Osteoporosis in Men: Epidemiology, Diagnosis, Prevention, and Treatment

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ABSTRACT

Background: Osteoporosis and fragility fractures in men account for substantial health care expenditures and decreased quality of life.

Objective: This article reviews the most current information about the epidemiology, diagnosis, prevention, and treatment of osteoporosis in men.

Methods: Relevant literature was identified through a search of MEDLINE (1966–June 2003) limited to English-language studies in men. The search terms included *fractures, bone density*, or *osteoporosis* plus either *epidemiology, diagnosis, prevention, control*, or *therapy*. Additional search terms included specific subtopics (eg, *bisphosphonates, calcium, exercise, parathyroid hormone*). The authors contributed additional relevant publications.

Results: Morbidity after fragility fracture is at least as high in men as in women, and the rate of fracture-related mortality 1 year after hip fracture is approximately double in men compared with women. The bioavailable fraction of testosterone slowly declines into the ninth decade in men. There is evidence that the effect of estrogens on bone is greater than that of testosterone in men. Diagnosing osteoporosis in men is complicated by a lack of consensus on how it should be defined. Significant risk factors for osteoporosis or fracture include low bone mineral density, previous fragility fracture, maternal history of fracture, marked hypogonadism, smoking, heavy alcohol intake or alcoholism, low calcium intake, low body mass or body mass index, low physical activity, use of bone-resorbing medications such as glucocorticoids, and the presence of such conditions as hyperthyroidism, hyperparathyroidism, and hypercalciuria. Prevention is paramount and should begin in childhood. During adulthood, calcium (1000–1500 mg/d), vitamin D (400–800 IU/d), and adequate physical activity play crucial preventive roles. When treatment is indicated, the bisphosphonates are the first choice, whereas there is less support for the use of calcitonin or androgen therapy. Parathyroid hormone (1-34) is a promising anabolic therapy. There is also strong evidence for the use of bisphosphonates for the treatment of glucocorticoid-induced osteoporosis.

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Conclusion: Osteoporosis and fragility fractures in men constitute a considerable health care burden. Proven preventive and therapeutic options are available. Bisphosphonates are currently the most efficacious treatments available for men with osteoporosis. Human parathyroid hormone promises to be an effective anabolic agent, provided no unexpected adverse events are discovered in the course of ongoing human trials. (*Clin Ther.* 2004;26:15–28) Copyright © 2004 Excerpta Medica, Inc.

Key words: men, fracture, osteoporosis, epidemiology, diagnosis, prevention, treatment.

INTRODUCTION

In recent years, there has been a dramatic increase in research investigating the epidemiology, pathophysiology, diagnosis, prevention, and treatment of osteoporosis and fragility fractures in men. Given the evidence for the benefits of healthy lifestyle choices[1–6] and the use of therapeutic agents to prevent and treat low bone mass in men,[7–12] it is important to raise awareness about the prevalence of osteoporosis in men and the value of early diagnosis to help avoid or delay fractures.

This article reviews the most current information about the epidemiology, diagnosis, prevention, and treatment of osteoporosis in men. Pertinent literature was identified through a search of MEDLINE (1966–June 2003) limited to English-language studies in men. The search terms included *fractures, bone density*, or *osteoporosis* plus either *epidemiology, diagnosis, prevention, control,* or *therapy*. Additional search terms included specific subtopics (eg, *bisphosphonates, calcium, exercise, parathyroid hormone*). The authors contributed additional relevant publications.

EPIDEMIOLOGY

Prevalence of Osteoporosis Based on Bone Mineral Density

Based on the World Health Organization [WHO] criteria and the US male standard for peak bone mass, the prevalence of osteoporosis of the hip was 3% to 6% in men aged >50 years in the National Health and Nutrition Examination Survey (NHANES III, 1988–1994); the corresponding rate among women in the same age group was 13% to 18%.[13] Similarly, in a large population-based random sample of Canadian men and women,[14] the prevalence of osteoporosis in men aged >50 years (based on a Canadian male standard for peak bone mass) was 2.9% at the lumbar spine and 4.8% at the femoral neck, with a combined prevalence of 6.6%, roughly half that in similarly aged women.

