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Osteoporosis Prevention, Screening, and Treatment: A Review

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Abstract

Osteoporosis, defined as low bone mass leading to increased fracture risk, is a major health problem that affects approximately 10 million Americans. The aging U.S. population is predicted to contribute to as much as a 50% increase in prevalence by 2025. Although common, osteoporosis can be clinically silent, and without prevention and screening, the costs of osteoporotic fracture–related morbidity and mortality will burden the U.S. healthcare system. This is a particularly relevant concern in the context of diminishing health care resources. Dual-energy X-ray absorptiometry is the most widely used, validated technique for measuring bone mineral density (BMD) and diagnosing osteoporosis. Cost-effectiveness analyses support early detection and treatment of high-risk patients with antiresorptive medications such as bisphosphonates. Moreover, optimization of bone health throughout life can help prevent osteoporosis. Current guidelines recommend screening women by age 65 years, but because no guidelines for screening intervals exist, decisions are made on the basis of clinical judgment alone. Although the recent literature provides some guidance, this review further explores current recommendations in light of newer evidence to provide more clarity on prevention, screening, and management strategies for patients with osteoporosis in the primary care setting.

Introduction

Osteoporosis is a major U.S. health problem affecting more than 10 million adults.[1] By 2025, costs and annual fracture incidence are anticipated to rise by almost 50%, with a greater than 87% rise for those aged 65 to 74 years.[2] In the United States, osteoporosis-related mortality and morbidity cost approximately $17 billion in 2005[2] and involved approximately 432,000 hospital admissions; 180,000 nursing home admissions; and 2.5 million office visits.[3] Osteoporotic fracture–related chronic pain and disability affect function and quality of life. The lifetime risk of any osteoporotic fracture is 40% to 50% for women and 13% to 22% for men,[4] a markedly higher risk when compared with other major diseases.

Osteoporosis is characterized by low bone mass, structural deterioration, and porous bone, which are associated with higher fracture risk.[4] Bone loss related to declining estrogen levels increases fracture risk in postmenopausal women, who make up the majority of osteoporosis cases. Screening and diagnosis use a bone mineral density (BMD) measurement that estimates bone strength.[4] Dual-energy X-ray absorptiometry (DXA) is the most widely used, validated technique to measure BMD.[5] Other techniques include a vertebral fracture assessment with a densitometer,[6] peripheral dual-energy X-ray absorptiometry, computed tomography–based absorptiometry (quantitative computed tomography), and quantitative ultrasound densitometry, but these are not as widely used for reasons such as radiation exposure, lack of standardization of techniques, and cost.[1]

BMD is reported as a T-score, defined as the difference in number of standard deviations (SDs) from the mean BMD of a normally distributed, healthy adult reference population[7]; it is expressed as a negative number. The World Health Organization (WHO) defines osteoporosis as a BMD greater than 2.5 SDs below the average. Normal bone is no more than 1 SD below this value, and osteopenia is 1 to 2.5 SD below average. Severe osteoporosis is BMD greater than 2.5 SD below average and one or more fragility fractures.[7] These criteria were developed using epidemiologic data.[7] The WHO BMD diagnostic classification should not be applied to men younger than 50 years or premenopausal women.[3] The International Society of Clinical Densitometry guidelines recommend preferential use of the Z-score—which is calculated in the same way as the T-score but uses an age-matched normal population for comparison—to evaluate

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Table 1. Professional Society Osteoporosis Screening Guidelines

Professional group	*Target population*	*BMD screening recommendation*
North American Menopause Society[11]	Postmenopausal women	Age ≥65 years without risk factors or ≤65 years with risk factors Postmenopausal women with medical causes of bone loss or fragility fracture, regardless of age Postmenopausal women ≥50 years with additional risk factors
National Osteoporosis Foundation,[3] American College of Preventive Medicine[12]	Postmenopausal women	Age ≥65 years without risk factors or ≤65 years with risk factors
	Men	Age ≥70 years without risk factors or ≥50 years with risk factors
U.S. Preventive Services Task Force[13]	Postmenopausal women Men	Age ≥65 years or ≤65 years with risk factors None[a]
Institute for Clinical Systems Improvement[14]	Postmenopausal women	Age ≥65 years and in younger women whose fracture risk is ≥9.3% from FRAX analysis or are considered to be at risk of fracture

[a]No recommendations were made for men due to lack of sufficient evidence.
BMD, bone mineral density; FRAX, Fracture Risk Assessment Tool.

