PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

NUMBER 129, SEPTEMBER 2012

(Replaces Practice Bulletin No. 50, January 2004)

Osteoporosis

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

Background

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

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

and homocysteine levels also appear to contribute to the complexity of bone quality (4).

Widely different age-adjusted hip fracture rates for women have been reported from around the world from 1 in 100,000 person-years among Nigerian black women to 421 in 100,000 person-years among Norwegian white women (5). Within the United States, there also is considerable variation in hip fracture rates, most notably between racial and ethnic groups. Caucasian women have the highest rates of hip fractures, African American women have the lowest rates, and Mexican American women have rates in between the other two groups (6). These racial and ethnic differences are important in counseling and management because fracture rates do not always correlate with BMD across ethnic groups. For example, Chinese American women typically have lower areal BMD than Caucasian American women, but lower rates of hip and forearm fracture (7). It is postulated that greater cortical density and thicker trabeculae compensate for less trabeculae in smaller bones. Thus, both
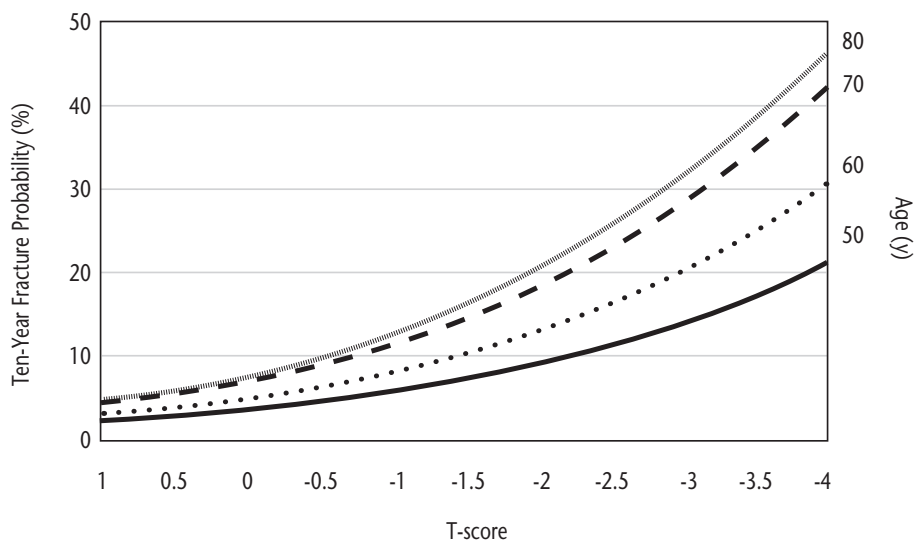
Fig. 1. Ten-year probability of sustaining any osteoporotic fracture in women by age and T-score.

Data from Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporos Int 2001;12(12):989–95.

BMD and microarchitecture appear to play distinct roles in fracture vulnerability. However, apart from Chinese Americans, fracture rates correlated with BMD data collected in the National Health and Nutrition Examination Survey (NHANES) 2005–2006, which reported the highest BMD in African American women, lower BMD in Mexican American women, and the lowest BMD in Caucasian American women (8).

Bone Physiology

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

for an earlier achievement of peak bone mass than previously reported (14). It is believed that peak bone mass correlates with fracture risk later in life.

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

All sex steroids play an important and complex role in adult bone development and maintenance. Hormonal activity at puberty appears to increase bone mineralization that leads to stronger bones and the reduction of the higher rate of fracture seen in prepubertal children. Estrogen is required by both males and females for optimal bone health, and the significant decline in estrogen levels at menopause triggers a time-limited rapid bone loss in women not seen in men. Although this menopausal loss in BMD is sometimes viewed as pathologic,

another paradigm views it as physiologic. It has been documented by some investigators that girls gain more bone mineral content per lean body mass than boys at puberty (16). It is hypothesized that this mechanically excess bone serves as a reservoir for pregnancy and lactation.

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

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

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

Diagnosing Osteoporosis

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

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

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

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

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

Table 1. Diagnosing Osteoporosis Using Bone Densitometry Criteria Developed by the World Health Organization

Category	T Score*
Normal	Greater than or equal to –1.0
Low Bone Mass (osteopenia)	Less than –1 to greater than –2.5
Osteoporosis	Less than or equal to –2.5

*T-score is the number of standard deviations above or below the mean average bone density value for young adult women.

situation that would not be expected to cause fractures in most individuals (eg, a vertebral fracture from opening a window or a simple fall from a standing position). These examples are in contradistinction to a fracture caused by falling off a ladder or a fracture resulting from a car accident where higher trauma is present.