According to the WHO definition of osteoporosis for postmenopausal white women—bone mineral density (BMD) <2.5 SDs below the young adult (age 30 years) mean—osteoporosis is less prevalent in men than in women. This advantage is at least partly due to men's greater body mass, greater bone size, greater accrual of bone during growth, absence of a punctuated decrease in endogenous sex hormones analogous to menopause, and shorter average lifespan compared with women.[15]

Prevalence of Fragility Fractures

Osteoporotic fractures, particularly those of the spine, are common in men; the age-related prevalence of vertebral fractures in men ranges from 29% in the sixth decade to 39% in the ninth decade.[16] Approximately 29% of 60-year-old men who do not receive preventive therapy will suffer a fracture in their remaining years.[17]

Although men generally have a higher areal BMD than women, vertebral fracture rates in persons aged >50 years are similar between the sexes[18–20] and perhaps even higher in men.[16] This discrepancy between areal BMD and vertebral fracture rates may be explained by the recognized size dependency of areal BMD measures[21] and is supported by findings of relatively equal vertebral volumetric density between the sexes on quantitative computed tomography (QCT).[22] In men, some vertebral fractures are symptomatic and come to clinical attention, but the majority are asymptomatic and often remain undiagnosed.[23]

At least one third of all hip fractures occur in men.[24,25] By 2050, the worldwide incidence of hip fracture in men is projected to increase by 310% (240% in women), assuming no change in the sex- and age-specific incidence.[26] This projected global increase in the rate of hip fracture is supported by the results of a Canadian study estimating that the rate of proximal femur fracture would increase exponentially between 1997 and 2037 in Canada.[27]

Morbidity and Mortality Associated with Fragility Fractures

Vertebral fractures commonly cause back pain, height loss, and impaired mobility and may cause equal morbidity in men and women.[23] In men, even asymptomatic subclinical vertebral fractures (found in 28% of men aged >50 years) are associated with decreased quality of life.[23] Hip fractures in men cause significant morbidity and loss of normal functioning.[23]

Although the overall prevalence of fragility fractures is higher in women, men generally have higher rates of fracture-related mortality. In a prospective investigation from Australia,[28] 5-year mortality after proximal femur or vertebral fracture was significantly higher in men than in women. Specifically, age-standardized mortality ratios in women were 2.18 (95% CI, 2.03–2.32) for proximal femur fracture and 1.66 (95% CI, 1.51–1.80) for vertebral fracture, compared with a respective 3.17 (95% CI, 2.90–3.44) and 2.38 (95% CI, 2.17–2.59) in men. Results of a recent investigation indicated that over a 10-year period, the risk of mortality was significantly higher in men who had vertebral fractures at baseline compared with age-matched men who did not (hazard ratio, 2.4; 95% CI, 1.6–3.9).[29]

A study by Trombetti et al[30] found that the rate of mortality after hip fracture was significantly greater in men than in women during the in-hospital period (15% vs 8%, respectively; $P < 0.03$), after 1 year (39% vs 19%; $P < 0.001$), and after 7 years (85% vs 67%; $P < 0.001$). However, the authors observed that the excess mortality in men was primarily restricted to the first year after hip fracture. Kanis et al[31] recently reported analogous findings; over the first 6 months, the mortality rate in men was approximately double that in similarly aged women. As in women, the mortality rate in men after hip fracture increased with age and was highest in the year after fracture.[30,31] The higher rates of mortality after fragility fractures in men compared with women are generally the result of higher rates of comorbidity in men.[28,32,33]

Economic Impact of Fragility Fractures

In the United States in 1995, medical expenditures for the treatment of osteoporotic fractures in American men were US $2.5 billion.[34] Similarly, in Canada in 1993, acute-care costs for osteoporosis and fractures in Canadian men aged >45 years were Can $104.4 million, compared with approximately Can $345 million in women of a similar age.[35] The costs of long-term care after fracture often exceed acute-care costs. A Canadian investigation reported that in men aged >50 years, the mean cost of hip fracture was Can $22,700 per person for the year after fracture, with yearly expenses for long-term care nearly double that.[36]

