Current approaches to the management of osteoporosis in men

SHERYL FOLLIN VONDRAECEK AND LAURA B. HANSEN

OSTEOPOROSIS is commonly considered a women’s health problem, especially for postmenopausal women. The vast number of published articles and guidelines reflect this emphasis. Recently, there has been an increased awareness that men are also at risk for osteoporosis and osteoporotic fractures. Osteoporosis manifests somewhat differently in men than in women; therefore, it is important to understand the distinguishing features of osteoporosis and treatment options for this population. This article reviews the epidemiology, pathophysiology, diagnosis, and management of osteoporosis in men. While a comprehensive review of osteoporosis is beyond the scope of this article, the reader is referred to several reviews on this topic.1-6

Epidemiology and prognosis

In 2002, it was estimated that 2 million U.S. men had osteoporosis and an additional 12 million had low bone mass.7 The lifetime risk for a clinical osteoporotic fracture in men is approximately 13%, with one third of all hip fractures occurring in men.8,9 The direct health care costs associated with osteoporosis in 2001 were estimated at $17 billion, with approximately one fifth, or $3.4 billion, due to osteoporosis-related care for men.10,11

Purpose. The epidemiology, pathophysiology, diagnosis, and management of osteoporosis in men are reviewed. Summary. Men with osteoporosis account for approximately one fifth of all patients with osteoporosis, and their morbidity and mortality rates from this disease are higher than in other patients. Guidelines specifically addressing the management of osteoporosis in men are not available. Lifestyle modifications, including smoking cessation, limited alcohol consumption, routine exercise, and fall prevention strategies, are beneficial to maintain bone health. Appropriate calcium and vitamin D intakes are critical components of any osteoporosis management strategy. Drug therapy should be initiated in all men at high risk for fracture. Alendronate is indicated for the treatment of osteoporosis. It is considered first-line therapy because of its efficacy and safety profiles. Teriparatide is indicated for the management of osteoporosis in high-risk men, but the drug’s cost, complex administration schedule, and potential risks have caused it to be restricted to a second-line therapy. Other options reserved for select patients include calcitonin and testosterone. Further studies are needed to better understand the distinctive features and management strategies for men with osteoporosis.

Conclusion. While the rate of osteoporosis in men is lower than in women, the consequences are possibly more devastating. Evaluation of secondary causes, especially hypogonadism, is important, as they can play a significant role in the development of osteoporosis in men. All men should be educated to improve modifiable risk factors and maintain recommended daily intakes of calcium and vitamin D. Bone mineral density should be evaluated in high-risk men using central dual energy x-ray absorptiometry, and drug treatment should be considered in those with a history of low-trauma fracture or significant bone loss.

Index terms: Alcohols, ethyl; Alendronate sodium; Androgens; Calcitonin; Calcium; Calcium regulators; Costs; Diagnosis; Dosage schedules; Epidemiology; Exercise; Hormones; Men; Minerals; Mortality; Osteoporosis; Parathyroid hormones; Protocols; Smoking; Teriparatide; Testosterone; Toxicity; Vitamin D; Vitamins

Am J Health-Syst Pharm. 2004; 61:1801-11

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Dr. Vondracek is a member of the speaker’s bureau for Merck, Proctor & Gamble, and Eli Lilly and is a member of the West Central Regional Osteoporosis Board, which is sponsored by the Alliance for Better Bone Health (a joint endeavor by Proctor & Gamble and Aventis Pharmaceuticals).

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risk for developing osteoporosis and osteoporotic fractures than do women, they have a greater risk for adverse consequences associated with the disease. In one study, a twofold to threefold increased risk for death was demonstrated in men with a history of a major osteoporotic fracture versus men without a history of fractures. This increased risk of death was higher than the increased risk of death in women with a history of fractures. According to a U.S. Congress report on outcomes associated with hip fractures, inhospital mortality rates and one-year mortality rates were greater for men than women: 8% versus 3%, respectively, and 36% versus 24%, respectively. Men who suffer symptomatic vertebral fractures also have a lower survival rate than do women. In a population-based study of 335 patients with vertebral fractures, the five-year relative probability of survival was lower for men than women (0.72 versus 0.84, respectively).