Bone Turnover Markers

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

Fracture Risk Assessment Tool

The fracture risk assessment tool (FRAX) was developed in collaboration with the WHO to predict the risk of osteoporotic fracture for a person in the next 10 years (http://www.sheffield.ac.uk/FRAX/). It was validated in 11 different cohorts (25). The clinical risk factors used in FRAX include, age, sex, body mass index, previous fragility fracture, parental hip fracture, current smoking status, corticosteroid use (greater than or equal to 5 mg prednisolone per day for 3 months), alcohol intake greater than or equal to 3 units per day (approximately three drinks), rheumatoid arthritis, and other secondary causes of osteoporosis. Results are specific for gender and race for various countries where fracture data were available to incorporate into the tool. In the United States, FRAX has been most widely used as an aid in decision making regarding treatment initiation when the patient's BMD score is in the low bone mass (osteopenia) range. It is recommended that DXA reports include a FRAX fracture risk score only when the patient's BMD is in the osteopenia zone. Treatment should be considered when there is a 3% risk of hip fracture or a 20% risk of a *major osteoporotic fracture* (defined as a fracture of

the forearm, hip, shoulder, or clinical spine) or both in the next 10 years. It is important to note that FRAX is valid with or without the incorporation of the femoral neck BMD score.

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

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

Treatment

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

Bisphosphonates

Bisphosphonates are in the antiresorptive class and have been the leading treatment for osteoporosis since the alendronate was approved in 1995. The four bisphosphonates approved in the United States, alendronate, risedronate, ibandronate, and zoledronate, have been extensively studied in large randomized controlled trials that have demonstrated antifracture benefit (27–31).

Table 2. Conditions, Diseases, and Medications That Cause or Contribute to Osteoporosis and Fractures

Rheumatic and autoimmune diseases

• Ankylosing spondylitis	• Lupus	• Rheumatoid arthritis

Endocrine disorders

• Adrenal insufficiency	• Diabetes mellitus	• Thyrotoxicosis
• Cushing's syndrome	• Hyperparathyroidism	

Gastrointestinal disorders

• Celiac disease	• Inflammatory bowel disease	• Primary biliary cirrhosis
• Gastric bypass	• Malabsorption	
• GI surgery	• Pancreatic disease	

Lifestyle factors

• Low calcium intake	• Vitamin D insufficiency	• Excess vitamin A
• High caffeine intake	• High salt intake	• Aluminum (in antacids)
• Alcohol (3 or more drinks/d)	• Inadequate physical activity	• Immobilization
• Smoking (active or passive)	• Falling	• Thinness

Medications

• Anticoagulants (heparin)	• Cancer chemotherapeutic drugs	• Gonadotropin releasing hormone agonists
• Anticonvulsants	• Cyclosporine A and tacrolimus	• Lithium
• Aromatase inhibitors	• Depo-medroxyprogesterone	
• Barbiturates	• Glucocorticoids (≥5 mg/d of prednisone or equivalent for ≥3 mo)	

Genetic factors

• Cystic fibrosis	• Homocystinuria	• Osteogenesis imperfecta
• Ehlers-Danlos	• Hypophosphatasia	• Parental history of hip fracture
• Gaucher's disease	• Idiopathic hypercalciuria	• Porphyria
• Glycogen storage disease	• Marfan syndrome	• Riley-Day syndrome
• Hemochromatosis	• Menkes steely hair syndrome	

Hypogonadal states

• Androgen insensitivity	• Hyperprolactinemia	• Turner's syndrome and Klinefelter's syndrome
• Anorexia nervosa and bulimia	• Panhypopituitarism	
• Athletic amenorrhea	• Premature ovarian failure	

Miscellaneous conditions and diseases

• Alcoholism	• Emphysema	• Muscular dystrophy
• Amyloidosis	• End stage renal disease	• Parenteral nutrition
• Chronic metabolic acidosis	• Epilepsy	• Post-transplant bone disease
• Congestive heart failure	• Idiopathic scoliosis	• Prior fracture as an adult
• Depression	• Multiple sclerosis	• Sarcoidosis

Hematologic disorders

• Hemophilia	• Multiple myeloma	• Systemic mastocytosis
• Leukemia and lymphomas	• Sickle cell disease	• Thalassemia