BMD in women from age 20 years through menopause.[8] A Z-score more negative than −2.0 would be considered clinically significant; in postmenopausal women, it may indicate secondary causes of osteoporosis.

Screening for osteoporosis may facilitate treatment before osteoporotic fracture occurrence. Cost-effectiveness analyses support early detection and treatment of high-risk patients with antiresorptive medications,[4] and optimization of bone health throughout life can help prevent osteoporosis.[9,10] Most guidelines recommend DXA screening for women 65 years and older (Table 1), but younger postmenopausal women and men aged 50 to 69 years should undergo screening only if they possess risk factors included in Table 2.[12] No current guideline addresses optimal screening intervals for osteoporosis, due to a lack of evidence. However, newer data provide insight into this question.[15] This review explores current recommendations for prevention, screening, and management strategies for osteoporosis in postmenopausal women, including discussion of some of the controversies regarding screening intervals, vitamin D and calcium supplementation, and bisphosphonate adverse effects, with the goal of aiding primary care physicians in the wake of ever-changing evidence and guidelines.

Prevention

Osteoporosis was previously considered a normal part of aging, but it is now understood to be preventable and treatable.[9] Many interventions reduce fracture risk in the general population and can be used for primary and secondary prevention. These strategies include adequate combined calcium and vitamin D intake (calcium alone has not been shown to reduce fractures), antiresorptive therapy, weight-bearing exercise, tobacco avoidance, moderate alcohol intake, and avoidance of trip or fall hazards.[3]

Calcium and Vitamin D Supplementation

Adequate calcium and vitamin D intake provides sufficient levels for bone formation and bone density maintenance; it ultimately reduces hip fracture risk in osteopenic and osteoporotic patients and decreases the incidence of falls in at-risk older adults. Supplementation has long been considered important for primary and secondary prevention, but concern about potential risks of supplementation and the unclear balance of benefits and harms has led to a recent change in guidelines. The U.S. Preventive Services Task Force (USPSTF) recently recommended ''against daily supplementation with 400 IU or less of vitamin D_3 and 1,000 mg or less of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women.''[16] They also cite insufficient evidence regarding the balance of benefits and harms of any daily supplementation of calcium and vitamin D for primary fracture prevention in premenopausal women or men[16] and are unable to make recommendations on higher doses of calcium and vitamin D, citing a lack of evidence. Their conclusions were based on a meta-analysis of 19 randomized controlled trials and 28 observational studies showing that the benefits of calcium and vitamin D supplementation for fracture risk reduction were setting-dependent. The prior USPSTF statement regarding the benefit of vitamin D supplementation to prevent falls in at-risk community-dwelling older adults has not changed.[16] In 2010, the Institute of Medicine published specific recommendations about calcium and vitamin D supplementation.[17] Daily calcium and vitamin D intake recommendations from various organizations are reviewed in Table 3.

The skeleton contains 99% of the body's calcium supply, which is mobilized when serum calcium levels are low.[3] Adequate calcium levels are crucial for bone health and muscle performance, which are closely associated with balance and fall risk.[3] The major biologic function of vitamin D is to maintain serum calcium levels through enhancement of small-intestine absorption.[18] Vitamin D sources include sunlight exposure, fortified foods, egg yolks, saltwater fish, liver, and supplements.[3,18]

Circulating 25-hydroxyvitamin D [25(OH) D] is the functional indicator of vitamin D status, reflecting the total amount from dietary intake, cutaneous synthesis, and oral supplementation.[19] These values should be measured in patients at risk of deficiency (e.g., elderly, immobile, or