It is well-known that previous low-trauma fracture is a strong predictor of future fractures. This association appears to be even stronger in men than women. In a population-based study of 820 subjects with a history of clinical vertebral fracture, the relative incidence rates for any new fracture was 4.2-fold higher for men and 2.7-fold higher for women when compared with the general population. The risk for a subsequent vertebral fracture was 33-fold higher in men and 11-fold higher in women.

Etiology and pathophysiology

Osteoporosis in men can be classified as either primary (age related or idiopathic) or secondary (a result of hypogonadism, chronic diseases, drug therapy, or adverse lifestyle practices that increase bone loss). Age-related osteoporosis tends to occur in men over the age of 70 years and is thought to result from a combination of a decreased absorption of calcium, reduced activation of vitamin D, a decline in the lifespan and function of osteoblasts, and decreased concentrations of sex hormones. Secondary causes are present in the majority of younger men (less than 70 years of age) with osteoporosis (Table 1). However, there are a significant number of men for whom no known cause of the disease can be identified. These patients are classified as having idiopathic osteoporosis.

The pathophysiology of osteoporosis and osteoporotic fractures is multifactorial, including inadequate peak bone mass, bone loss leading to low bone density, impaired bone strength, and falls. Men are at a lower risk for developing osteoporosis and osteoporotic fractures than women due to several gender differences. Men have larger bones and reach a greater peak bone mass at skeletal maturity. They also do not undergo the period of accelerated bone loss that women do during menopause. There are differences in bone quality between the sexes, mainly because of differences in the pattern of bone loss. Women tend to have an increase in the number of resorption sites and deeper resorption sites. This can cause trabecular perforations, leading to a decrease in structural integrity and an increase in fracture risk. Men, on the other hand, have a more uniform thinning of trabeculae, leading to fewer perforations.

Men are less likely to fall than women, thereby placing them at a potentially lower risk for both hip and wrist fractures. The major risk factors that influence peak bone mass and bone loss, such as genetics, nutritional intake (calcium, vitamin D, and protein), exercise, adverse lifestyle practices (e.g., smoking), sex hormone levels, diseases, and medications, are similar between men and women.

Assessment and diagnosis

The early identification of men at risk for osteoporosis, as well as the diagnosis of men with established disease, can be challenging. Several risk factors for osteoporosis in men have been identified, and many are similar to risk factors in women (Table 1). Because secondary causes are common in men with osteoporosis, several laboratory tests are routinely recommended to rule out the presence of a treatable cause of osteoporosis (Table 2).

The diagnosis of osteoporosis can only be made based on central bone density results from the hip or spine or both using dual energy x-ray absorptiometry (DEXA). There are no consensus guidelines for when to perform bone densitometry in men. Based on expert reviews, central

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*Potentially modifiable factors or causes.
DEXA testing is recommended in men who meet the following criteria: age over 70 years, presence of multiple risk factors for osteoporosis, evidence of a low-trauma fracture, evidence of a prevalent vertebral deformity, documented osteopenia via a standard x-ray, and conditions known to increase the risk for bone loss and fracture, such as hypogonadism and glucocorticoid use (Figure 1).9,21,37,41,42

The World Health Organization (WHO) diagnostic criteria established for postmenopausal women is often used for the diagnosis of osteoporosis in men.40,43 Based on these criteria, osteoporosis is defined as a T score of ≤ -2.5, which equates to a bone mineral density (BMD) value that is 2.5 standard deviations or more below the mean BMD of a healthy, young reference population. Osteopenia, or low bone mass, is defined as a T score between -1.0 and -2.5, and normal bone density is a T score of at least -1.0.43 One of the greatest issues of contention with the WHO criteria is the chosen reference population.9,37,40,44 The International Osteoporosis Foundation recommends that BMD in men be evaluated using data from a healthy female population, while the International Society for Clinical Densitometry recommends using sex-matched reference data for the diagnosis of osteoporosis.9,41 It is important to note that the major drug trials of osteoporosis in men used male reference data to determine T score criteria.54-46 In addition, it has been argued that the use of female population data will significantly underdiagnose osteoporosis in men.41,47

The use of heel ultrasound devices to measure BMD has become increasingly popular for osteoporosis screening. Currently, the use of peripheral bone densitometry devices is only recommended for postmenopausal women.48 Studies evaluating the ability of peripheral-screening devices to predict fracture risk in men are limited, and male reference databases for peripheral devices tend to be small and inadequate for accurate comparisons.49 Until further data become available on the benefit of peripheral-screening devices in men, it is most appropriate to refer men at risk for osteoporosis for central DEXA testing.

