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NAMS Position Statement

Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society

Abstract

Objective: To review evidence regarding osteoporosis screening, prevention, diagnosis, and management in the past decade and update the position statement published by The North American Menopause Society (NAMS) in 2010 regarding the management of osteoporosis in postmenopausal women as new therapies and paradigms have become available.

Design: NAMS enlisted a panel of clinician experts in the field of metabolic bone diseases and/or women's health to review and update the 2010 NAMS position statement and recommendations on the basis of new evidence and clinical judgement. The panel's recommendations were reviewed and approved by the NAMS Board of Trustees.

Results: Osteoporosis, especially prevalent in older postmenopausal women, increases the risk of fractures that can be associated with significant morbidity and mortality. Postmenopausal bone loss, related to estrogen deficiency, is the primary contributor to osteoporosis. Other important risk factors for postmenopausal osteoporosis include advanced age, genetics, smoking, thinness, and many diseases and drugs that impair bone health. An evaluation of these risk factors to identify candidates for osteoporosis screening and recommending nonpharmacologic measures such as good nutrition (especially adequate intake of protein, calcium, and vitamin D), regular physical activity, and avoiding smoking and excessive alcohol consumption are appropriate for all postmenopausal women. For women at high risk for osteoporosis, especially perimenopausal women with low bone density and other risk factors, estrogen or other therapies are available to prevent bone loss. For women with osteoporosis and/or other risk factors for fracture, including advanced age and previous fractures, the primary goal of therapy is to prevent new fractures. This is accomplished by combining nonpharmacologic measures, drugs to increase bone density and to improve bone strength, and strategies to reduce fall risk. If pharmacologic therapy is indicated, government-approved options include estrogen agonists/antagonists, bisphosphonates, RANK ligand inhibitors, parathyroid hormone-receptor agonists, and inhibitors of sclerostin.

Conclusions: Osteoporosis is a common disorder in postmenopausal women. Management of skeletal health in postmenopausal women involves assessing risk factors for fracture, reducing modifiable risk factors through dietary and lifestyle changes, and the use of pharmacologic therapy for patients at significant risk of osteoporosis or fracture. For women with osteoporosis, lifelong management is necessary. Treatment decisions occur continuously over the lifespan of a postmenopausal woman. Decisions must be individualized and should include the patient in the process of shared decision-making.

Key Words: Bisphosphonates – Bone mineral density – Calcium – Estrogen agonists/antagonists – Falls – Fractures – Osteoporosis – Parathyroid hormone-receptor agonists – Postmenopause – Prevention – RANK ligand inhibitors – Vitamin D.

Osteoporosis can be a serious health threat for postmenopausal women by predisposing them to fractures that may be associated with substantial morbidity and mortality, especially in older women. Clinical management cannot be defined or confined only by ''evidence.'' There is no single or optimal management strategy for a chronic disorder such as osteoporosis. When evidence is lacking, clinicians use clinical judgement, consisting of

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individualized management decisions for each patient and for different stages in the course of the disease and based on a combination of known evidence, knowledge of the physiology of the problem being addressed, and their experience.[1]

The North American Menopause Society (NAMS) creates position statements on specific disorders to provide reliable and accurate information regarding management of menopause-associated health conditions. Here, NAMS provides guidance on the diagnosis, assessment, prevention, and treatment of osteoporosis in postmenopausal women in North America.

The recommendations herein are based, where possible, on evidence provided by clinical trials and, where evidence does not exist, current best clinical practice in the opinions and clinical judgment of an editorial panel consisting of clinicians and researchers with expertise in metabolic bone diseases or women's health. These statements do not represent guidelines or codified practice standards as defined by regulating bodies and insurance agencies. Rather, the editorial panel has attempted to provide sufficient information for clinicians to approach postmenopausal women with or at risk for osteoporosis with a confident understanding of management options. The recommendations are focused on the perceptions of the needs of healthcare professionals caring for the skeletal health of postmenopausal women in the primary care setting. The guidance provided herein is generally consistent with recommendations for the assessment and treatment of postmenopausal osteoporosis available from several other North American societies and organizations.[2-8]

This position statement is an update of the 2010 position statement, ''Management of Osteoporosis in Postmenopausal Women.''[9] Since then, several new medications with sophisticated mechanisms of action have received government approval on the basis of randomized, controlled trial (RCT) data. In addition, new knowledge about the pathophysiology and epidemiology of postmenopausal osteoporosis has become available, as have new perspectives about the role of hormone therapy (HT) in the management of skeletal health, longer experience with the efficacy and safety of older osteoporosis drugs, the potential role of drug holidays for bisphosphonates, and new paradigms regarding sequential use of and anabolic and antiremodeling osteoporosis therapies. These advances have created the need to update the position statement.

METHODS

For this revision, NAMS enlisted a six-person editorial panel composed of clinicians and researchers with expertise in metabolic bone diseases or women's health to review the 2010 position statement, identify key studies and evidence published subsequently, and reach consensus on recommendations. The editorial panel reviewed clinical studies published in English related to osteoporosis management in postmenopausal women. Priority was given to evidence from RCTs and meta-analyses of such trials, followed by evidence from systematic reviews and controlled observational studies, using criteria described elsewhere.[10] Because standards of care and available treatment options differ throughout the world, the focus is limited to therapies for postmenopausal osteoporosis available in North America. The NAMS Board of Trustees was responsible for the final review and approval of this position statement.

EVALUATING PATIENTS FOR AND WITH OSTEOPOROSIS

Background

Osteoporosis—the most common bone disorder affecting humans—is a generalized skeletal disorder characterized by compromised bone strength, predisposing a person to an increased risk of fracture, most importantly of the spine and hip.[11] These and other serious fractures occur most commonly in older postmenopausal women and are often life-altering events. However, the bone loss that results in osteoporosis is most marked during the menopause transition and early menopause. Less serious fractures, such as wrist fractures, occur in young postmenopausal women and are important warning signs of osteoporosis.

Persons with osteoporosis and high risk of fracture can be readily identified. Both general and pharmacologic management strategies are available to slow or prevent bone loss and to reduce fracture risk. Because osteoporosis is such a common disorder, skeletal health assessment should be a part of the routine evaluation of all postmenopausal women, and all professionals caring for postmenopausal women should be competent and confident about undertaking that evaluation.

Pathophysiology

In adults, bone tissue undergoes constant change by a process called *bone remodeling*. Old bone material (mineral and protein matrix) is resorbed (removed) by osteoclasts and replaced with new healthy bone by osteoblasts. Osteocytes interconnect in the solid matrix of bone via an extensive canalicular network that senses both mechanical loading and focal bone damage. Osteocytes secrete molecules that regulate both the location of and the rate of bone remodeling. These include receptor activator of nuclear factor kappa-β (RANK) ligand, a growth-promoting factor whose interaction with its receptor RANK is required for the proliferation, differentiation, and activity of osteoclasts; and sclerostin, an inhibitor of bone formation. Osteocyte activity is, in turn, regulated by mechanical loading and circulating hormones including parathyroid hormone (PTH) and estrogen.

Bone strength (and, hence, fracture risk) is dependent on many qualities of bone, of which bone mineral density (BMD) is the most commonly measured.[11] Bone density at any given age is a function of both peak bone mass (reached by age 30) and how much bone is subsequently lost. In healthy premenopausal women, bone mass is quite stable. The amount of old bone resorbed is replaced with an almost equal amount of new bone.[12] During perimenopause, estrogen deficiency results in increased expression of RANK ligand, activating osteoclasts. Bone resorption becomes more rapid, exceeding the ability of

osteoblasts to form new bone, resulting in an accelerated phase of bone loss during the menopause transition.[12,13]

The average annual rate of bone loss is about 2%, beginning 1 to 3 years before menopause and lasting for 5 to 10 years, resulting in an average loss of BMD of 10% to 12% in the spine and hip across the menopause transition.[12] Rates of loss are somewhat greater in thin versus heavy women. After this interval of relatively rapid bone loss, bone density decreases about 0.5% per year. This imbalance in remodeling continues into advanced age in which an additional deficit in osteoblast function limits bone formation. By age 80 years, women have lost, on average, approximately 30% of their peak bone mass.[4]

Bone loss after menopause results in a gradual but progressive deterioration of the microarchitecture of both trabecular and cortical bone, weakening the skeleton and increasing the risk of fracture. The thick and numerous trabeculae seen in the spine and ends of long bones in premenopausal women become thinned and perforated and may be completely resorbed, resulting in empty spaces where bone tissue once existed. The thick outer shell of cortical bone is thinned from the inside and becomes more porous because of the dominance of bone resorption over formation. This imbalance in bone remodeling can be accentuated by a very sedentary lifestyle, contributing to accelerated bone loss in older inactive women. Many diseases and medications can amplify these effects by either increasing bone resorption or inhibiting bone formation.

Other factors, including bone mineralization, matrix composition, microstructure, and microdamage, as well as age-related factors such as the accumulation of advanced glycation end products, affect the quality and integrity of bone tissue. These factors cannot be directly measured in clinical practice. These combined changes in bone mass, structure, and quality result in impaired bone strength and the increased fracture risk of postmenopausal osteoporosis.

Bone mineral density

The measurement of areal bone density (the amount of bone mineral divided by the area of the bone scanned) by dual-energy X-ray absorptiometry (DXA), is the principal clinical tool used to assess skeletal health. Careful attention to the quality of both the acquisition and interpretation of DXA bone density tests is necessary.[14]

To standardize bone density values from different skeletal sites, results are reported as T-scores or Z-scores:

- The T-score compares a woman's bone density to the average value of healthy young women and is expressed in standard deviation (SD) units. A T-score of +1 represents a value 1 SD above the young normal mean, whereas a value 2.5 SDs below the young normal mean would equate to a T-score of −2.5. By convention, the White (non-race adjusted), young, normal value serves as the reference for T-scores in women of all races.
- The Z-score is the number of SDs above or below the average bone density for the average person of the same age, sex, and ethnicity. The normal range for Z-score is −2.0 to +2.0. The Z-score has limited value in postmenopausal women.

