiometer.

Acute or chronic back pain should raise suspicion of vertebral fractures. These fractures typically cause chronic back pain and fatigue, especially in the middle back. The mid-back vertebrae T12 and L1 are the most common fracture sites, followed by T6 through T9.<sup>41,42</sup> Ultimately, multiple vertebral compression fractures result in the most obvious sign of osteoporosis, kyphosis (abnormal curvature of the thoracic spine). Because back pain, height loss, and kyphosis may occur without osteoporosis, vertebral fractures should be confirmed by radiography. Similarly, height loss without back pain requires radiologic evaluation for spine fractures, which can be asymptomatic in two-thirds of the cases. Also, women with a vertebral fracture are at high risk for subsequent fracture,<sup>12</sup> making identification of even greater clinical importance. Wrist fracture, which tends to occur at an earlier age than vertebral or hip

fracture, may also be an early clinical expression of osteoporosis.<sup>43</sup>

### Bone mineral density measurement

BMD testing is the preferred method to diagnose osteoporosis. BMD is a strong predictor of fracture risk because bone mass accounts for 75–85% of the variation in bone strength.<sup>44</sup> Testing of BMD should be performed based on a woman's risk profile. Testing is not indicated unless the results will influence a treatment or management decision.

Although not all experts agree, NAMS recommends that BMD be measured in all women with medical causes of bone loss and in those who are at least 65 years of age, regardless of additional risk factors. Testing is also indicated for all postmenopausal women younger than age 65 with one or more of the following risk factors for fracture: a nonvertebral fracture after menopause, low body weight (<127 lbs), or a history of a first-degree relative who has experienced a hip or vertebral fracture. For elderly women who have experienced an osteoporotic vertebral fracture, treatment may be given without BMD measurement, although baseline BMD testing may be useful to follow the effects of therapy. A nonvertebral fracture in the absence of low BMD is not an indication for treatment. Testing of BMD in early postmenopause may be valuable in helping women make a decision about preventive therapy.

Healthy premenopausal women do not require BMD testing because of the low prevalence of osteoporosis in this population. BMD testing is indicated only in premenopausal women who experience a low-trauma fracture or who have known secondary causes of osteoporosis.

Analyses performed by the National Osteoporosis Foundation show that BMD testing is cost-effective for postmenopausal women aged 50 to 60 years with risk factors or for those beyond the age of 60 to 65 with or without risk factors.<sup>45</sup> Several tests to measure BMD are available, either radiation-based or radiation-free. Dual-energy x-ray absorptiometry (DXA) is the technical standard for measuring BMD. All the recent large, randomized, controlled clinical trials have used DXA of the hip and spine to determine therapeutic efficacy. DXA is the preferred technique because it measures BMD at the important sites of osteoporotic fractures, especially the hip.<sup>46</sup>

The total hip is the preferred site for BMD testing, especially in women older than age 60, primarily because of the high prevalence of extraosseous ossification that makes spinal measurements unreliable. The spine, however, is a useful site for BMD measurement

**TABLE 2.** Definition of osteoporosis based on BMD of total hip

Normal	<i>T</i> score above (i.e., better than) -1	BMD within 1 SD of a young normal adult
Low bone mass (i.e., osteopenia)	<i>T</i> score between -1 and -2.5	BMD between 1 and 2.5 SD below that of a young normal adult
Osteoporosis	<i>T</i> score below (i.e., worse than) -2.5	BMD is more than 2.5 SD below that of a young normal adult

BMD, bone mineral density.

Adapted from the World Health Organization.<sup>46</sup>

in early postmenopausal women, because they tend to lose bone faster in the spine than in the hip. Although tests at peripheral sites (e.g., wrist, calcaneus) can identify women with low bone mass, they may not be as useful as central-site tests (e.g., hip, spine) because the results are not as precise. Peripheral site measurements should be limited to the assessment of fracture risk when DXA is not available. They should not be used to diagnose osteoporosis or to follow response to therapy.<sup>47</sup>

To standardize values from different bone densitometry tests, results are reported as standard deviations, either as a *Z* score or a *T* score. A *Z* score is based on the standard deviation (SD) from the mean BMD of a reference population of the same sex, ethnicity, and age. A *T* score is based on the mean peak BMD of a normal, young adult population and is expressed in terms of standard deviations from the average value of this reference population.

In general, lower BMD *T* scores indicate more severe osteoporosis and higher risk of fracture. Every decrease of one standard deviation from age-adjusted bone density represents approximately a 10–12% change in BMD and an increase in the risk of fracture by a factor of approximately 1.5.<sup>46</sup>

Repeat DXA testing in *untreated* postmenopausal women typically is not useful until 3 to 5 years have passed. In general, postmenopausal women lose about 0.5 in standard deviations from the mean in both *T* and *Z* scores every 5 years.

