Osteoporosis in men

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ABSTRACT

Osteoporosis and fragility fractures are more prevalent in men than previously assumed and mortality rates following a major osteoporotic fracture are higher in men as compared with women. There is still uncertainty on how to interpret bone mineral density (BMD) in men, and few prospective studies exist that have examined the association between BMD and fracture risk. Prospective studies that have evaluated fracture risk suggest that risk increases as BMD decreases in men in a similar way as described in women. Although data are limited, prior fragility fractures also increase subsequent fracture risks in both men and women. Prevention of osteoporosis in men is important and should begin during childhood. During adulthood, calcium and vitamin D and adequate physical activity play major preventative roles. There is minimal data to suggest treatment of osteoporosis in men on the sole basis of t-score BMD measurement. However, if therapy is necessary, bisphosphonate use should be the first choice for treatment in men.

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Until recently, the observation of osteoporosis in men was uncommon and when present it was typically described as a consequence of secondary causes rather than to slow bone loss as a natural process of aging. However, mounting epidemiological evidence is revealing that men have higher rates of osteoporosis[1] and fragility fracture[2,3] than previously assumed. Given the availability of therapeutic agents for the prevention and treatment of osteoporosis in men it is important to raise awareness as to its prevalence and the value of early diagnosis to help avoid or delay future fracture.

Epidemiology. Osteoporosis, as defined by bone mineral density (BMD) measurement, is less prevalent in men than in women. In the third National Health and Nutrition Examination Survey (NHANES III), a total of 14,636 men (3,090 >50) had their BMD measure at the proximal femur.[4] Data suggested that (using male-specific hip BMD cutoffs), approximately 3-6% and 28-47% of American men $\geq$50 years of age had osteoporosis, and osteopenia. The corresponding figures in women were 13–18% for osteoporosis and 37–50% for osteopenia. These data are very consistent with those of a European study, based on femoral neck BMD, in which the prevalence of osteoporosis was found to be 6% in men and 23% in women aged 50 years of age and older.[5] Greater accumulation of skeletal mass during growth and slower rate of bone loss contribute to the lower prevalence of osteoporosis relative to women.[6,7] Moreover, the shorter life expectancy of men further reduces the risk of fractures compared with women.[6,7]

Despite the lower prevalence of osteoporosis in men on the basis of BMD assessment, approximately 29% of 60-year-old men who do not receive preventive therapy will experience a fracture in their remaining lifespan.[8,9] In men, vertebral deformities occur with a similar prevalence as compared with women.[2] A total of 25-30% of hip fractures occur in men and they represent the most clinically serious fragility fractures.[10] Men have been shown to have higher rates of mortality associated with their fractures. Center et al[11] followed 2413 women and 1898 men to examine the mortality rates after different types of osteoporotic fractures. Data from the study indicated that 356 women and 137 men had a low trauma fracture (average follow-up is 5 years). For hip-proximal femur and vertebral fractures. the standardized mortality ratio was 3.17 (2.90-3.44) and 2.38 (2.17–2.59) for men as compared with 2.18

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(2.03–2.32) and 1.66 (1.51–1.80) for women. For other major fractures, including pelvic, distal femur, proximal tibia, multiple rib, and proximal humerus fractures, the standardized mortality ratio was 2.22 (1.91–2.52) for men and 1.92 (1.70–2.14) for women.