Etiology and Pathophysiology

Although idiopathic and involutional osteoporosis are common, secondary causes of diminished BMD—including hypogonadism, glucocorticoid excess, alcoholism, hypercalciuria, malabsorption, and hyperthyroidism—are also frequently found in referred osteoporotic men.[37] In 70 men with vertebral crush fractures,[38] 54% were found to have such underlying secondary causes of osteoporosis as hypogonadism, use of oral corticosteroid therapy, neoplastic disease, and chronic alcoholism. Because of the high prevalence of secondary causes of bone loss in men, laboratory testing should be performed to determine whether a patient's low bone mass has a secondary origin.

Because of the longer and larger magnitude of pubertal bone accrual in men, men have greater peak bone mass than women.[39] During growth, which is the time of most rapid bone accrual, positive stimuli will have their greatest impact on peak bone mass; correspondingly, any perturbations will have devastating consequences on the amount of peak bone mass attained. With aging, both sexes experience slow losses in cancellous bone, resulting in significant trabecular thinning and increased fracture risk, particularly after menopause in women and after the age of 70 years in men.[40,41] In men with idiopathic osteoporosis, bone loss has been linked to osteoblastic depression.[40,42] Bone strength in the cortical shell is somewhat preserved in men during aging through minimal periosteal apposition, despite large endosteal losses[43]; the small increases in bone diameter mechanically compensate for the endosteal losses in bone mass. Consequently, differences in bone strength and fracture prevalence between the sexes may be the result of larger bones in men; bones of larger diameter are biomechanically stronger and less apt to fail under load.

Men have a slow decline in bioavailable androgens with age (~60% decrease between the ages of 20 and

79 years).[44] Although total serum testosterone and estrogen levels remain relatively unchanged with age, their bioavailable fractions (not bound to sex hormone–binding globulin) diminish progressively to 30% to 50% of the young adult male value after the age of 80 years.[45] Testosterone deficiency caused by endocrine abnormalities[46] or pharmacologic suppression of the pituitary–gonadal axis (eg, with the use of luteinizing hormone–releasing hormone [LHRH] for prostate cancer)[47] results in accelerated bone loss. The increase in BMD observed in mature hypogonadal men receiving testosterone treatment supports the osteotrophic properties of androgens, either through augmented bone formation or diminished bone resorption.[48] The results of studies in patients with syndromes of androgen-receptor insensitivity also suggest a direct role for androgens in the development of the male skeletal phenotype, particularly bone size.[49]

Aromatization of androgens to estrogen may indirectly account for the majority of testosterone's anabolic actions.[50] Investigations in men with an inherited deficiency of either the estrogen receptor or aromatase, both of which are required for estrogen synthesis,[51,52] have shown the importance of estrogen in bone regulation and maturation in males. Estrogen treatment resulted in augmented bone mass and fusion of the epiphyseal growth plates in aromatase-deficient men.[51] In the Rancho Bernardo cohort,[53] vertebral fracture status after 4 years of follow-up was predicted significantly only by concentrations of bioavailable estradiol ($P < 0.01$) and not by concentrations of testosterone. In fact, most studies have shown a closer correlation in men between serum estradiol concentrations and BMD than between serum testosterone concentrations and BMD.[45,50,54] Analyses of data from the Framingham Study[50,55] found that the difference in mean BMD between men in the lowest and highest quartiles of estradiol concentration was similar to the effect of 10 years of aging. In an investigation of alternating systemic blockade and replacement of estrogen and testosterone in men,[56] estrogen was found to be the dominant sex steroid regulating bone resorption, whereas both estrogen and testosterone were important in bone formation. Furthermore, there is evidence that idiopathic osteoporosis in men may be at least partly the result of deficient expression of estrogen receptor–alpha protein.[57]

Finally, insulin-like growth factor–I has been implicated in male idiopathic osteoporosis, although its direct or indirect actions have not yet been defined.[58,59]