Nonpharmacologic management

The nonpharmacologic management of osteoporosis in men includes modification of adverse lifestyle practices, exercise, fall prevention strategies, and adequate calcium and vitamin D intake.50,51 Cigarette smoking is an independent risk factor for the development of osteoporosis in men.34-36,52-56 Studies have demonstrated greater increases in bone loss and higher fracture rates in smokers. Based on data from a large meta-analysis, it was estimated that smoking increases the lifetime risk for vertebral and hip fractures in men by approximately 32% and 40%, respectively.56 Studies suggest that fracture risk declines over time in ex-smokers, especially men.55,56 Therefore, current smokers should be encouraged to quit and given assistance when needed.

The effect of alcohol consumption on bone density and fracture risk in men has not been clearly defined.9,39,53,57-59 While there is a well-established link between alcoholism and osteoporosis, several studies have demonstrated increases in BMD with moderate alcohol consumption.9,39,52,58-61 Alcohol abuse may decrease BMD through multiple mechanisms in men: reductions in free serum testosterone concentrations, nutritional deficiencies, and a direct toxic effect on osteoblasts.52,63 The cessation of alcohol consumption may stop the progression of bone loss in alcoholics, as osteoblast function has been shown to be restored within two weeks of abstinence.63 There are no data to suggest that BMD lost due to alcohol abuse can be regained with abstinence. To minimize negative bone effects, consumption of alcohol should be limited to two servings or less per day.

Appropriate physical activity in men can increase BMD and decrease the risk of falls through improvements in muscle strength, balance, and agility.39,52,54,64-66 Studies have shown a reduced risk of hip fracture in men who are physically active compared with those who are sedentary.54,65,67,68 Evidence linking physical activity to reductions in other types of osteoporotic fractures (e.g., vertebral) is lacking.65,67 Weight-bearing exercises (e.g., walking) are recommended at least three days per week for 30–45 minutes. Resistance exercises (using free weights, weight machines, or resistance bands) should be performed at least two days per week for 20–30 minutes per day. Men with severe osteoporosis or other comorbid diseases should check with their physician before beginning any exercise regimen. In addition, all patients should be educated on proper form and technique before performing resistance exercises.

Calcium and vitamin D are essential for the appropriate mineralization of bone. Inadequate intake of these nutrients has been linked to increases in bone loss and fractures.69 Studies evaluating the efficacy of vitamin D or calcium supplementation...
alone have demonstrated conflicting results. The combined administration of calcium and vitamin D is most beneficial and has been shown in men and women to increase BMD and decrease the risk of fractures. The effects of calcium 500-mg/day and vitamin D 700-IU/day supplementation were compared with placebo in a prospective, double-blind, randomized study of 389 healthy, ambulatory men and women 65 years of age or older. After three years, femoral neck, lumbar spine, and total body BMD were significantly higher in the calcium–vitamin D group compared with the placebo group. When men and women were evaluated separately, only total BMD was significantly increased in women taking calcium–vitamin D whereas the BMD at all sites was significantly higher in men. A total of 37 subjects had at least one nonverte-
bral fracture (5 men and 32 women) during the study period. The relative risk for first fracture was reduced by 50% in the calcium–vitamin D group compared with the placebo group (relative risk [RR], 0.50; 95% confidence interval [CI], 0.20–0.90) (p = 0.02).

