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The Medical Management of Bone Health and Osteoporosis

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Definition of Osteoporosis and Impact on Public Health

At the 2000 National Institutes of Health (NIH) Consensus Conference, osteoporosis was defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture (1). As are many medical conditions associated with aging, osteoporosis is common, underrecognized as a public health concern, underdiagnosed, and inadequately treated by medical providers (2). The current estimates of 8 million osteoporotic women and 2.5 million osteoporotic men in the United States are expected to increase by about 40% by 2020, with estimated direct costs in 2002 dollars of $12.2 to $17.9 billion (3).

Yet recent clinical trials have shown that public health interventions and medical practices for the diagnosis, prevention, and treatment of osteoporosis are effective. The U.S. Surgeon General's Report of 2004 on Bone Health and Osteoporosis (4) was published in two forms: one for patient information and a separate guide for medical professionals, with the goal of addressing the lack of public awareness and neglect by medical providers that osteoporosis, or bone fragility with aging, is preventable and treatable, and not an inevitable consequence of aging.

Bone Metabolism Changes with Aging, Disease, and Environmental Influences

Throughout life, bone is a metabolically active body organ with a complex physiology that is a function of aging, gender, ethnicity, nutrition, physical activity, environmental exposures, and disease (Tables 3.1 and 3.2).

Physiology and Genetics

Men and women usually achieve peak bone mass by approximately age 30 years, but that peak bone mass can be influenced by genetic factors. Genetically based diseases can result in osteoporosis by young

Table 3.1. Determinants of Peak Bone Mass.

Parameter	Normal Peak Bone Mass	Low Peak Bone Mass
Genetics	Vitamin D and lipoprotein 5 receptors	Homocysteinuria
Metabolism	Normal gastrointestinal motility/absorption	Gastrointestinal malabsorption/celiac disease
	Euthyroid state	Hyperthyroid states/Graves' disease
		Sex hormone deficiency
		Amenorrhea
		Hypothalamic-pituitary disease
Body mass	Body mass Index >20 kg/m^2	Anorexia nervosa
Weight-bearing exercise	Physical activity 3 hours weekly	Trauma-induced immobility
Nutrition	Calcium intake, 1,000 mg daily	Inadequate calcium and vitamin D intake
	Vitamin D intake, 400 IU daily	Phosphate-containing sodas
Medications	Estrogen-containing oral contraceptives	Steroid medications
		Phenytoin
		Warfarin
Environmental exposures	Fluorinated drinking water	Tobacco use
		Excessive alcohol intake

Table 3.2. Determinants of Bone Loss with Aging.

Parameter	Positive Impact on Bone Health	Contributors to Bone Loss
Genetics	Vitamin D and lipoprotein 5 receptors	Excessive calcium excretion in urine
Metabolism	Estrogen synthesis in adipose tissue	Menopause
		Age-related testosterone deficiency in men
		Hyperparathyroidism
		Renal failure
Body mass index	>24 kg/m^2	<20 kg/m^2 (or cycled weight loss/gain)
Weight-bearing exercise	Walking 30 minutes daily	Immobility secondary to hemiparesis from stroke or prolonged bed rest for medical illness
	Resistance training	
Medical conditions	None	Rheumatoid arthritis
Nutrition	Calcium intake, 1,200–1,500 mg daily	Inadequate calcium and vitamin D intake
	Vitamin D intake, 600–800 IU daily	Phosphate-containing sodas
Medications	Hormone replacement therapy	Steroid medications
	Antiresorptive agents	Phenytoin
	Thiazide diuretics	Gonadotropin antagonists
	Calcium carbonate antacids	Phosphate-binding antacids
Environmental exposures	Sunlight exposure	Tobacco use
		Excessive alcohol intake

adulthood (5). For example, homocysteinuria, a metabolic defect in cobalamin metabolism, produces impairments in cross-linking of collagen that result in fragile bone. Genetic variants in vitamin D receptors and lipoprotein receptor-related protein 5 and vitamin D are known to result in strong bone, whereas others result in fracture syndromes (6). Calcium excretion by the kidney is mediated genetically, and excess calcium loss in urine results in the formation of kidney stones and predisposes to demineralization of bone when dietary intake of calcium is insufficient to compensate for the urinary losses.

