Osteoporosis in Men

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Osteoporosis is a chronic, progressive disease characterized by low bone mass, bone deterioration, and decreased bone strength resulting in bone fragility and increased fracture risk.[1] Osteoporosis increasingly is being recognized as an important cause of morbidity and mortality in older men. Approximately 2 million men in the United States have osteoporosis,[2] and 1.5 million of these men are over the age of 65 years.[3]

The risk of osteoporosis increases with age but develops in men approximately 5 to 10 years later than in women.[4] The estimated lifetime risk of developing an osteoporotic fracture after the age of 50 years is 13% for men versus 40% for women.[5] Between 25% and 35% of hip fractures occur in men.[6] For reasons that are unclear, the mortality associated with hip fractures is higher in men than in women.[7] Men are twice as likely to die in the hospital following a hip fracture (14% versus 6% for women),[7] and it is estimated that 31% of men with hip fracture die within 1 year of the fracture versus 17% of women.[8]

Although osteoporosis is recognized as a debilitating condition in older men and a cause of significant morbidity and mortality, it remains poorly understood and is frequently overlooked in clinical practice. As the population of men over age 65 years continues to grow, physicians in various settings are increasingly likely to encounter male patients with or at risk for osteoporosis. Early recognition of these patients is essential to achieving better outcomes of care in men with osteoporosis. This article provides an overview of osteoporosis in men, with a focus on causes and risk factors, use of dual-energy x-ray absorptiometry (DXA) for screening and diagnosis, and treatment options.

TAKE HOME POINTS

- Osteoporosis is usually asymptomatic in men and commonly presents initially with low trauma fractures or an incidental finding of osteopenia on radiographs.
- About one third of men with osteoporosis have idiopathic disease; common identifiable causes of osteoporosis include hypogonadism, alcohol abuse, gastrointestinal diseases, vitamin D deficiency, anticonvulsant therapy, and glucocorticoid therapy.
- A bone mineral density more than 2.5 standard deviations below that of normal men is diagnostic of osteoporosis according to World Health Organization criteria.
- Once osteoporosis is diagnosed, secondary causes should be identified and treated, patients should receive calcium and vitamin D supplementation to achieve an adequate daily intake (≥ 1000 mg and 800 IU), and a weight-bearing exercise regimen should be recommended. Bisphosphonates are currently the pharmacologic therapy of choice.
- Serial bone mineral testing should be performed every 1 to 2 years to assess response to therapy.

BONE DEVELOPMENT AND CAUSES OF BONE LOSS

Bone mineral density in men increases markedly during puberty in response to sex hormone production. Peak bone mass is attained by age 20 years in men and women.[9] Men achieve greater peak bone mass than women. Areal bone mineral density is 8% to 10% greater in men,[10] and men have a greater bone width, resulting in a greater peak vertebral size and greater bone strength.[11] Men also have increased periosteal bone formation compared with women and thus undergo less disruption in their bone architecture due to age-related changes.[11,12] Men lose less bone mass due to a cessation of hormone production as there is no menopause equivalent in men.[10] All of these factors contribute to a greater total bone mass, a lower incidence of fragility fractures, and a lower prevalence of osteoporosis in men.

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Table 1. Causes of Osteoporosis in Men

Endocrine disorders
Hypogonadism
Hypercortisolism
Hyperparathyroidism
Hypercalcemia
Thyrotoxicosis
Vitamin D deficiency
Diabetes mellitus
Growth hormone deficiency
Delayed puberty
Hypervitaminosis A
Acromegaly
Dietary/lifestyle factors
Smoking
Alcohol abuse
Low calcium intake
Decreased physical activity/immobilization
Weight reduction
Drugs
Glucocorticoids
Thyroxine
Heparin
Anticonvulsants
Cyclosporine A and other immunosuppressants
Genetic disorders
Osteogenesis imperfecta
Homocystinuria
Marfan syndrome
Neoplastic disorders/hematologic disorders
Metastatic tumors
Multiple myeloma
Lymphoma
Leukemia
Chronic hemolytic anemia
Gastrointestinal disorders
Inflammatory bowel disease
Malabsorption syndromes
Cirrhosis
Renal disease
Renal failure
Hypercalciuria
Psychiatric
Anorexia nervosa
Other
HIV infection
Aging
Idiopathic