Diagnosis and risk factors. The diagnosis of osteoporosis is presently based on dual x-ray absorptiometry (DXA) BMD measurement. The World Health Organization's defines osteoporosis as a BMD t-score of ≤2.5. Bone mineral density measurements have been extensively used to identify asymptomatic individuals at risk for fracture and also to monitor the efficacy of treatment. This diagnosis is restricted for use in only postmenopausal white women. However, BMD has been used for comparable purposes for different races and in men without comprehensive investigation of the utility and validity of this measurement in these populations. As a consequence, there is still some uncertainty on how to interpret BMD measurements in men. Currently, there are no diagnoses or intervention thresholds for men. Nevertheless, BMD is an important determinant of fracture risk in men,[2,10,12,13] and has been found to be similar between sexes.[12,13] There are number of epidemiological studies which suggest the presence of a prevalent fragility fracture. This is an important factor for future fracture risk in both men and women. In an American study, pervious Colles fractures were significantly related to an increased risk of hip fracture in both men (RR=2.3; 95% CI=1.2–4.5) and women (RR=1.5; 95% CI=1.2–1.9).[14] In addition, a prior vertebral fractures were associated with high risks for subsequent vertebral fractures (standardized incidence 12.6; 95% CI=11–14), with men having a greater risk of refracture compared with women.[15] In a Scandinavian study, the association between prior forearm fracture and any future fracture was similar between the sexes.[16] Furthermore, in European Vertebral Osteoporosis Study it was concluded that a past hip fracture in men was a significant risk factor for future multiple vertebral fractures.[17] The largest study to date determined the risk of fractures requiring hospital admission following a vertebral deformity. The survey comprised 13.4 million hospital admissions of which 28,000 were for thoracic or lumbar vertebral fractures. The risks for subsequent fractures were generally similar in men and women.[18] There are several other risk factors that have been associated with developing osteoporosis in men. They include advanced age,[13,19] maternal history of fracture[20] marked testosterone deficiency,[21,22] low body mass index,[20] heavy alcohol consumption,[23-25] smoking,[20,26] low levels of physical activity[20,27] and corticosteroid use.[17,28]

Prevention of osteoporosis. The goal of preventive therapy is to avert bone loss and maintain bone mass. The prevention of osteoporosis in men must begin at childhood to ensure optimal attainment of peak bone mass during young adult life and should include assessment and advice regarding diet and lifestyle risk factors. Particular consideration should be given to low dietary calcium and vitamin D intake, sedentary lifestyle, excessive alcohol consumption, and smoking.

Calcium and vitamin D. A majority of studies report a slowing of bone loss with calcium and vitamin D therapy. A randomized controlled trial which supplemented community-living men and women (>65 years) with calcium (500 mg) and vitamin D (700 IU) for 3 years found significant treatment effects for BMD at the femoral neck, lumbar spine and total body and a significantly lower rate of non-vertebral fracture as compared with the placebo group.[29] Other investigations have reported positive effects of adequate calcium intake on BMD and fracture in men.[30,31]

Exercise. Exercise during growth is a influential stimulus that can augment peak bone mass and possibly decrease fracture risk.[31] Large, prospective epidemiological studies have shown that involvement in vigorous physical activity significantly decreases the risk of hip,[32,33] but not vertebral[34] fracture. The non-beneficial effect at the spine may reflect increased risk of traumatic vertebral fracture during activity. Unfortunately, in men most, the anti-fracture benefit observed with physical activity is lost after the cessation of exercise.[35] Perhaps the main role of exercise has on decreased fracture risk is strengthening muscle and enhancing muscular coordination, thereby decreasing the likelihood of falling.

Alcohol and smoking. There is abundant evidence supporting the argument that lifestyle choices have a noteworthy impact on bone health. For instance, in men, there is a significant risk of vertebral and hip fracture with heavy long-term alcohol consumption.[23,36] Tanaka et al[20] found that in Japanese men (>50 years) past and present smoking was significantly associated with low bone mass at the proximal femur.

Treatment. There is minimal evidence to recommend treatment of osteoporosis in men on the exclusive basis of t-score BMD measurement. Although, the prevention of low bone mass may be the best approach for life-long skeletal adequacy, there have been a number of promising therapies for the treatment of low BMD in men. To date, there has been a relatively large amount of data for the bisphosphonates.