Environmental Factors

Environmental influences also are important to bone development. In children, low dietary calcium intake (7), vitamin D intake of less than 200 IU, consumption of carbonated beverages such as soda (8), and physical activity of less than 3 hours per week (9) all have been shown to contribute to low bone mass. Body weight is highly correlated with bone mass, and anorexia nervosa results in low peak bone mass (10). Skin is able to synthesize a precursor of vitamin D when exposed to ultraviolet light, but circulating vitamin D levels are known to decrease when sun exposure is limited, as during winter months, in northern climates, and in home-bound older adults who have limited dietary intake of dairy products fortified with vitamin D.

Aging

On average, men achieve greater bone size, although a quantitative computed tomography (CT) study has shown that women have greater trabecular bone mass by volume (11). After peak bone mass is achieved, little bone loss occurs in healthy adults until advanced age or, in women, menopause. With aging, the balance of bone formation to bone resorption is altered greatly by decreases in postpubertal circulating levels of sex hormones. Most common and most important is the universal menopause in women (12), but osteoporosis also results from androgen deprivation in men with aging.

Disease States

Disease states that alter gastrointestinal absorption of calcium and vitamin D (13); hepatic (14) and renal metabolism (15) of vitamin D; the endocrine systems of the hypothalamus and pituitary, thyroid, parathyroid (16), adrenal, and pancreatic glands; and the paracrine functions of the bone marrow all regulate bone formation and/or bone resorption and contribute to disease-related osteoporosis. A recently discovered hormone from fat cells, leptin, also has been shown to have effects on bone (17). Calcitriol, or 1,25-dihydroxyvitamin D_3, is the metabolically active hormone that increases intestinal absorption of calcium and phosphorus. Because dietary forms and skin-derived precursors of vitamin D are metabolized in the liver and kidney, severe impairments in renal function result in calcitriol deficiency,

malabsorption of calcium through the gut, hypocalcemia, and ultimately a compensatory rise in parathyroid hormone and active bone resorption.

Celiac disease, one cause of gastrointestinal malabsorption, has a prevalence of 1 in 266 adults and may present solely as osteoporosis in approximately 15% of cases (13). Hyperthyroidism and hyperparathyroidism result in excessive bone resorption, and excess secretion of cortisol associated with clinical depression has been associated with osteopenia. Bacterial infections, such as periodontal disease and osteomyelitis, can produce localized bone loss. The alterations in molecular growth factors associated with rheumatoid arthritis and multiple myeloma are thought to result in osteopenia even without systemic glucocorticoid therapies. Repetitive weight loss is another risk for bone loss, although attention to nutrition and physical activity may limit this risk. Medical therapies of corticosteroids, anticoagulants that impair vitamin K metabolism (such as warfarin), and anticonvulsants that impair vitamin D metabolism (such as phenytoin, valproic acid, and carbamazepine) may impair bone formation, whereas antiestrogens used for breast cancer treatment in women and antiandrogens used for prostate cancer treatment in men result in excessive bone resorption.

Bone Strength and Fracture

Bone strength is achieved through a combination of three-dimensional architecture and the mineralization of the bone matrix proteins. Vitamin K is essential for the carboxylation of bone matrix proteins, whereas vitamin B complex mediates collagen cross-linking. The systemic hormones that regulate blood calcium levels, such as parathyroid hormone and calcitonin, do so, in part, through their mediation of bone mineralization. Calcium is an important mediator of cell communications in multiple body tissue, and, because bone serves as the reservoir of this mineral, limited dietary intake results in increased circulation of parathyroid hormone and bone demineralization (18).

The coupling of bone formation to bone resorption is controlled locally by signaling proteins under the control of the systemic hormones and growth factors (Figure 3.1). Marcrophage colony-stimulating factor and receptor activator of nuclear factor kappa B ligand (RANKL) are osteoblastic-derived proteins that bind to receptors on the osteoclast precursors and stimulate bone resorption (19). In contrast, a third protein, osteoprotegerin, binds RANKL and prevents osteoclastic activity (20). The systemic hormones and local growth factors that stimulate bone resorption regulate the amounts of RANKL and osteoprotegerin. For example, estrogen deficiency results in an increase in RANKL. A second signaling pathway involves lipoprotein receptor-related protein 5 (21).

