

Osteoporosis in Men

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Abstract

Osteoporosis is a significant threat to aging bone in men. Thirty percent of hip fractures occur in men; during initial hospitalization and the first year after fracture, the mortality rate is twice that of women. Nevertheless, osteoporosis in men is grossly underdiagnosed and undertreated. The most frequent factors associated with osteoporosis in men are age >75 years, low baseline body mass index (<24 kg/m²), weight loss >5% over 4 years, current smoking, and physical inactivity. Osteoporosis in men is either secondary to a primary disease or is idiopathic. It exhibits a bimodal age distribution, with peaks at age 50 years (secondary disease) and at age 70 years (idiopathic). Prevention and early detection currently are the best forms of management. Alone or in combination, calcium, vitamin D, bisphosphonates, and human parathyroid hormone are all effective management options. In the acute setting of fragility fracture, the orthopaedic surgeon is key in identifying patients at risk because the surgeon provides primary care and may initiate prophylactic measures to prevent future fractures.

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It is estimated that more than 2 million men in the United States currently have osteoporosis.^{1,2} Although a threat to successful aging, this issue is largely unrecognized. Osteoporosis in men silently progresses, with initial diagnosis typically made after hip or spine fracture. Even after such fragility fractures, osteoporosis in men is grossly underdiagnosed and undertreated.³ As the primary physician treating fractures, the orthopaedic surgeon can play a greater role in identifying men with osteoporosis for targeted intervention to prevent the possibility of future fractures.

Thirty percent of hip fractures occur in men, and during the initial hospitalization and in the first year following fracture, men have twice the mortality rate of women.³ Loss of independence often is a result of hip fracture; consequently, one third of men in this population move into

a nursing facility or the home of a relative.⁴ With the potential for 77 million men entering the at-risk age group in the next 15 to 20 years, the prevention, diagnosis, and treatment of men with osteoporosis is crucial to prevent fragility fractures.

Etiology

Although osteoporosis historically has been perceived as a disease of aging women, in 1992, the Framingham study indicated that loss of femoral neck bone density was linear with age and equivalent in men and women.⁵ In fact, osteoporosis is a disease of both young and old men, with a prevalence of 4% to 6% in men older than age 50 years. An additional 33% to 47% of men have osteopenia.¹ In absolute terms, 2.3 million men in the United States currently have osteoporosis, and 11.8 million have low bone densi-

Table 1
Comparison of Osteoporosis and Fracture Occurrence in Men and Women

Factor	Men	Women
Lifetime risk of osteoporosis ⁷	13%-25%	50%
Usual presentation	Fragility fracture, back pain, loss of height	Asymptomatic via DXA scan
Onset of osteoporosis ⁷	10 years later than in women; bimodal prevalence (at ages 50 and 70 years)	Prevalence skewed toward later years
Prevalence of osteopenia after age 50 years ^{7,15}	33%-47%	50%
Prevalence of osteoporosis after age 50 years ¹⁵	3%-6%	13%-18%
Causes of osteoporosis	50% idiopathic, 50% secondary	Most idiopathic
Peak bone mass	10% greater than in women	—
Lifetime risk of hip fracture at age 50 years ¹⁶	6%	17%
Incidence of hip fracture after age 65 years ¹⁶	5/1,000	10/1,000
Mortality within 1 year after hip fracture ¹⁷	31%	17%
Number of patients receiving treatment for osteoporosis 1-5 years after fragility fracture ¹	27%	71%
Prevalence of osteoporotic spine fracture	After age 50 years, 5% ¹¹	By age 60 years, 11.6%; by age 90 years, 51.7% ¹⁸

DXA = dual-energy x-ray absorptiometry

ty.² Evaluated according to race, the prevalence of osteoporosis in the United States is highest in Caucasian men (7%), followed by African-American men (5%) and Hispanic men (3%).⁶ The World Health Organization definition of osteoporosis is a T-score of at least 2.5 standard deviations below the mean bone mineral density (BMD) of young men (age 30 years). Although this standard was developed for women, it is currently being used in diagnosing osteoporosis in men. However, controversy exists as to whether the use of a standard developed for women accurately reflects the measure of BMD loss necessary for diagnosis of osteoporosis in men.⁷

As many as 85% of all hip fractures and 90% of all vertebral fractures in men are attributed to osteoporosis.⁸ Unlike the usual situation in women, however, osteoporosis in men typically is undiagnosed until the patient sustains a fragility fracture. Because men start with a higher peak BMD, they begin to experience fragility fractures 10 years later than the age at which women do (ie, 75 years). Thus, at approximately age 85 years, absolute BMD in a man generally is the same as that of a woman who began to sustain fragility fractures at approximately age 75 years. This is true for hip, vertebral, and distal radius fractures.