Studies to date provide inadequate data on racial inequities in health care. Individual- and system-level issues that promote inequality need to be addressed in further research studies.[15]

Diagnosing osteoporosis

Diagnostic categorization by bone density is based on recommendations of a World Health Organization Study Group (Table 1).[16] In North America, the standard criterion for the diagnosis of osteoporosis in postmenopausal women is a T-score of −2.5 or less at the lumbar spine (LS; at least two vertebral levels measured in the posterior-anterior projection but not the lateral projection), femoral neck (FN), or total hip (TH) by DXA testing. If anatomic factors such as arthritis or hip replacement make measurements of the spine and hip invalid, bone density of the distal one-third site of the radius (forearm) may be considered a diagnostic site, but other methods of diagnosing osteoporosis and assessing fracture risk also should be considered. When a woman's T-score increases with treatment from less than −2.5 to values above −2.5, the diagnosis of osteoporosis persists.[17]

The diagnosis of low BMD, or *osteopenia,* does not necessarily indicate that bone loss has occurred. This term has limited clinical use because it includes young postmenopausal women without other risk factors who are at low risk of fracture as well as older women with other risk factors who are at very high risk of fracture.

T-scores can be generated from other methods of BMD assessment, and some of those measurements have been shown to predict fracture risk. In general, however, T-scores from those other methods should not be used to diagnose osteoporosis.[18]

In addition to BMD, the clinical diagnosis of osteoporosis can be made in postmenopausal women who present with fractures of their spine or hip or who have other risk factors resulting in high fracture risk (Table 2).[7]

Osteoporosis is categorized as either *primary* or *secondary*. Primary osteoporosis refers to bone loss that occurs after menopause and with aging. Secondary osteoporosis is diagnosed when medications such as glucocorticoids or diseases contribute to bone loss.

Prevalence

In the 2013-2014 National Health and Nutrition Examination Survey, 16.5% of American women aged 50 years or older had osteoporosis, defined as a BMD T-score of −2.5 or lower at either the FN or LS.[19] Similar prevalence has been observed in Canada and Mexico.[20,21] The prevalence of osteoporosis by low FN BMD increases with age, from

TABLE 1. *Diagnostic categories based on femoral neck T-scores*

Normal	T-score ≥ −1.0
Low bone mass[a]	T-score between −1.0 and −2.5
Osteoporosis	T-score ≤ −2.5

[a]This category is often referred to as osteopenia.
Kanis JA, et al.[16]

TABLE 2. *Diagnosing osteoporosis in postmenopausal women*

1. BMD T-score by DXA of −2.5 or lower in the LS or proximal femur (TH or FN)
2. History of vertebral (spine) or hip fracture, irrespective of BMD or other risk factors
3. Low bone mass (T-score between −1.0 and −2.5) and any of the following
   a. History of fracture of proximal humerus, pelvis, or distal forearm
   b. History of multiple fractures at other sites (excluding face, feet, and hands)
   c. Increased fracture risk using FRAX country-specific thresholds

BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; FN, femoral neck; FRAX, Fracture Risk Assessment Tool; LS, lumbar spine; TH, total hip.
Camacho PM, et al.[7]

6.8% in women aged 50 to 59 years to 34.9% in women aged 80 years and older.[22] In the United States, the rates of osteoporosis vary with ethnicity: Black Americans have the highest BMD, whereas Asian Americans have the lowest.[23] These differences, however, may be related more to body weight than to race.[24]

More than 2 million fractures related to osteoporosis occur each year in the United States, including more than 700,000 clinical vertebral fractures and 300,000 hip fractures, resulting in more than 500,000 hospital admissions.[25] Most of these fractures occur in older postmenopausal women, with two-thirds of the fractures occurring after age 75.[26] For a White American woman aged 50 years, the risk of suffering an osteoporotic fracture in her remaining lifetime has been estimated at 40%, and for hip, forearm, and symptomatic vertebral fracture is at 17.5%, 16.0%, and 15.6%, respectively.[27] Lifetime risks for hip fracture are 17% for White Americans, 14% for Hispanic Americans, and 6% for Black Americans.[28]

Age-adjusted rates of hip fracture in women in the United States and Canada appeared to be decreasing after 1997. However, recent data suggest that those rates have plateaued and may even be increasing again, perhaps related to the declining use of osteoporosis medications since 2008.[29,30] The absolute number of patients who have fractures will continue to increase because of population growth.[22]

Morbidity and mortality

Hip fractures, occurring on average at age 82, elicit a particularly devastating toll, resulting in higher cost and disability than all other fracture types combined.[31] Hip fractures cause up to a 25% increase in mortality within 1 year of the incident.[32] Up to 25% of women require long-term care after a hip fracture, and 50% will have some long-term loss of mobility. The annual incidence of experiencing a second hip fracture is 2% to 10%, with the second fracture occurring, on average, about 2 years after the first.[33]

Fractures at other sites, including the spine, humerus, and pelvis, also can result in serious morbidity.[34] Multiple or severe vertebral fractures may cause substantial pain as well as loss of height and exaggerated curvature of the thoracic spine (kyphosis), restricted movement, and impaired lung function.[35] Only about one-third of vertebral fractures that can be diagnosed radiographically come to clinical attention.[35,36] Existing vertebral fractures increase the risk of subsequent vertebral fracture by five- to seven-fold.[37] The relative risk for mortality after vertebral fracture is as high as with hip fracture.[38] Postfracture pain, loss of mobility, changed body image, and loss of independence can have strong effects on self-esteem and mood.[39]

Clinical assessment

Evaluation of skeletal health, including the assessment of risk factors for low BMD and fracture, should be undertaken in all postmenopausal women. This information can identify women for BMD testing and shape recommendations for clinical management.

Risk factors and risk assessment

It is important to distinguish between risk factors for osteoporosis as defined by BMD and risk factors for fracture. Major risk factors for low BMD in postmenopausal women include menopause status, advanced age, genetics, thinness, and diseases or drugs with adverse skeletal effects. Low BMD, as well as a history of previous fracture, older age, parental history of hip fracture, frailty, and other medical problems are important risk factors for fracture. Tools to assess the risk of low BMD and of osteoporotic fracture are available.

Risk factors for low bone density.

- **Advanced age**. Bone loss decreases progressively with advancing age, and the prevalence of osteoporosis increases as women grow older.
- **Thinness.** Bone density in healthy women is strongly correlated with body weight.[40] Being thin—often cited as body weight less than 127 lb (57.7 kg), the lower quartile of weight for US women aged older than 65 years, or body mass index (BMI) less than 21 kg/m^2—is a risk factor for low BMD.
- **Genetics**. Family studies demonstrate that 50% to 85% of the variance in BMD is genetically determined.[41] Many genes have been weakly associated with low bone mass in humans.
- **Smoking.** Women who currently smoke have lower BMD than do nonsmokers.[42] Smokers are generally thinner and have earlier menopause and lower serum estradiol levels than nonsmokers.
- **Diseases and drugs**. Many diseases and drugs adversely affect the skeleton (Table 3).[4,7] These include eating disorders, chronic inflammatory illnesses (ie, rheumatoid arthritis), diseases causing malabsorption (ie, celiac disease), and various endocrinopathies (hyperparathyroidism, Cushing syndrome). Drugs can cause bone loss by increasing bone resorption (aromatase inhibitors [AIs]), impairing vitamin D metabolism (phenytoin), or reducing bone formation (glucocorticoids), as can surgeries such as gastric bypass.

Notable factors not predictive of low BMD include daily or lifetime intake of calcium or vitamin D, alcohol or caffeine

TABLE 3. *Common or important medications and medical conditions that can adversely affect bone health*

Medications	
Medications causing bone loss	
Aromatase inhibitors	Glucocorticoids for >3 mo
Thyroid hormone in excess	Immunosuppressive agents (eg, cyclosporine)
Gonadotropin-releasing hormone agonists or antagonists	Some anticonvulsants (eg, phenytoin)
Cytotoxic agents	Intramuscular medroxyprogesterone
Medications associated with increased fracture risk	
Proton pump inhibitors	Thiazolidinediones
SGLT2-inhibitors	Insulin with hypoglycemia
Selective serotonin-reuptake inhibitors	Selective norepinephrine-reuptake inhibitors
Medical conditions	
Genetic disorders	
Osteogenesis imperfecta	Hypophosphatasia
Thalassemia	Hemochromatosis
Endocrinopathies	
Gonadal insufficiency (primary and secondary)	Type 1 and type 2 diabetes mellitus
Hyperthyroidism	Primary hyperparathyroidism
Hypercortisolism, including Cushing syndrome	
Nutritional disorders	
Eating disorders	Obesity
Disorders of calcium balance	
Vitamin D deficiency	Hypercalciuria
Gastrointestinal diseases	
Malabsorption syndromes (eg, celiac disease)	Inflammatory bowel disease
Gastrectomy	Chronic liver disease
Other disorders and conditions	
Chronic renal disease	Systemic mastocytosis
Rheumatologic diseases (eg, rheumatoid arthritis)	Hematologic malignancies (eg, leukemia, multiple myeloma)
Frailty	Neuromuscular or visual impairment

SGLT2, sodium glucose cotransporter 2.
Cosman F, et al[4]; Camacho PM, et al.[7]

intake, current or past physical activity, and reproductive history.

Tools to predict low bone mineral density in postmenopausal women.

Several simple tools are available to identify postmenopausal women likely to have low BMD. The Osteoporosis Self-Assessment Tool combines age and body weight in this formula: Osteoporosis Self-Assessment Tool T-score = 0.2 × (weight in kg minus age in years), truncated to yield integer.[43] Using a definition of less than 2 as high risk, the performance of the Osteoporosis Self-Assessment Tool in identifying postmenopausal White women with BMD T-score values of −2.5 or lower at either the LS or FN demonstrated a sensitivity of 95.3% and a corresponding specificity of 39.6%. The Osteoporosis Risk Assessment Instrument demonstrated sensitivity of 93.3% and 94.4% for selecting Canadian women with low BMD and osteoporosis, respectively.[44] These tools are most useful for selecting young postmenopausal women for BMD testing.

Risk factors for fracture.

The most important risk factors for fracture in postmenopausal women are history of previous fracture or falls, older age, and low BMD. Combining these and other independent risk factors improves the ability to identify patients at high risk of fracture.[45] Several fracture risk-assessment tools are available to estimate a person's risk of fracture, including the Canadian Association of Radiologists and Osteoporosis Canada calculator.[46] This computer-based algorithm is available online (www.sheffield.ac.uk/FRAX/) and in common DXA software. In addition to age, sex, and BMI, FRAX combines age, sex, BMI, and independent risk factors on the basis of meta-analyses of large observational cohorts (Table 4).[47] Separate databases are used to estimate fracture risk in White, Black, Asian, and Hispanic women in the United States. Details of the use of the FRAX tool, including its strengths and limitations, have been reviewed elsewhere.[48]

- **Prior fracture**. Having or having had a fracture since menopause is the most important and powerful risk factor for having another fracture.[49] The risk of refracture is especially high (up to 19% within 12 mo) in patients with recent fractures.[37,50] This has led some organizations to describe patients with a recent osteoporotic fracture as being at very high or imminent risk of fracture.[7,51] This increased risk gradually diminishes but persists for at least 10 years, with the average risk over that time being about two-fold higher than expected for their age and BMD.
  - In the past, terms such as *fragility* or *nontraumatic* fractures were used to define fractures related to osteoporosis and that predicted future fractures.
  - Recent evidence suggests that all fractures, except those of the face, skull, hands, and feet, are associated with low BMD and future fracture risk, irrespective of association with trauma.[52]
- **Low bone density**. The strongest correlation of BMD and fracture risk is with hip bone density.[53] Hip fracture risk increases by 2.6-fold for each age-adjusted SD (one Z-score unit) decrease in FN BMD. The magnitude of risk associated with low BMD is modulated by age and other risk factors.