DIAGNOSIS

Bone Mineral Density Measurement

The diagnosis of osteoporosis is currently based on BMD measurement by dual-energy x-ray absorptiometry (DXA). The WHO definition of osteoporosis (BMD T-score <2.5) was developed for use in postmenopausal white women[60]; however, this standard has been applied to different races and to men without thorough investigation of the utility or validity of this standard for these groups. Nevertheless, apart from an existing fragility fracture, BMD is the most robust determinant of fracture risk in men.[18,24,61–63]

Influence of Assessment Site and Machine

The prevalence with which osteoporosis is diagnosed is largely dependent on the instrument used to assess BMD and the site of assessment; different instruments and sites result in vastly different rates of osteoporosis.[64] The reference standard for the diagnosis of osteoporosis is DXA measurement of the proximal femur,[65] but the possibility of osteoporosis at other sites also warrants close clinical consideration. Generally, fracture risk should be assessed based on the lowest BMD of the total hip, femoral neck, and lumbar spine as measured by DXA. DXA is the most commonly used technique for diagnosing BMD because of its reliability, accuracy, speed, ease of use, and relatively low levels of ionizing radiation.[66] However, measurement of vertebral BMD in older men (aged >60 years) may be misleading because of the presence of common degenerative changes that may increase BMD without decreasing fracture risk.[67]

The measurement of areal BMD is significantly affected by bone size, resulting in systematic overestimation of density in larger bones and underestimation in smaller bones.[21] Attempts to correct this size-mediated problem have demonstrated little additional benefit in the prediction of fracture risk beyond standard measurement of areal BMD.[63,64,68]

The T-Score

The T-score is defined as the number of SDs by which a given BMD measurement exceeds or falls below the young normal mean BMD (usually for the

average healthy 30-year-old). The reported prevalence of osteoporosis in a population is highly dependent on the reference range adopted. The male and female population standard for proximal-femur BMD in the United States is derived from the NHANES III database,[69] whereas in Canada, the reference standard is based on data from the Canadian Multicentre Osteoporosis Study (CaMos).[14] In 2000, reports from NHANES III and CaMos presented epidemiologic data that altered the reference ranges that had been recommended by the manufacturers of some DXA equipment; the young normal mean was lower and the SD higher than was previously assumed, dramatically shifting the T-score ranges. Because of differing rates of bone loss and composition (proportions of cortical and trabecular bone), T-scores from different sites cannot be used interchangeably,[70] nor should T-scores from different machines be used interchangeably.

Female or Male Cutoff Points for Diagnosing Male Osteoporosis?

In NHANES III, rates of proximal-femur osteoporosis in white, Hispanic, and black men were 4%, 2%, and 3%, respectively, when the absolute BMD cutoff for women (0.56 g/cm^2) was used.[13] When a male-specific BMD cutoff (0.59 g/cm^2) was created, however, the corresponding rates were 7%, 3%, and 5%. These American data are consistent with those for Canadian men.[14] In the Rochester Epidemiology Project,[63] the use of female cutoff values for white men aged >50 years resulted in a 3% rate of osteoporosis at the hip, spine, or distal forearm, whereas the use of male cutoff values resulted in a rate of 19%, which is more consistent with the 13% lifetime fracture risk. However, because research has shown that men and women sustain fractures at the same absolute BMD,[71] there is much controversy about the proper BMD cutoff point for the definition of male osteoporosis.

Prospective data are needed for the determination of valid cutoff points for the diagnosis of osteoporosis in men. Until such data are available, it may be most prudent to use a combination of male cutoff points and other clinical risk factors to diagnose osteoporosis in men. In addition, DXA bone density testing should be offered to men aged >50 years with a family history of osteoporosis, height loss, fragility fracture, or use of medications or the presence of diseases associated with a predisposition to bone loss. Men of advanced age (>70 years) should have a bone density evaluation regardless of risk factors, because the risk of hip fracture increases significantly in this age group.[62,67] Osteoporosis is asymptomatic until the occurrence of fracture, and there is currently little evidence to support the treatment of osteoporosis in men solely on the basis of BMD measurements expressed as T-scores; however, there is a need for treatment in men who have suffered fragility fractures. Despite the paucity of data, therapy to reduce the risk of fracture should be considered in men with low bone mass (T-score <2.5), age >55 years with ≥1 risk factor, or age >65 years with no additional risk factors.