Several organizations have published recommendations regarding appropriate intakes of calcium and vitamin D. The recommended elemental calcium intake ranges from 1000 mg/day for men 65 years of age or younger to 1500 mg/day for men over 65 years. Ideally these intake goals should be met by eating foods high in calcium; however, most men do not consume the recommended amounts of calcium on a daily basis. According to a National Health and Nutrition Examination Survey conducted from 1999 through 2000, the average dietary intake of calcium for men 60 years of age or older was only 797 mg/day.78 Based on this information, most men require education on appropriate calcium supplementation to achieve the recommended daily intakes. Calcium carbonate is a cost-effective calcium supplement for most men. It contains the highest possible content of elemental calcium (40%) and is available in a variety of formulations. Because calcium carbonate requires an acidic environment for maximal absorption, it should be taken with food. Calcium citrate does not require an acidic environment for absorption; therefore, it may be considered a better choice for elderly men, many of whom have achlorhydria or are taking acid-suppressing medications. Calcium citrate can be taken without regard to food and may cause less bloating and constipation in the elderly than do other calcium supplements; however, it is more expensive and available in limited dosage forms.

Recommended vitamin D intakes for men range from 400 to 800 IU/day. These levels can be achieved relatively easily by most men through the consumption of fortified milk and a daily multivitamin (most contain 400 IU of vitamin D) and exposure to ultraviolet light. Calcium supplements that contain vitamin D or separate vitamin D supplements are also available.

While the recommended intakes of calcium and vitamin D are adequate for most men, substantially higher dosages of calcium and vitamin D may be necessary in men with certain medical conditions (e.g., inflammatory bowel disease, pancreatitis) that impair the absorption of vitamins and minerals or when a deficiency is documented. Several studies have demonstrated a high rate of vitamin D deficiency in elderly men and women, especially those residing in long-term-care facilities or living in the northern United States or Canada. A baseline serum 25-hydroxyvitamin D level should be obtained in men considered at risk for insufficiency or deficiency. Vitamin D insufficiency is defined as a serum 25-hydroxyvitamin D level of less than 20 ng/mL and deficiency as less than 5 ng/mL. However, most experts agree that vitamin D levels of 30 ng/mL or higher are necessary to prevent signs of secondary hyperparathyroidism. In men with a documented vitamin D deficiency, the recommended daily intake is insufficient to replete their vitamin D stores. There is no standard guideline for repletion of vitamin D, and a variety of oral regimens have been used to accomplish this goal (e.g., 1,600 IU/day, 50,000 IU/week for eight weeks followed by 800 IU/day, 100,000 IU every four months). Hypercalcemia is a risk with high-dose vitamin D supplementation; therefore, close monitoring of serum calcium is warranted.

**Pharmacologic management**

Drug therapy, in conjunction with calcium and vitamin D supplementation and lifestyle modification, is an important part of the management of osteoporosis in men at high risk for osteoporotic fractures. There are no guidelines for when drug therapy should be initiated in men. Most expert reviews recommend starting pharmacologic interventions when the T score is ≤–2.5 or below or there is evidence of a low-trauma fracture. However, the two largest treatment trials of osteoporosis in men enrolled subjects who had T scores of ≤–2.0. Therefore, similar to guidelines for women, drug therapy may be considered for men who have additional risk factors for fracture and a T score of ≤–2.0.

**Drug therapy options for the treatment of osteoporosis in men are limited.** While there are five agents currently indicated by the Food and Drug Administration for the management of osteoporosis in postmenopausal women, there are only two agents, oral alendronate sodium and teriparatide injection, for the treatment of primary or hypogonadal osteoporosis in men. Risedronate sodium is the only other agent that is anticipated to be indicated for use in men with osteoporosis in the near future.

**Bisphosphonates.** Bisphosphonates are structural analogs of pyrophosphate, a naturally occurring bone-resorption inhibitor. They work by inhibiting osteoclastic bone resorption and increasing osteoclastic apoptosis. Only a few published studies have evaluated the effects of alendronate in men with primary or hypogonadal osteoporosis. The largest trial was a prospective, double-blind, randomized comparison of alendronate 10 mg/day with placebo in 241 men (mean age, 63 years) with osteoporosis. Subjects were enrolled if they had a femoral neck BMD that was at least two standard deviations (T score of –2.0 or less) and a lumbar spine BMD that was at least one standard deviation (T score of –1.0 or less) below the mean for a young healthy male. Men could also be enrolled if they had a
femoral neck T score of ≤-1.0 and at least one vertebral deformity or a history of osteoporotic fracture. Men with secondary causes for osteoporosis except hypogonadism were excluded from the trial. All subjects received 500 mg of calcium daily and 400 IU/day of vitamin D supplementation. The primary endpoint was change in lumbar spine BMD. After two years, mean ± S.D. lumbar spine BMD increased by 7.1% ± 1.3% and femoral neck BMD by 2.5% ± 0.4% in the alendronate-treated group. This increase was significantly greater than placebo (p < 0.001).