The incidence of fracture becomes similar between men and women with advancing age.⁹ Older age at fracture and increased age-related medical comorbidities result in men dying at twice the rate of women after hip fracture.¹⁰ More than 50% of the remaining men have chronic pain and require assistive devices for walking at 6 months.² After age 50 years, the prevalence of osteoporosis fragility fractures in men increases by 5%. These data are based on male life expectancy and comorbidity factors that may produce osteoporosis.¹¹

One recent study³ found the care of men with osteofragility to be limited. Conducted at a large tertiary medical center, the study compared the diagnosis and treatment of osteoporosis in men and women after hip fracture. Although both groups were matched for age, fracture, and fracture care, only 4.5% of men were referred for treatment of osteoporosis at the time of discharge versus 27% of women. At 1- to 5-year follow-up, treatment of men continued to lag behind women at a rate of more than 2.5:1. Further, most of the men who were treated received only calcium and vitamins without antiresorptive therapy to reduce osteoclast activity. At 1- to 5-year follow-up, only 11% of men had a BMD measurement, compared with 27% of women.

The economic costs of fragility fracture are high, for the individual patient as well as to the health care system in general. It is estimated that \$2.5 billion is spent annually in the United States in caring for men with osteoporotic fractures.¹² More hospital days are used to care for men with osteoporotic fractures than those with prostate cancer.¹³ The number of hip fractures in men is expected to increase 310% by 2050, versus 240% in women.¹⁴

Table 1 compares osteoporosis and fragility fracture occurrence in men and women. The prevalence of osteoporosis in men is lower than that in women for four primary rea-

sons. First, men accumulate more bone mass during development. Second, men do not experience the same abrupt hormone decline that women do at approximately age 50 years; rather, men experience a slow, steady decline in testosterone and bioavailable estrogen. Third, men historically have had shorter life spans than women and therefore have had less time to develop fragility fractures.¹⁹ With increased life expectancy, however, more men are now living long enough to develop osteofragility. Finally, although both men and women with age lose cancellous bone at peripheral sites, men begin with greater bone mass; thus, over their lifetimes, women lose more central trabecular bone and cortical bone than do men.^{20,21}

Risk Factors

Multiple risk factors have been attributed to the development of osteoporosis in men. Approximately half of these factors are a result of either genetics or age, with the remainder secondary to modifiable variables (Table 2). Bakhireva et al²² prospectively examined the predictors of bone loss in older men (aged 45 to 92 years) and determined that the most important factors were age >75 years, low baseline body mass index (<24 kg/m²), weight loss >5% over 4 years, current smoking, and physical inactivity. Sedentary men had greater BMD loss in the femoral neck and lumbar spine than did physically active men. Fracture risk increases, not only with low BMD (<18.5 kg/m²) but also with history of previous fracture, maternal history of hip fracture, and weight loss >10%.²³

Classification

Men develop osteoporosis as a result of primary or secondary causes. This results in a bimodal prevalence over time. Cross-sectional studies have shown that men have two distinct

Table 2

Risk Factors for the Development of Osteoporosis in Men^{7,22}

Modifiable lifestyle risk factors

- Excessive alcohol use (>7 oz/wk)
- Tobacco use
- Sedentary lifestyle
- Low body mass index
- Low calcium and vitamin D intake
- Medication
 - Anticonvulsants
 - Oral glucocorticoids
 - Cyclosporin
 - Methotrexate
 - Heparin

Nonmodifiable risk factors

- Age
- Family history of fragility fractures
- Prostate cancer with luteinizing hormone–releasing hormone analogue use
- Testosterone and estrogen deficiency
- Peptic ulcer disease
- Rheumatoid arthritis
- Hyperthyroid
- Hyperparathyroid
- Hypercalciuria

time frames for presenting with osteoporosis. The first, resulting from secondary or disease-related causes, occurs at approximately age 50 years; the second wave—idiopathic or age-related osteoporosis—occurs after age 70 years.¹⁹

Secondary Osteoporosis

It is more common for men than women to develop osteoporosis secondary to an underlying disease or metabolic derangement. At least 50% of the causes of osteoporosis in men are ascribed to other diseases or to lifestyle choices.¹ Categorically, these include genetic disorders, lifestyle choices, drug-induced bone loss, malabsorptive diseases, and endocrine disorders. Of these, the most frequent causes of secondary osteoporosis in men are excessive alcohol consumption, corticosteroid therapy, and hypogonadism.¹

Genetic Causes

The genes predisposing men to osteoporosis have not yet been identified. Several case reports, however, have implicated estrogens as key

players in the regulation of peak BMD in men. In these case reports, in which each patient was osteoporotic, estrogen was not available to bone, either because of a mutation in the estrogen receptor gene or an inability to convert androgens to estrogen.^{24,25} Several genetic disorders, including homocystinuria, Marfan syndrome, and osteogenesis imperfecta, are known to cause osteoporosis and osteopenia.^{26,27}

Lifestyle Factors

Lifestyle choices can have a profound impact on bone health. Chronic alcohol use (>7 oz/wk) directly suppresses osteoblast activity. Smoking lowers BMD and increases the risk of hip and vertebral fracture.^{28,29} Smoking also increases the risk of hip fracture by 40%. Low calcium and vitamin D levels, as well as insufficient sun exposure, also contribute to the development of osteoporosis. Although the literature shows mixed results, in general, inactivity is thought to contribute to loss of BMD.