Table 2. Risk Factors for Osteoporosis and Fractures

Risk factor	*Example*
Lifestyle factors	Alcohol (≥3 drinks/day) Aluminum (e.g., antacids) Excess vitamin A Frequent falls High caffeine intake High salt intake Immobilization (e.g., bedrest) or inadequate physical activity (e.g., behavior) Low body mass index Low calcium intake Tobacco use (active or passive) Vitamin D insufficiency
Genetic factors	Cystic fibrosis Ehlers-Danlos syndrome Gaucher disease Glycogen storage disease Hemochromatosis Homocystinuria Hypophosphatasia Idiopathic hypercalciuria Marfan syndrome Menkes disease Osteogenesis imperfecta Parental history of hip fracture Porphyria Riley-Day syndrome
Hypogonadal state	Androgen insensitivity Anorexia nervosa and bulimia Athletic amenorrhea Hyperprolactinemia Panhypopituitarism Premature ovarian failure Turner syndrome, Klinefelter syndrome
Endocrine disorders	Adrenal insufficiency Cushing syndrome Diabetes mellitus Hyperparathyroidism Thyrotoxicosis
Gastrointestinal disorders	Celiac disease Gastric bypass Inflammatory bowel disease Malabsorption Pancreatic disease Previous gastrointestinal surgery Primary biliary cirrhosis
Hematologic disorders	Hemophilia Leukemia and lymphomas Multiple myeloma Sickle cell disease Systemic mastocytosis Thalassemia
Rheumatic and autoimmune diseases	Ankylosing spondylitis Rheumatoid arthritis Systemic lupus erythematosus
Miscellaneous conditions and diseases	Alcoholism Amyloidosis Chronic metabolic acidosis Congestive heart failure Depression Emphysema End-stage renal disease Epilepsy Idiopathic scoliosis Multiple sclerosis Muscular dystrophy Parenteral nutrition Posttransplant bone disease Prior fracture as an adult Sarcoidosis
Medications	Anticoagulants (heparin) Anticonvulsants Aromatase inhibitors Barbiturates Chemotherapeutic agents Cyclosporine A Depo-medroxyprogesterone Glucocorticoids (≥5 mg/day of prednisone or equivalent for ≥3 months) Gonadotropin-releasing hormone agonists Lithium Oral hypoglycemics Proton pump inhibitors Tacrolimus Selective serotonin reuptake inhibitors

Adapted from the National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation, 2013.

chronically ill patients).[3] No serologic test for adequate calcium nutritional status exists, but a normal 24-hour urinary calcium level suggests adequate nutritional intake and absorption.[20]

The most common adverse effects of vitamin D supplementation are hypercalcemia and hypercalciuria.[19] Limited studies have observed a small increase in nephrolithiasis.[19,21] Recent research suggests that vitamin D deficiency is associated with cardiovascular risk factors, including hypertension, diabetes mellitus, and metabolic syndrome, and increased risk of cardiovascular events, whereas supplementation is associated with better survival.[22–24] This has yet to be confirmed by a randomized clinical trial, but such studies are underway.[24]

Calcium intake above 1,200 to 1,500 mg/day has limited benefit and possibly an increased risk of cardiovascular disease and nephrolithiasis.[3] Supplementation recently has become controversial. Whereas some authors have shown a positive correlation between calcium supplementation and cardiovascular risk, presumably through vascular calcifications and increased coagulability,[24] the Women's Health Initiative showed no statistically significant effect on any cardiovascular outcome with combined vitamin D (400 IU)

Table 3. Vitamin D and Calcium Supplementation Recommendations

Source	*Recommendation*	*Target population*
National Osteoporosis Foundation[3]	Calcium: 1,200 mg/day (from diet or supplement)	All
	Vitamin D: 800–1,200 IU/day	Adults age ≥50 years[a]
National Academy of Sciences[18]	Calcium: 1,200 mg/day (diet or supplement)	All
	Vitamin D: 400 IU/day	Adults age ≥50 years[a]
	Vitamin D: 600 IU/day	Adults age ≥70 years[a]
Institute of Medicine[17]	Calcium: 1,000 mg/day	Women 19–50 years, men 19–70 years
	Calcium: 1,200 mg/day	Women >50 years, men >70 years
	Vitamin D: 600 IU/day	All <70 years[b]
	Vitamin D: 800 IU/day	All >70 y[b]
U.S. Preventive Services Task Force[16]	Recommend *against* daily supplementation with ≤400 IU of vitamin D3 and ≤1,000 mg of calcium for the primary prevention of fractures	Noninstitutionalized, postmenopausal women
	Insufficient evidence to make recommendations	Premenopausal women; men

[a]Goal serum level 25(OH)D (hydroxyvitamin D) ≥30 ng/mL.
[b]Goal serum level 25(OH)D ≥20 ng/mL.

and calcium supplementation (1,000 mg calcium carbonate).[25] Moreover, results 4.9 years after the combined supplementation intervention showed no effect on cardiovascular disease or all-cause mortality and no decrease in hip fracture or colorectal cancer incidence.[26] Dietary calcium has not been linked to increased cardiovascular risk at normal levels,[24] but one study observed increased cardiovascular risk when dietary calcium intake exceeded 1,400 mg/day and supplements were also taken.[27] More research is needed to clarify the relationship between calcium and cardiovascular risk. Meanwhile, patients should strive to obtain sufficient calcium through their diets. Table 4 reviews literature regarding calcium and vitamin D supplementation.