Table 3. Government-Approved Drugs for Postmenopausal Osteoporosis

Generic (Brand name)	Dose and Route	Indication	Contraindications
Bisphosphonates (oral unless otherwise specified)			
Alendronate (Fosamax)	5 mg/d or 35 mg/wk tablet or oral solution	Prevention	• Abnormalities of the esophagus
	10 mg/d or 70 mg/wk tablet or oral solution	Treatment	• Inability to stand or sit upright for at least 30 minutes
Alendronate + vitamin D_3 (Fosamax Plus D*, Fosavance†)	70 mg + 2,800 IU/wk; 70 mg + 5,600 IU/wk	Treatment	• Hypersensitivity to any component of this product
Risedronate (Actonel)	5 mg/d p.o.; 35 mg/wk; 75 mg in 2 consecutive d/mo; 150 mg/mo	Prevention + Treatment	• Hypocalcemia
Risedronate (Atelvia)	35 mg/wk (delayed release)	Treatment	• Patients at increased risk of aspiration should not receive Fosamax oral solution
Risedronate + calcium carbonate (Actonel with Calcium)	35 mg/wk (day 1) + 1,250 mg Ca for no-risedronate days (days 2–7 of 7-d treatment cycle)	Prevention + Treatment	
Ibandronate (Boniva*)	150 mg/mo; 2.5 mg/d	Prevention + Treatment	
	3 mg every 3 mo I.V.	Treatment	
Zoledronic acid (Reclast*)	5 mg/2 y I.V.	Prevention	• Hypocalcemia
	5 mg/y I.V.	Treatment	• Creatinine clearance < 35 mL/min and acute renal impairment
			• Hypersensitivity to Zoledronic acid or any components of this product
Estrogen agonist/antagonist			
Raloxifene (Evista)	60 mg/d	Prevention + Treatment	• Venous thromboembolism
			• Pregnancy, women who may become pregnant, and nursing mothers
Calcitonin			
Calcitonin-salmon (Fortical)	200 IU/d nasal spray	Treatment (>5 y postmenopause)	• Allergy to calcitonin-salmon
Calcitonin-salmon (Miacalcin)	200 IU/d nasal spray	Treatment (>5 y postmenopause)	• Allergy to synthetic calcitonin-salmon
	100 IU/every other day s.c. or i.m.	Treatment (>5 y postmenopause)	

(continued)

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

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

*Available in the United States but not Canada. †Available in Canada but not the United States. Products not marked are available in both the United States and Canada.

Abbreviations: p.o., by mouth; I.V., intravenous; s.c.,subcutaneous; i.m., intramuscular.

Modified from North American Menopause Society. Government-approved drugs for postmenopausal osteoporosis in the United States and Canada. Mayfield Heights (OH): NAMS; 2012. Available at http://www.menopause.org/otcharts.pdf. Retrieved July 27, 2012. Reprinted with permission from the North American Menopause Society.

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

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

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

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

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

Partial Estrogen Agonists and Antagonists

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

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

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

Denosumab

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

Calcitonin

Salmon calcitonin, an antiresorptive treatment, is available as a nasal spray and a subcutaneous injection. It has been shown to reduce vertebral fractures and to reduce

bone pain associated with vertebral fractures (40, 41). Fracture reduction is less robust than with other agents and was not seen in early postmenopausal women. It should not be used until women are 5 years from menopause. Adverse effects include flushing and nausea with subcutaneous injection and local irritation with nasal spray.

Parathyroid Hormone

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

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

Clinical Considerations and Recommendations

▶ When should bone health be addressed?

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

▶ Are lifestyle changes beneficial?

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

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

▶ What are the current calcium and vitamin D guidelines?

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

Table 4. Institute of Medicine Recommended Dietary Allowances for Calcium and Vitamin D

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

Data from Institute of Medicine. Dietary reference intakes: calcium, vitamin D. Washington, DC: National Academies Press; 2011.

97.5% of the population. Routine screening of vitamin D levels is not recommended. For individuals at high risk of vitamin D deficiency, such as those with certain medical conditions that may affect vitamin D absorption and those taking medications that affect vitamin D levels, screening is recommeneded (52).

Among postmenopausal Caucasian women, vitamin D levels above 30 ng/mL have been associated with a reduced rate of fractures compared with lower levels; however, in the same study, higher levels of vitamin D were associated with an increased risk of fracture among African Americans (53). Another study that used an annual dose of 500,000 international units of cholecalciferol in older women (older than age 70 years) reported an increase in falls and fractures in the women who received the high dose of vitamin D (54). There is emerging evidence of a U-shaped curve with respect to risks associated with vitamin D. Both low and high levels appear to carry risks. These risks include cardiovascular disease, some types of cancer, falls, fractures, and all-cause mortality (51). The IOM recommended upper limit of vitamin D intake for adolescents and adults is 4,000 international units/d.