In addition to these sex-related factors, high levels of physical activity along with adequate intake of calcium and vitamin D help in achieving maximal peak bone mass.[13] Growth hormone, thyroid hormone, and the gonadal steroids all play an important role in skeletal development. The gonadal steroids are especially important, as shown by the fact that men who suffer constitutionally delayed puberty typically have lower bone mineral densities than age-matched normal counterparts.[14] In men, bone loss may begin at age 30 years, and within their lifetime, men lose approximately 30% of their trabecular bone and 20% of their cortical bone.[11] Lifestyle factors such as cigarette smoking and alcohol abuse accelerate bone loss.[15]

Osteoporosis may be classified as primary or secondary. In primary osteoporosis, bone loss results from age-related or unidentified causes. Secondary osteoporosis is caused by various chronic medical conditions, nutritional deficiencies, and medications (**Table 1**).[16,17] Epidemiologic studies suggest that a cause for osteoporosis can be identified in 40% to 60% of men presenting with osteoporotic fractures,[18] while approximately one third of men with osteoporosis have idiopathic disease.[16] Hypogonadism, alcohol abuse, gastrointestinal diseases, vitamin D deficiency, anticonvulsant therapy, and glucocorticoid therapy are among the more common identifiable causes of osteoporosis.[16,17]

CLINICAL FEATURES AND DIAGNOSIS

Osteoporosis is usually asymptomatic in men and commonly presents initially with low trauma fractures or an incidental finding of osteopenia on radiographs. Loss of height of more than 1.5 inches should prompt further evaluation for osteoporosis. In some cases, the diagnosis is suspected when a patient has a medical condition or drug exposure associated with osteoporosis.

Measurement of bone mineral density is considered the most accurate test for diagnosing osteoporosis, and it allows one to assess a patient's risk for fracture.[19] Prospective studies have suggested that a 1 standard deviation decrease in bone mass at the spine, hip, or wrist is associated with an approximate doubling of fracture risk.[20] The gold standard for diagnosing osteoporosis is measurement of hip or spine bone mineral density using DXA. This modality assesses the cortical and trabecular bone together but does not allow different rates of bone loss in the 2 compartments to be assessed. However, DXA remains the best noninvasive assessment of overall bone strength. The results are reported as density measurements in g/cm^2 as well as T-score and Z-score measurements. The T-score refers to the number of standard deviations from the mean

Table 2. World Health Organization Criteria for Diagnosis of Bone Status

T-Score	Classification
> –1.0	Normal
–1.0 to –2.5	Osteopenia or low bone mass
< –2.5	Osteoporosis
< –2.5 plus fractures	Severe osteoporosis

bone density values in normal sex-matched adults at age 20 years or at peak bone mass. The Z-score refers to the number of standard deviations from the mean bone mineral density of a normal age- and sex-matched reference population.

In current practice, the diagnostic criteria for men are the same as those used to diagnose osteoporosis in women; however, the T-score is computed by comparing the measured bone density to that of young men of the same race. A bone mineral density greater than 2.5 standard deviations below that of normal men is diagnostic of osteoporosis according to World Health Organization criteria (**Table 2**).[21,22] The International Society for Clinical Densitometry (ISCD) has provided recommendations on how to use T-scores to diagnose osteoporosis in specific age-groups (**Table 3**).[23] According to the ISCD, osteoporosis should be diagnosed for a T-score of –2.5 or less that is derived using a male reference database in men 65 years or older or in men 50 to 64 years who have other risk factors (eg, hypogonadism, alcohol abuse, glucocorticoid therapy).

It must be noted, however, that the definition for osteoporosis in men continues to be controversial. A consensus has not been achieved in defining the reference population for men, be it young men at peak bone density or premenopausal women at peak bone density. In addition, prospective studies are needed to define what criteria should be used to predict fracture risk in men or determine whether male-specific reference values for determining fracture risk should be established.