When bone resorption exceeds bone formation, bone fragility occurs, putting the skeletal system at risk for fracture, even when the injuring force is relatively minor, such as that from a fall (22). The risk of a fall increases with sensory deficits (such as inadequate vision and hearing), neurologic impairments (such as peripheral neuropathy, Parkinson's

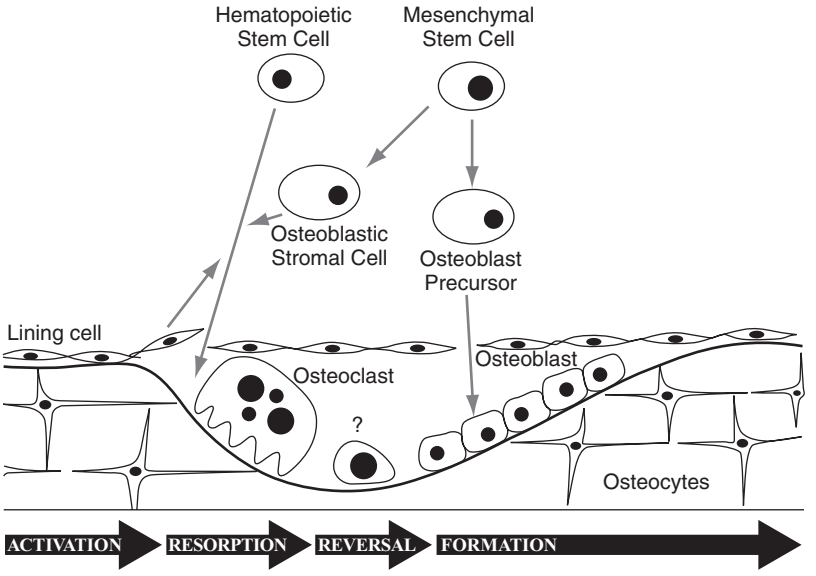

Figure 3.1. Systemic and local mediators of bone formation and bone resorption. (From Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, 2004.)

disease, and stroke), and loss of muscle strength from deconditioning (such as results from a bed-bound state, the most severe form of disuse, which results in rapid bone loss).

Assessing Bone Health and Osteoporosis Screening

The U.S. Preventive Task Force recommends assessment of bone mass/density for all women aged 65 years or older or those aged 60 years or older who have one or more osteoporosis risk factors (Table 3.1) (23). The National Osteoporosis Foundation guidelines recommend an initial assessment at age 70 years for men with no risk factors other than advanced age (24). All adults receiving systemic glucocorticoids and all young adults with sex hormone deficiency for whatever cause should be assessed, including women treated with antiestrogens and men treated with androgen deprivation. Bone fracture that occurs from a fall at standing height and age-related height loss of more than 1.5 inches suggest fragility fractures for which osteoporosis or other metabolic bone disorders may be an underlying cause.

Diagnostic Tools

Dual energy x-ray absorptiometry (DEXA) of the central skeleton is the most commonly used diagnostic procedure for assessing bone mineral density. The technology requires less than 30 minutes to measure multiple sites of spine, hip, and forearm; involves low-dose radiation comparable with background environmental exposures; and can be used to monitor osteoporosis treatments. The World Health Organization (25)

has established definitions for normal, osteopenia, and osteoporosis based on standard deviations from peak bone health (Table 3.2). The International Society for Clinical Densitometry (26) has established standards that include assessment of at least three lumbar vertebral bodies, three hip sites (total hip, femoral neck, and trochanter), and the proximal third of the nondominant arm radius (27). This society also has established standards for DEXA diagnosis of osteoporotic versus normal in premenopausal women and men aged 50 years and older (Table 3.3). Pitfalls in DEXA technology include assessment of the spine in older adults who may have degenerative changes or dense vertebra from compression fractures and assessment in limited positioning of the hip due to arthritic conditions. Recently, some DEXA devices have been upgraded to assess vertebral deformity associated with vertebral compression fractures, termed an *instant vertebral assessment* (28), that may be useful when the DEXA spine image shows deformity. Serial DEXA measurements for monitoring osteoporosis treatments should be performed with the same device because different devices calculate bone mineral density with different computer algorithms. An appropriate interval for testing is every 2 years. Exceptions are made for individuals with high bone turnover (such as that related to untreated hyperparathyroidism, uncontrolled hyperthyroidism, and drugs that reduce sex hormone levels) or low bone formation (such as that related to systemic glucocorticoid use). For these high-risk groups, a yearly DEXA measurement is recommended.