High intake of calcium also has been associated with risks. A 2009 Cochrane analysis of 11 trials reported a statistically significant increase in renal stones or renal insufficiency (relative risk, 1.16; 95% confidence interval, 1.02–1.33) (55). Controversy exists regarding the possible association of calcium supplementation and coronary artery calcification and coronary artery events. In a secondary analysis of a randomized controlled trial designed to assess the effect of calcium supplements on bone, a trend toward an increase in cardiovascular events was noted (56). In a reanalysis of the Women's Health Initiative (WHI) data that involved only those participants who were not using personal calcium supplements at randomization, the authors found a statistically significant increase in cardiovascular events in those women randomized to calcium supplementation (57). The authors recommended dietary sources of calcium as potentially safer sources of calcium than supplements. Other reports, including a meta-analysis, dispute the findings and report no beneficial or detrimental effects to the cardiovascular system (58, 59).

▶ *Do soy isoflavones have a beneficial effect on bone mineral density?*

Studies of soy isoflavone supplements have produced mixed results; some have suggested a beneficial effect on BMD and some have not. There are no prospective trials on the effect of soy isoflavones on fracture rate. Two extensive reviews of the effect of soy isoflavones concluded that soy supplements were not likely to have a significant effect on BMD (60, 61).

▶ *When should bone density screening be initiated?*

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

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

Although the use of DMPA is associated with loss of BMD, current evidence suggests that partial or full recovery of BMD occurs at the spine and at least partial recovery occurs at the hip after discontinuation of DMPA. Practitioners should not perform BMD monitoring solely in response to DMPA use because any observed short-term loss in BMD associated with DMPA use may be

---

Box 2. When to Screen for Bone Density Before Age 65 Years

Bone density should be screened in postmenopausal women younger than 65 years if any of the following risk factors are noted:

- Medical history of a fragility fracture
- Body weight less than 127 lb
- Medical causes of bone loss (medications or diseases)
- Parental medical history of hip fracture
- Current smoker
- Alcoholism
- Rheumatoid arthritis

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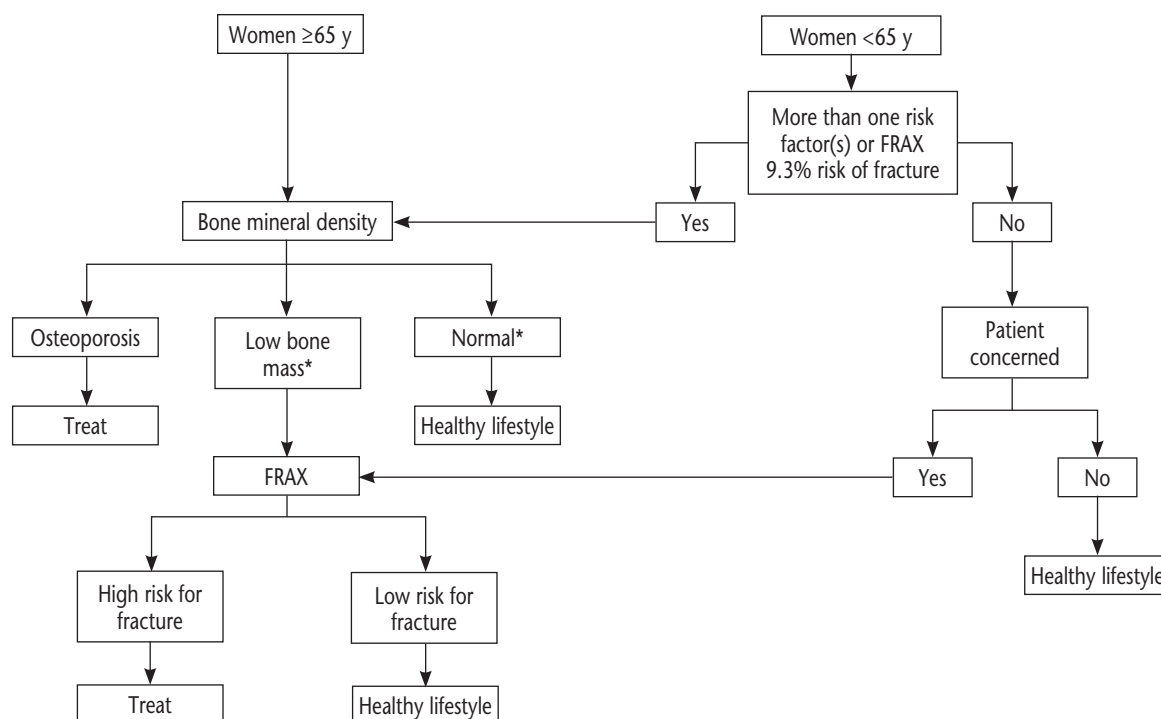
*Fragility fracture is an indication for treatment despite lack of osteoporosis on DXA.