Vertebral fractures were assessed by two methods. The semiquantitative method graded the degree of compression on a scale of 0–3 (0 equals no fracture, and 3 equals severe fracture). The quantitative method measured the change in vertebral body height. A decrease of over 20% indicated the presence of a fracture. A significant reduction in vertebral fractures in the alendronate group was noted when the quantitative method was used, but not with the semiquantitative method of assessment (six fractures [7.1%] in the placebo group versus one fracture [0.8%] in the alendronate-treated group) (p < 0.02). There was no significant difference in the rate of non-vertebral fractures between the placebo and alendronate-treated groups (5.3% versus 4.1%, respectively).

Risedronate is indicated for the prevention and treatment of glucocorticoid-induced osteoporosis in men. Studies have demonstrated significant increases in BMD and reductions in fracture risk associated with risedronate use in this population.88-91 Studies evaluating risedronate in men with primary or hypogonadal osteoporosis are ongoing; preliminary results are available in abstract form.92,93 In an open-label trial, 280 men (mean age, 57 years) with primary or secondary osteoporosis were allocated to receive either calcium and vitamin D supplements alone or risedronate 5 mg/day plus calcium and vitamin D supplements. After one year of treatment, risedronate significantly increased lumbar spine BMD by 4.5%, compared with 0.8% with calcium and vitamin D supplementation alone (p < 0.0001). The risk of new vertebral fractures was significantly reduced in the risedronate-treated group versus those receiving calcium and vitamin D alone (7 fractures versus 17 fractures, respectively) (p = 0.033).92

Currently alendronate is the only bisphosphonate approved by FDA for the management of osteoporosis in men. Studies, while small, have demonstrated increases in BMD comparable with those observed in postmenopausal women. Evidence for its efficacy in fracture prevention is not as strong in men, and further studies using vertebral and hip fracture reduction as a primary endpoint are needed. The recommended dosage of alendronate for the treatment of osteoporosis in men is 70 mg p.o. once weekly or 10 mg p.o. once daily. The most common adverse effects are similar between men and women and involve the upper gastrointestinal tract (e.g., dyspepsia, abdominal pain). Alendronate is contraindicated in patients with significant kidney disease (creatinine clearance of <30 mL/min) and abnormalities of the esophagus that delay esophageal emptying, such as stricture or achalasia.94 Education on the proper administration of bisphosphonates is essential. The average wholesale price for alendronate is approximately $65.00 per month.

Parathyroid hormone. Teriparatide injection, recombinant (rDNA origin) human parathyroid hormone (PTH) (1-34), is the first anabolic agent approved by FDA for the treatment of osteoporosis. It increases new bone formation by increasing osteoblast differentiation, function, and survival.95 Two studies have evaluated the effect of PTH in men.44,96 The first trial included 23 men (average age, 50 years) with idiopathic osteoporosis, defined as a lumbar spine or femoral neck BMD at least 2 standard deviations below the mean for age-matched men or at least 2.5 standard deviations below the mean for young, healthy men.96 Seventy-eight percent of patients had a history of fracture as an adult. All patients received 1500 mg of calcium and 400 IU of vitamin D and were randomized to receive a daily subcutaneous injection of either PTH (1-34) 400 IU (equivalent to approximately 20 µg) or placebo. After 18 months of therapy, lumbar spine and femoral neck BMD significantly increased in the PTH group, compared with those receiving placebo (lumbar spine, 13.5% ± 3.0% versus no change, respectively; p < 0.001) (femoral neck, 2.9% ± 1.5% versus no change, respectively; p < 0.05). There were not enough fractures in the trial to allow for an adequate comparison.