For women receiving osteoporosis therapy, BMD monitoring before 2 years of therapy are completed may not provide clinically useful information. Not observing an increase in BMD is not evidence of treatment failure. In one study,<sup>48</sup> most women who appeared to have lost more than 4% of BMD during the first year of treatment (with either alendronate or raloxifene) showed substantial gains the second year while remaining on the same therapy. The decrease in BMD could be due to imprecision in the DXA measurement. However, an apparent decrease in vertebral BMD greater than 4–5% would indicate a need to

evaluate compliance with therapy and dosing instructions as well as to search for secondary causes of bone loss.

In 1994, the World Health Organization (WHO) defined osteoporosis as a BMD *T* score below -2.5 SD based on measurements of any skeletal site. A revised WHO report published in 2000<sup>46</sup> stated that a measurement at either the total hip or femoral neck is preferred, but that posterior-anterior (not lateral) vertebral BMD can be used to make the diagnosis (Table 2). The current industry standard for hip BMD is the total hip, and the accepted reference populations used by all DXA densitometers come from the Third National Health and Nutrition Examination Survey (NHANES III). NAMS supports the use of the revised WHO guidelines.

Interpretation and clinical application of *T* scores are made after all other pertinent data are evaluated, particularly the age and fracture history of the woman. For example, at the same *T* score of -2.5, a 75-year-old woman has about 8 to 10 times the 10-year hip fracture risk of a 45-year-old woman.<sup>49</sup>

The fracture risk, however, depends on other factors, such as frailty, falls, and previous fractures. For example, a woman who has had a vertebral fracture has a 5-fold increased risk of sustaining another vertebral fracture during the first year after the fracture and twice the risk of a hip fracture as a woman with the same BMD *T* score who has not had a fracture.<sup>12</sup>

### Biochemical markers

Biochemical markers of bone turnover cannot diagnose osteoporosis, predict bone density, or predict fracture risk. However, these tests have been studied as a means of assessment that could be used earlier in the course of therapy to show therapeutic response. Bone turnover changes can provide evidence of osteoporosis therapy efficacy much earlier than BMD changes (sometimes within weeks). The value of such markers in routine clinical practice, however, has not been established.<sup>50,51</sup>

**TABLE 3.** Routine laboratory tests for osteoporosis evaluation

Test	Diagnostic result	Possible secondary cause
Complete blood cell count	Anemia	Multiple myeloma
Serum calcium	Elevated	Hyperparathyroidism
	Low	Vitamin D deficiency, malabsorption
Serum alkaline phosphatase	Elevated	Vitamin D deficiency, malabsorption, hyperparathyroidism
Serum albumin	Used to interpret serum calcium	
Urinary calcium excretion	Elevated	Renal calcium leak, multiple myeloma, metastatic bone cancer, hyperparathyroidism, hyperthyroidism
	Low	Malabsorption, vitamin D deficiency
Thyroid-stimulating hormone	Low	Hyperthyroidism

**Tests for secondary causes of osteoporosis**

Once osteoporosis is diagnosed, any secondary causes of osteoporosis should be identified. Various laboratory tests can help identify secondary causes of osteoporosis (Table 3). Tests that should be performed routinely include a complete blood cell count and serum levels of calcium, alkaline phosphatase, thyroid-stimulating hormone, and albumin, as well as urinary calcium excretion to identify calcium malabsorption or renal calcium leak. Special tests may be appropriate, including measurement of serum protein electrophoresis, parathyroid hormone, and 25-hydroxyvitamin D.

**LIFESTYLE APPROACHES**

All postmenopausal women, regardless of their osteoporosis risk factors, should be encouraged to engage in steps to prevent bone loss and fractures, such as eating a balanced diet (including adequate intakes of calcium and vitamin D), participating in appropriate exercise, not smoking, avoiding excessive alcohol consumption, and instituting measures to prevent falls. Some of these steps, such as smoking cessation and exercising, offer health benefits beyond their effects on osteoporosis.

**Nutrition**

A balanced diet is important for bone development as well as for general health. Some women, such as elderly women with reduced appetites or women who diet frequently or have eating disorders, may not consume adequate vitamins and minerals to maintain optimal bone mass. In general, women should be advised to eat more fruits and vegetables and minimize consumption of fats.

For women 75 years of age and older, observational research suggests that adequate protein intakes may

help minimize bone loss.<sup>52</sup> Protein supplements (20 g/day) in elderly patients (mean age 82) who have sustained a hip fracture have been shown to significantly shorten the hospital stay (median stay 69 days vs 102 days for placebo recipients) after the hip fracture and improve the clinical outcomes while in the hospital.<sup>53</sup> Protein recipients also had significantly lower rates of complications and mortality than the controls 7 months after their hip fracture.