TABLE 4. *Risk factors used in FRAX*

- Age (40-90 y)
- Sex
- Weight[a]
- Height[a]
- Previous fracture
- Parental history of hip fracture
- Current tobacco smoking
- Use of glucocorticoids
- Rheumatoid arthritis
- Alcohol intake of more than two units daily
- Secondary osteoporosis[b]
- FN BMD if available

BMD, bone mineral density; FN, femoral neck; FRAX, Fracture Risk Assessment Tool.
[a]Body mass index is automatically computed from height and weight.
[b]Only included in calculation when BMD is not available.
Kanis JA, et al.[47]

- **Age**. For any BMD value, older women are at higher fracture risk than are younger postmenopausal women.[45]
- **Parental history of hip fracture**. The strongest component of a family history to predict fracture risk is a parental history of hip fracture.[54]
- **Smoking**. Fracture risk in postmenopausal women who smoke is increased about 30%, independent of BMD.[55]
- **Excessive alcohol intake**. Consuming more than three servings of alcohol daily is associated with a 38% and 68% increase risk of major osteoporotic and hip fracture, respectively.[56]

Risk factors not incorporated into FRAX include those not available in the databases on which FRAX was based (eg, falls) or were not known when FRAX was developed (diabetes):

- **Falls**. Most fractures, including many vertebral fractures, occur after a fall from a standing height or less.[57,58] As a result, risk factors for falls, including a history of recent falls; weakness; impaired balance, coordination, vision, or hearing; obesity; and arthritis, are also risk factors for fracture.
- **Diseases and drugs**. Poor health is a risk factor for fracture; most diseases are associated with a general increase in fracture risk (Table 3).[4,7] Diseases and drugs such as type 2 diabetes, obesity, and proton pump inhibitors are associated with increased fracture risk without causing bone loss. Disorders and drugs that affect muscle strength and balance such as frailty, stroke, and antidepressant medications increase risks of falls and fracture.

Other known risk factors for fracture include dementia, low physical activity, thoracic kyphosis, rates of bone loss, and both weight and height loss.[52,59]

Other risk-assessment methods.

Bone density can be assessed by techniques other than DXA, including ultrasound and quantitative computed tomography (CT). T-score values obtained with these techniques are not substitutes for T-scores of the hip or spine obtained with DXA because they may overestimate or underestimate BMD and thus fracture risk.[60] For those few patients who cannot have DXA measurements at the hip or spine, assessing fracture risk with FRAX without BMD provides more useful information than does BMD measured by alternate techniques.

Biomechanical CT analyzes quantitative CT scans of the LS and hip with an algorithm called *finite element analysis* that provides validated estimates of bone strength in individual patients.[61] Biomechanical CT predicts fracture risk, although its advantage over DXA is small. Access to biomechanical CT is limited, and its role in routine clinical practice has not been defined.

Trabecular bone score is a special software available for DXA machines that analyzes the heterogeneity of density distribution on routine LS DXA images. Trabecular bone score measurements correlate with trabecular microarchitecture and predict fracture risk independently from bone density.[62] Trabecular bone score has recently been incorporated into FRAX.[63] Using trabecular bone score is most helpful in women whose fracture risk is near the treatment threshold.

Assessing fall risk, with special emphasis on a history of a recent fall, is an important part of risk assessment in older women.[57] The Stopping Elderly Accidents Deaths and Injury initiative developed by the Centers for Disease Control and Prevention provides an algorithm for fall-risk screening (www.cdc.gov/steadi/pdf/STEADI-Algorithm-508.pdf).

Limitations to fracture-risk assessment.

There are limitations to the use of any of the individual fracture-risk assessment tools and of the FRAX assessment tool. FRAX underestimates fracture risk in patients with falls or diabetes and in those with low spine but not FN BMD.[64] In addition, current FRAX scoring does not allow input for quantification of risk factors, including dose of glucocorticoid, amount of alcohol intake, duration and amount of cigarette smoking, or the number, type, or recency of prior fractures.[47] Despite these limitations, FRAX has been validated as an accurate predictor of fracture probability in large populations in the United States and Canada.[65,66] However, its performance in identifying individual patients who will or will not fracture is less robust.[67] FRAX does not accurately predict BMD, but that is not what it was designed to do.[68] Until there are practical and inexpensive methods to measure bone strength accurately, estimating fracture risk with FRAX will remain one of the most useful tools.

Indications for bone density testing

Bone density should be measured in postmenopausal women with risk factors for low bone density where knowing the result will influence clinical management:

- Those with a history of fracture since menopause
- Those with known medical causes of bone loss or fracture
- Those aged 65 years and older
- Those aged 50 years and older with one or more of these additional risk factors:
  - Body weight less than 127 lb (57.7 kg) or BMI less than 21 kg/m^2
  - History of hip fracture in a parent
  - Current smoker

– Discontinuing estrogen with additional risk factors for fracture

In healthy postmenopausal women without osteoporosis, repeat BMD testing after 3 years does not enhance fracture risk prediction.[69] For postmenopausal women aged 50 to 64 years with baseline T-scores greater than −1.5, retesting could be deferred to age 65, the age at which routine BMD screening is recommended for all women.[70] Earlier retesting should be considered in women within 5 years of menopause whose initial BMD T-score was lower than −1.5 or in those with other important risk factors such as prior fracture or with medical problems or medications predisposing to bone loss.

Physical examination

The goals of evaluating postmenopausal women with osteoporosis or important risk factors are to identify modifiable risk factors and secondary causes of bone loss, to quantify fracture risk and the severity of osteoporosis, and to determine appropriate candidates for pharmacologic therapy. This evaluation requires a detailed history of risk factors for fractures and falls, other diseases and medications, previous fractures, and family history. A thorough physical examination should include evaluation of kyphosis, muscle strength, and balance. Standing height should be measured annually with an accurate method, such as a wall-mounted ruler or a stadiometer. Height loss of 1.5 in (3.8 cm) or more increases the likelihood that a vertebral fracture is present. This calls for evaluation by a lateral thoracolumbar radiograph or vertebral fracture assessment by DXA to identify asymptomatic compression vertebral fractures.[71,72] Weight should be recorded to identify those women with low BMI and to be aware of weight changes, which may interfere with the interpretation of changes in BMD over time. For women with osteoporosis, examination also should include specific skeletal assessments such as bone tenderness (best elicited over the anterior tibia or thoracic vertebrae), indicating osteomalacia or focal bone disease, and joint laxity or blue sclera, features of osteogenesis imperfecta.

Laboratory evaluation

For women with osteoporosis considering pharmacologic therapy, laboratory testing is performed to evaluate for secondary causes of bone loss and to identify contraindications to specific therapies (Table 5).[4,5,7] Routine tests include complete blood cell count and general serum chemistry, especially serum calcium, creatinine, alkaline phosphatase, albumin, and serum phosphate. Measurement of 24-hour urinary calcium excretion is useful to detect patients with poor calcium absorption (<100 mg/d) and those with hypercalciuria (>250 mg/d). Special laboratory tests should be considered in the presence of abnormal routine laboratory tests, clinical clues of other diseases, or unusual cases of osteoporosis.

Biochemical markers of bone turnover.

Bone turnover markers are serum tests that reflect either bone resorption by osteoclasts (fasting serum C-telopeptide of type I collagen) or bone formation by osteoblasts (bone-specific alkaline phosphatase or serum procollagen type I N-terminal propeptide).[73] Bone turnover markers cannot diagnose osteoporosis and have varying ability to predict

TABLE 5. *Suggested laboratory tests for osteoporosis evaluation*

	Diagnostic result	Possible secondary cause
Routine tests		
Complete blood count	Anemia	Multiple myeloma; celiac disease
	Elevated	Hyperparathyroidism
Serum calcium	Low[a]	Vitamin D deficiency; GI malabsorption; hypoparathyroidism
Serum albumin (used to interpret serum calcium)	Low	Nutritional deficiencies; renal protein loss
Serum phosphate	Elevated	Renal failure
	Low	Hyperparathyroidism; renal phosphate wasting
Serum creatinine	Elevated[b]	Renal failure; osteodystrophy
Serum alkaline phosphatase	Elevated	Vitamin D deficiency; GI malabsorption; liver/biliary tract disease; Paget disease
	Low	Hypophosphatasia
Special tests		
Serum 25-hydroxyvitamin D	Low	Vitamin D deficiency; GI malabsorption
Serum PTH	Elevated	Hyperparathyroidism, primary or secondary
24-hour urinary calcium	Low	Vitamin D deficiency; GI malabsorption
	Elevated	Renal calcium leak; cancer involving bone, including myeloma; hyperthyroidism, hyperparathyroidism
24-hour urinary cortisol	Elevated	Cushing syndrome
Serum protein electrophoresis	Monoclonal band	Multiple myeloma; MGUS
Tissue transglutaminase	Elevated	Celiac disease
Serum tryptase	Elevated	Mast cell disease
Serum TSH	Low	Hyperthyroidism

Decisions about laboratory testing depend on the clinical picture.
GI, gastrointestinal; MGUS, monoclonal gammopathy of undetermined significance; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.
[a]Contraindication for bisphosphonates, denosumab, and romosozumab.
[b]Caution or contraindication for bisphosphonate therapy.
Cosman F, et al[4]; Eastell R, et al[5]; Camacho PM, et al.[7]

fracture risk in clinical trials.[74] Bone turnover markers have been used primarily in clinical trials to demonstrate group responses to treatment. Although used by some osteoporosis specialists, the routine use of bone turnover markers in the evaluation of patients with osteoporosis is not recommended.