A cause for osteoporosis should be sought when the diagnosis is made. If a cause is not apparent after the initial history and physical examination, then further evaluation is warranted and may include the following laboratory tests: complete blood count; liver function tests; serum calcium, phosphorus, and creatinine levels; serum testosterone, thyroid-stimulating hormone, parathyroid hormone, and 25-hydroxyvitamin D levels; serum and urine protein electrophoresis; and levels of urine calcium and creatinine as well as 24-hour urinary free cortisol level. Multiple myeloma, kidney or liver disease, hypogonadism, hyperthyroidism, hyperparathyroidism, vitamin D deficiency, hypercalciuria, and Cushing's syndrome are a few of the causes of osteoporosis (Table 1) that should be identified and treated appropriately to prevent further deterioration in bone quality.

Table 3. International Society for Clinical Densitometry Recommendations on Using T-Scores to Diagnose Osteoporosis in Men

Population	Recommended Approach to Diagnosis of Osteoporosis
Men aged ≥ 65 yr	Base diagnosis on T-scores using World Health Organization criteria (see Table 2)
Men aged 50–64 yr	Both T-score ≤ –2.5 and other risk factors for fracture must be present
Men < 50 yr	Diagnosis should not be made on the basis of T-score alone

Adapted with permission from Indications and reporting for dual-energy x-ray absorptiometry. Writing Group for the ICSD Position Development Conference. J Clin Densitom 2004;7:37–44.

TREATMENT

Secondary causes of osteoporosis should be identified and treated. For example, patients with primary hyperparathyroidism have improved bone density after parathyroidectomy and patients with thyrotoxicosis do not experience further bone loss if thyroid levels are normalized. Adequate intake of calcium (≥ 1000 mg/day) and vitamin D (800 IU/day)[24] and a regimen of weight-bearing exercise are essential in preserving and enhancing bone mass in men with osteoporosis.[25] The National Institutes of Health consensus guidelines also suggest that men should increase their daily elemental calcium intake to 1500 mg after age 65 years.[24,26]

Several pharmacologic therapies have been shown to enhance bone mineral density in men. Bisphosphonates are currently the therapy of choice for the treatment of osteoporosis in men. Teriparatide is most commonly used as a second-line agent in patients who do not respond to bisphosphonate therapy, but it should also be considered in men with very low bone mineral density and fracture complications.[2]

Bisphosphonate Therapy

Bisphosphonates block the absorption of bone by inhibiting osteoclast activity. These agents were initially approved for the treatment of osteoporosis in women and have since been found to be effective in treating men. In 2001, alendronate was the first bisphosphonate to be approved by the US Food and Drug Administration for the

treatment of osteoporosis in men. A randomized, controlled, multicenter trial conducted in the United States and 10 other countries compared the effects of alendronate (10 mg/day) versus placebo on bone density in 241 men with osteoporosis; all patients received calcium and vitamin D supplementation.[27] After 2 years of therapy, men in the alendronate group had a 7.1% increase in lumbar spine density compared with men in the placebo group. Bisphosphonates (including risedronate) are effective in treating glucocorticoid-induced osteoporosis in both men and women.[28,29] The once weekly formulation of 70 mg of alendronate is the most commonly used treatment for male osteoporosis. In 2006, risedronate was approved for treatment of osteoporosis in men. Oral bisphosphonates are contraindicated in patients with hypocalcemia, untreated vitamin D deficiency, a history of hypersensitivity reaction, creatinine clearance of less than 35 mL/min, and esophageal strictures. Bisphosphonates should be taken at least 30 minutes prior to eating breakfast or taking other medications.