The second trial included 437 men (average age, 59 years) with osteoporosis, defined as a lumbar spine or femoral neck BMD at least two standard deviations below the mean of a young, healthy male reference population.44 Men with secondary causes of osteoporosis except hypogonadism were excluded. Subjects were randomized to receive a daily subcutaneous injection of placebo, 20 µg of teriparatide, or 40 µg of teriparatide. All subjects received 1000 mg of calcium and 400-1200 IU of vitamin D per day. The primary endpoint of this trial was change in lumbar spine BMD. The planned duration of the trial was 24 months; however, it was stopped at 11 months because of an observed increased risk for osteosarcoma in parallel rat studies. Lumbar spine BMD significantly increased in the 20-µg teriparatide group, compared with the placebo group (5.9% ± 4.5% versus 0.52% ± 3.9%, respectively) (p < 0.001). Femoral neck BMD also significantly increased with 20 µg of
teriparatide versus placebo (1.5% ± 4.0% versus 0.31% ± 4.1%, respectively) (p = 0.029). The response to treatment was independent of age, body mass index, baseline testosterone level, and history of smoking and alcohol consumption. The number of fractures was too low to evaluate the effect of treatment.

Because of the increased rate of osteosarcoma in rats, teriparatide contains a black-box warning that it should not be administered to any patient with an increased baseline risk for developing osteosarcoma.97 This includes patients with Paget’s disease or unexplained elevations of alkaline phosphatase, pediatric patients or young adults with open epiphyses, and patients with prior radiation therapy involving the skeleton. The drug is also not recommended in patients with a history of hypercalcemia or hyperparathyroidism or for a duration of over two years because of a lack of efficacy and safety data. The most common adverse effects of teriparatide are transient hypercalcemia, dizziness, and leg cramps. The recommended dosage is 20 µg once daily administered subcutaneously to the abdomen or thigh through a prefilled pen delivery device.93 Teriparatide is expensive, with an average wholesale price of approximately $500–$600 per month, and requires significant patient education for proper administration and storage.

Teriparatide is a promising new agent for the management of osteoporosis in men. Small studies of short duration have demonstrated impressive increases in BMD, although evidence for its efficacy in fracture prevention is lacking. Because of its high cost, warnings and contraindications, and complex administration and storage requirements, teriparatide is currently considered a second-line agent for men who cannot take bisphosphonates. More information is needed to clarify the role of teriparatide to maximize its anabolic effect on bone.

**Testosterone.** Androgens appear to play a significant role in bone homeostasis by stimulating osteoblasts and inhibiting osteoclasts.26 It is unknown if androgens exert their effects directly or through their conversion to estradiol, as studies have indicated a correlation between estradiol levels and low BMD and vertebral fractures in men.22,98,99 The normal physiological range for total serum testosterone is typically 300–800 ng/dL. Hypogonadism (i.e., total serum testosterone of <300 ng/dL) is the most common secondary cause of osteoporosis in men and has been shown to result in bone loss and increased fracture risk.9,26,37,100 Testosterone therapy in men with documented hypogonadism can significantly increase BMD.9,101-103 The impact of testosterone therapy on fracture risk in this population has not been prospectively evaluated.

Total and free testosterone levels decline with aging and may play a role in the development of osteoporosis in elderly men.33,104 However, there are limited data to indicate that elderly men with low bone mass but without overt hypogonadism derive a bone benefit from testosterone treatment.105-107 In one study, testosterone therapy using a patch was compared with a patch containing placebo in 108 healthy men over 65 years of age.106 Subjects were included if they had a serum testosterone concentration at least one standard deviation below the mean for healthy young men (<475 ng/dL) and a low baseline lumbar spine BMD. After 36 months of therapy, there was no significant difference in the mean ± S.D. percent change in spinal BMD between the testosterone- and placebo-treated groups (4.2% ± 0.8% versus 2.5% ± 0.6%, respectively). However, subjects with low baseline testosterone concentrations had greater increases in BMD versus subjects with baseline testosterone levels in the normal range (5.9% ± 1.0% versus 0.9% ± 1.0%, respectively). No significant changes in hip BMD were noted, and no fractures were observed in either group.