Corticosteroid Therapy

Although multiple drugs are associated with osteoporosis and fragility fracture, chronic corticosteroid use (>5 mg/day for 6 months) is most commonly implicated. Potent inhaled corticosteroids also may affect bone health.³⁰ In a large retrospective study, Van Staa et al³¹ found a dose-dependent increase in the risk of vertebral, hip, and wrist fractures with corticosteroid use.

The negative effects of corticosteroids are mediated via several mechanisms. They inhibit intestinal calcium absorption with resultant secondary hyperparathyroidism. This leads to increased osteoclast activity and bone turnover in combination with decreased osteoblast activity.³² Corticosteroids also suppress sex hormone production at the gonads and through the pituitary gonadotropin pathway.

Hypogonadism

Testosterone deficiency, secondary to endocrine abnormality or pharmacologic suppression for prostate cancer, leads to decreased peak bone mass before puberty and bone loss after puberty.³³ It is unclear whether this is the result of increased bone resorption or of decreased bone formation. Stanley et al³⁴ reported a 6.5-fold increase in hip fracture in hypogonadal men. This is thought to be secondary to higher levels of sex hormone-binding globulin and resultant low levels of bioavailable androgen rather than to the absolute androgen level.²⁸

Idiopathic Osteoporosis

Primary, or idiopathic, osteoporosis is generally attributed to aging, although in actuality the exact cause is unknown. Idiopathic loss of BMD is credited to a variety of metabolic alterations, such as diminished androgen levels, decreased bioavailable estrogen levels, and reduction in insulin-like growth factor-I levels.³⁵

Although testosterone often is implicated as the key sex hormone

for male growth, the level of bioavailable estrogen is the major factor in maintaining bone density in men.³⁶⁻³⁸ Fracture status also is predicted by levels of bioavailable estrogen but not levels of testosterone.³⁹ Absolute levels of estrogen remain relatively stable over time; however, the amount available to interact on behalf of bones is dependent on the level of steroid hormone-binding globulin.⁴⁰ As levels of this molecule increase with age, the level of free estrogen available to interact with tissues decreases. By age 80 years, levels decline progressively to 30% to 50% of young adult values.⁴⁰ Estrogen prevents bone resorption; without adequate levels, the rate of bone turnover is greater than that of bone formation. This is evidenced by higher levels of urinary markers of bone turnover in the absence of bioavailable estrogen.⁴¹ Deficiencies in estrogen receptor- α also have been implicated in idiopathic osteoporosis.⁴²

Presentation and Screening

Often, men are first diagnosed with osteoporosis in association with a fracture. This need not be the case, however, if physicians remain cognizant of the man at risk for osteoporosis. Any man with a history of low-energy fracture to the hip, spine, or distal radius; radiographic osteopenia; chronic corticosteroid use; primary or secondary hypogonadism; chronically low body mass index; acute weight loss; or any of the other medication or lifestyle risks previously discussed should be considered for BMD screening. Even men with none of these factors but with height loss >1.5 inches should be tested because they may have asymptomatic vertebral fractures. Given that osteoporosis is greatest for men aged 70 years and older, physicians should consider routine screening at that age.

Treatment

Prevention

Treatment options for osteoporosis in men currently are limited; therefore, prevention is the rule. Boys should be encouraged to engage in weight-bearing sports exercise to maximize peak bone mass before puberty. In adulthood, men require calcium 1,000 mg/day to 1,500 mg/day and vitamin D 400 IU/day to 800 IU/day.⁴³ Oral supplementation is necessary because only 60% of older adults receive these levels from their diets,⁴⁴ and intestinal calcium and vitamin D metabolism are impaired with age.⁴⁵ Mechanical stimuli for bone formation should be provided via weight-bearing exercise to reduce the risk of hip fracture.⁴⁶ This exercise should continue throughout life because the bone benefits decrease when exercise is stopped. Alcohol intake must be limited to <60 g/day (four cans of beer or 2 oz of liquor), and tobacco use should be avoided.

Medical Treatment

A standard of care for treatment of osteoporosis in men is still being established, and currently, there are no guidelines for initiating therapy based on BMD alone. In general, however, treatment should be considered in the patient with a fragility fracture or in the presence of low BMD plus age >55 years and one risk factor, or age >65 years with no risk factors.⁷ When osteoporosis is secondary to another primary disease, addressing the osteoporosis by treating the underlying cause is usually effective only when the bone loss incurred thus far is not severe (Table 3).