An adequate intake of both calcium and vitamin D is recognized as an essential component of any osteoporosis prescription drug regimen. For example, a review of 31 clinical trials evaluating estrogen and calcium supplements found annual BMD gains at the hip were significantly greater for the 20 trials testing estrogen plus calcium (2.4%) compared with the 11 trials evaluating estrogen alone (0.9%).<sup>54</sup>

*Calcium*

Evidence has clearly established the importance of adequate calcium intake in programs focused on bone. Calcium requirements rise after midlife, particularly in postmenopausal women, owing in large part to estrogen-related shifts in intestinal calcium absorption and renal conservation. The primary factor influencing the amount of calcium absorbed is the amount of calcium ingested.

Most experts support the published recommendations for daily calcium consumption from either the National Institutes of Health (revised in 1994)<sup>16</sup> or the National Academy of Sciences (revised in 1997).<sup>55</sup> Recommendations related to perimenopausal and postmenopausal women are presented in Table 4.

The recommended calcium intakes are based on the total calcium content of various foods. To achieve maximum calcium absorption, food selection decisions should reflect the food’s calcium bioavailability and

**TABLE 4.** Recommended daily elemental calcium intakes in peri- and postmenopausal women

National Academy of Sciences	
Age 31–50	1,000 mg
Age 51 and older	1,200 mg
National Institutes of Health	
Premenopausal women aged 25–50	1,000 mg
Postmenopausal women younger than age 65 using estrogen replacement therapy (ERT)	1,000 mg
Postmenopausal women not using ERT	1,500 mg
All women older than age 65	1,500 mg

Adapted from the National Institutes of Health<sup>16</sup> and the National Academy of Sciences.<sup>55</sup>

the presence in the meal of other foods that may inhibit calcium absorption (e.g., oxalic acid-containing foods, such as spinach, and phytate-rich grains, such as wheat bran). Calcium requirements should optimally be met by food sources, with a calcium supplement added only if needed.<sup>26</sup>

The side effect profile from recommended levels of calcium intake is insignificant. No calcium intervention trials have reported any serious side effects associated with these intakes. Nevertheless, some women have difficulty tolerating some calcium supplements, requiring a switch to a different type of supplement.

Higher than recommended calcium intakes produce no currently recognized health benefits to women, and side effects can occur. Intakes greater than 2,500 mg/day (the upper limit for healthy adults set by the National Academy of Sciences) can increase the risk for hypercalciuria and, possibly, hypercalcemia, which, in extreme cases, can lead to kidney damage.

No single laboratory test can accurately detect calcium deficiency. In general, postmenopausal women in the United States and Canada have dietary calcium intakes that are low, with median intakes of approximately 600 mg/day.<sup>56,57</sup> Specific populations of postmenopausal women at increased risk for inadequate calcium intake include women who are elderly, lactose intolerant, follow a vegetarian diet, or have poor eating habits.

Dietary sources should be the primary source of calcium intake because there are other essential nutrients found in high-calcium food. Dairy products are among the best sources of calcium based on their high elemental calcium content, high absorption rate, and low cost relative to total nutritional value. Supplements and fortified foods are an alternative source for women not able to consume enough dietary calcium; most women need an additional 600 to 900 mg/day (2 to 3 dairy portions) over their daily dietary intake to reach the recommended levels. However, a level of caution may be needed to avoid consuming more than 2,500 mg/day.<sup>26</sup>

Calcium intakes of up to 1,500 mg/day do not appear to increase the risk of developing renal calculi and may actually reduce the risk.<sup>26</sup> For perimenopausal and postmenopausal women at high risk for developing renal calculi, foods may be the best sources of calcium. If calcium supplementation is needed, each dose should be taken with meals. Calcium supplements should be considered contraindicated in a woman with a calcium-containing renal calculus until her urinary biochemical profile has been assessed.

#### Vitamin D

The nutrient vitamin D is essential for the intestinal absorption of calcium. Ensuring sufficient vitamin D intake is fundamental to all prevention and treatment programs for postmenopausal osteoporosis.

The current recommended dietary intake for vitamin D is 400 IU/day for women aged 51 to 70 years and 600 IU/day for women older than age 70.<sup>55</sup> The National Osteoporosis Foundation recommends intakes of up to 800 IU/day for women at risk of deficiency because of inadequate sunlight exposure, such as elderly, chronically ill, housebound, institutionalized women, or those who live in northern latitudes.<sup>58</sup> The safe upper limit of vitamin D is 2,000 IU/day.<sup>55</sup> Higher doses may introduce risks such as hypercalciuria and hypercalcemia and should be avoided.

Sources of vitamin D include sunlight, vitamin D-fortified dairy products, fatty fish, and supplements. Daily requirements can usually be met with a multivitamin supplement (typically containing 400 IU vitamin D) plus moderate sun exposure. Many women over the age of 65 who have little or no sun exposure and rely on multivitamins alone for vitamin D intake may have suboptimal vitamin D levels.<sup>59</sup> Currently, there is no worldwide consensus on criteria for acceptable serum 25-hydroxyvitamin D values, but if minimization of parathyroid hormone concentration is used, as some suggest, the lower end of the normal 25-hydroxyvitamin D concentration would be in the range of 28 to 32 ng/ml (70 to 80 nmol/L).<sup>60</sup> Vitamin D is very long-acting, and thus, taking vitamin D at the same time as a calcium supplement is not necessary, although it can be a convenient way to obtain adequate levels of both nutrients.