Bisphosphonates. In a randomized placebo-controlled trial of osteoporotic men (a third with low serum testosterone) 2 years of alendronate (10 mg/d) therapy significantly increased BMD at

all measured skeletal sites and significantly decreased vertebral fracture incidence as compared with the control group (0.8% versus 7.1%; p=0.02).[37] In a 2-year open-label randomized controlled trial of 134 men with primary established osteoporosis and normal serum testosterone levels, the alendronate (10 mg/d) group exhibited significantly greater gains in lumbar spine (10.1% versus 2.8%) and femoral neck BMD (5.2% versus 2.2%) as compared to the alfacalcidol treated group (1 mg/day). The incidence rate of patients with new vertebral fracture was 18.2% and 7.4% for the alfacalcidol and alendronate groups (p=0.071).[38]

The utilization of bisphosphonates in the prevention and treatment of corticosteroid-induced osteoporosis is well documented.[39-43] In exclusive men study, the authors concluded that 5 mg/d risedronate was effective in both the treatment (lumbar spine only) and prevention (all skeletal sites) of corticosteroid-induced osteoporosis (>7.5 mg/d for >12 months) and significantly decreased the prevalence of vertebral fractures after one year of treatment.[44]

Sex hormones. Androgen replacement therapy has positive effects on BMD in hypogonadal men[45,46] particularly those with open epiphyses.[47] Testosterone replacement appears to be useful for increasing BMD at the lumbar spine in hypogonadal men; nonetheless, it has not been found to have a positive effect on BMD at cortical sites such as the hip or radius.

In men with normal gonadal function, who represent the majority of men with osteoporosis,[48] the impact of androgen therapy is less understandable. Anderson et al[49] conducted an open label, prospective trial to examine the effects of regular moderate androgen supplementation on BMD in 23 eugonadal men (mean age 58 years) with severe (all had vertebral fractures) idiopathic osteoporosis. Patients were treated every 2 weeks with intramuscular injections of 250 mg testosterone esters (Sustanon 250 (R)) for 6 months. Mean BMD at the lumbar spine increased 5% in 6 months whereas BMD did not change at the femoral neck.

Parathyroid hormone (PTH). Twelve months of daily subcutaneous injection of a synthetic PTH (1-34), combined with daily supplements of 1,25 (OH)2 vitamin D in middle-aged men with idiopathic osteoporosis and one or more vertebral fractures, significantly increased BMD at the spine, while no changes occurred at the radius.[50]

In a recent 18-month randomized controlled trial of idiopathic osteoporotic men, 400 IU of PTH (1-34) daily significantly increased lumbar spine BMD by 13.5% (QCT) and femoral neck BMD by 2.9% as compared with the control group.[51] Bone mineral density of the 1/3 distal radius showed no change from baseline in the PTH-treated group.[51] Parathyroid hormone is a potent anabolic agent for bone, particularly at cancellous sites. While changes in BMD in woman administered PTH for one year[52] were similar to what was observed in the trial for men,[51] the anti-fracture efficacy of this medication still needs to be established in men.

In conclusion, osteoporosis and fragility fracture are more widespread in men than previously assumed and carry significant consequences. The diagnosis of osteoporosis in men is complex due to methodological issues and a lack of consensus on how it should be defined. While there are less data available on men as compared with women concerning the relationship between BMD and fracture risk, BMD can precisely be measured in men and low BMD levels are associated with an increase in risk of fracture. Significant risk factors for osteoporosis and/or fracture risk in men include previous fragility fracture, family history of fracture, marked hypogonadism, heavy smoking, alcoholism, low calcium and vitamin D intake, body mass index, low physical activity, and medications such as corticosteroids. Although an increasing number of studies are designed at unraveling the prevention and treatment of osteoporosis in men, the field is still relatively new and more evidence is required to be collected before solid evidence-based recommendations can be developed. Prevention of osteoporosis is important and should start during childhood. When treatment is indicated, bisphosphonates and parathyroid hormone have been shown to be the most effective treatment for men with osteoporosis .

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