Bisphosphonates

Two bisphosphonates currently are approved for use in men with osteoporosis: alendronate and risedronate. Etidronate currently is not approved for use in osteoporosis, although it is sometimes prescribed

off-label for this purpose. These pharmaceutical agents work by inhibiting osteoclastic bone resorption and stimulating osteoclast apoptosis (programmed cell death).

Alendronate was the first antiresorptive therapy approved for use in men and is an effective treatment for both primary and secondary osteoporosis. In a double-blind, randomized controlled trial of men aged 60 to 90 years with primary osteoporosis conducted by Orwoll et al,⁴⁸ subjects took alendronate 10 mg/day for 2 years. In subjects taking alendronate, bone loss was reversed in the hip and in the lumbar spine by 2.5% and 7.1%, respectively, and there was a decreased incidence of vertebral fracture. In addition, men in the study group lost 1.8 mm less height than did the control group. Alendronate is administered as either a daily oral dose of 10 mg or a once-weekly dose of 70 mg.

Recently, Ringe et al⁴⁹ completed a 1-year follow-up of 316 men with osteoporosis who were treated with daily dose of risedronate 5 mg. These patients had significant increases in lumbar spine (5%) ($P < 0.001$), femoral neck (2%) ($P < 0.001$), and acetabular (3%) BMD. The treatment group had a 60% reduction in new vertebral fractures and less height loss and back pain than did the control group.

Currently, bisphosphonates are the first line of treatment in men with osteoporosis. They are well tolerated, relatively inexpensive, and effective. In men unable to take bisphosphonates, human parathyroid hormone (PTH) may be considered.

Human Parathyroid Hormone

PTH, or teriparatide, was recently approved by the US Food and Drug Administration at a dose of 20 µg/day for treatment of osteoporosis. The drug increases bone formation by stimulating osteoblast differentiation, function, and survival.⁵⁰ This anabolic agent has been shown to increase BMD in men with primary or

Table 3

Summary of Risk Factors for and Treatment of Osteoporosis in Men⁴⁷

Risk Factor	Treatment
Glucocorticoid therapy: Long-term treatment with 5 mg/d for 6 mo	Bisphosphonate supplement with calcium 1,500 mg/d plus vitamin D 500 IU/d
Anticonvulsant therapy: phenytoin and phenobarbital decrease intestinal calcium absorption	Calcium plus vitamin D daily with antiresorptive therapy when BMD is low
Hypogonadal states	Testosterone replacement therapy
Low estrogen levels	No treatment currently proved effective. Use calcium plus vitamin D supplementation with or without antiresorptive therapy
Tobacco: Dose-dependent, multiple mechanisms	Cessation and calcium 1,500 mg/d plus vitamin D 500 IU/d with or without antiresorptive therapy
Excess alcohol: Toxic to osteoblastic function	Cessation and supplementation
Low body weight	Supervised muscle-building program
Existing fragility fracture	Obtain dual x-ray absorptiometry scan
Idiopathic age-related osteoporosis	Calcium 1,500 mg/d plus vitamin D 500 IU/d with or without antiresorptive therapy

secondary hypogonadism, who are at high risk of fracture upon falling.⁵¹ Lumbar spine and femoral neck density increased (13.5% and 2.9%, respectively) on intermittent doses of PTH 40 µg/day.⁵² A larger double-blind randomized study found that lumbar spine BMD improved substantially with use of PTH at either 20 µg/day or 40 µg/day. Vertebral density improved 12% to 18% over that of the control group.⁵³ PTH, however, is contraindicated in men with hyperparathyroidism, Paget's disease, renal disease, or bone cancer. Finkelstein et al⁵⁴ compared the use of either alendronate and PTH alone and both together over 2.5 years. PTH increased BMD in both the femoral neck and vertebrae more than did alendronate, either alone or in combination.

Summary

Recognition is the main hurdle to the effective treatment of osteoporosis

in men and subsequent prevention of fragility fractures. The consequences of low BMD in men can be greater than those seen in elderly women, yet osteoporosis in men remains underdiagnosed and undertreated. The pattern of osteoporosis in men has two age peaks, with secondary osteoporosis presenting at approximately age 50 years and primary osteoporosis at approximately age 70 years. Many of the risk factors for osteoporosis, including activity level, low body weight, smoking, alcohol use, and corticosteroid use, can be modified with proper patient education. When treatment is initiated, men must take calcium, vitamin D, and, when necessary, antiresorptive therapy. With heightened awareness, the orthopaedic surgeon not only can identify the men at risk for fragility fracture and act preemptively but also ensure that the patient who presents with fragility fracture is effectively treated with medical intervention.

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