Single x-ray absorptiometry devices and ultrasound devices are portable and often used to assess forearm and heel sites in community settings such as health fairs and nursing facilities (29). With aging, discordance of bone loss between the axial and appendicular skeleton is common, with vertebral bone loss occurring at more accelerated rates (11). Thus, limiting assessment to a forearm or heel scan may be insufficient for assessing bone health in an adult who is in the early stages of sex hormone deficiency or glucocorticoid use. At present, the heel ultrasound devices report a T-score that is not comparable to DEXA.

Table 3.3. International Society for Clinical Densitometry Criteria for Diagnosis by DEXA.

	Women		
Status	**Premenopausal (Z-scores)**	**Postmenopausal (T-scores)**	**Men ≥50 Years Old (T-scores)***
Normal		**−1.0 or above**	**−1.0 or above**
Osteopenia		**Between −1.0 and −2.5**	
Osteoporosis	**Low bone mineral density with secondary causes or risk factors**	**−2.5 or below**	**−2.5 or below†**

* Diagnosis in men <50 years old should not be made on the basis of densitometric criteria alone.

† Plus clinical risk factors in men 50 to 64 years old.

For example, a T-score of –1.8 in heel ultrasound may predict a fracture risk equivalent to a DEXA T-score of –2.5 (30). However, ultrasound is useful in identifying older adults who may benefit from full DEXA assessment, especially those in a nursing home environment and those with a physical dependence that may limit full DEXA assessment.

Compared with DEXA, quantitative computerized tomography of the spine results in less artifact from spinal deformity but has higher levels of radiation and cost and, in general, has been used less widely in clinical practice. However, high-resolution computerized tomography is emerging as a novel technology for assessing the trabecular architecture of bone and has the potential for better prediction of bone strength and fracture risk than DEXA (31).

Medical Evaluation

Standard

The medical evaluation for the underlying cause of osteoporosis begins with a careful history of medical, family, medication, and social factors to assess risks for low peak bone mass, rapid adult bone loss, and medical diagnoses and treatments associated with osteoporosis. One study identified secondary causes of osteopenia in 51% of men and 41% of women studied (32). Tannenbaum et al. (32) found that, in women, the most common secondary causes were vitamin D deficiency (20%), hypercalciuria (10%), and gastrointestinal malabsorption (7%).

The medical history should elicit information about fractures (including peripheral sites of the forearm and ankle), disease states (such as rheumatoid arthritis, kidney stones, hyperthyroidism, gastrointestinal malabsorption, multiple myeloma, depression, and renal insufficiency), and surgical interventions (such as gastric stapling, partial gastrectomy, and small bowel resection) that may have resulted in impaired absorption of nutrients. A family history of fractures and disease states also should be obtained. Assessment of the patient's reproductive function should include the age of pubertal development, evaluation for prolonged amenorrhea after menarche in women, the age of cessation of menses in postmenopausal women, and evidence of sexual dysfunction in men.

The medication and nutritional history should determine exposure to medications that contain sex hormones, antiestrogens (such as aromatase inhibitors), medroxyprogesterone acetate (which can cause a hypoestrogen state in premenopausal women), systemic glucocorticoid, vitamin K–depleting anticoagulants (such as warfarin), antiseizure medications that impair vitamin D (such as phenytoin), and thyroxine supplements. The nutritional assessment should also determine routine dietary sources of calcium, vitamin D, vitamin B complex, and nutritional supplements.

Other information obtained should include a social history and systems review. The social history should include assessment of physical activity, history of smoking, and intake of alcohol, phosphate-containing beverages (such as sodas), and caffeine. The systems review should address sensory deficits and physical function (including a

history of falls) and longitudinal changes in body weight. Bone pain is often caused by degenerative or inflammatory processes distinct from osteoporosis, although diffuse bone and muscle pain is associated with vitamin D deficiency.