It is well established that supplemental calcium can reduce the rate of postmenopausal bone loss, especially 5 or more years after menopause,<sup>61</sup> and can reduce the risk of fracture, particularly in the elderly.<sup>62,63</sup> However, calcium, either alone or with vitamin D, is not as effective as are estrogen replacement therapy (ERT), hormone replacement therapy with estrogen plus pro-

gestogen (HRT), selective estrogen-receptor modulators (SERMs), or bisphosphonates. Nevertheless, calcium and vitamin D are both essential components of osteoporosis therapy in combination with all antiresorptive agents.

### *Magnesium*

Another nutrient, magnesium, is sometimes mentioned as a necessary supplement for the protection of bone health and/or for absorption of calcium. Although magnesium is a necessary nutrient for the metabolic activity of all cells, in most trials focused on BMD or osteoporotic fracture, benefits of calcium were observed without magnesium supplementation. Moreover, a study with calcium absorption as the endpoint found that 789 to 826 mg/day of magnesium, more than double the daily average magnesium intake (280 mg) for postmenopausal women, had no effect on calcium absorption.<sup>64</sup>

Two studies<sup>65,66</sup> that did report an increase in BMD in postmenopausal women who received magnesium-containing supplements were small and not well controlled, and they do not present persuasive evidence of a beneficial effect from magnesium. However, in frail elderly women and women with gastrointestinal disease, magnesium supplements may be needed.<sup>67,68</sup>

### *Isoflavones*

Studies to date do not support the use of isoflavones to prevent or treat osteoporosis. Although some data suggest that isoflavones (a class of phytoestrogens found in rich supply in soybeans and soy products as well as in red clover) may favorably affect bone health, few randomized, controlled clinical studies with humans have been conducted, and all involved small numbers of subjects in trials of short duration.<sup>69</sup> Ipriflavone, a synthetic isoflavone available without a prescription in the United States, has not demonstrated a positive effect on bone density, bone turnover markers, or fracture risk in osteoporotic women.<sup>70</sup>

### **Exercise**

Physical activity plays an important role in reducing the risk of falls in elderly women with osteoporosis. Exercise programs for the elderly reduce their risk of falling by 10%, and programs that include training for balance reduce the risk by nearly 20%.<sup>71</sup> Exercise for women with established osteoporosis should not include heavy weight bearing or activity so vigorous that it may trigger a fracture.

Exercise is also important for early postmenopausal

women. For bone benefits, they should be advised to add muscle strength training to their exercise program.

Postmenopausal women who do not use either ERT or HRT often lose bone mass. Some evidence shows that strength training may curb bone loss in these women.<sup>72,73</sup> For women who do use ERT/HRT, strength training provides additional benefits, allowing them to increase bone mass rather than just maintain it with ERT/HRT alone.<sup>74</sup> Strength training can be performed as little as twice a week and need not involve special equipment other than simple weights or elastic bands.

### **Smoking cessation**

Because smoking can lead not only to lower BMD but also to a wide range of health problems and increased fracture risk, smoking cessation should be encouraged for all women who are smokers. A wide array of smoking cessation aids are available, including prescription products (with and without nicotine) and behavior-modification smoking cessation programs.

### **Alcohol avoidance**

The level of alcohol consumption associated with an increased risk of falls is more than seven drinks a week, as established by the Framingham Study.<sup>75</sup> Postmenopausal women who drink should be advised to drink moderately and not to exceed seven drinks a week. One drink is considered to be one beer, 4 oz of wine, or 1 oz of liquor.

### **Fall prevention**

In the United States, about 30% of people over age 60 fall at least once a year.<sup>76</sup> The incidence of falls increases with age, rising to a 50% annual rate in people over 80 years of age. Elderly women have a significantly higher risk for falls than do men of the same age. As a result, prevention of falls that can cause fractures should be an aspect of routine care for all elderly women.

After menopause, a woman's risk for falls should be assessed at least annually. Clinical factors related to an increased risk for falls include a history of falls, fainting, or loss of consciousness; muscle weakness, dizziness, or balance problems; problems with muscle coordination; and impaired vision. Medications that affect balance and coordination (e.g., sedatives, narcotic analgesics, anticholinergics, and antihypertensives) are also risk factors. Safety hazards in the home and work environment, such as obstacles and poor lighting, also contribute to the risk of falls.