Several options are available for testosterone therapy. Intramuscular injections of testosterone, while the least expensive route for the patient, are not ideal because they can lead to wide fluctuations in hormone levels, may be painful, and require frequent physician office visits for drug administration.98 A typical dosing regimen is 100–150 mg administered intramuscularly every two weeks.104 A transdermal patch or topical gel is more expensive; however, physiological diurnal testosterone concentrations are achieved. One or two patches (equivalent to 5 mg of testosterone per day) can be applied once daily in the evening or 50 mg of a 1% testosterone topical gel can be applied once daily in the morning to various areas of the body (upper arm, back, thighs, abdomen, or upper buttocks), depending on the product. Local skin reactions can be a problem and are less frequent with the gel formulation.98,104 A transcr nal patch is another option for testosterone therapy and, like the transdermal route, results in more consistent testosterone levels. A 4- or 6-mg patch is applied daily to clean, dry-shaven scrotal skin each morning and worn for 22–24 hours.

Weight gain, acne, edema, sleep apnea, dyslipidemia, polycythemia, azospermia, gynecomastia, and prostate disorder are all possible adverse effects associated with testosterone therapy.26,104 The use of testosterone is contraindicated in men with a history of prostate cancer.104 Routine monitoring should include hematocrit, lipid panel, and prostate-specific antigen testing at baseline and every six months to yearly.26,104 The goal is to achieve a total serum testosterone level within the physiological range; therefore, testosterone levels should be monitored to determine if dosage adjustments are necessary.26,104 More studies are needed to clarify the role of testosterone and possibly...
estradiol in the development of osteoporosis. In addition, evidence is lacking regarding the efficacy and safety of testosterone therapy in men with low bone mass. On the basis of current evidence, testosterone therapy is an option for the prevention of osteoporosis in men with documented hypogonadism, as long as the benefits outweigh the risks.26,98,104 Men with osteoporosis, regardless of their testosterone level, should receive therapy with an agent that has demonstrated significant improvements in BMD and reductions in fracture risk. Alendronate and teriparatide have demonstrated efficacy in men with osteoporosis, regardless of their hypogonadism and therefore should be the drugs of choice in this population.

**Calcitonin.** Calcitonin is a polypeptide hormone that inhibits bone resorption by decreasing the number and activity of osteoclasts. The efficacy of intranasal calcitonin in men with idiopathic osteoporosis was evaluated in a 12-month, prospective, controlled trial.108 Twenty-eight men (average age of approximately 52 years) with T scores for the lumbar spine or femoral neck of ≤−2.5 were randomized to receive either intranasal calcitonin 200 IU once daily or intranasal placebo. All men received a 500-mg calcium supplement daily. Men with secondary causes of osteoporosis were excluded from the study. Lumbar spine BMD increased by 7.1% ± 1.7% over baseline in the men treated with calcitonin and 2.5% ± 1.5% in the placebo group (p < 0.05). No significant changes were noted in femoral neck BMD. One vertebral fracture occurred in the calcitonin-treated group and two in the placebo group. The increases in spinal BMD demonstrated in this study were much higher than those demonstrated in other intranasal calcitonin studies. Further studies are needed to validate these results.

There are some data showing that intranasal calcitonin has an analgesic effect in osteoporotic men with acute vertebral fracture pain.109 Two small, prospective, randomized trials showed significantly lower pain scores and reduced analgesic consumption after four weeks in patients receiving 200 IU of intranasal calcitonin daily, compared with placebo.110,111 Larger controlled trials with a longer duration of follow-up would be helpful to better clarify the benefits of calcitonin in acute fracture pain.