The routine annual physical examination of all adults should include measurement of height, with loss of 1.5 or more inches prompting assessment for asymptomatic vertebral compression, and examination of the spine for kyphosis. Practical examinations that identify clinically significant kyphosis include assessment of whether the occiput can be positioned against the wall and whether the distance from the ribs to the pelvis is less than four finger breadths. Examinations to assess the risk of a fall include vision and hearing assessment, observation of gait, and neurologic assessment for balance, peripheral sensation, and muscle strength.

All patients about to undergo pharmacologic therapy for osteoporosis should receive basic laboratory screening for calcium, phosphorus, creatinine, alkaline phosphatase, albumin, and globulin and a complete blood count as a screen for multiple myeloma. A serum 25-hydroxyvitamin D level is recommended for older adults who limit sun exposure and dietary intake of vitamin D and for adults with conditions that predispose to gastrointestinal malabsorption. A 24-hour urine collection for calcium is recommended for patients with a history of kidney stones to assess for hypercalciuria. This evaluation can determine inadequate dietary intake of calcium when levels are low, but patient compliance is challenging.

Expanded Diagnostics

More extensive diagnostics are recommended when the degree of osteopenia as defined by the DEXA scan is greater than expected, when a fracture occurs without a substantial risk thereof based on history, or when serial DEXA scans show continued bone loss despite an adequate treatment plan. For men, measurement of the serum testosterone level is useful. For premenopausal women with menstrual irregularities, measurements of gonadotropin levels may uncover premature menopause. Measuring estrogen levels in postmenopausal women has no diagnostic utility. Elevations in serum intact molecule parathyroid hormone with normal serum 25-hydroxyvitamin D levels are diagnostic for asymptomatic primary hyperparathyroidism and may occur in the presence of normal serum calcium. Measurement of 1,25-dihyroxyvitamin D_3 levels is needed for patients with severe renal insufficiency. Urine and serum protein electrophoresis tests assess monoclonal gammopathy associated with multiple myeloma. The presence of serum antiglidian antibodies (such as endomysial antibody) suggests celiac disease, although small-bowel biopsy for villous atrophy is the gold standard for diagnosis. To assess adequately the hypothalamic–pituitary–adrenal regulation of cortisol, a 24-hour urine collection for cortisol or a dexamethasone suppression test is recommended. It is also recommended that the serum thyroid-stimulating hormone levels of patients receiving thyroxine supplements be maintained within normal range, as a suppressed level may cause bone resorption.

In addition, biochemical markers of bone turnover can be measured to assess a patient for a high bone-turnover state such as hyperparathyroidism, thyrotoxicosis, or sex-hormone-deficient states (33). In general, markers are not used to monitor treatments, except for individuals in high bone-turnover states.

Prevention and Treatment

Nutrition and Bone Health

The current U.S. recommended dietary allowances of daily elemental calcium are, for adults aged 19 to 50 years, 1,000 mg; and for adults more than 50 years old, 1,200 mg (34). The current recommended dietary allowance for vitamin D is 400 IU for adults aged 50 to 70 years and 600 IU for adults more than 70 years old, although the clinical guidelines followed in Canada include 800 IU for individuals more than 50 years old (35). A recent study has found that higher doses of vitamin D (such as 1,300 IU daily) may reverse bone pain and muscle weakness associated with aging (36).

The average American diet that excludes dairy products achieves only 300 mg of elemental calcium because little vitamin D is present naturally in other foods. With increased awareness of bone health, calcium and vitamin D fortification of fruit juices, breakfast cereals, skim milk puddings, and yogurts is increasing (Table 3.4). On average, 8 oz of calcium-fortified fruit juice contains 300 mg of elemental calcium, comparable with the level in milk.

There are multiple commercial formulations of calcium and vitamin D to supplement dietary sources. Although there are subtle differences in absorption, in general, all are clinically effective (37). Calcium

Table 3.4. Calcium-Enriched Foods.