## PHARMACOLOGIC APPROACHES

A management strategy focused on lifestyle approaches may be all that is needed for women who are at low risk for osteoporotic fracture. NAMS recommends considering osteoporosis therapy in the following populations (these recommendations represent a change from previous NAMS recommendations<sup>77</sup> based on additional published data regarding fracture efficacy):

- All postmenopausal women with total hip or spine *T* scores worse than  $-2.5$ .
- All postmenopausal women with total hip or spine *T* scores from  $-2.0$  to  $-2.5$  and at least one additional risk factor for fracture.
- All postmenopausal women with an osteoporotic vertebral fracture (no BMD is needed).

Several pharmacologic options are available for the prevention and treatment of osteoporosis, including ERT/HRT, bisphosphonates, SERMs, and calcitonin.

### ERT/HRT

As estrogen levels decline, the rate of bone remodeling increases, with an imbalance favoring bone resorption over bone formation. Both ERT and HRT reduce the rate of bone turnover and resorption.<sup>78</sup> In many postmenopausal women, ERT lowers the elevated resorption rates to premenopausal rates. Adding a progestogen (to protect against an increased endometrial cancer risk from unopposed estrogen) does not reduce the bone-preserving effects of ERT and may enhance those effects.<sup>79,80</sup>

The positive BMD effects of systemic estrogen (oral or transdermal), with or without a progestogen, are well established. More than 50 randomized, placebo-controlled clinical trials have demonstrated that ERT/HRT initially increases spine BMD 4–6% and hip BMD 2–3%, and maintains those increases after 3 years of treatment.

In the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial,<sup>81</sup> a randomized, controlled, multicenter study of 875 postmenopausal women (average age 56 years), oral intakes of 0.625 mg conjugated equine estrogens (CEE), with or without a progestogen (medroxyprogesterone acetate or micronized progesterone), increased BMD at the spine (3.5–5%) and hip (1.7%) over a 3-year period. Both gains were significant compared with placebo recipients. Low-dose CEE (0.3 mg/day), in a continuous combined formulation including medroxyprogesterone acetate (2.5 mg/day),

increased spinal bone density 3.5–5.2% in older (age >65 years) postmenopausal women with low bone mass.<sup>82</sup>

In another study of postmenopausal women, 0.3 mg/day of oral esterified estrogens, administered unopposed by progestogen for 24 months, resulted in positive bone changes without inducing endometrial hyperplasia.<sup>83</sup> A randomized, controlled clinical trial of unopposed transdermal 17 $\beta$ -estradiol found that doses ranging from 0.025 to 0.1 mg/day significantly increased BMD of the spine and hip compared with placebo.<sup>84</sup>

The optimal time to initiate therapy and optimal duration of therapy have not been determined. Generally, ERT/HRT is believed to work best if started during the first 5 to 10 years after menopause. Even if started long after menopause, ERT/HRT produces substantial gains in bone mass.<sup>85–87</sup> In the Framingham Study,<sup>88</sup> elderly women (mean age 76 years) with 7 or more years of ERT/HRT use had significantly higher BMD than nonusers, although the effect diminished somewhat in those older than 75 years. When ERT/HRT is discontinued, however, bone loss tends to accelerate.<sup>89</sup> Over time, their bone mass approaches that of women who have not used hormones. Fracture rates are also indistinguishable.

Regarding fracture prevention, observational studies have indicated a significant reduction in hip fracture risk in women who use systemic ERT/HRT. A meta-analysis of studies published up to 1992<sup>90</sup> yielded evidence of a 25% reduction in the risk of hip fracture for postmenopausal women who had ever used ERT/HRT. A more recent meta-analysis<sup>91</sup> found that ERT/HRT use for at least 1 year significantly reduced the risk of nonvertebral fracture (relative risk 0.73), although the effect was somewhat reduced in women beginning therapy when they were older than 60 years. A large prospective, cohort study of elderly women, the Study of Osteoporotic Fractures,<sup>92</sup> found a significant fracture risk reduction of 34% for nonspine fractures in current long-term users of ERT/HRT compared with never users. The investigators also found that ERT/HRT is more effective in reducing fracture risk if started within 5 years of menopause and if used longer than 10 years.

In the Heart and Estrogen/Progestin Replacement Study (HERS),<sup>93</sup> a randomized, controlled trial of 2,763 postmenopausal women, no reduction in fracture risk was observed after 4 years of HRT (0.625 mg/day CEE plus 2.5 mg/day medroxyprogesterone acetate). These women did not have osteoporosis and were at relatively low risk for fracture. Adequate randomized

trials evaluating the effectiveness of estrogen therapy on reducing fracture risk in women with osteoporosis have not been undertaken.

In the absence of randomized, prospective trials with osteoporotic fractures as the outcome, the FDA has withdrawn the osteoporosis *treatment* indication from estrogen products; the osteoporosis *prevention* indication was retained. In Canada, ERT/HRT is approved only for prevention.