Key points

- Osteoporosis is a common disorder with potentially serious consequences.
- Assessment of skeletal health should be a part of routine care for all postmenopausal women.
- The annual examination should include measurements of height and weight; assessment for chronic back pain and kyphosis; and clinical risk factors for osteoporosis, fractures, and falls.
- The most important risk factors for future fracture are a history of previous fracture, older age, and low BMD.
  - Fracture risk is especially high in the first 2 years after an incident fracture.
- Bone mineral density testing is indicated for all postmenopausal women with risk factors for low BMD or fracture.
  - DXA is the preferred technique for BMD testing.
  - For untreated postmenopausal women at low fracture risk, repeat DXA testing is not useful until at least 5 years have passed, unless rapid bone loss is anticipated.
- Vertebral imaging is appropriate for postmenopausal women aged 70 years and older or with historical height loss.
- Secondary causes of osteoporosis should be evaluated before osteoporosis treatment has begun.
- The routine use of biochemical markers of bone turnover in clinical practice is not recommended.

NONPHARMACOLOGIC TREATMENTS AND LIFESTYLE MODIFICATIONS

The objectives of managing skeletal health in postmenopausal women are to prevent or minimize bone loss and to reduce the likelihood of fractures. All postmenopausal women, regardless of their BMD, clinical risk factors, or fracture risk, should be encouraged to adopt nonpharmacologic measures and lifestyle modifications, such as eating a balanced diet with adequate intakes of calcium and vitamin D, being physically active, and avoiding harmful lifestyle habits such as smoking, to support both general and bone health.[4,5,7,75] These general approaches, however, will not prevent bone loss in early menopause, will not significantly increase BMD in postmenopausal women, and are certainly not adequate treatment for women with osteoporosis. For women at high risk of fracture, pharmacologic therapy to strengthen the skeleton is required to reduce fracture risk.

With obvious exceptions, such as the Women's Health Initiative (WHI), most studies evaluating the effects of nonpharmacologic treatments and lifestyle modification are small and of short duration. As a result, recommendations here will be based on systematic reviews, meta-analyses, and expert opinion.

Nutrition

Calcium and vitamin D

Sufficient intakes of calcium and vitamin D are necessary for normal skeletal growth during childhood and adolescence. The importance of these nutrients in healthy postmenopausal women is less clear. An Institute of Medicine (IOM; now called the National Academy of Medicine) committee concluded that scientific evidence supports important roles for calcium and vitamin D in skeletal health. Their proposed daily intakes of calcium for postmenopausal women were 1,000 mg to 1,200 mg, with an upper limit of 2,000 mg (Table 6).[76] The IOM commented that the recommendation for women aged 51 to 70 years is based on uncertain and inconsistent data.

The average dietary calcium intake in postmenopausal women in the United States and Canada is 700 mg to 800 mg, about one-third of which comes from dairy products, meaning that an average dairy-free diet contains up to 500 mg of calcium. Few healthy women need to take more than 50 mg to 600 mg of a calcium supplement to achieve the IOM-recommended daily intake. Patients with malabsorption or disorders of calcium metabolism such as hypoparathyroidism may require higher daily intakes of calcium and vitamin D. A listing of calcium content of foods and supplements is available from the National Institutes of Health Osteoporosis and Related Bone Diseases National Resource Center (www.bones.nih.gov/health-info/bone/bone-health/nutrition/calcium-and-vitamin-d-important-every-age). No serious adverse events (AEs) have been observed with daily calcium intakes of less than 600 mg. Larger daily intakes are associated with gastrointestinal symptoms including bloating and constipation.

In the WHI Calcium and Vitamin D study, the average dietary calcium intake was about 1,100 mg daily. In the group that took an additional 1,000 mg of a calcium supplement daily, the risk of kidney stones was increased by 17%.[77] The possibility that a calcium supplement of 1,000 mg daily (with total daily intake approximately 2,000 mg) is associated with increased cardiovascular risk was raised in a clinical trial and a subsequent meta-analysis.[78,79] That association was not observed in the WHI.[80] A subsequent meta-analysis found that a calcium intake level of 2,000 mg to 2,500 mg per day was not associated with cardiovascular risk in healthy adults.[81] However, in the absence of proof of benefit, a total daily calcium intake of more than 1,200 mg is not recommended for healthy postmenopausal women or those with osteoporosis.

TABLE 6. *Institute of Medicine recommendations for daily intakes of calcium and vitamin D for women aged older than 50 years*

	Calcium, mg		Vitamin D, IU	
Age range, y	EAR[a]	RDA[b]	EAR[a]	RDA[b]
51-70	1,000	1,200	400	600
Over 70	1,000	1,200	400	800

EAR, estimated average requirement; IU, international units, RDA, recommended dietary allowance.
[a]Expected to satisfy the needs of 50% of persons in that age group.
[b]Daily dietary intake level of a nutrient considered sufficient to meet the requirements of 97.5% of healthy persons in that group.
Institute of Medicine.[76]

Skeletal benefits of vitamin D supplementation in healthy adults are uncertain. The IOM recommends 600 IU for women aged between 50 and 70 years and 800 IU daily for those aged older than 70 years, stating that these intakes were sufficient to achieve serum 25-OHD levels of at least 20 ng/mL in most postmenopausal women. Meta-analyses of the effects of calcium and/or vitamin D on fracture risk provide inconsistent conclusions, with most reporting no benefit on fracture risk.[82,83] In the bone health substudy in the Vitamin D and Omega-3 Trial, the bone density effects of 2,000 IU of cholecalciferol (vitamin D_3) daily were evaluated over 24 months in healthy women (average age, 63 y) with baseline serum 25-OHD levels of 27.6 ng/mL.[84] No effect was observed in the entire study group or in the subgroup with baseline serum 25-OHD levels less than 30 ng/mL. The inability to demonstrate effectiveness may be related to calcium and vitamin D being threshold nutrients; severe deficiencies may be harmful, but intakes more than the threshold to avoid deficiency does not provide additional benefit. Salutary effects of vitamin D with calcium on fracture risk have been observed most often in institutionalized or vitamin D-deficient older adults.[85] Most studies evaluating the effects of calcium or vitamin D have not restricted the study population to deficient participants. The US Preventive Services Task Force (USPSTF) concluded that there was insufficient evidence to assess the balance of the benefits and harms of daily supplementation with vitamin D 400 IU or more and calcium 1,000 mg or more daily for the primary prevention of fractures in community-dwelling, postmenopausal women.[86] They also recommended against the use of vitamin D supplements to prevent falls.[87]

Women with osteoporosis do not require more calcium than women with normal BMD, and there is no convincing evidence that taking calcium and vitamin D supplements improves the effectiveness of osteoporosis drugs.[88] Adequate intakes of calcium and vitamin D are recommended when taking osteoporosis drugs to reduce the risk of treatment-induced hypocalcemia.[5]

Protein intake

Studies of relationships between protein intake and BMD or fracture risk have been inconsistent. In fall-prone older adults who were losing weight, higher protein intake was associated with reduced fall frequency.[89]

Probiotics

The gut microbiota can influence several aspects of bone health, including the absorption of calcium and vitamin D and immune response. In animal models, probiotics may prevent bone loss associated with estrogen deficiency, and preliminary studies in humans suggest that probiotics could have a role in preventing bone loss.[90]

Other supplements

Strontium is a heavier divalent cation than calcium and increases BMD by being deposited in the skeleton. *Strontium ranelate*, a proprietary strontium salt, reduced the risk of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis.[91] This drug was never approved in the United States or Canada, and it is no longer available in the rest of the world because of concerns about increased cardiovascular risk. Other strontium salts (citrate, chloride) are promoted to support bone health in the United States, but there is no evidence for their effectiveness or safety.

Meta-analysis found no meaningful relationship between *magnesium* intake and skeletal health.[92] Routine magnesium supplementation is not recommended in healthy adults with normal diets.

Various *vitamin K* supplements have been promoted to improve bone health. A recent meta-analysis found no evidence that vitamin K affects bone density or vertebral fracture risk in postmenopausal women and that the evidence was insufficient to confirm a reduction in clinical fractures.[93]

Phytoestrogens, including isoflavones, are plant-derived compounds with weak estrogenic activity. In a systematic review, some isoflavones (aglycone form) had a moderately beneficial effect against estrogen-deficiency bone loss.[94] Isoflavones are not recommended as effective strategies to prevent or treat postmenopausal osteoporosis.[95]

There is also no compelling evidence for a beneficial effect of boron, zinc, black cohosh, berberine, or dehydroepiandrosterone on BMD or fracture risk in postmenopausal women.

Avoiding harmful lifestyle factors

Cessation of smoking and limiting alcohol intake are important general health measures. The AEs of smoking on bone health appear to reverse when smoking is stopped.[96]

Physical activity and exercise

Skeletal mass is strongly influenced by mechanical loading. During growth in children, impact-loading exercise programs induce small gains in BMD, whereas diseases causing immobilization are associated with low bone mass. A *Cochrane* review and several meta-analyses found relatively small, statistically significant effects of exercise on BMD compared with control groups in postmenopausal women.[97-99]

The perception that exercise can reverse osteoporosis in postmenopausal women by inducing new bone formation is unfounded. Programs of regular exercise for general health can be recommended, especially those that increase muscle strength and improve balance, leading to fewer falls. Women with osteoporosis, especially those with vertebral fractures, should avoid activities that involve lifting or pulling with forward spine flexion or rotation and may benefit from an exercise program to stretch and strengthen the extensor muscles of the spine.[100]

Fall prevention

At least one-third of women aged 65 years and older experience one or more falls each year, and the risk of falling and of fracture increases with advancing age.[101] Because most fractures occur as a result of a fall, attempts to reduce the

incidence of falls should be important components of reducing fracture risk in older postmenopausal women.[4,7] A recent USPSTF report and a *Cochrane* review found that multicomponent exercise programs such as tai chi that target balance, gait, and muscle strength were the most effective ways to prevent falls and perhaps fractures in older adults.[86,101] Tapering the use of benzodiazepines, neuroleptic agents, and antidepressants reduced the risk of falling by more than 60%. Hip protectors may be considered in patients at high risk for falling, especially for patients in supervised settings such as long-term care facilities.[102] The Centers for Disease Control and Prevention's Stopping Elderly Accidents, Deaths, and Injuries initiative, based on published guidelines, provides useful tools for fall risk assessment and management (www.cdc.gov/steadi/).

Key points

- Recommending and promoting healthy habits, including attention to nutrition, adequate calcium and vitamin D intake, physical activity, and avoidance of harmful habits is appropriate for all postmenopausal women.
- None of these approaches can significantly improve BMD or correct the architectural abnormalities of osteoporosis.
- The modest skeletal benefits of nonpharmacologic measures should not be construed as sufficient or effective therapies for postmenopausal women with osteoporosis at high risk of fracture.
- The likelihood of falls can be decreased, however, and fracture risk may be reduced in older women. Prevention of falls is especially important in older women or those with decreased mobility.