**Thiazide diuretics.** Hypercalciuria has been associated with low BMD, and men are twice as likely as women to have hypercalciuria.9 Approximately 10% of men with osteoporosis have hypercalciuria.37 Thiazide diuretics decrease the urinary excretion of calcium and improve calcium balance. Data indicating the benefit of thiazide diuretics on BMD and fracture risk are conflicting.112-119 In a four-year, prospective cohort study of 9518 elderly men and women (mean age, 74 years), the use of thiazide diuretics was associated with a significant reduction (32%) in the relative risk of hip fracture.118 In another study, 320 healthy, normotensive adults (mean age, 67 years) were randomized to receive hydrochlorothiazide 12.5 or 25 mg/day or placebo for three years.117 Based on the intention-to-treat analysis, hydrochlorothiazide 12.5 and 25 mg/day increased total hip BMD by 0.79% and 0.92%, respectively, compared with placebo (p = 0.03). Overall, there was no significant difference in spine BMD at 36 months. In a case series of five osteoporotic men with idiopathic hypercalciuria, treatment with hydrochlorothiazide 25 mg/day for a mean of eight months resulted in normalization of urinary calcium excretion and significant increases in lumbar spine and femoral neck BMD.120

Patients enrolled in the only prospective, randomized evaluation of thiazide diuretics did not have hypercalciuria or low bone mass; therefore, it is difficult to determine the true benefit of thiazide diuretics in this population. More data are needed on the effect of thiazide diuretics on BMD and fracture risk before they can be routinely recommended in the management of osteoporosis in men. For men with documented hypercalciuria (24-hour urine calcium concentration of >300 mg/dL), the administration of hydrochlorothiazide 12.5–25 mg/day may be beneficial.37

**Combination therapy.** There have been no combination antiresorptive trials in men. One combination therapy trial evaluating alendronate and PTH use in men has been published.121 Eighty-three men were randomly assigned to receive alendronate 10 mg p.o. once daily for 3 months, PTH 40-µg s.c. injection once daily for 24 months, or both for 24 months. At the end of the trial, PTH alone had a significantly greater effect on spine and femoral neck BMD than did alendronate alone or combination therapy. The mean ± S.D. percent increase in BMD at the posteroanterior spine and femoral neck was 7.9% ± 1.6% and 3.2% ± 1.7% in the alendronate group, 18.1% ± 3.2% and 9.7% ± 3.7% in the PTH group, and 14.8% ± 2.4% and 6.2% ± 2.2% in the combination group, respectively. Total body BMD was similar in all groups. Fractures were not evaluated. This study suggests that the addition of an anabolic agent, alendronate, to an anabolic agent, PTH, results in a reduced benefit on BMD. The effect of this combination on fracture risk is unknown. Further studies evaluating combination antiresorptive-anabolic therapy are needed.

**Summary of management strategies**

An algorithm for the management of osteoporosis in men is depicted in Figure 1.122 Men who are at high risk for developing osteoporosis should undergo central BMD testing. Regardless of the BMD results, all men should be educated on lifestyle modifications and the recommended dai-
ly intake of calcium and vitamin D to prevent osteoporosis. If BMD is low, the presence of a secondary cause should be ruled out. In men with osteopenia and documented hypogonadism, testosterone therapy can be considered to prevent further bone loss. Drug therapy for osteoporosis should be considered in men with a history of low-trauma fracture, a T score of −2.5, or a T score of −2.0 to −2.4 with risk factors. Based on available safety and efficacy data and the convenience of once-weekly administration, alendronate should be considered first-line therapy for the management of primary or hypogonadal osteoporosis in men. Based on similar safety and efficacy in the management of postmenopausal women and glucocorticoid-induced osteoporosis and promising preliminary results in men, risedronate can be considered a reasonable alternative to alendronate. Because of its high cost, requirement for daily subcutaneous administration, and strict storage conditions, teriparatide is currently considered a second-line option for patients who are intolerant of or have contraindications to bisphosphonate therapy. Until more information is available about the efficacy of intranasal calcitonin in men, it is considered a third-line option. Thiazide diuretics may be considered adjunctive therapy in men with documented hypercalcemia.

Conclusion

While the rate of osteoporosis in men is lower than in women, the consequences are possibly more devastating. Evaluation of secondary causes, especially hypogonadism, is important, as they can play a significant role in the development of osteoporosis in men. All men should be educated to improve modifiable risk factors and maintain recommended daily intakes of calcium and vitamin D. BMD should be evaluated in high-risk men using central DEXA, and drug treatment should be considered in those with a history of low-trauma fracture or significant bone loss.

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