In the Swedish Hip Fracture Study,<sup>94</sup> a large, population-based, case-control study of women aged 50 to 81 with hip fractures, only recent use of ERT/HRT was associated with optimal fracture protection. However, this study suggested that therapy can be beneficial even if started several years after menopause. The overall fracture risk appeared to decrease with duration of estrogen use and addition of a progestogen.

Despite the potential advantages, an estimated 50–75% of women who begin ERT/HRT discontinue within 6 months; often cited among the reasons for discontinuance are concerns about the link between estrogen and an increased risk of breast cancer. The magnitude of the link, however, remains unresolved.<sup>95,96</sup> ERT/HRT also carries a 3-fold increased risk of venous thromboembolic events. Furthermore, the HRT-induced uterine bleeding is unacceptable to some women.

### Bisphosphonates

This class of drugs works by inhibiting osteoclast activity, thus reducing bone resorption. Unlike ERT/HRT, bisphosphonates do not have beneficial effects on the body other than on bone. However, they do not exhibit estrogen's adverse effect on the uterus and breast. Clinical trials have demonstrated that these agents increase BMD at the spine and hip in a dose-dependent manner; they also reduce the risk of vertebral and nonvertebral fracture by 30–50%.<sup>5</sup>

Bisphosphonates may cause upper gastrointestinal (GI) disorders, and are contraindicated in those with esophageal abnormalities that delay esophageal emptying or who are unable to stand or sit upright for at least 30 minutes after ingestion. Also, as less than 1% of a bisphosphonate dose is normally absorbed, and food or drink further decreases absorption, the agent must be taken when the stomach is empty. Food or drink must be avoided for at least 30 minutes after dosing.

#### *Alendronate*

This bisphosphonate is approved in both the United States and Canada for postmenopausal osteoporosis

prevention (5 mg/day or 35 mg/wk) and treatment (10 mg/day or 70 mg/wk). It has been shown in large, randomized, controlled clinical trials to increase BMD and reduce fracture risk.<sup>97–100</sup>

For women in early postmenopause, 2 to 4 years of treatment with alendronate (5 mg or more daily) increased BMD at the spine and hip from 1–4% from baseline, whereas placebo recipients had decreases of 2–4% during that time, a statistically significant intergroup difference.<sup>97,98</sup> In a 7-year trial, alendronate was associated with BMD increases from baseline of 5–10% at the spine and hip in postmenopausal women who had low BMD or established osteoporosis.<sup>99</sup>

The efficacy of alendronate in decreasing fracture risk has been demonstrated only in postmenopausal women with osteoporosis, defined as having either an existing vertebral fracture or a *T* score worse than –2.5. In the Fracture Intervention Trial,<sup>100</sup> 3 years of alendronate therapy significantly reduced the risk of non-spine fracture by 27% and new spine fracture by 50% in women with osteoporosis; however, it had no statistically significant effect in women without osteoporosis.

#### *Risedronate*

This bisphosphonate, approved for the prevention and treatment of postmenopausal osteoporosis in both the United States and Canada, has established antiresorptive activity. In clinical trials, risedronate has been shown to prevent BMD loss and reduce fracture risk.<sup>101–104</sup>

In a trial of early postmenopausal women (40 to 60 years of age) with normal bone mass, doses of 5 mg/day for 2 years produced significant BMD increases of 5.7% in the lumbar spine and 5.4% in the hip compared with placebo.<sup>101</sup> In older postmenopausal women (mean age approximately 69 years),<sup>102</sup> 3 years of risedronate therapy significantly increased BMD compared with placebo in the spine (4.3%) and femoral neck (2.8%).

Several studies have found fracture risk reductions with risedronate. In two studies of postmenopausal women with established osteoporosis,<sup>102,103</sup> 1 to 3 years of treatment with 5 mg/day of risedronate significantly reduced the risk of vertebral fracture compared with placebo. After 1 year of therapy, the relative risk of vertebral fracture was reduced by 61–65%. After 3 years of therapy, vertebral fracture risk reductions were still statistically significant relative to placebo. In one of these studies,<sup>102</sup> the risk of nonvertebral fracture was significantly reduced by 39%.

In the Hip Intervention Program Study Group,<sup>104</sup>

risedronate significantly reduced the relative risk for hip fracture by 40% among women 70 to 79 years of age with confirmed osteoporosis; however, it did not significantly lower the risk in women 80 years of age and older who had risk factors for falling but who did not have osteoporosis confirmed by BMD.

### *Etidronate*

The bisphosphonate etidronate is approved in Canada for osteoporosis prevention and treatment in postmenopausal women. Although it is available in the United States, it is FDA-approved only for treatment of Paget's disease, not for osteoporosis prevention or treatment, and the dose approved for Paget's disease is considerably higher than that used in osteoporosis therapy.