Risk Factors Other Than Reduced Bone Mineral Density

In men as in women, an existing fragility fracture is perhaps the most significant indicator of future risk for fracture, with a minimum doubling of risk.[72–74] Thus, fracture history should be obtained, and patients with fragility fractures should be considered for therapy regardless of the presence of additional risk factors.[75]

As with all other health characteristics, osteoporosis and fragility fracture have genetic components. In a cohort of 12,816 men and women aged 50 to 75 years, a maternal history of hip fracture was associated with a modest increase in the risk for vertebral deformity in men (odds ratio [OR] = 1.3; 95% CI, 1.0–1.8).[76] Results of another study supported the increased risk of fracture with a history of maternal hip fracture.[77] Further, advancing age is itself a significant risk factor for low BMD in men.[78–80]

Because low body mass and low body mass index (<18.5 kg/m^2) are significant risk factors for both osteoporosis[77,79,81,82] and fragility fractures ($P < 0.05$),[73] patients should attempt to stay within a healthy weight range for their height. Furthermore, substantial weight loss (>10%) has been shown to significantly increase the risk for hip fracture compared with no weight loss (relative risk, 2.27; 95% CI, 1.13–4.59).[24]

Marked testosterone deficiency is a risk factor for low BMD in men. Stanley et al[83] reported that hypogonadism in men was significantly associated with hip fracture (6.5-fold increase vs eugonadal men; $P < 0.01$). Up to 20% of men with symptomatic vertebral fractures are reported to have some degree of hypo-

gonadism.[38] In contrast, a case-control study comparing 91 men with vertebral fractures (median age, 64 years) with 91 age-matched control subjects[84] found that androgen deficiency was not associated with an increased risk of fracture; however, levels of sex hormone–binding globulin were significantly higher and the free androgen index was significantly lower in men with vertebral fractures compared with control subjects (both comparisons, $P < 0.001$).

Lifestyle Factors

There is ample evidence to support the significant impact of lifestyle choices on bone health. The risk for vertebral and hip fractures in men increases greatly with heavy alcohol intake (≥7 oz/wk), particularly with long-term intake.[85] However, moderate intake of alcohol (1–6 oz/wk) may augment BMD.[79,86] Other factors associated with alcoholism, such as an increased risk of falling and malnutrition, may mask the direct effects of alcohol on BMD and fracture risk.

Most evidence suggests that cigarette smoking reduces BMD,[77,81,82,87] and smoking has been significantly associated with an increased risk of vertebral fracture (OR = 2.8; 95% CI, 1.2–6.7)[84] and hip fracture ($P < 0.05$).[88] However, smoking had no effect on the risk of vertebral fracture in the European Prospective Osteoporosis Study.[89] A meta-analysis[90] concluded that smoking has an independent, dose-dependent effect on bone loss that could increase the risk for hip fracture in men by as much as 40%.

Low intake of calcium (<800 mg/d) in men is associated with low bone mass,[80,91,92] and physical inactivity has a negative impact on both BMD[77] and fracture risk.[88,93] Although low calcium intake and low levels of physical activity do not in themselves justify BMD testing, these details should be included in the general assessment of osteoporosis risk.

Numerous medications increase the fracture risk in men (eg, anticonvulsants, nonsteroidal anti-inflammatory drugs, antiarrhythmics, hypnotics/anxiolytics, antidepressants, and anti-Parkinson drugs[94]), but oral glucocorticoids are the most commonly used agents associated with increased fracture risk in men. In a retrospective trial that included 244,235 users of oral glucocorticoids and 244,235 control subjects,[95] the risk for vertebral, hip, and wrist fractures in men receiving glucocorticoids increased significantly in a dose-response manner (all sites, $P < 0.05$). Further data have confirmed glucocorticoid use as a significant risk factor for fragility fractures in men ($P < 0.05$).[73,84]

As mentioned earlier, other risk factors for bone loss in men include LHRH analogue use, gastrectomy, peptic ulcer disease, rheumatoid arthritis, chronic lung disease, hyperthyroidism, hyperparathyroidism, and hypercalciuria.[47,79] Assessment of height changes, measures of kyphosis, and lateral radiographs of the spine may provide additional useful diagnostic information. Radiologists should be encouraged to quantitatively report any vertebral deformities noted on radiography.