Weight-bearing exercise

Multiple studies demonstrate the health benefits of exercise, including reduced risk of falls and fractures. Weight-bearing and muscle-strengthening exercise is recommended for osteoporosis prevention because it improves agility, posture, balance, and strength to prevent falls.[3] For some patients, exercise increases their risk of fracture and falls, and physicians must keep this in mind, making recommendations for type and degree of activity based on individual risk.

A recent Cochrane review[10] included 43 randomized controlled trials investigating whether exercise could prevent bone loss and fractures in postmenopausal women. A small but statistically significant effect of exercise on BMD was observed. Specifically, non-weight-bearing, high-force exercise (e.g., lower-limb, progressive-resistance strength training) was the most effective exercise for femur neck BMD. Combination exercise programs were the most effective for the spine.

Additional interventions

Tobacco and excessive alcohol intake are detrimental to bone health. The amount of daily alcohol intake that is harmful is unclear. Based on 2013 Institute for Clinical Systems Improvement (ICSI) guidelines,[14] >1 unit/day for women and >2 units/day for men is harmful, but the Fracture Risk Assessment Tool (FRAX)[12] incorporates >3 units/day as a risk factor. However, in several studies, moderate alcohol intake appeared to be associated with slightly higher BMD and lower fracture risk in postmenopausal women.[3,32,33] Clearly, more research is needed to clarify this relationship, but a judicious recommendation is for postmenopausal women to moderate their alcohol intake according to current

Table 4. Calcium and Vitamin D Evidence of Benefit

Source	*Supplement*	*Comment*
Cranney[19]	Vitamin D (>700 IU/day) + calcium (500-1,200 mg/day)	Systematic review Prevents bone loss compared with placebo
Women's Health Initiative[21,28]	Vitamin D (400 IU) + calcium (dose unspecified)	Decreased total hip bone loss No reduction in incidence of hip fracture
Cranney,[19] Chung[29]	Vitamin D (400-800 IU/day) without calcium	No decrease in fractures Decreased risk of nonvertebral and hip fractures in older patients in institutionalized settings with higher vitamin D dose Decreased falls with vitamin D and calcium
Dawnson-Hughes,[30] Chapuy[31]	Dietary calcium and vitamin D	Decreased fracture incidence

guidelines. We recommend no more than 1 unit of alcohol daily for women and no more than 2 units daily for men.

Fall prevention helps prevent osteoporosis-related morbidity. Interventions include vision and hearing correction, removing trip or fall hazards, evaluating suspected neurologic problems, avoiding medications that cause imbalance, and advising hip pad protectors for those with significant risk.[3]

Lastly, antiresorptive medications or selective estrogen-receptor modulators can be initiated in patients with osteopenia who have significant risk of osteoporosis. The American College of Preventive Medicine and USPSTF recommend that clinicians consider using osteoporosis risk-assessment tools to estimate absolute fracture risk when considering pharmacologic agents to prevent osteoporosis.[12]

FRAX score and risk-assessment tools

FRAX is a computerized fracture-risk algorithm developed by the WHO that uses global models of population-based cohorts combined with clinical risk factors.[12] Designed for primary care use in postmenopausal women and men older than 50 years (but validated for men and women aged 40–90 years), it is most useful in patients with low hip BMD.[34] Risk factors are combined with femoral neck BMD to calculate major osteoporotic and hip fracture risk within 10 years,[34] although the tool can be used without a DXA. These values can be used to decide if treatment should be initiated; for example, U.S. Food and Drug Administration (FDA)–approved therapy can be initiated for patients with osteopenia and a 10-year risk of hip fracture of at least 3% or a risk of a major osteoporotic fracture 20% or higher.[3] It should not be used on patients already receiving bisphosphonate therapy.