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

recovered and is unlikely to place an adolescent or adult woman at risk of fracture during use or in later years.

▶ *When should treatment for osteoporosis be recommended?*

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

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

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

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

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

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

Bisphosphonates are generally considered first-line therapy, but raloxifene can be a good first choice in younger postmenopausal women for the previously described reasons. A woman using raloxifene can be transitioned to another therapy, such as a bisphosphonate, in her

Box 3. Fall Prevention Measures

Lighting

Provide accessible lighting for each part of the home

Use night-lights

Floors

Remove throw rugs or secure them to the floor

Remove all clutter from the floor

Move cords and cables away from traffic path

Use nonskid wax

Storage

Store items at a height that does not require a step stool to reach

Bathroom

Install safety grab bars in bath and shower

Apply nonskid strips to bath and shower floor

Indoors and Outdoor Stairs

Install handrails for the entire length of the stairs

Provide adequate lighting

Add nonskid treads or secure carpet indoors

60s. This strategy reduces the duration of exposure to bisphosphonates, while providing protection from osteoporosis and breast cancer.

Bisphosphonates can be selected on the basis of patient preference for a certain route of delivery or insurance coverage. Patients who have gastrointestinal problems or had gastrointestinal adverse effects with oral preparations may be better served with a parenteral bisphosphonate. For patients with adherence issues, an annual infusion of zoledronic acid may be preferred.

Denosumab also is a good treatment option for the woman with a high risk of fracture. The subcutaneous injections every 6 months may appeal to some patients and not others. Teriparatide is usually reserved for cases of severe osteoporosis and for patients who have experienced fractures. The daily subcutaneous injections and cost are considerations. Teriparatide therapy is limited to 24 months. Calcitonin is an approved therapy that has weaker data than other available options. It should be reserved for less serious cases of osteoporosis when other treatments are not tolerated.

Combination therapy is not usually recommended. Although it may increase BMD to some degree, fracture data are not available. Risks, adverse effects, and cost with the use of two drugs may be higher than with one

drug. The previously mentioned drugs provide many options for patients and physicians.

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

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

▶ *What is the role of hormone therapy?*

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

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

Deciding on the duration of HT is a challenge because recent HT guidelines specify using the lowest dose for the shortest amount of time, especially when using

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

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

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

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

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

The initial assessment should determine whether there has been a significant decrease in BMD. Every DXA center should periodically test the equipment and the technicians who perform the test to determine the margin of error for that DXA center. The information should be specified in the DXA report or the report should state that there is a significant change in BMD so that the clinician will know if the patient's loss is greater than the margin of error for that office. It also is important to determine if the patient was taking the medication correctly and consistently. Next, a thorough evaluation for secondary causes of osteoporosis (Box 1 and Table 2),

or referral to a specialist are appropriate. One common cause of bone loss during treatment was found to be insufficient vitamin D levels (78). Other secondary causes of osteoporosis that are not uncommon are idiopathic hypercalciuria and celiac disease.

Summary of Recommendations and Conclusions

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

▶ Treatment should be recommended for:
   — Women with a T-score of –2.5 or less
   — Women who have had low-trauma fracture
   — Women who have a T-score from –1 to –2.5 and a FRAX score greater than or equal to 3% for risk of hip fracture or a FRAX score greater than or equal to 20% for risk of a major osteoporotic fracture (defined as forearm, hip, shoulder, or clinical spine fracture) or both in the next 10 years

▶ FDA-approved therapies should be used for medical treatment: raloxifene, bisphosphonates, PTH, denosumab, calcitonin.

▶ Bone density screening for women should begin at age 65 years. Dual-energy X-ray absorptiometry screening can be used selectively for women younger than 65 years if they are postmenopausal and have other significant risk factors for osteoporosis or fracture.

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

▶ In the absence of new risk factors, DXA screening should not be performed more frequently than every 2 years.

▶ In the absence of new risk factors, DXA monitoring of therapy should not be repeated once BMD has been determined to be stable or improved.

▶ Women should be counseled about lifestyle factors that may affect BMD and fracture risk: smoking, poor nutrition and excessive weight loss, weight-bearing and muscle-strengthening exercise, and fall-prevention measures.

▶ Women should be advised of current IOM calcium and vitamin D recommendations.