Food	Serving Size (mg equivalent)	Calcium (mg)
Tofu	½ cup (400 mg)	434
Low-fat yogurt	8 oz (300–400 mg)	300
Fortified orange juice	1 cup (300–400 mg)	300
Fortified soy milk	1 cup (300–400 mg)	300
Skim, 1%, or 2% milk	1 cup (300–400 mg)	321
Fortified cereal	¾ cup (300–400 mg)	Varies by brand
Fortified oatmeal	1 packet (300–400 mg)	350
Cheddar, Monterey, or provolone cheese	1 oz (200–300 mg)	206
Spinach (cooked)	1 cup (200–300 mg)	237
Pizza	1 slice (100–200 mg)	100
Mustard greens (cooked)	1 cup (100–200 mg)	104
Cottage cheese	1 cup (100–200 mg)	138
Frozen yogurt or pudding	½ cup (100–200 mg)	152
American, feta, or mozzarella cheese	1 oz (100–200 mg)	174

Source: United States Department of Agriculture Nutrient Database for Standard Reference, http://www.nal.usda.gov/fnic/foodcomp.

carbonate tablets provide the greatest concentration of calcium per tablet (500 to 600 mg), although they are associated with more gas, bloating, and constipation than calcium citrate supplements (300 to 325 mg per tablet). Chewable tablets, powders that dissolve in beverages, calcium-enriched candies and chocolates, and liquid preparations offer a wide range of personal choice. Nutritional labels on commercial packages report the number of tablets per serving and the amount of elemental calcium. Many calcium supplements also contain 125 to 200 IU of vitamin D. Multiple vitamins marketed for older adults and women may also include 200 to 450 mg of elemental calcium per tablet. Gastrointestinal absorption of calcium is maximal at 600 mg, hence the need to ingest calcium-enriched dietary sources and supplements throughout the day.

Vitamin K, vitamin B complex with folate, and vitamin A also are essential for bone health. The daily U.S. recommended dietary allowances are vitamin K, 90 µg for women and 120 µg for men; vitamin B complex and folate, 400 IU; and vitamin A, 2,000 IU. Vitamin A in excess of 2,500 IU may increase risk of fracture. Older adults for whom warfarin has been prescribed should not take calcium or vitamin supplements that contain vitamin K.

Trace elements, such as magnesium, copper, zinc, and boron, play a role in bone metabolism, but there is inadequate evidence to support the routine use of dietary supplements to achieve intakes beyond those achieved through a well-balanced diet (38). Plants such as soy contain substances with estrogen-like activity. However, a recent randomized trial of a commercially prepared soy protein supplement showed that it did not prevent menopausal loss of bone density (39).

Although the effects of caffeine and alcohol on bone have not been well described, recommendations include limiting intake to two or less exposures of each of these substances daily. Carbonated beverages also should be limited to two or less daily, and they should not be ingested at the same time as calcium-enriched foods or supplements because they may impair calcium absorption (8).

Physical Activity

Exercise has been shown to increase bone mass and morphology during childhood bone development, prevent bone loss with aging, and reduce the risk of falls that result in fracture (40). In young adults, low-magnitude strains achieved through walking can maintain bone (40). Bed rest results in 1% loss of bone per week, which can be recovered at a rate of 1% per month when weight-bearing activity resumes (41), but building bone requires high-magnitude and novel, not customary, physical activity. Increases in the level or amount of such physical activity can raise issues of concern, including endurance loading and fatigue microdamage secondary to repetitive high-impact exercise (such as jogging), nerve entrapment syndromes of the spine and extremities secondary to poor body mechanics, and vertebral compression fractures secondary to flexion exercises of the spine in patients with severe osteopenia. Walking in appropriate footwear for

30 minutes daily is a safe and reasonable exercise prescription. Many community centers offer Tai Chi, of proven benefit for the prevention of falls. The management of newly diagnosed osteoporosis should include a physical therapy referral for instruction in proper technique for resistance exercise; for assessments of gait, balance, and leg-length discrepancies; for fitting of assistive devices to improve gait disorders; and for balance exercise to prevent falls.

Devices that convey vibrations to bone are under investigation and, if proved effective, potentially can be useful particularly for individuals with impaired mobility, such as stroke victims.

Prevention After Menopause and in High-Risk Conditions

Bone loss occurs in all women in the setting of estrogen deficiency. The lower the bone mass in a postmenopausal woman, the greater the risk of future fracture. Women begin menopause with different levels of bone mass, and women lose bone at different rates. The best predictor of early menopausal bone loss is low body weight. Thus, there will be differences among women in short- and long-term fracture risks (11).