Combining BMD and clinical risk factors increases sensitivity and maintains specificity. Disadvantages to FRAX include an inability to incorporate all known clinical risk factors (e.g., tobacco history) that are important in considering treatment options. It also does not incorporate spine BMD.[35] Moreover, it does not reflect the variation in fracture probability in different regions of the world and therefore must not be viewed as the ''gold standard,'' but rather as a tool to enhance patient assessment.[35]

Other osteoporosis risk-assessment tools include the Male Osteoporosis Risk Estimation Score, the Osteoporosis Self-Assessment Screening Tool, the Osteoporosis Risk-Assessment Instrument, the Simple Calculated Osteoporosis Risk Estimation Score, the Osteoporosis Index of Risk, the Women's Health Initiative hip fracture risk calculator, and the Osteoporosis Society of Canada and Canadian Association of Radiologists Working Group tool.[12] These tools are helpful when BMD testing is unavailable.

Screening

Osteoporosis screening is based on BMD measurement, usually by DXA, which is then used to predict fracture risk.[4,36] Hip BMD measurement by DXA is the best predictor of future hip fracture risk.[36] Advantages include its noninvasive nature, low level of radiation exposure, and short test time. Disadvantages include the inability to accurately compare results from one center to another or to account for bone architecture.[12]

Multiple organizations have developed evidence-based osteoporosis screening recommendations (Table 1). However, the rationale for screening is based largely on indirect evidence. Although no randomized controlled studies have demonstrated that screening affects fracture outcome,[12] a recent observational study showed that hip DXA screening was associated with a 36% lower hip fracture incidence during 6 years of follow-up compared with usual medical care.[37] Several studies indicated that low BMD predicts fracture occurrence,[36,38,39] and numerous randomized controlled studies demonstrate that treatment of osteoporosis significantly reduces fracture risk.[40] Therefore, screening for and treating low BMD before fractures occur should improve fracture outcome.

Most guidelines recommend initiating screening of postmenopausal women by age 65 or younger postmenopausal women with risk factors. However, the latter group can be difficult to identify clearly. The North American Menopause Society suggests testing for women age 50 and older with one or more risk factors, including >2 alcoholic drinks per day, rheumatoid arthritis, current smoker, history of hip fracture in a parent, thin with body mass index $<21\ kg/m^2$, or fracture after menopause.[11] For women aged 50 to 64 years, the USPSTF recommends screening those whose fracture risk is equal to or greater than that of a 65-year-old white woman with no additional risk factors, which correlates with a 10-year risk of 9.3% for any osteoporotic fracture using the FRAX tool.[13]

Screening intervals

No guidelines have been issued regarding screening intervals or cessation of screening due to insufficient data. The USPSTF suggests a minimum of 2 years between screenings to reliably measure BMD change because of limitations in test precision.[13]

Only three published studies have tried to identify appropriate screening intervals. In 2007, a prospective cohort study was conducted to determine whether repeated BMD screening measurements aided fracture-risk prediction beyond the initial measurement.[41] They studied 4,124 women aged 65 years and older and reported that in healthy, postmenopausal women, BMD measurement repeated up to 8 years after the initial measurement did not predict incident fractures. In 2009, a study of 1,008 nonosteoporotic women aged 60 years and older attempted to identify the ideal timing for repeat screening of BMD measurements by using fracture as the outcome metric.[42] They reported that age and T-score could be used to estimate the optimal interval through an absolute risk-based prognostic model. For example, a 65-year-old woman with a baseline T-score of -1.5 has a 9.6% five-year risk of developing osteoporosis, which increases to 14.9% if her baseline T-score is -2.2. Both studies used risk of or development of fracture as the primary outcome, rather than identification of osteoporosis before fracture, illustrating a limitation in applying the findings to the establishment of guidelines for screening intervals.

A 2012 study investigated how BMD testing interval related to osteoporosis development before fracture occurrence.[15] The investigators studied 4,957 women aged 67 years and older for up to 15 years; patients had baseline normal BMD or osteopenia. The objective was to estimate the

interval needed for osteoporosis development in 10% of the subjects (before a hip or clinical vertebral fracture and before initiation of osteoporosis treatment). Estimates were adjusted for major clinical risk factors such as smoking, glucocorticoid use, and rheumatoid arthritis. For women with normal BMD (T-score, −1.00 or more negative) or mild osteopenia (T-score, −1.01 to −1.49), osteoporosis developed by 15 years. For women with moderate osteopenia (T-score, −1.50 to −1.99), osteoporosis developed by 5 years. However, for women with advanced osteopenia (T-score, –2.00 to −2.49), it was only 1 year to osteoporosis development. Only 1% of women with baseline normal BMD and 5% of women with mild osteopenia had osteoporosis develop during the 15-year study period. Thus, based on this study, the key determinant of the BMD testing interval appears to be baseline T-score. For those with initial normal BMD or mild osteopenia, the screening interval could be 15 years. For women with moderate osteopenia, screening every 5 years may be sufficient, and for women with advanced osteopenia, screening should likely be performed yearly. Notably, the estimated time to osteoporosis decreased with increasing age. These were the first evidence-based estimates for optimal screening intervals before the development of osteoporotic fractures and before initiation of treatment for older postmenopausal women.