The following conclusion is based primarily on consensus and expert opinion (Level C):

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

Proposed Performance Measure

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

References

1. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. J Bone Miner Res 2007;22:465–75. (Level III)

2. Boonen S, Autier P, Barette M, Vanderschueren D, Lips P, Haentjens P. Functional outcome and quality of life following hip fracture in elderly women: a prospective controlled study. Osteoporos Int 2004;15:87–94. (Level II-2)

3. Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ 3rd. Population-based study of survival after osteoporotic fractures. Am J Epidemiol 1993;137:1001–5. (Level II-3)

4. Ralston SH. Genetics of osteoporosis. Proc Nutr Soc 2007;66:158–65. (Level III)

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

6. Melton LJ 3rd, Kearns AE, Atkinson EJ, Bolander ME, Achenbach SJ, Huddleston JM, et al. Secular trends in hip fracture incidence and recurrence. Osteoporos Int 2009;20:687–94. (Level II-3)

7. Walker MD, Liu XS, Stein E, Zhou B, Bezati E, McMahon DJ, et al. Differences in bone microarchitecture between postmenopausal Chinese-American and white women. J Bone Miner Res 2011;26:1392–8. (Level II-3)

8. Looker AC, Melton LJ 3rd, Harris TB, Borrud LG, Shepherd JA. Prevalence and trends in low femur bone density among older US adults: NHANES 2005–2006 compared with NHANES III. J Bone Miner Res 2010;25:64–71. (Level II-3)

9. Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Marcus R, Matkovic V, et al. Peak bone mass. Osteoporos Int 2000;11:985–1009. (Level III)

10. Baxter-Jones AD, Faulkner RA, Forwood MR, Mirwald RL, Bailey DA. Bone mineral accrual from 8 to 30 years of age: an estimation of peak bone mass. J Bone Miner Res 2011;26:1729–39. (Level III)

11. Cvijetic S, Colic Baric I, Keser I, Cecic I, Satalic Z, Blanusa M. Peak bone density in Croatian women: varia-

tions at different skeletal sites. J Clin Densitom 2008;11:260–5. (Level II-3)

12. Lorentzon M, Mellstrom D, Ohlsson C. Age of attainment of peak bone mass is site specific in Swedish men—The GOOD study. J Bone Miner Res 2005;20:1223–7. (Level III)

13. Matkovic V, Jelic T, Wardlaw GM, Ilich JZ, Goel PK, Wright JK, et al. Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. Inference from a cross-sectional model. J Clin Invest 1994;93:799–808. (Level III)

14. Recker RR, Davies KM, Hinders SM, Heaney RP, Stegman MR, Kimmel DB. Bone gain in young adult women. JAMA 1992;268:2403–8. (Level II-2)

15. Greendale GA, Young JT, Huang MH, Bucur A, Wang Y, Seeman T. Hip axis length in mid-life Japanese and Caucasian U.S. residents: no evidence for an ethnic difference. Osteoporos Int 2003;14:320–5. (Level II-3)

16. Jarvinen TL, Kannus P, Sievanen H. Estrogen and bone-a reproductive and locomotive perspective. J Bone Miner Res 2003;18:1921–31. (Level III)

17. Manolagas SC. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. Endocr Rev 2010;31:266–300. (Level III)

18. Bass S, Pearce G, Bradney M, Hendrich E, Delmas PD, Harding A, et al. Exercise before puberty may confer residual benefits in bone density in adulthood: studies in active prepubertal and retired female gymnasts. J Bone Miner Res 1998;13:500–7. (Level II-2)

19. Kannus P, Haapasalo H, Sankelo M, Sievanen H, Pasanen M, Heinonen A, et al. Effect of starting age of physical activity on bone mass in the dominant arm of tennis and squash players. Ann Intern Med 1995;123:27–31. (Level II-3)

20. Bass SL, Saxon L, Daly RM, Turner CH, Robling AG, Seeman E, et al. The effect of mechanical loading on the size and shape of bone in pre-, peri-, and postpubertal girls: a study in tennis players. J Bone Miner Res 2002;17:2274–80. (Level II-3)

21. Eser P, Hill B, Ducher G, Bass S. Skeletal benefits after long-term retirement in former elite female gymnasts. J Bone Miner Res 2009;24:1981–8. (Level II-3)

22. Howe TE, Shea B, Dawson LJ, Downie F, Murray A, Ross C, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. 2011, Issue 7. Art. No.: CD000333. DOI: 10.1002/14651858.CD000333.pub2. (Meta-analysis)

23. National Osteoporosis Foundation. Clinician›s guide to prevention and treatment of osteoporosis. Washington, DC: NOF; 2010. Available at: http://www.nof.org/sites/default/files/pdfs/NOF_ClinicianGuide2009_v7.pdf. Retrieved March 26, 2012. (Level III)