A meta-analysis of 13 trials investigating intermittent cyclic etidronate therapy (14 days every 3 months) for postmenopausal osteoporosis found that, relative to control groups, 1 to 3 years of therapy (400 mg/day) increased BMD by 4.1% in the lumbar spine and 2.3% in the femoral neck.<sup>105</sup> This analysis concluded that etidronate significantly reduced the risk for vertebral fracture (37%) but not the risk for nonvertebral fracture.

Etidronate is typically administered in 2-week cycles that are repeated every 3 months; calcium is taken between the cycles of etidronate. Administration is cyclic because daily use may cause abnormalities in bone mineralization.<sup>106</sup>

### **SERMs**

The drugs in this class act as weak estrogen agonists in some organ systems and as estrogen antagonists in others. The goal of SERM therapy is to provide the benefit of estrogen on bone without adverse effects on the endometrium and breast.

Raloxifene is the only SERM approved for osteoporosis prevention and treatment in both the United States and Canada (60 mg/day). In postmenopausal women, raloxifene has been shown to significantly reduce serum and urinary markers of bone turnover compared with controls.<sup>107</sup> At 2 years, it produces significant BMD increases of 2.4% for both the spine and hip relative to placebo.<sup>108</sup> Over 3 years, raloxifene reduces the risk of vertebral fracture in postmenopausal women with osteoporosis by 35–50%,<sup>109</sup> although a reduction in fracture risk at other sites was not demonstrated.

Unlike estrogen, raloxifene apparently does not stimulate the endometrium. Like estrogen, it decreases bone turnover by inhibiting resorption and lowers total and low-density lipoprotein cholesterol levels,<sup>108</sup> al-

though it does not raise high-density lipoprotein cholesterol. Also, raloxifene does not have the unfavorable effect of raising triglycerides, as oral estrogen sometimes can. In addition, 3 to 4 years of raloxifene administration has been shown to reduce the risk of invasive breast cancer in postmenopausal women by 76%.<sup>110,111</sup> However, it should be noted that the patient population in that study was elderly and selected based on osteoporosis criteria and, as such, participants were not at increased risk for breast cancer. As of yet, there are no published studies on raloxifene use in younger women with a history of breast cancer.

Hot flashes are the most common side effect of raloxifene, so the medication cannot be used to treat vasomotor symptoms associated with menopause and might even exacerbate the symptoms. Raloxifene carries the same risk as ERT/HRT of venous thromboembolic events, such as deep vein thrombosis. Therefore, like ERT/HRT, raloxifene should not be given during periods of prolonged immobilization.

### **Calcitonin**

Both intranasal and injectable formulations of salmon calcitonin have been approved in the United States for postmenopausal osteoporosis treatment but not for prevention. Although an injectable formulation is available in Canada, it is not approved for any osteoporosis indication.

Calcitonin inhibits bone resorption; however, the reduction in bone turnover is much less than with other antiresorptive agents. Calcitonin therapy has produced positive spinal BMD effects, but at the hip, its efficacy is less clear. A small, dose-finding study of intranasal calcitonin in postmenopausal women with osteoporosis showed significantly increased spinal BMD of 3% relative to baseline.<sup>112</sup> Significant BMD effects were not seen at the hip.

In the Prevent Recurrence of Osteoporotic Fractures (PROOF) study,<sup>113</sup> a large randomized, double-blind, placebo-controlled study of intranasal calcium, doses of 200 IU/day for 5 years significantly reduced the risk of new vertebral fracture by 33% compared with placebo in postmenopausal women with established osteoporosis. However, at either 100 IU/day or 400 IU/day, statistically significant reductions were not observed. After 5 years, a significant spinal BMD increase compared with placebo was seen only for the 400-mg dose recipients. No significant effect on hip BMD occurred at any dose. The absence of a dose response as well as a 60% dropout rate have led some experts to doubt the reliability of these data.

Calcitonin has also been found to reduce bone pain

from osteoporotic vertebral compression fractures.<sup>114</sup> Calcitonin has few adverse effects other than nausea, local inflammation, and flushing of the face or hands when given as an injection and local nasal irritation with the nasal spray formulation.

Because calcitonin is a less potent agent than other pharmacologic therapies for osteoporosis, it is reserved as an alternative for women who cannot or choose not to take one of the other osteoporosis agents. It is recommended for use in women with osteoporosis who are at least 5 years beyond menopause. The efficacy of calcitonin has not been observed in early postmenopausal women.

### Other therapies

Several additional therapies have shown some efficacy for bone health. The statins and thiazides have FDA approval for cardiac indications but not for skeletal effects. Parathyroid hormone (PTH) and tibolone have new drug applications pending.