In 2011, Nayak et al.[43] demonstrated through modeling analysis that screening for postmenopausal osteoporosis leads to more quality-adjusted life years compared with no screening. In addition, DXA scans were cost effective, especially when treatment was started for women with a T-score of −2.5 or more negative, with screening repeated every 5 years. Their model showed that the most effective and best value strategy (i.e., for diagnostic yield and healthcare cost) would be to start screening postmenopausal women at age 55 years. This study, as well as the other studies described, did not address screening intervals for younger postmenopausal women, nor did it indicate the appropriate time to consider cessation of screening.

Treatment

Abundant evidence demonstrates that treatment reduces fracture risk due to postmenopausal osteoporosis.[40] Moreover, all osteoporosis treatment options reduce vertebral and nonvertebral fractures in high-risk groups.[40] Bisphosphonates such as alendronate are considered first-line therapy, based on head-to-head trials demonstrating increased BMD.[44,45] Other factors affecting treatment choice include adverse effects and cost (Table 5). Additionally, potential harms of screening and treatment include anxiety from perceived vulnerability to fracture,[51] false-negative results leading to lack of treatment and false reassurance,[52,53] and potential harm from radiation exposure.

The National Osteoporosis Foundation recommends that postmenopausal women and men 50 years and older should be considered for treatment if they have a hip or vertebral fracture including fragility fracture, a T-score more negative than −2.5 at the femoral neck or spine (with secondary causes excluded), or osteopenia and a FRAX 10-year risk score of at least 3% for hip fracture or at least 20% for major osteoporotic fracture.[3] A fragility fracture is one occurring in the absence of trauma or with minimal trauma such as a fall from a standing height or less.[54] A 1996 systematic review supports this recommendation, stating that it was cost effective to recommend medical therapies that reduce hip fracture risk in women with low BMD.[55] Potential secondary causes must be considered for appropriate treatment. A thorough history, physical examination, and routine blood work [including complete blood count, comprehensive metabolic panel, thyroid stimulating hormone, calcium and serum 25(OH) D] can identify most secondary causes.[3,56]

Bisphosphonates inhibit bone resorption through osteoclast function effects and are well tolerated.[46,47] They are taken up by bone at active sites of resorption. All bisphosphonates can reduce the incidence of vertebral and nonvertebral fractures, but only some reduce hip fractures. Recently, concerns have been raised about the long-term safety of bisphosphonate therapy. Multiple case series have illustrated a link between prolonged bisphosphonate use and atypical fractures, as characterized by clinical and radiographic features.[57] The proposed pathophysiology is suppressed bone turnover resulting in accumulated microdamage and a subsequent insufficiency fracture at the point of maximal stress.

A 2010 systematic review[58] evaluated 32 case series reporting 141 atypical femur fractures and showed that ethnicity and undiagnosed skeletal disorders may have a role in these atypical fractures. Alendronate was the most commonly used bisphosphonate, and risk factors included concurrent glucocorticoid or proton-pump inhibitor use and prodromal thigh or hip pain. Retrospective studies of subtrochanteric femur fractures identified additional risk factors, including prolonged glucocorticoid therapy, active rheumatoid arthritis, and low serum 25(OH) D levels.[59]

Although multiple case series demonstrate a possible association between atypical fractures and bisphosphonate therapy, results have conflicted among several population-based studies. Cumulatively, the current body of evidence is thought to support this association.[59] Although more research is needed to understand causality, the evidence supporting the use of bisphosphonates to reduce overall fracture risk greatly outweighs the risk of an atypical fracture.[60] Many institute a drug holiday at the recommendation of the FDA to reduce potential adverse effects because bisphosphonates are incorporated into the skeleton and continue to exert effects after discontinuation.[60] No specific guidelines exist for long-term bisphosphonate therapy and risk of atypical fracture, so regular assessment of the need for bisphosphonates by treating physicians is recommended.