24. Miller PD, Hochberg MC, Wehren LE, Ross PD, Wasnich RD. How useful are measures of BMD and bone turnover? Curr Med Res Opin 2005;21:545–54. (Level III)

25. Kanis JA, Oden A, Johnell O, Johansson H, De Laet C, Brown J, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and

osteoporotic fractures in men and women. Osteoporos Int 2007;18:1033–46. (Level III)

26. Kanis JA, Hans D, Cooper C, Baim S, Bilezikian JP, Binkley N, et al. Interpretation and use of FRAX in clinical practice. Task Force of the FRAX Initiative. Osteoporos Int 2011;22:2395–411. (Level III)

27. Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995;333:1437–43. (Level I)

28. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11:83–91. (Level I)

29. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. Hip Intervention Program Study Group. N Engl J Med 2001;344:333–40. (Level I)

30. Chesnut CH 3rd, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoieth A, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE). J Bone Miner Res 2004;19:1241–9. (Level I)

31. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. HORIZON Pivotal Fracture Trial. N Engl J Med 2007;356:1809–22. (Level I)

32. Ensrud KE, Barrett-Connor EL, Schwartz A, Santora AC, Bauer DC, Suryawanshi S, et al. Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the Fracture Intervention Trial long-term extension. Fracture Intervention Trial Long-Term Extension Research Group. J Bone Miner Res 2004;19:1259–69. (Level I)

33. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 2004;350:1189–99. (Level I)

34. Wasnich RD, Bagger YZ, Hosking DJ, McClung MR, Wu M, Mantz AM, et al. Changes in bone density and turnover after alendronate or estrogen withdrawal. Early Postmenopausal Intervention Cohort Study Group. Menopause 2004;11:622–30. (Level I)

35. Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston CC Jr. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. J Clin Endocrinol Metab 1998;83:396–402. (Level I)

36. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, pre-

37. Migliorati CA, Schubert MM, Peterson DE, Seneda LM. Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy. Cancer 2005;104:83–93. (Level III)

38. McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, et al. Denosumab in postmenopausal women with low bone mineral density. AMG 162 Bone Loss Study Group. N Engl J Med 2006; 354:821–31. (Level I)

39. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. FREEDOM Trial [published erratum appears in N Engl J Med 2009;361:1914]. N Engl J Med 2009;361:756–65. (Level I)

40. Pun KK, Chan LW. Analgesic effect of intranasal salmon calcitonin in the treatment of osteoporotic vertebral fractures. Clin Ther 1989;11:205–9. (Level I)

41. Chesnut CH 3rd, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000;109:267–76. (Level I)

42. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434–41. (Level I)

43. Kurland ES, Heller SL, Diamond B, McMahon DJ, Cosman F, Bilezikian JP. The importance of bisphosphonate therapy in maintaining bone mass in men after therapy with teriparatide [human parathyroid hormone(1-34). Osteoporos Int 2004;15:992–7. (Level III)

44. Black DM, Bilezikian JP, Ensrud KE, Greenspan SL, Palermo L, Hue T, et al. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. PaTH Study Investigators. N Engl J Med 2005;353:555–65. (Level I)

45. Matkovic V, Kostial K, Simonovic I, Buzina R, Brodarec A, Nordin BE. Bone status and fracture rates in two regions of Yugoslavia. Am J Clin Nutr 1979;32:540–9. (Level II-3)

46. Heaney RP. Calcium in the prevention and treatment of osteoporosis. J Intern Med 1992;231:169–80. (Level III)

47. Kalkwarf HJ, Khoury JC, Lanphear BP. Milk intake during childhood and adolescence, adult bone density, and osteoporotic fractures in US women. Am J Clin Nutr 2003; 77:257–65. (Level II-3)

48. Winzenberg T, Shaw K, Fryer J, Jones G. Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomised controlled trials. BMJ 2006;333:775. (Meta-analysis)

49. Bonjour JP. Dietary protein: an essential nutrient for bone health. J Am Coll Nutr 2005;24:526S–36S. (Level III)

50. Tkatch L, Rapin CH, Rizzoli R, Slosman D, Nydegger V, Vasey H, et al. Benefits of oral protein supplementation in elderly patients with fracture of the proximal femur. J Am Coll Nutr 1992;11:519–25. (Level I)

51. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011;96:53–8. (Level III)

52. Institute of Medicine. Dietary reference intakes: calcium, vitamin D. Washington, DC: National Academies Press; 2011. (Level III)