### Parathyroid hormone

Daily subcutaneous injections of recombinant human PTH activate bone formation and result in substantial increases in trabecular bone density and connectivity in women with postmenopausal osteoporosis, regardless of whether they are receiving estrogen therapy.<sup>115–117</sup> In postmenopausal women with prior vertebral fracture, 19 months of PTH (20 or 40 µg daily) reduced the incidence of new vertebral fractures by 65% and 69%, respectively, and new nonvertebral fractures by 53% and 54%.<sup>117</sup>

### Tibolone

This synthetic steroid has estrogenic, androgenic, and progestogenic properties. At a dose of 2.5 mg/day for 2 years, tibolone has been shown to be effective in preventing bone loss in postmenopausal women and increasing bone mass in women with established osteoporosis.<sup>118,119</sup> A more recent study showed that lower doses (0.625 and 1.25 mg/day) are effective for preventing postmenopausal bone loss.<sup>120</sup> However, 2.5 mg/day of tibolone is needed to treat menopausal symptoms, such as hot flashes.

### Statins

The discovery that potent bisphosphonates suppress osteoclast activity by inhibiting a step in the cholesterol synthesis pathway led to speculation that other drugs that impair cholesterol synthesis, such as the HMG

CoA-reductase inhibitors known as statins, would have similar effects on the skeleton. In the laboratory, statins inhibit osteoclast bone resorption. However, it is not known whether lipid-lowering doses of statins inhibit osteoclast activity in the clinical setting. Reports from several observational studies have not consistently demonstrated a reduction in fracture incidence in patients receiving statins.<sup>121–124</sup> Formal clinical trials are needed to further the understanding of the effects of statins on skeletal health.

### Thiazide

Thiazide therapy does not prevent bone loss. However, in healthy elderly women, 25 mg/day for 3 years of the widely used diuretic hydrochlorothiazide has been shown to significantly reduce the rates of bone loss at the hip and spine by 1.4% and 1.3%, respectively, relative to placebo.<sup>125</sup> A lower daily dose of 12.5 mg was not effective. No prospective studies have evaluated the effect of thiazides on fracture risk.

### Combination therapies

Combining therapies in an attempt to gain greater benefits is common in medical practice. Some recent studies have evaluated the efficacy of combining ERT/HRT with other osteoporosis therapies in postmenopausal women.

In one study,<sup>126</sup> BMD improvements in the spine and hip with combined alendronate and CEE were significantly greater than results for either agent alone. In another study,<sup>127</sup> combined alendronate and HRT produced significantly greater gains in BMD at the lumbar spine (3.6% vs 1%) and hip trochanter (3.7% vs 0.5%) than HRT alone. Combined risedronate and ERT/HRT also has shown favorable, although modest, BMD effects compared with either agent alone.<sup>128</sup> A study of combined cyclic etidronate and HRT found BMD gains were 3% higher at the spine and 2% higher at the hip than gains made with HRT alone.<sup>129</sup> Concomitant ERT/HRT and calcitriol therapy also produced larger increases in BMD than with ERT/HRT alone.<sup>87</sup> Whether increases in BMD result in better fracture protection is not known, and the long-term safety of combination therapies has not been evaluated.

## RESEARCH NEEDS

Although much can be ascertained regarding the prevention and treatment of postmenopausal osteoporosis, additional research is needed to clarify related issues. Some suggested areas for research include the following:

- Identify genetic factors relating to bone mass.
- Develop strategies to identify women at higher fracture risk.
- Establish standards for BMD readings to enable cross-comparison of studies and measurements at different sites.
- Determine the clinical value of bone turnover markers in the pathogenesis and treatment of bone diseases, including predicting fracture.
- Determine the long-term effects of calcium intake on bone remodeling.
- Ascertain the influence on BMD of age at which ERT/HRT is initiated.
- Determine when to initiate and when to discontinue ERT/HRT.
- Determine the duration of the protective effect of ERT/HRT on BMD after treatment is withdrawn.
- Evaluate the efficacy of different ERT/HRT regimens on BMD and/or fractures.
- Determine the relationship of androgens and bone.
- Evaluate the impact of combination therapy, including pharmacologic, nutritional, and lifestyle interventions, in the management of postmenopausal osteoporosis.
- Evaluate strategies to improve long-term adherence to therapies.

### SUMMARY

Postmenopausal osteoporosis is a serious health threat that affects nearly 20% of North American women over the age of 50. Nearly half of all white women over age 50 will suffer an osteoporotic fracture during their remaining lifetime. Among elderly women who suffer a hip fracture, about half have long-term disability. Within 1 year, nearly a quarter will be confined to long-term care, and about a fifth will die as a direct consequence of the fracture. A vertebral fracture results in deformity and significant pain for many women.

Management of the postmenopausal woman involves identifying the potential risk for osteoporosis and osteoporotic fracture through an assessment of risk factors and BMD testing. Osteoporosis prevention focuses on a combination of adequate nutrition (including sufficient calcium and vitamin D), exercise, avoidance of excessive alcohol consumption, smoking cessation, and the prevention of falls. In women who require pharmacologic therapy because of high risk for fracture, available options include ERT/HRT, bisphosphonates, SERMs, and calcitonin.

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