Parathyroid Hormone

Teriparatide (human recombinant parathyroid hormone [PTH 1-34]) stimulates bone formation. It is a portion of human PTH, the primary regulator of calcium and phosphorus metabolism in bone. Teriparatide has been approved for use in men at high risk for fracture or for those who have failed previous treatment with bisphosphonates. A randomized trial involving 437 men with spine or hip bone mineral density more than 2 standard deviations below the young adult male mean showed that teriparatide increased spine and femoral neck bone density compared to placebo.[30] It is administered by daily injection (20 µg subcutaneously) for a maximum duration of 2 years. Adverse effects include lightheadedness, nausea, arthralgias, and leg cramps. In addition, there is a potential risk for developing osteosarcoma. In the teriparatide randomized trial,[30] osteosarcoma occurred in Fischer 344 rats receiving high doses of teriparatide but did not occur in primates. Teriparatide should not be used in patients with a history of bone tumors, Paget's disease of the bone, hypercalcemia, and skeletal radiation exposure. Although teriparatide has been shown to reduce the incidence of fractures in women,[31] there have been no comparable controlled clinical trials in men.

Testosterone Therapy

Many studies have demonstrated that testosterone therapy increases bone mineral density in hypogonadal men with osteoporosis. In a study of 36 men with acquired hypogonadism, spinal bone density increased by 5% after 12 to 18 months of testosterone replacement therapy.[32] At this point, further studies are needed to demonstrate that androgen replacement therapy reduces the incidence of fractures in men. Before starting treatment with testosterone, all patients should undergo assessment of prostate-specific antigen (PSA) level and liver function tests. Patients with a history of prostate cancer or with elevated levels of PSA should not be prescribed testosterone, and a urologic examination should be recommended.

Calcitonin

Calcitonin has been approved only for treatment of postmenopausal osteoporosis, but its analgesic effect on the bone pain of acute vertebral fracture makes it an attractive off-label alternative treatment of osteoporosis in the acute phase of a bone fracture.[33] The analgesic effect is more pronounced during the first weeks of use after a fracture, and it helps decrease the use of other analgesic medications and the duration of immobilization.[34] Calcitonin is administered as a nasal spray, and the recommended dose is 200 IU daily in alternating nostrils. The side effects are minimal, with mild rhinitis being the most common.

Monitoring Therapy

The ISCD guidelines recommend that serial bone mineral testing should be performed every 1 to 2 years to assess response to therapy.[23] However, the testing interval may be adjusted based on the patient's clinical status. Serial testing should be performed with the same machine in order to improve accuracy. Other laboratory studies may also be appropriate on follow-up visits, depending on the choice of therapy. Monitoring renal function during bisphosphonate therapy and liver function and PSA level during androgen replacement therapy is essential. No special monitoring is necessary with the use of teriparatide. However, it can affect calcium levels, and mild hypercalcemia has been observed in some cases. Serum calcium should be checked 1 month after initiation of treatment with teriparatide. If hypercalcemia occurs, patients should be advised to stop taking dietary calcium supplements, reduce the dosing frequency of teriparatide to every other day, or both.[35]

PREVENTION AND SCREENING

Osteoporosis in men commonly presents with a vertebral or hip fracture, whereas in women it is more often diagnosed by routine screening.[36] Screening of asymptomatic men would be beneficial since a reliable test is available to establish diagnosis (DXA) and

appropriate intervention may decrease fracture risk as well as morbidity and mortality. The goal is to achieve earlier diagnosis and treatment of men at risk of developing osteoporosis. The ISCD expert panel suggests the following as indications for bone mineral density testing in men:[23]

- Age 70 years or greater
- History of fragility fracture as an adult
- History of conditions associated with low bone mass or bone loss as an adult
- Treatment with medications associated with low bone mass or bone loss
- Being considered for pharmacologic treatment
- Monitoring following diagnosis of osteoporosis or bone loss
- Not being treated for low bone mass but would be if evidence of bone loss were revealed

The International Osteoporosis Foundation[37] also recommends that men over age 70 years be screened for osteoporosis regardless of other risk factors, and both the foundation and the ISCD recommend screening earlier in life if there are identifiable risk factors.[23,37]

CONCLUSION

Osteoporosis in men remains a frequently overlooked condition even though it is recognized as a debilitating condition and a cause of significant morbidity and mortality in older men. A high index of suspicion must be maintained for men at risk and physicians of all specialties should be able to recognize the problem, initiate an appropriate work-up, and select treatment. **HP**

Test your knowledge and comprehension of this article with the *Clinical Review Quiz* on page 28.

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