53. Cauley JA, Danielson ME, Boudreau R, Barbour KE, Horwitz MJ, Bauer DC, et al. Serum 25-hydroxyvitamin D and clinical fracture risk in a multiethnic cohort of women: the Women's Health Initiative (WHI). J Bone Miner Res 2011;26:2378–88. (Level II -2)

54. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial [published erratum appears in JAMA 2010;303:2357]. JAMA 2010;303:1815–22. (Level I)

55. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. 2009, Issue 2. Art. No.: CD000227. DOI: 10.1002/14651858.CD000227.pub3. (Meta-analysis)

56. Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ 2008;336:262–6. (Level I)

57. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ 2011;342:d2040. (Level III)

58. Lewis JR, Calver J, Zhu K, Flicker L, Prince RL. Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up. J Bone Miner Res 2011;26:35–41. (Level I)

59. Wang L, Manson JE, Song Y, Sesso HD. Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. Ann Intern Med 2010; 152:315–23. (Meta-analysis)

60. Liu J, Ho SC, Su YX, Chen WQ, Zhang CX, Chen YM. Effect of long-term intervention of soy isoflavones on bone mineral density in women: a meta-analysis of randomized controlled trials. Bone 2009;44:948–53. (Meta-analysis)

61. The role of soy isoflavones in menopausal health: report of The North American Menopause Society/Wulf H. Utian Translational Science Symposium in Chicago, IL (October 2010). North American Menopause Society. Menopause 2011;18:732–53. (Level III)

62. Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. Menopause 2010;17:25–54; quiz 55–6. (NAMS 2010) (Level III)

63. International Society for Clinical Densitometry. Official positions of the International Society for Clinical Densitometry. West Hartford (CT): ISCD; 2007. Available at: http://www.iscd.org/Visitors/pdfs/ISCD2007Official Positions-Adult.pdf. Retrieved March 26, 2012. (Level III)

64. Screening for osteoporosis: U.S. preventive services task force recommendation statement. U.S. Preventive Services Task Force. Ann Intern Med 2011;154:356–64. (Level III)

65. Watts NB, Bilezikian JP, Camacho PM, Greenspan SL, Harris ST, Hodgson SF, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis. AACE Osteoporosis Task Force. Endocr Pract 2010;16(suppl 3):1–37. (Level III)

66. World Health Organization. Prevention and management of osteoporosis: report of a WHO scientific group. WHO Technical Report Series No. 921. Geneva: WHO; 2003. Available at: http://libdoc.who.int/trs/WHO_TRS_921.pdf. Retrieved March 26, 2012. (Level III)

67. Bell KJ, Hayen A, Macaskill P, Irwig L, Craig JC, Ensrud K, et al. Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data. BMJ 2009;338:b2266. (Level I)

68. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. Women's Health Initiative Investigators. JAMA 2003;290:1729–38. (Level I)

69. Jackson RD, Wactawski-Wende J, LaCroix AZ, Pettinger M, Yood RA, Watts NB, et al. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. Women's Health Initiative Investigators. J Bone Miner Res 2006; 21:817–28. (Level I)

70. The 2012 hormone therapy position statement of the North American Menopause Society. Menopause 2012;19:257–71. (Level III)

71. Santen RJ, Allred DC, Ardoin SP, Archer DF, Boyd N, Braunstein GD, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. Endocrine Society. J Clin Endocrinol Metab 2010;95:s1–66. (Level I)

72. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. WHI Investigators. JAMA 2003;289: 3243–53. (Level I)

73. Chen WY, Manson JE, Hankinson SE, Rosner B, Holmes MD, Willett WC, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. Arch Intern Med 2006; 166:1027–32. (Level II-2)

74. Ascott-Evans BH, Guanabens N, Kivinen S, Stuckey BG, Magaril CH, Vandormael K, et al. Alendronate prevents loss of bone density associated with discontinuation of hormone replacement therapy: a randomized controlled trial. Arch Intern Med 2003;163:789–94. (Level I)

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

76. Cohen A, Fleischer JB, Johnson MK, Brown IN, Joe AK, Hershman DL, et al. Prevention of bone loss after withdrawal of tamoxifen. Endocr Pract 2008;14:162–7. (Level I)

77. Gourlay ML, Fine JP, Preisser JS, May RC, Li C, Lui LY, et al. Bone-density testing interval and transition to osteoporosis in older women. Study of Osteoporotic Fractures Research Group. N Engl J Med 2012;366:225–33. (Level II-2)

78. Geller JL, Hu B, Reed S, Mirocha J, Adams JS. Increase in bone mass after correction of vitamin D insufficiency in bisphosphonate-treated patients. Endocr Pract 2008;14:293–7. (Level II-3)

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

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

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

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

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

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

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

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

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

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

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