PHARMACOLOGIC THERAPY TO PREVENT BONE LOSS

Several drugs with differing mechanisms of action have demonstrated the ability to prevent bone loss in postmenopausal women and to reduce fracture risk in women with postmenopausal osteoporosis. The mechanisms of action of all osteoporosis drugs are to modulate (either to inhibit or to activate) bone metabolism. Antiremodeling agents, often called antiresorptive drugs, include estrogen, estrogen agonists/antagonists (EAAs), bisphosphonates, and denosumab. They inhibit bone resorption, and to a lesser extent, bone formation. These drugs maintain or improve BMD and reduce fracture risk, but they do not improve or repair disruption of trabecular structure. In contrast, osteoanabolic agents, by stimulating new bone formation, improve cortical and/or trabecular bone structure and induce large increases in BMD, reducing fractures more quickly than do antiremodeling drugs.

Prevention versus treatment

Drugs are approved by North American regulatory agencies for either preventing or treating osteoporosis or both. Since 2008, North American guidelines have focused on using osteoporosis drugs to reduce fracture risk. The concept of preventing osteoporosis by halting postmenopausal bone loss and its attendant damage to skeletal architecture is not recognized in those guidelines.

On the basis of studies demonstrating prevention of bone loss in postmenopausal women without osteoporosis, various oral and transdermal estrogen preparations, alone or in combination with progestogens or bazedoxifene (BZA), as well as raloxifene, tibolone (in Mexico only), and four bisphosphonate drugs (alendronate, risedronate, ibandronate, and zoledronate) have government approval for prevention of osteoporosis (Table 7). Bone density responses to these agents over 2 years in prevention studies are varied. The bone density benefits of therapy persist as long as therapy is continued, but the effects of estrogen-like drugs abate when treatment is discontinued. Markers of bone turnover return to pretreatment values within a few months, and BMD falls to pretreatment levels within 1 to 2 years of stopping therapy, effects prevented by switching to a bisphosphonate.[103,104]

Although using drugs to prevent osteoporosis is not included in national osteoporosis guidelines, a strong clinical argument can be made for doing so, especially in women who come to menopause with low bone mass.[105,106] On average, women lose about one T-score unit (10-12%) of bone mass across a normal menopause transition.[12,107,108] With this rapid bone loss, significant and irreversible deterioration in trabecular microarchitecture occurs. These effects are preventable with estrogen and bisphosphonates.[106,109,110] However, with the exception of the WHI, strong evidence that preventing bone loss in young postmenopausal women results in fewer fractures in later life is lacking. A modeling exercise suggested that infrequent infusions of zoledronate at menopause would substantially reduce fracture risk and the number of women aged older than 65 years who had osteoporosis.[111] Support for the concept of osteoporosis prevention by antiremodeling agents also is found in the treatment of women with AIs for nonmetastatic breast cancer who experience bone loss and increased fracture risk.[112] In these patients, bisphosphonates and denosumab prevented bone loss, and denosumab reduced the incidence of vertebral fractures by 50% within the first year of treatment, including in women with normal BMD values at baseline.[113-115]

Hormone therapy

Several oral and transdermal systemic estrogen products are government approved in the United States and Canada for prevention of postmenopausal osteoporosis. Although no clear differences in the BMD responses among different estrogen preparations or between oral and transdermal administration have been observed, transdermal estrogen appears to have less risk of venous thrombotic events and possibly stroke.

Bone mineral density

The beneficial effects of systemic standard doses of oral or transdermal HT on BMD, including estrogen plus progestogen therapy (EPT) for women with a uterus or estrogen-alone therapy (ET) for women without a uterus, have been shown in

TABLE 7. *Drugs approved in North America for preventing osteoporosis*

Drug	Trade name(s)	Drug class	Dose, route of administration, and dosing interval
CE	Premarin	Estrogen	Oral; various doses and intervals (0.3, 0.45, 0.9, 1.25, 2.5 mg)
Estradiol	Various[a]	Estrogen	Oral and transdermal, various doses and intervals
Estradiol + NETA	Activella, Amabelz	Estrogen-progestin combination	Estradiol 1 mg + NETA 0.5 mg; estradiol 0.5 mg + NETA 0.1 mg; PO daily
Ethinyl estradiol + NETA	FemHRT, Jinteli	Estrogen-progestin combination	Ethinyl estradiol 2.5 μg + NETA 0.5 mg; ethinyl estradiol 5 μg + NETA 1 mg; PO daily
CE + MPA	PremPro	Estrogen-progestin combination	CE + MPA doses: CE 0.625 mg + MPA 2.5 mg or 0.45 mg + 1.5 mg; 0.3 mg+1.5 mg; 0.625 mg + 5 mg; PO daily
CE + BZA	Duavee	Estrogen-EAA combination	CE 0.45 mg + BZA 20 mg PO daily
Tibolone *	Livial; generics	Synthetic estrogen agonist	2.5 mg PO daily
Raloxifene	Evista; generics	EAA	60 mg PO daily
Alendronate	Fosamax; generics	Bisphosphonate	35 mg PO q wk
Risedronate	Actonel; Atelvia; generics	Bisphosphonate	35 mg PO q wk or 150 mg PO q mo
Ibandronate	Boniva; generics	Bisphosphonate	150 mg PO q mo
Zoledronate	Reclast; Aclasta; generics	Bisphosphonate	IV q 2 y

* available only in Mexico.
BZA, bazedoxifene; CE, conjugated estrogens; EAA, estrogen agonist/antagonist; IV, intravenous; MPA, medroxyprogesterone acetate; NETA, norethindrone acetate; PO, orally.
[a]Trade names of estrogens approved for prevention of osteoporosis include Climara, Estrace, Minivelle, Premarin, Vivelle dot.

RCTs in both younger and older postmenopausal women.[116-120] In the Postmenopausal Estrogen/Progestin Interventions trial (N = 875), 0.625 mg conjugated estrogens (CE), with or without a progestogen (either medroxyprogesterone acetate [MPA] or micronized progesterone [MP]), for 3 years significantly increased LS BMD by 3.5% to 5.0%, with a 1.7% increase in hip bone density.[116] In the WHI, a 5-year RCT in postmenopausal women aged 50 to 79 years (N = 16,608), standard daily EPT doses (0.625 mg CE plus 2.5 mg MPA) significantly increased LS and TH bone density by 4.5% and 3.7%, respectively, relative to placebo.[121] Oral 17-β estradiol in daily doses of 0.25 mg, 0.5 mg, and 1.0 mg increased LS BMD after 2 years by 0.4%, 2.3%, and 2.7%, respectively.[122] Combining those doses of estradiol with norethindrone acetate 0.5 mg daily resulted in larger increases in BMD. In a meta-analysis of 57 RCTs in postmenopausal women, consistent BMD increases with ET or EPT were observed at all skeletal sites versus placebo.[123] In trials of 2 years' duration, the mean difference in BMD after EPT was 6.8% at the LS and 4.1% at the FN. Similarly, daily doses of 0.05 mg and 0.1 mg of estradiol acetate delivered via a vaginal ring significantly increased hip BMD (1.7% and 1.8%, respectively) and LS BMD (2.7% and 3.3%, respectively) compared with baseline.[124] Lower-than-standard doses of ET and EPT are associated with significant, albeit smaller, improvements in BMD, although the number of women experiencing bone loss on lower doses is likely higher.[118,120,122,125-127]

Fracture risk

In the WHI, ET with CE alone and EPT reduced the combined risk of vertebral fractures, hip fractures, and total fractures by 34% compared with placebo in a low-risk fracture population.[121,128] Hip fracture risk was reduced by 30% (hazard ratio [HR], 0.7; unadjusted 95% confidence interval [CI], 0.4-1.0), vertebral fractures by 30% (HR, 0.7; unadjusted 95% CI, 0.4-1.0), and other osteoporotic fractures by 20% (HR, 0.8; 95% CI, 0.7-0.9). Meta-analysis and a systematic review, dominated by WHI results, demonstrated that 5 to 7 years of HT significantly reduced risk of spine, hip, and nonvertebral fractures.[129,130] Because no study, including the WHI, has evaluated the effects of estrogen on fracture risk in women with osteoporosis, estrogen is not approved as a treatment for postmenopausal osteoporosis. Doses of ET or EPT lower than used in the WHI have not been studied with regard to fracture efficacy.

Safety

In the WHI, initial reports of systemic EPT showed statistically significant increased risks of breast cancer, stroke, and thromboembolic events.[131-133] In women with prior hysterectomy, CE alone for 6.8 years resulted in a statistically significant increased risk of stroke and deep venous thrombosis, whereas breast cancer, coronary heart disease, total venous thromboembolism (VTE), and pulmonary embolism were not statistically increased.[134] In the WHI Memory Study, a statistically significant increase in probable dementia was noted in women aged 65 to 79 years who received EPT for a mean of 4.0 years.[135] After a mean follow-up of 5.2 years, there was a nonsignificant trend for increased probable dementia in women allocated to ET.

Subgroup analyses suggest that the timing of initiation of HT influences the benefit-risk balance, with more favorable effects observed in women aged 60 years and younger or within 10 years of menopause, including less risk of cardiovascular disease and possibly cognition.[136-138] In women aged older than 60 years or more than 10 years past the menopause

transition, beginning HT was associated with increased risks of stroke (relative risk [RR], 1.21; 95% CI, 1.06-1.38) and VTE (RR, 1.96; 95% CI, 1.37-2.80).

Discontinuing hormone therapy

The beneficial effects of estrogen on the skeleton begin to abate within a few months of stopping therapy. Bone mineral density loss of 3% to 6% occurs during the first year after cessation of systemic ET or EPT, and markers of bone turnover return to pretreatment values within a few months.[103,139] Within 2 years, BMD falls to levels seen in women who never took estrogen.[140] In the WHI, discontinuation of HT was associated with a return of fracture risk to levels seen in women who had received placebo, with no excess fracture risk observed.[141]

The primary indication for systemic HT is for relief of vasomotor (VMS) and other menopause symptoms in postmenopausal women aged younger than 60 years and within 10 years of menopause, with secondary benefit on bone protection.[142,143] However, well-counseled women with persistent menopause symptoms and those at high risk of fracture who cannot tolerate the other therapies may be candidates for HT for prevention or treatment of osteoporosis if benefits outweigh risks. Extended use of HT is an option for well-counseled women who have low bone mass, regardless of menopause symptoms, for prevention of further bone loss and/or reduction of fracture risk when alternate therapies are not appropriate or when the benefits of extended use are expected to exceed the risks.[142,144,145]

Despite positive effects on bone, initiating HT in women aged older than 60 years or more than 10 years beyond menopause is generally not recommended because of concerns about cardiovascular safety.[142,146]

Although the optimal time to initiate ET or EPT and the optimal duration of therapy have not been established, ET or EPT should largely be used in the early years after menopause. Women with primary ovarian insufficiency, premature menopause, or early surgical menopause experience long-term AEs on bone, cognition, mood, cardiovascular health, sexual health, and mortality.[147] For these women, an estrogen preparation should be considered, unless there are contraindications, to prevent bone loss as well treat menopause symptoms, at least until the average age of natural menopause.[142] Higher doses of HT may be needed to provide protection against bone loss in younger women, particularly those aged younger than 40 years.[125]

Estrogen-receptor agonists/antagonists

Raloxifene

Estrogen agonists/antagonists, previously known as selective estrogen-receptor modulators, have weak estrogen-like antiresorptive properties in bone. Raloxifene is the only EAA approved for the prevention and treatment of postmenopausal osteoporosis.