A multidisciplinary approach to bone health after menopause is recommended, including advice about nutrition, physical activity, and healthy behaviors; medical assessment of osteoporosis risk by the primary medical provider; and appropriate referrals for DEXA before age 65 years for women with additional risk. The optimal daily calcium intake is 1,500 mg in combination with 400 to 600 IU of vitamin D. The diet should include more than five daily servings of fresh fruits and vegetables to achieve adequate vitamin B complex, folate, and vitamin K levels. Healthy behaviors include avoiding phosphate-containing beverages and limiting caffeine and alcohol use. Maintenance of a healthy body weight and of a body mass index of 24 to 25 kg/m^2 without cycled weight gain and loss is optimal. Walking 30 minutes daily in appropriate footwear and performing resistance exercises with a proper technique complete the behavioral approaches to optimal bone health.

Clinical trials of antiresorptive therapies of estrogens, selective estrogen receptor modulators (such as raloxifene) (42), and oral bisphosphonates (such as alendronate [43] and risedronate [44]) have shown prevention of menopausal bone loss and preservation of the microarchitecture of trabecular bone. The Women's Health Initiative Study, published in 2003, dramatically halted the routine medical practice of prescribing estrogens to postmenopausal woman for preventive health purposes (45). Although the Women's Health Initiative Study documented that conjugated estrogen reduced the rate of hip and symptomatic vertebral fractures by approximately one third, the adverse events of thromboembolic disorders, cardiovascular endpoints of myocardial infarction and stroke, and breast cancer outweighed the benefits to bone health (46). Raloxifene and alendronate therapies have been shown to result in statistically significant reductions in the incidence of vertebral fractures in postmenopausal women with normal or mild bone loss (42,43). However, the low incidence of bone fractures in

healthy women under the age of 70 years may limit the clinical utility of these therapies for women with osteopenia and normal bone density.

Bisphosphonate therapies are used to prevent osteoporosis in high-risk patients, including hypogonadal men (47), adults treated with systemic glucocorticoids (48), and those with primary hyperparathyroidism (49). Because of the risk of falls, stroke patients should be considered for preventive therapies. Patients receiving systemic glucocorticoids and antiseizure medications that impair vitamin D metabolism should receive at least 1,000 IU of vitamin D daily.

For early postmenopausal women treated with estrogen or selective estrogen receptor modulators, the inhibition of bone loss erodes rapidly after discontinuation of drug therapy. Thus, maintenance may require long-term therapy. In contrast, bisphosphonates are deposited in bone and may have long-term effects after routine administration ceases (50). Clinical trials are underway to determine whether a drug holiday may be feasible after several years of oral bisphosphonate therapy.

Pharmacologic Therapies for the Treatment of Established Osteoporosis

Age-related fracture risk and bone mineral density should be considered before recommending pharmacologic intervention. A 50-year-old woman with bone mineral density within the World Health Organization's (51) definition of osteoporosis has a 2.5% risk of fracture within 5 years, whereas a 65-year-old woman with the same bone density has a 13% 5-year fracture risk (52). The number of osteoporotic women needed to be treated with pharmacologic therapy at age 50 to prevent one fracture is 100, but the number of older women is only 19 (52). Recently, the cost-effectiveness of alendronate therapy for osteopenic postmenopausal women with femoral neck T-scores better than –2.5 and no history of clinical fractures or other bone mineral density–independent risk factors for fracture has been questioned (53). It is expected that future recommendations for pharmacologic therapy will advocate intervention when the 5-year fracture rate is 10% at 1 year based on a combination of age, a few easily identified clinical risk factors, and bone mineral density (54).

Attention to adequate calcium and vitamin intake is needed to achieve normal bone architecture and strength in the setting of all pharmacotherapies. Indeed, one early study of fluoride had unfavorable results, likely secondary to inadequate mineralization of bone from excessive doses and vitamin D deficiency (55).

Until recently, the principal action of all drug therapies, including estrogens, selective estrogen receptor modulators, bisphosphonates, and calcitonin, was to decrease active bone resorption. Recently, synthetic derivatives of parathyroid hormone have offered an anabolic approach, although fracture data to date show no greater benefit, and long-term safety and efficacy data are lacking (56). Novel osteoporosis treatments under development are targeting the signaling pathways that couple bone resorption to bone formation and stimulate bone matrix protein synthesis.