An additional, less common adverse effect of bisphosphonates is osteonecrosis of the jaw.[12] It has been seen in cancer patients receiving intravenous bisphosphonates, but a causal relationship has not been established.[12]

Selective estrogen-receptor modulators (e.g., tamoxifen, raloxifene) bind estrogen receptors and subsequently agonize or antagonize estrogen receptor activity in different tissues.[61] Raloxifene also decreases breast cancer risk in high-risk postmenopausal women through estrogen antagonist activity in breast tissue.[8] However, although raloxifene is appropriate therapy for osteopenia and osteoporosis, tamoxifen is not used for this purpose.

Calcitonin is a naturally occurring peptide that strongly inhibits osteoclast function through a receptor-mediated process. Synthetic or salmon-derived preparations are available as a parenteral injection, but they are most commonly administered intranasally. Calcitonin was previously approved by the

Table 5. Benefits and Adverse Effects of Osteoporosis Treatment Options

Agent	*Benefit*[a]	*Adverse effects*
Bisphosphonate[3,46,47,b,c,d]	Decreases vertebral fracture (41%–70%) Decreases spine and hip fracture 50% over 3 years (alendronate) Decreases nonvertebral fracture 36% over 3 years (risedronate) Decreases nonvertebral fracture 25% over 3 years (zoledronic acid)	Gastrointestinal tract (nausea, vomiting, abdominal pain, dyspepsia, esophagitis, reflux)[e]
Selective estrogen-receptor modulators (raloxifene, tamoxifen)[3,40]	Increases BMD, decreases bone turnover, decreases vertebral and nonvertebral fracture (30%–50%) No hip fracture prevention	Increases risk of VTE (deep vein thrombosis, pulmonary embolism, cardiovascular accident), vasomotor symptoms, urogenital symptoms Increases risk of CV events (raloxifene)
Hormone therapy[3,27,40,48]	Decreases BMD loss Decreases hip, vertebral, and nonvertebral fracture (23%–40%)	Increases risk of VTE Increases risk of CV disease in older postmenopausal women (probably >10 years after menopause)
Parathyroid hormone[3,27,f]	Decreases vertebral fracture (65%–69%) Decreases nonvertebral fracture (35%–40%) No hip fracture prevention	Injection site reactions Nausea, dizziness Leg cramps
Calcitonin[3,49]	Stabilizes BMD loss Increases BMD (modest) in cervical spine Decreases vertebral fracture (200 IU/day, intranasal)[g] Decreases fracture-associated pain	Rhinitis, epistaxis (intranasally administered)
Denosumab[50]	Reduces risk of vertebral and nonvertebral fractures and risk of hip fracture Increases BMD at the lumbar spine and total hip	Gastrointestinal tract symptoms (diarrhea, nausea, vomiting), dermatitis, rash, arthralgia, limb and back pain, peripheral edema, nasopharyngitis, headache, hypocalcemia, hypercholesterolemia

[a]Percentages denote relative risk.
[b]First-line therapy.
[c]Alendronate, risedronate, and zoledronic acid are FDA approved for prevention and treatment of postmenopausal osteoporosis.
[d]Alendronate and risedronate are FDA approved for male osteoporosis and glucocorticoid-related osteoporosis.
[e]Overall mild but is the reason for discontinuation of therapy for 11%–25% of patients.
[f]FDA approved for postmenopausal osteoporosis, men at high fracture risk, men and women at risk due to glucocorticoids.
[g]No advantage to higher or lower doses.
CV, cardiovascular; FDA, Food and Drug Administration; VTE, venous thromboembolism.

FDA for treatment of osteoporosis in women who are postmenopausal for at least 5 years.[3] It appears to reduce acute fracture-related pain, although long-term fracture prevention data are limited.[62] A recent FDA panel voted against continued use of calcitonin for treatment of osteoporosis, citing a possible link to increased cancer risk and a lack of evidence of benefit. The cancer link was not clear but was believed to be plausible after considering the available evidence.[63]

Estrogen decreases BMD loss by suppressing osteoclast cytokine release while inducing osteoclast death.[64] Hormone therapy is no longer considered first-line therapy for osteoporosis. Important adverse effects include increased risk of thromboembolic events[40] and cardiovascular disease in older postmenopausal women.[27] Although the risk likely is greatest in women more than 10 years postmenopause, the FDA recommends alternative treatment options if estrogen is being considered solely for osteoporosis treatment.[3] If estrogen is used, the lowest effective dose for the shortest time possible is recommended.[48]