In a 2-year RCT of 601 postmenopausal women without osteoporosis (mean age, 55 y), raloxifene 60 mg per day improved BMD by 1.6% at the LS and 1.2% at the FN compared with placebo (decreases of 0.8% and 1.2%, respectively).[148] Bone loss resumes when raloxifene therapy is stopped.[149] Raloxifene is associated with bone loss when given to premenopausal women.[150]

Adverse events with raloxifene include increased hot flashes, leg cramps, and an increased risk of VTE.[151,152] In postmenopausal women with osteoporosis, raloxifene significantly reduced the incidence of invasive breast cancer by 76% after 3 years and by 59% after 8 years of therapy.[153,154]

Bazedoxifene with conjugated estrogens

Bazedoxifene is an EAA that has effects similar to raloxifene on bone density and fracture risk in women with osteoporosis.[155] It is not approved as monotherapy in the United States or Canada.

A daily fixed-dose combination of BZA 20 mg with CE 0.45 mg improved VMS, decreased bone turnover markers, and prevented bone loss over 2 years in young postmenopausal women.[156-158] In a pooled analysis from phase 3 trials in young postmenopausal women with normal or low BMD, bone density changes versus placebo with BZA plus CE were 2.3% and 1.4% at the LS and TH, respectively.[159] Because BZA is a uterus antagonist, and the rates of endometrial hyperplasia were less than 1% and comparable to placebo, progestogens do not need to be taken with this combination therapy, based on safety data up to 2 years.[158,160]

In RCTs of up to 2 years with the combination of CE and BZA, mammographic breast density and rates of breast tenderness, breast cancer, vaginal bleeding, cardiovascular events, and VTE were similar to placebo.[157] This combination has been approved in the United States, Canada, and Mexico for the management of moderate to severe VMS and in the United States and Mexico for prevention of postmenopausal osteoporosis. This product contains a warning similar to other estrogen-containing products.

The best candidates for BZA with CE are postmenopausal women with a uterus who need relief from hot flashes and prevention of bone loss. Caution should be exercised in beginning any HT in women aged older than 60 years.

Tibolone

Tibolone, a synthetic hormone derived from the Mexican yam, has metabolites with estrogenic, androgenic, and progestogenic effects.[161] In young postmenopausal women, tibolone prevented hot flashes, bone loss, and vaginal atrophy.[162] In women with postmenopausal osteoporosis, tibolone 1.25 mg daily significantly reduced the risk of vertebral and nonvertebral fracture but increased stroke risk.[163] It has not been approved in the United States or Canada but is used in Mexico for osteoporosis prevention.

Bisphosphonates

These analogs of pyrophosphate bind to bone matrix and are absorbed into osteoclasts at sites of active bone remodeling. By interfering with important intracellular processes,

bisphosphonates impair osteoclast function. Bone remodeling decreases, and BMD increases.[164] There are bisphosphonates approved for both the prevention and treatment of postmenopausal osteoporosis.

In young postmenopausal women, bisphosphonates increase BMD over 24 months by 3.1% to 6.0% in the LS and by 1.8% to 4.0% in the proximal femur.[165-168] Doses of zoledronate and alendronate approved for prevention are 50% smaller than the doses approved for osteoporosis treatment. Bone mineral density decreases slowly on stopping alendronate or zoledronate.[103,169]

Bisphosphonates can be considered to prevent bone loss in early menopause if estrogen cannot be taken or when ET or raloxifene therapy is discontinued.

Key points

- Intervening to prevent rapid bone loss and deterioration of skeletal structure is a unique opportunity to maintain bone health.
- Such intervention would be most appropriate in women with low BMD who are experiencing relatively rapid bone loss because of acute estrogen deficiency in the perimenopausal and early postmenopausal periods or on discontinuing ET.
- For younger, healthy postmenopausal women, particularly those with VMS, who are candidates for prevention of bone loss, estrogen alone (if no uterus) or combined with progestogen or BZA are the most appropriate therapies.
  - A bisphosphonate could be chosen if estrogen is contraindicated or on stopping ET.
  - Raloxifene is a good option for prevention of bone loss in postmenopausal women with an elevated risk of breast cancer and infrequent VMS.
- Bisphosphonates to prevent bone loss can be considered in postmenopausal women with low BMD (T-score < -1) and other risk factors for fracture (eg, family history) who do not meet criteria for osteoporosis treatment.

PHARMACOTHERAPY TO TREAT OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

The primary objective of treating women with osteoporosis is to reduce the risk of fracture. All drugs approved for osteoporosis treatment have been shown in RCTs to reduce fracture risk (Table 8).[151,170-189]

These drugs vary considerably in their mechanisms of action and their effectiveness. Details and nuances of their use are found in cited reviews. Combining therapies is not generally recommended to treat osteoporosis, although sequential therapies may play a role in preventing loss after certain therapies.

Antiremodeling drugs

Antiremodeling agents inhibit bone resorption by osteoclasts, and secondarily, bone formation. Treatment results in the filling in of remodeling spaces in bone that are present at the beginning of therapy and in opening of fewer new remodeling spaces, resulting in increased BMD and skeletal strength and decreased fracture risk. These drugs do not repair deficits in trabecular architecture. Denosumab, the most potent inhibitor of bone remodeling, does reduce porosity in cortical bone. Protection from fractures occurs within 1 year of beginning therapy, persists as long as treatment is given, and wanes when treatment is stopped. Hypocalcemia has been reported with some of these agents. Low serum calcium should be corrected before beginning therapy.

Raloxifene

In a pivotal RCT of postmenopausal women with osteoporosis, raloxifene significantly reduced the incidence of vertebral fractures after 3 years by 30% and 50% in women with and without prevalent vertebral fracture, respectively.[151] Hip and nonvertebral fracture risk was not reduced with raloxifene therapy for up to 8 years.[152]

TABLE 8. *Drugs approved in North America for treating women with postmenopausal osteoporosis*

Drug	Trade names	Drug class	Dose, route of administration, and dosing interval	Fracture risk reduction (in primary analyses of registration trials)		
				Vertebral fracture	Nonvertebral fracture	Hip fracture
Raloxifene[151]	Evista; generics	EAA	60 mg/d PO	✓		
Alendronate[170-172,184]	Fosamax; Binosto; generics	Bisphosphonate	70 mg q wk PO	✓		✓
Risedronate[173-175,185-187]	Actonel; Atelvia; generics	Bisphosphonate	35 mg q wk PO; 150 mg q mo PO	✓	✓	✓
Ibandronate[176,188,189]	Boniva; generics	Bisphosphonate	150 mg PO q mo; 3 mg IV q 3 mo	✓		
Zoledronate[177]	Reclast; Aclasta; generics	Bisphosphonate	5 mg IV q y	✓	✓	✓
Denosumab[178,179]	Prolia	RANK ligand inhibitor	60 mg SQ q 6 mo	✓	✓	✓
Teriparatide[178,179]	Forteo; Teribone	PTH-receptor agonist	20 μg SQ daily	✓	✓	
Abaloparatide[179,180]	Tymlos	PTH-receptor agonist	80 μg SQ daily	✓	✓	
Romosozumab[181,182]	Evenity	Sclerostin inhibitor	210 mg SQ q mo	✓	✓	✓
Calcitonin-salmon[183]	Calcimar; Fortical; generics	Calcitonin	200 USP units by nasal spray daily	✓		

Available only in the United States.
EAA, estrogen agonist/antagonist; IV, intravenous; PTH, parathyroid hormone; SQ, subcutaneous.
Ettinger B, et al[151]; Liberman UA, et al[170]; Black DM, et al[171];Cummings SR, et al[172]; Harris ST, et al[173]; Reginster J, et al[174]; McClung MR, et al[175]; Chesnut CH 3rd, et al[176]; Black DM, et al[177]; Cummings SR, et al[178]; Neer RM, et al[179]; Miller PD, et al[180]; Cosman F, et al[181]; Saag KG, et al[182]; Chesnut CH 3rd, et al[183]; Schnitzer T, et al[184]; Brown JP, et al[185]; Delmas PD, et al[186]; McClung MR, et al[187]; Miller PD, et al[188]; Delmas PD, et al.[189]

In the pivotal study, raloxifene use was associated with a significant threefold increase in the risk of VTE without a significant difference in coronary or cerebrovascular events between placebo and raloxifene.[151] In postmenopausal women with risk factors for coronary heart disease, no significant effects of raloxifene on the risk of primary coronary events or stroke were observed over a median of 5.6 years.[190] However, the risk of fatal stroke was increased (HR, 1.49).

Therapy considerations.

Raloxifene is an option for the treatment of postmenopausal osteoporosis in women with a low risk of hip fracture, an elevated risk of breast cancer, and low risk of stroke and VTE.