PREVENTION

Prevention of osteoporosis begins during childhood. Factors that augment bone mass should be encouraged and those that diminish it should be discouraged. These healthful practices should be maintained over a lifetime.

Calcium and Vitamin D

Most studies report a slowing of bone loss when patients take supplemental calcium and vitamin D. A randomized controlled trial (RCT) in community-dwelling elderly men and women (age >65 years) examined the effects of supplementation with calcium (500 mg/d) and vitamin D (700 IU/d) for 3 years.[1] The authors reported significant treatment effects on BMD at the femoral neck ($P = 0.02$), lumbar spine ($P = 0.04$), and total body ($P < 0.001$), and a significantly lower rate of nonvertebral fracture in the group that received supplementation compared with the placebo group ($P = 0.02$). Other investigators have reported positive effects of adequate calcium ingestion on BMD and fracture risk in men.[2,80] A recent trial investigating the administration of high doses of cholecalciferol (100,000 IU) every 4 months for 5 years in community-dwelling men aged 65 to 85 years reported a nonsignificant effect on fracture risk.[96]

Both intestinal calcium absorption[97,98] and vitamin D metabolism[99] are impaired as men age, highlighting the importance of adequate calcium and vitamin D intake during these years. In addition, inadequate exposure to sunlight is a significant risk factor for hip fracture in men.[88,100] Between the ages of 19 and 50 years, men should ingest ≥1000 mg/d calcium and 400 IU/d vitamin D from dietary and (if necessary)

supplemental sources; at >50 years, they should ingest 1500 mg/d calcium and 800 IU/d vitamin D.[75] Calcium and vitamin D are necessary adjuncts to the treatment of low bone mass but are not themselves sufficient.[75]

Exercise

Weight-bearing exercise during growth is a potent stimulus that augments peak bone mass and may decrease fracture risk.[3] Participation in vigorous physical activity has been shown to significantly decrease the risk of hip fracture compared with no such participation (relative risk, 0.38; 95% CI, 0.16–0.91; $P = 0.03$),[4] but the same has not been found for vertebral fracture risk.[101] This discrepancy may reflect an increased risk for traumatic vertebral fracture during vigorous competitive activities. Unfortunately, much of the beneficial effect of physical activity is lost when men stop exercising.[5] Perhaps the most important role of exercise in decreasing fracture risk is in strengthening muscles and improving muscular coordination, thereby decreasing the likelihood of falling.[6]

Other Lifestyle Factors

Prevention of osteoporosis in men should include evaluation of and advice about diet and lifestyle risk factors. Particular consideration should be given to sedentary lifestyle, smoking, excessive alcohol consumption, low dietary calcium intake, low vitamin D intake, and inadequate sun exposure.

TREATMENT

Although several fracture prevention treatments have been approved for use in postmenopausal women, comparatively few have been approved for use in men, most likely because of the paucity of trials in men. Most trials that have been conducted have been small. More studies investigating nonhormonal therapies that have shown efficacy in women are needed to guide clinical decision-making in men.

Antiresorptive Therapies

Bisphosphonates

Bisphosphonates are the first choice for the treatment of osteoporosis in men, particularly the second-generation amino-bisphosphonates (alendronate and risedronate). In an RCT in men with osteoporosis (one third with low serum testosterone levels),[7] 2 years of alendronate 10 mg/d significantly increased BMD at all measurement sites ($P < 0.001$ vs baseline and placebo) and significantly decreased the incidence of vertebral fracture compared with the placebo group (0.8% vs 7.1%, respectively; $P = 0.02$). In a 2-year, open-label RCT in 134 men with established primary osteoporosis and normal serum testosterone levels,[8] the group that received alendronate 10 mg/d had significantly greater gains in BMD at the lumbar spine compared with the group that received alfacalcidol 1 µg/d (10.1% vs 2.8%, respectively; $P < 0.001$) and significantly greater gains in BMD at the femoral neck (5.2% vs 2.2%; $P < 0.009$). The incidence of new vertebral fractures was 7.4% in the alendronate group and 18.2% in the alfacalcidol group; this difference was not statistically significant.