Based on large clinical trials with fracture outcomes, the first-line treatment for established osteoporosis is oral bisphosphonates (44,46–48). Bisphosphonates, although limited in gastrointestinal absorption, are bone specific and have little systemic effects, hence their overall more desirable benefit-to-risk profile compared with estrogens and selective estrogen receptor modulators. The mechanism of action is impairment in cholesterol synthesis, although specific to osteoclasts secondary to the hydroxyapatite side chains. Current U.S. FDA-approved agents in this class include alendronate and risedronate in daily and once-weekly formulations and ibadronate in a once-monthly dose. Withdrawal of alendronate was shown to have no significant loss of bone density after 7 years (57). The most common adverse reactions are gastrointestinal and occur less frequently when dose intervals are less frequent than daily. Osteonecrosis with long-term oral bisphosphonates has been reported rarely (58). For patients who have had several years of oral bisphosphonate therapy and who have low biochemical markers of active bone resorption, clinicians are now considering at least a 1-year drug-free holiday with serial monitoring at 3, 6, and 12 months and resumption of bisphosphonate therapy when markers increase.

Treatment failure is difficult to assess because the pharmacologic intervention studies show that the various agents have a 30% to 60% efficacy in preventing fractures. Trials of oral bisphosphonate suggest that an adequate clinical response is achieved if serial bone density testing using the same DEXA device shows no loss of bone mineral density.

Intravenous administration of more potent bisphosphonates (such as zolendronic acid) may extend the dosing interval to once yearly and may offer therapy to those who do not tolerate oral therapy (59). The long-term benefits and risks of this approach are as yet unknown, and this intervention should be reserved for those who cannot tolerate standard oral therapies.

Selective estrogen receptor modulators, although effective antiresorptive agents, and estrogen are considered second-line therapies because of the systemic adverse effects that promote thrombosis. Of less concern with selective estrogen receptor modulators are the antiestrogen effects of hot flushes and vaginal atrophy. Long-term cardiovascular effects of raloxifene are currently under large-scale clinical investigation in a study analogous to the Women's Health Initiative Study of conjugated estrogen (45). Other trials are assessing the potential of raloxifene to prevent breast cancer in high-risk women (60). Newer compounds in this class are under development, with the goals of estrogenic effects on bone and the temperature-regulating center of the brain, antiestrogen effects on the breast and uterus, and no effect on the clotting cascades that result in thromboembolic events, myocardial infarction, and stroke. Testosterone replacement therapy for men 50 years of age or older is not recommended at present because of the potential adverse effects on the prostate gland, nor are there synthetic testosterone-like compounds analogous to selective estrogen receptor modulators.

Calcitonin, administered subcutaneously or intranasally, has weaker antiresorptive properties than the agents listed above, but without the systemic allergic reaction as an adverse effect. However, fracture data show that this compound offers no benefit in the prevention of hip fracture (61). With the increase in alternative therapies, calcitonin is used rarely in the clinical management of osteoporosis. Worldwide, strontium is available as an antiresorptive agent (62). It is too soon to determine how its risk-to-benefit profile compares with that of bisphosphonates. An in vitro study of statins, prescribed to impair hepatic metabolism of cholesterol, suggested that they may be effective antiresorptive agents with a mechanism of action similar to that of bisphosphonates (63). Cohort studies have shown fewer hip fractures with statin therapy, although these studies had no control for body weight, a strong predictor of bone mass (64,65). Clinical trials are needed to determine whether statins may be useful in the treatment of osteoporosis.

Anabolic agents that increase bone formation over resorption are in development. Parathyroid hormone derivatives synthesized by recombinant techniques are currently FDA approved or in clinical trials. Current data support their efficacy for the prevention of vertebral fractures (66), but no clinical trials have reported hip fracture endpoints. The bone mineral density increases are greater than those of bisphosphonates as a class, but the fracture data are insufficient for recommending parathyroid hormone derivatives over bisphosphonates as a first-line therapy. Safety, ease of administration, and cost of drugs are issues. At present there are insufficient data to support combination therapy with antiresorptive agents (67).

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