Bisphosphonates

In RCTs, daily oral therapy with alendronate, risedronate, and ibandronate and annual intravenous dosing with zoledronate reduced the risk of vertebral fractures by 41% to 70% over 3 years in postmenopausal women with osteoporosis.[191] Alendronate, risedronate, and zoledronate also reduced the risk of hip and nonvertebral fractures by 28% to 50% and 20% to 38%, respectively, in long-term extension studies. Bone mineral density in the TH and FN plateaus after about 5 years, with no further increases over the next 4 to 5 years.[192,193] Registration for government approval of the commonly used weekly and monthly dosing regimens of the oral agents was based on studies comparing BMD responses to daily therapy rather than on fracture endpoint studies (Table 8).[151,170-189]

Adverse events include diffuse bone and muscle pain of unknown mechanism, worsening upper gastrointestinal symptoms with oral bisphosphonates, and flu-like symptoms in about one-third of patients with the first infusion of zoledronate. Renal failure has occurred with zoledronate in patients with compromised renal function. Oral bisphosphonates are to be used with caution, and zoledronate is contraindicated in patients with markedly impaired renal function. Osteonecrosis of the jaw (ONJ) occurs infrequently (1 in 10,000-100,000 patient-years) with osteoporosis doses of bisphosphonates.[194] Invasive dental procedures and poor oral hygiene are risk factors for ONJ. Discontinuing therapy before an invasive dental procedure does not reduce the risk of ONJ,[195] but improving oral hygiene preoperatively and using topical antimicrobial therapy with dental extraction does appear to reduce risk.[196,197]

A duration-dependent risk of subtrochanteric or femoral shaft fractures with atypical radiologic features becomes evident after 2 to 3 years of therapy, with an incidence of about 1 in 1,000 patients after 8 to 10 years of therapy.[198] The risk of these fractures appears to be greater in Asian women, in younger postmenopausal women with low BMD rather than osteoporosis, and in patients with some genetic skeletal disorders such as hypophosphatasia.[199] Pain in the thigh or groin is usually present for weeks to months before the atypical fracture occurs. Patients on bisphosphonates for more than 3 years should be cautioned to report new thigh or groin pain so that radiographic evaluation can be undertaken. The risk of atypical fracture may decrease on discontinuation of oral bisphosphonates.[200]

Duration of therapy and bisphosphonate drug holiday.

The effects of bisphosphonate therapy on bone remodeling and protection from fracture wane slowly (over 1-5 y) when treatment is stopped.[192,193,201] Because of this unique pharmacology, a temporary withdrawal of therapy (''bisphosphonate holiday'') can be considered after 3 to 5 years of therapy in patients at low or moderate fracture risk and who no longer meet criteria for therapy.[5,7,130,202] Fracture risk increases again when patients have been off oral bisphosphonate therapy for 2 years.[203] Osteoporosis treatment should be restarted with a significant decline in BMD, an intervening fracture, or other factors altering clinical risk.[5,191,202] For patients remaining at high risk after 3 to 5 years of bisphosphonate therapy (history of previous spine or hip fracture or multiple other fractures, hip BMD values remaining in the osteoporosis range, or who have other important risk factors), continuing on the bisphosphonate or switching to denosumab or an osteoanabolic agent is recommended.[5,7,202]

Therapy considerations.

Bisphosphonates are appropriate to reduce fracture risk in women with postmenopausal osteoporosis. Use with caution in patients with significantly impaired renal function. Consider a bisphosphonate holiday only in women at low or moderate fracture risk.

Denosumab

This fully human monoclonal antibody inhibits RANK ligand, the principal stimulator of bone resorption. Treatment with denosumab 60 mg by subcutaneous injection every 6 months results in marked inhibition of bone remodeling, with resorption inhibited more than formation.[204] In a pivotal RCT, denosumab therapy for 3 years reduced the risk of vertebral fractures by 68% and hip fractures by 40% in postmenopausal women with osteoporosis.[178] Over 10 years, BMD increased by 21.7% and 9.2% in the LS and TH, respectively, and protection from fracture persisted or improved.

In that trial, skin rash and skin infection occurred more frequently with denosumab than placebo but did not increase in frequency with long-term therapy. Denosumab can be used in patients with impaired renal function, but hypocalcemia is more common. Rare cases of atypical femoral fractures and ONJ were observed with long-term therapy. The relationship between duration of denosumab therapy and these possible AEs is unclear. No other AEs were observed over 10 years of treatment.[192]

Discontinuing denosumab.

On stopping denosumab treatment, bone turnover markers quickly rise above baseline levels before returning to pretreatment levels after 1 to 2 years. Bone mineral density

decreases rapidly, and vertebral fracture protection is lost. Vertebral fractures, often multiple, occurring 3 to 18 months after stopping denosumab treatment have been reported.[205] There is no justification for a ''holiday'' with denosumab therapy. Whenever denosumab is stopped, therapy with a bisphosphonate should be used to prevent bone loss.[206,207]

Therapy considerations.

Denosumab is appropriate for women with postmenopausal osteoporosis, including those at high risk of fractures. There is no limit to the duration of denosumab therapy. Administration of denosumab should not be delayed or stopped beyond 7 months without subsequent therapy to prevent bone loss and vertebral fractures.

Calcitonin-salmon

Nasal spray calcitonin-salmon is recommended for the treatment of osteoporosis only for women who cannot tolerate other therapies.[5] Calcitonin-salmon may reduce pain and shorten time to mobilization after an acute vertebral fracture.[208]

Osteoanabolic therapies

These bone-building drugs stimulate bone formation and restore the structure of trabecular bone by increasing the number and width of trabeculae and improving cortical thickness.[209] The bone-forming effects of these agents diminish over several months (antisclerostin therapy) to a few years (PTH-receptor agonists). For these and other reasons, therapy with anabolic agents is limited to treatment intervals of 12 to 24 months. Bone mineral density is lost rapidly when osteoanabolic agents are discontinued. To maintain the treatment benefits, these therapies should always be followed by an antiremodeling drug. Osteoanabolic therapies are more effective than antiremodeling agents at increasing BMD and reducing fractures and should be the initial therapy for osteoporosis in women at very high or imminent risk of fracture.[6,7,51]

Parathyroid hormone receptor agonists

Teriparatide and abaloparatide activate the PTH receptor, stimulating bone formation on trabecular and endocortical bone surfaces, leading to increased skeletal mass and volume, improved trabecular microarchitecture, increased cortical width, and increased bone strength.[210,211] Both drugs, administered by daily subcutaneous injection, significantly reduce risks of vertebral and nonvertebral fracture. Hip fracture efficacy was not demonstrated in individual randomized trials (limited by sample size), but a meta-analysis showed hip fracture efficacy with teriparatide.[212] Orthostatic hypotension with first doses and hypercalcemia are possible AEs. High doses of both drugs induced bone tumors in rats, but this risk has not been observed in clinical studies. Neither drug should be used in patients with hypercalcemia, at risk for osteosarcoma, or with skeletal metastases. Previously, treatment with both agents was limited to 2 years in one's lifetime. The teriparatide label changed (November 2020) to allow a repeat teriparatide course in appropriate patients. Abaloparatide is not yet available in Canada.

Teriparatide.

Teriparatide is a synthetic peptide comprised of the first 34 amino acids of PTH.[210] In a phase 3 pivotal trial, teriparatide therapy for 18 to 19 months resulted in increases of LS bone density by 9.5% and TH bone density by 2.6%.[179] The risks of vertebral and nonvertebral fracture were reduced by 65% and 35%, respectively. In women with postmenopausal osteoporosis at high fracture risk, teriparatide reduced risks of vertebral fracture by 56% and clinical fractures by 52% compared with risedronate.[213]

Abaloparatide.

Abaloparatide is a synthetic analog of PTH-related peptide analog, modified to potentiate its anabolic effect.[211] In a pivotal fracture trial, women with postmenopausal osteoporosis were randomized to blinded abaloparatide 80 μg, placebo, or open label teriparatide for 18 months.[214] Bone mineral density increased with abaloparatide by 11.2% in the LS and by 4.2% after 18 months in TH BMD. Over 18 months, risks of vertebral fracture and nonvertebral fracture were reduced by 86% and 43%, respectively. These fracture-prevention benefits achieved with abaloparatide were maintained for 2 additional years when women were switched to alendronate. Increases in BMD, especially at the hip, were greater with abaloparatide than with teriparatide, but there were no significant differences in fracture risk between the two therapies.

Romosozumab

Romosozumab is a humanized antisclerostin monoclonal antibody that stimulates bone formation while inhibiting bone resorption.[215] It is administered monthly as two subcutaneous injections totaling 210 mg for 12 months. In women with postmenopausal osteoporosis, average BMD increases with romosozumab at 1 year were 13.3% in the LS and 6.8% in the TH. With 12 months of romosozumab followed by 24 months of alendronate or denosumab, total increases in LS BMD were 14.9% and 18.1%, respectively, whereas increases in TH BMD were 7.0% with alendronate and 9.4% with denosumab.[181,182]

In a pivotal RCT in women with postmenopausal osteoporosis, romosozumab, compared with placebo, significantly reduced vertebral fracture risk by 73% and clinical fractures (>85% of which were nonvertebral) by 36% after 12 months of therapy.[181] The 25% reduction in nonvertebral fracture risk was not statistically significant.

In a second pivotal trial in women at high risk of fracture, romosozumab was compared with alendronate.[182] At 12 months, vertebral fracture risk was reduced by 37% with romosozumab compared with alendronate. After that 12 months, all women received alendronate. At the end of the study (average, 33 mo; 21 mo on alendronate),

nonvertebral fractures were significantly reduced by 19% and hip fractures by 38% in patients receiving romosozumab during the first year of the study compared with those who received only alendronate throughout. The reduction in vertebral fracture risk observed during the 12 months of romosozumab compared with placebo or alendronate was maintained for at least 2 years while women took denosumab or alendronate.

Romosozumab can produce mild injection-site reactions and hypersensitivity reactions. Compared with alendronate, romosozumab was associated with a higher risk of major cardiovascular AEs (heart attack, stroke, and cardiovascular death), but there was no difference in rates of these events with romosozumab versus placebo. The explanation for the disparity in the results of the two studies is unclear.[216] Romosozumab is not recommended for women at high risk of cardiovascular disease, particularly those who have had recent heart attacks or strokes.

Therapy considerations.

Osteoanabolic therapy results in larger, faster gains in BMD and better protection from fractures than do bisphosphonates. Anabolic therapy should be followed by a potent antiremodeling agent to maintain gains in BMD. Bone mineral density gains, particularly in the hip, are greater when the anabolic drug is administered before the antiremodeling drug compared with the opposite sequence. The best candidates are women at very high risk of fracture, including those with prior and especially recent fractures, very low BMD (T-score below −3.0), and those who sustain fractures or lose BMD while taking antiremodeling therapy.

DEVELOPING AN OSTEOPOROSIS TREATMENT PLAN

Osteoporosis is a chronic, progressive, and currently incurable disease requiring life-long management. There is no single treatment paradigm. Rather, treatment must be individualized and then monitored and altered depending on the course of the patient. Different medications are chosen depending on the patient's age, BMD, fracture risk, and other considerations. Moreover, different medications may be chosen for the same patient at different stages of life. Optimal management will entail the use of osteoporosis therapies in various sequences to maximize benefits and minimize risks across the lifespan of a postmenopausal woman.