Bisphosphonates for Glucocorticoid-Induced Osteoporosis

Prolonged glucocorticoid therapy (>3 mo) at prednisone-equivalent doses >7.5 mg/d is associated with a high risk for bone loss and corresponding fracture.[75] However, use of consistent doses of <7.5 mg/d (as low as 2.5 mg/d) may increase fracture risk.[95] The use of bisphosphonates in the prevention and treatment of glucocorticoid-induced osteoporosis is well established.[9,10,102–105] Effective therapies for the prevention and treatment of bone loss due to glucocorticoid-induced osteoporosis in men include cyclic etidronate (Canada),[102] alendronate 10 mg/d and 70 mg/wk,[10] risedronate 5 mg,[104,105] and intravenous pamidronate (recently approved in Canada for use in patients who are unable to tolerate oral bisphosphonates).[106]

The most commonly reported adverse event with bisphosphonate therapy is gastrointestinal upset, particularly with a daily dosing regimen.[7,10,104] However, the use of a weekly dosing schedule and findings that the incidence of gastrointestinal upset is no greater with bisphosphonates than with placebo[7,10,105] have somewhat minimized this concern. Other adverse events are uncommon with bisphosphonate use.

Calcitonin

There is limited information on the effects of calcitonin use in men. In a 12-month RCT in 28 men (age 27–74 years) with idiopathic osteoporosis,[11] intranasal salmon calcitonin 200 IU/d increased lumbar spine BMD significantly more than did placebo (7.1% vs 2.4%, respectively; $P < 0.05$). However, there were no

significant changes at any other site measured, and no fracture data were collected. Adverse events with intranasal calcitonin were rare in this study, although rhinitis was reported in 22% of the active-treatment group and 15% of the placebo group in a large trial in postmenopausal women ($P < 0.01$).[107]

Androgen Therapy

Androgen replacement therapy improves BMD in hypogonadal men,[108] particularly those with open epiphyses.[109] In a trial in hypogonadal men who received transdermal testosterone,[108] after 2 years of therapy, BMD had increased by 7.7% at the lumbar spine ($P < 0.001$) and by 4.0% at the femoral trochanter ($P = 0.02$). Although testosterone replacement has been reported to significantly increase BMD at the lumbar spine and trochanteric region in hypogonadal men ($P < 0.01$),[108,110] it has not shown a beneficial effect on BMD at more cortical sites, such as the hip or radius.

The impact of androgen therapy is less clear in men with normal gonadal function, who represent the majority of men with osteoporosis.[111] Anderson et al[112] conducted a prospective, open-label trial of the effects of regular moderate androgen supplementation on BMD in 23 eugonadal men (mean age, 58 years; age range, 34–73 years) with severe idiopathic osteoporosis and vertebral fractures. Patients received intramuscular injections of testosterone esters 250 mg every 2 weeks for 6 months. Mean BMD at the lumbar spine increased by 5% in 6 months, whereas BMD at the femoral neck did not change.

Results of a 36-month RCT in men aged >65 years indicated that transdermal testosterone therapy was effective with respect to BMD of the spine in men with low testosterone levels, but had an insignificant effect in those with normal testosterone levels.[111]

Testosterone may have a role in the treatment of glucocorticoid-induced osteoporosis. An RCT assessed the effects on bone and muscle mass of injections of mixed testosterone esters 200 mg, nandrolone decanoate 200 mg, or placebo every 2 weeks for 12 months in a group of eugonadal men receiving long-term, high-dose glucocorticoids (mean prednisone-equivalent dose, 12 mg/d).[113] After 12 months, lumbar spine BMD increased significantly only in the group of men who received testosterone (4.7%; $P < 0.01$); there were no changes in hip or total body BMD.

Data on fracture rates with testosterone treatment in hypogonadal or eugonadal men are not available at this time.

Anabolic Therapies

Human Parathyroid Hormone

Human parathyroid hormone (PTH [1-34]) therapy is a promising anabolic approach to the treatment of osteoporosis in men. Preliminary results indicate positive effects on both BMD and fracture risk.