Human recombinant parathyroid hormone 1–34 (also termed teriparatide) is an anabolic agent that increases BMD by stimulating bone formation and inhibiting resorption. It is administered by daily subcutaneous injection and is recommended for up to 2 years because of the short duration of safety and efficacy testing.[3] To maintain or increase BMD, teriparatide therapy is commonly followed by bisphosphonate therapy. Studies in rats have demonstrated an increased incidence of osteosarcoma, so it is contraindicated for patients with increased risk for osteosarcoma or a history of radiotherapy.[3]

Denosumab is a human monoclonal antibody against the receptor activator of nuclear factor–κB ligand, an essential osteoclast cytokine. By binding this ligand, denosumab ultimately inhibits osteoclast-mediated bone resorption.[50] It is administered subcutaneously every 6 months. The international, randomized, placebo-controlled Fracture Reduction Evaluation of Denosumab in Osteoporosis (FREEDOM) trial showed that 36 months of denosumab significantly reduced the risk of vertebral and nonvertebral fractures in women aged 60 to 90 years with a diagnosis of osteoporosis. It is generally not used as initial treatment for osteoporosis, given the efficacy, cost, and long-term safety data of bisphosphonates, but it may be used in high-risk women.

Biochemical markers of bone turnover

Biochemical markers (e.g., bone-specific alkaline phosphatase, osteocalcin, urinary hydroxyproline, and collagen crosslinks such as β-C-terminal-telopeptide and N-terminal-telopeptide) can be used to identify the balance of bone formation and resorption; these are useful for aiding in osteoporosis diagnosis and monitoring treatment response.[65,66] High bone turnover, reflected by elevated marker levels, might predict fracture development.[66,67] Given limitations such as biologic variability and difference in assays, these markers are not yet included in algorithms that calculate fracture risk, but they are being used to monitor osteoporosis treatment.[34,66,68]

Minorities

All ethnic groups are at risk of osteoporosis, but prevalence of osteoporosis is increasing most rapidly in Hispanic women.[69] The prevalence of osteoporosis in postmenopausal white and Asian women is 21% in the United States[70] and approximately 52% more are estimated to have low BMD.[69] The prevalence of osteoporosis is 16% for Hispanic women and 10% for African American women.[70] Osteoporosis is underrecognized and undertreated in white and African American women, with only about one-third of eligible women referred for screening. A recent study demonstrated that significantly fewer African American women are referred for DXA and osteoporosis treatment compared with white women, highlighting the persistence of ethnic disparities in medical care.[71]

Conclusion

Osteoporosis affects an estimated 10 million Americans and will increase as the population ages. Recommended measures include sufficient calcium and vitamin D levels, regular weight-bearing exercise, fall prevention, and avoidance of tobacco and excessive alcohol. Recently, the USPSTF recommended against specific dosages of calcium and vitamin D supplementation in noninstitutionalized postmenopausal women and premenopausal women. Guidelines recommend screening women 65 years and older and men 70 years and older. However, all high-risk postmenopausal women and male patients older than 50 years should be screened. A recent model suggests that initiating screening at age 55 in postmenopausal women may be more cost-effective than current USPSTF guidelines. The most important factors for determining optimal screening intervals appear to be T-score and age. For older postmenopausal women with normal BMD or mild osteopenia at baseline, clinicians may wait up to 15 years before repeat screening. Older postmenopausal women with moderate osteopenia at baseline can be screened every 5 years, and those with advanced osteopenia likely should be screened yearly.

Osteoporosis treatment reduces fracture risk and is recommended after hip or vertebral fracture for patients with a T-score that is -2.5 or more negative at the femoral neck or spine without secondary causes. Treatment also is recommended for patients with a FRAX 10-year risk of at least 3% for hip fracture or at least 20% for major osteoporotic fracture with osteopenia. Bisphosphonates are generally well tolerated and are considered first-line treatment.

Primary care physicians have an important role in the prevention and treatment of osteoporosis, especially as the population ages. This review attempts to help primary care physicians inform patients about their risks, provide helpful information to aid shared decision-making, and assist in deciding on early interventions to prevent the mortality and morbidity associated with osteoporosis-related fractures.

Disclosure Statement

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