Goal-directed therapy, or ''treat-to-target,'' is an emerging concept to aid in the selection of initial therapy or when and how to change therapy for postmenopausal osteoporosis.[217] The fundamental principle of this concept is that the goal of treatment is to reach an acceptable level of fracture risk or suitable surrogate. The initial treatment is selected according to the likelihood of that treatment achieving this goal. If the response to the initial treatment does not achieve this goal, a change in treatment is considered.

The value of BMD as an appropriate target as a surrogate of fracture risk is supported by recent studies documenting that the level of BMD achieved on osteoporosis treatments correlates strongly with a person's current risk of fracture; the higher the TH BMD is on treatment, the lower the fracture risk.[218,219] Those studies suggested that optimal treatment benefit is achieved at TH T-score values between −2.0 and −1.5. These data are bolstered by robust evidence from meta-regressions of published clinical trials of many medications demonstrating a strong correlation between the magnitude of BMD increase with treatment and reduction of vertebral, nonvertebral, and hip fracture risk.[220,221]

These results suggest that, for patients with very low BMD or very high risk of fracture, beginning therapy with an osteoanabolic agent followed by an antiremodeling drug is most likely to achieve osteoporosis treatment goals.[51,222] The studies documenting the superiority of osteoanabolic treatments over antiremodeling drugs for reducing fracture risk in patients at very high risk of fracture strongly support this recommendation.[182,213] This approach is even more attractive on recall that the increase in BMD and fracture protection achieved with 12 to 18 months of osteoanabolic treatment persists for at least 2 years after patients are transitioned to a bisphosphonate or denosumab.[223,224]

Based on these concepts, the choice of the initial treatment is based on the patient's current BMD and fracture risk (Table 9).[6,7,51] If the response to the initial treatment does not achieve this target, a change in treatment is considered. If

TABLE 9. *Choosing an initial treatment for postmenopausal osteoporosis*

Fracture risk	Example	Recommended starting therapy
Moderate	Patient aged 62 y T-score: LS -2.6, FN -1.8 No other risk factors	Raloxifene or a bisphosphonate
High	Patient aged 68 y, mother with hip fracture T-score: FN -2.8 Wrist fracture at age 60	Bisphosphonate or denosumab
Very high	Patient aged 72 y T-score: FN -3.0 Humerus fracture age 68 Two recent vertebral fractures	Osteoanabolic drug

FN, femoral neck; LS, lumbar spine.
Shoback D, et al[6]; Camacho PM, et al[7]; Kanis JA, et al.[51]

the treatment goal has not been achieved with bisphosphonate therapy, switching to denosumab or an osteoanabolic drug should be considered. If the treatment target is reached after 3 to 5 years of bisphosphonate therapy, discontinuation of treatment for an interval could be considered, with plans to restart therapy if bone loss or fractures occur. If raloxifene or denosumab therapy is stopped, switching to a bisphosphonate would be indicated to prevent the rapid decrease in BMD and loss of fracture protection. Osteoanabolic therapy should always be followed by a bisphosphonate or by denosumab.

Monitoring osteoporosis therapy

Bone mineral density testing should be repeated 1 to 2 years after beginning osteoporosis therapy (depending on the drug used), with careful attention to quality control of the repeat testing.[4,7] For patients on bisphosphonates, repeating BMD testing again at 5 years is used to determine whether a ''bisphosphonate holiday'' would be considered.[202]

Although changes in bone turnover markers are used by some specialists to assess adherence and effectiveness of therapy, routine use of bone markers is not recommended. Follow-up contact by an office nurse may be the most effective means to enhance adherence to therapy.[225]

Key points

- The choice of the initial treatment for osteoporosis is based on the patient's current BMD and fracture risk.
- Raloxifene is an option for the treatment of postmenopausal osteoporosis in women with a low risk of hip fracture, an elevated risk of breast cancer, and low risk of stroke and VTE.
- Bisphosphonates are appropriate to reduce fracture risk in women with postmenopausal osteoporosis.
  - Use with caution in patients with significantly impaired renal function.
  - Consider a bisphosphonate holiday only in women at low fracture risk who no longer meet criteria for therapy.
    - Restart therapy if bone loss or fractures occur or when patient again meets criteria for treatment.
  - For patients remaining at high fracture risk after 3 to 5 years of bisphosphonate therapy, continue treatment or switch to another drug.
- Denosumab is appropriate for women with postmenopausal osteoporosis, including those at high risk of fracture.
  - There is no limit to the duration of denosumab therapy.
  - Administration of denosumab should not be delayed or stopped beyond 7 months without subsequent therapy to prevent bone loss and vertebral fractures.
- Osteoanabolic therapies are most appropriately used in women at very high risk of fracture, including those with prior and especially recent fractures, very low BMD (T-score below −3.0), and those who sustain fractures or lose BMD while taking antiremodeling therapy.
  - Osteoanabolic therapies increase bone mass more rapidly and reduce fracture risk more effectively than do bisphosphonates.
  - Anabolic therapy should be followed by an antiremodeling agent to maintain bone density gains.
  - Bone mineral density gains, particularly in the hip, are greater when an anabolic drug is administered before an antiremodeling drug, compared with the opposite sequence.
- Bone mineral density measured while on therapy correlates with current fracture risk.
- If the response to the initial treatment does not achieve preventing bone loss or reducing the risk of fracture, a change in treatment should be considered.
- If drug-related AEs occur, appropriate management strategies should be instituted. If AEs persist, switching to another agent may be required.
- Identify barriers to nonadherence to therapy and encourage adherence to the treatment plan. Providing clear information to women regarding their risk for fracture and the purpose of osteoporosis therapy may be an optimal way to improve adherence.
- Depending on the treatment, an appropriate interval for repeat BMD testing is 1 to 2 years after beginning treatment or when a change in therapy is considered.
  - Initial DXA and follow-up scans should ideally be performed on the same instrument, using the same procedure. Interpretation of BMD changes requires careful attention to DXA quality control.
- If progressive loss of BMD or fractures occurs while on therapy, evaluate for reasons for suboptimal response to therapy, including poor adherence and underlying medical conditions or medications.
- Even when treatment increases T-score values above −2.5, the patient still has the diagnosis and risks of osteoporosis.
- Referral to bone specialists is recommended for women with very low T-scores, inadequate treatment response, including progressive decline in BMD or fractures while on therapy, or additional factors (eg, renal failure, hyperparathyroidism) requiring special management.

CONCLUSIONS

- Osteoporosis is a chronic, progressive health issue affecting a large proportion of postmenopausal women.
- Menopause practitioners should be familiar and comfortable with approaches to the assessment and management of bone health in their patients.
- Once diagnosed, patients with osteoporosis require lifelong management.
- Management of bone health in postmenopausal women involves assessment of risk factors for low BMD and fracture, encouraging healthy lifestyle habits to reduce risk factors, and if indicated, pharmacologic therapy.
- Effective tools for diagnosing osteoporosis and assessing fracture risk are available, and well-studied strategies exist for managing bone health in women at both low and high risk of fracture.
- By individualizing treatment approaches and monitoring and adjusting those approaches if the clinical picture changes, the consequences of osteoporosis on a menopausal woman's activity and well-being can be minimized.

RECOMMENDATIONS

- Encourage all postmenopausal women to employ lifestyle practices that reduce the risk of bone loss and osteoporotic

fractures: maintaining a healthy weight, eating a balanced diet, obtaining adequate calcium and vitamin D, participating in regular physical activity, avoiding excessive alcohol consumption, not smoking, and using measures to prevent falls.
- The annual examination should include measurements of height and weight, assessment for chronic back pain, kyphosis, and clinical risk factors for osteoporosis, fractures, and falls.
- Evaluate BMD in all women
  - Aged 65 years and older.
  - With history of fracture (other than skull, facial bone, ankle, finger, and toe) after menopause.
  - With medical causes of bone loss such as AE therapy and systemic glucocorticoid therapy of more than 3 months.
- Consider BMD testing for postmenopausal women aged younger than 65 years who have one or more of these risk factors:
  - Discontinued estrogen with additional risk factors for fracture.
  - Thinness (body weight < 127 lb [57.7 kg] or BMI $< 21\ kg/m^2$)
  - History of hip fracture in a parent.
  - Current smoking.
  - Excessive alcohol intake.
  - Long-term use of medications associated with bone loss such as prednisone or an AI.
- Use DXA as the preferred technique for BMD testing and the lowest T-scores at the LS, TH, or FN for diagnostic categorization.
- Vertebral imaging is appropriate for women aged 70 years and older or with historical height loss of more than 1.5 in.
- The IOM recommends daily intake of calcium 1,000 mg to 1,200 mg and vitamin D_3 400 IU to 800 IU for women aged 50 years and older.
- Routine use of calcium and vitamin D supplements is not recommended. Supplements should only be used when daily targets of calcium and vitamin D are not achieved from dietary sources.
- Drug therapy is recommended to prevent bone loss in postmenopausal women with
  - Premature menopause, at least until the average age of natural menopause.
  - Low BMD (T-score < -1.0) and experiencing relatively rapid bone loss because of acute estrogen deficiency in the menopause transition or on discontinuing ET.
  - Low BMD (T-score < -1.0) and other risk factors for fracture (eg, family history) but who do not meet the criteria for osteoporosis treatment.
- Drug therapy is recommended to treat osteoporosis in these populations:
  - All postmenopausal women who have had a vertebral or hip fracture.
  - All postmenopausal women who have BMD values consistent with osteoporosis (ie, T-scores < -2.5) at the LS, FN, or TH region.
  - All postmenopausal women who have T-scores from -1.0 to -2.5 and any one of
    - History of fracture of proximal humerus, pelvis, or distal forearm.
    - History of multiple fractures at other sites (excluding face, feet, and hands).
    - Increased fracture risk according to country-specific thresholds using FRAX. In the United States, those thresholds are a 10-year risk of major osteoporotic fracture (spine, hip, shoulder, and wrist) of at least 20% or of hip fracture of at least 3%.
- Perform comprehensive evaluation, including thorough medical history, physical examination, laboratory evaluation and, in women with historical height loss and kyphosis, vertebral imaging before beginning osteoporosis therapy.
- Ensure adequate total daily intake of calcium (1,000-1,200 mg) and vitamin D (400-800 IU) as adjunct therapy for all postmenopausal women receiving pharmacologic interventions for osteoporosis.
- Consider osteoanabolic therapies for patients at very high risk of fracture, including older women with recent fractures, T-scores -3.0 and lower, or multiple other risk factors.
- During therapy, reevaluate the treatment goals and the choice of medication on an ongoing basis through periodic medical examination and follow-up BMD testing.
- Once diagnosed, patients with osteoporosis require lifelong management to prevent fractures.

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