Middle-aged men (age 37–62 years) with idiopathic osteoporosis and ≥1 vertebral compression fracture received daily subcutaneous injections of a synthetic PTH (1-34) combined with daily $1,25(OH)_2$ vitamin D for 12 months.[114] Treatment significantly increased spinal trabecular BMD ($P < 0.01$), whereas no changes occurred at the one-third distal radius (one third of the distance from the distal to the proximal end). In an 18-month RCT in men with idiopathic osteoporosis,[115] PTH (1-34) given at 400 IU/d significantly increased lumbar spine BMD (as measured by QCT) by 13.5% ($P < 0.001$) and femoral neck BMD by 2.9% ($P < 0.05$) compared with the control group. As in the trial by Slovik et al,[114] the PTH group had no change from baseline in the one-third distal radius. Orwoll et al[12] conducted an RCT of the effects of daily injections of PTH (1-34) given at 20 or 40 µg or placebo in men with low spine or hip BMD (T-score <2). After a median of 11 months, BMD had increased significantly in both PTH groups at the spine (20 µg: 5.9%; 40 µg: 9.0%; both, $P < 0.001$) and the femoral neck (20 µg: 1.5%, $P < 0.03$; 40 µg: 2.9%, $P < 0.001$) compared with the placebo group.

A recent trial compared the effects on BMD of alendronate 10 mg/d and PTH (1-34) 40 µg/d SC alone and in combination for 30 months (PTH was begun at 6 months) in men aged 46 to 85 years.[116] Both femoral neck and lumbar spine BMD increased significantly more with PTH alone than with either of the other treatments (femoral neck, $P < 0.01$; lumbar spine, $P < 0.001$). In the 2 groups with smaller increases in BMD, lumbar spine BMD increased significantly more in the combination-therapy group than in the alendronate-only group ($P < 0.001$). The investigators suggested that alendronate impairs the ability of PTH to increase BMD at the lumbar spine and femoral neck in men, possibly by attenuating PTH-induced stimulation of bone formation.

PTH is a potent anabolic agent for bone, particularly at cancellous sites. Changes in bone mass at 1 year have been reported to be similar in women[117] and men[115] who received PTH, and any antifracture efficacy of PTH in men must be established through large RCTs. Adverse events are uncommon with PTH injection; headache (10%) and nausea (4%) are the most commonly reported drug-associated adverse effects.[12]

Fluoride

There are scant data supporting the use of fluoride in men. A 3-year RCT[118] compared the effect of intermittent (3 months on, 1 month off) low-dose fluoride (114 mg/d) plus calcium or calcium alone in 64 men (mean age, 53 years) with idiopathic osteoporosis and no existing vertebral fractures. The group that received fluoride had significantly greater gains in BMD at all sites investigated (lumbar spine and one-third distal radius, $P < 0.001$; femoral neck, $P < 0.01$) and had significantly fewer vertebral fractures compared with the placebo group (4 vs 17, respectively; $P = 0.008$). Fluoride had no significant effect on the incidence of nonvertebral fractures compared with placebo. Adverse events with fluoride therapy in this study included lower-limb pain syndrome (~20%) and mild epigastric symptoms (<10%). Fluoride requires further study before it can be recommended for use in men with osteoporosis.

Other Therapies

The efficacy of antiresorptive agents other than the bisphosphonates or anabolic therapies other than PTH for the treatment of idiopathic osteoporosis in men remains largely unproven.

CONCLUSIONS

An increasing number of investigations are attempting to clarify the epidemiology, prevention, and treatment of osteoporosis in men. Nevertheless, the field is relatively new, and many more data are needed before evidence-based recommendations can be made. All men should be encouraged to engage in physical activity, maintain a healthy body mass, minimize use of tobacco and alcohol, ingest appropriate amounts of calcium and vitamin D, and avoid bone-resorbing drugs if possible. Bisphosphonates are currently the most efficacious treatments available for men with osteoporosis. Human PTH promises to be an effective anabolic agent, provided no unexpected adverse events are discovered in the course of ongoing human trials.

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