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Osteoporosis in men: An underrecognized and undertreated problem

Important risk factors for male osteoporosis include a prior fragility fracture, glucocorticoid use or alcohol consumption, a family history of osteoporosis, and hypogonadism.

ABSTRACT: Osteoporosis is a well-recognized problem in older women. However, there has been insufficient awareness among both the public and the medical profession that osteoporosis is also a common problem in older men. It is estimated that one in five 50-year-old men will sustain a fragility fracture during the remainder of his life. Although treatments that increase bone density are available, few men receive treatment. Until recently, treatment decisions in osteoporosis have been based almost entirely on bone density measurements. Recently, tools have been developed that enable a more precise assessment of absolute fracture risk, which is expected to significantly facilitate treatment decisions. It is hoped that a greater awareness of the problem of osteoporosis in men will lead to better treatment, and ultimately to a decrease in fractures and their associated morbidity and mortality.

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Although traditionally regarded as a disease of women, especially after menopause, osteoporosis also occurs frequently in men. Men steadily lose bone mineral density with aging, and one in five men over 50 will suffer an osteoporotic fracture. Almost 30% of all hip fractures are in men, and the mortality following a hip fracture is substantially higher in men than in women.[1,2]

Epidemiology

Trauma (usually falls), reduced bone density, and impaired bone quality all contribute to fracturing. Before age 50, men fracture bones more than women, probably because of exposure to more trauma. After 50, fractures increase with age in both sexes, but more so in women. So-called fragility fractures, occurring with minimal trauma such as a fall from standing height or less, frequently affect the hip, vertebrae, forearm (wrist), and humerus. Men represent between 20% and 40% of all patients with each of these types of fracture.

In men, the incidence of hip fractures increases sharply after age 75 and is greater at higher latitudes. There are racial differences in the frequency of hip fractures. There is evidence of a decline in age-standardized rates of hip fracture in men and women in Canada since 1985,[3] which may help to offset the increase resulting from aging of the population. Although both the 1-year mortality and the need for institutional care after a hip fracture are higher in men than women, men are less likely to receive investigation or treatment for their underlying osteoporosis.[4]

Vertebral fractures are often asymptomatic, and also often overlooked on X-rays (such as lateral chest X-rays);

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accurate data on the prevalence of such fractures are therefore difficult to obtain. Vertebral fractures are commoner in men younger than 50, but after 50, vertebral fractures, like other osteoporotic fractures, increase more rapidly in women. It is very important to identify vertebral fractures, as their presence is predictive of both further fractures at any site and increased mortality.

The simple question "How common is osteoporosis in men?" is unfortunately not as easy to answer as the corresponding question for women. The female patient's bone density is compared with that of a normal young (20- to 29-year-old) woman to derive a T-score. There has been debate about whether the bone density of male patients should be compared with that of normal young males (gender-specific) or with that of normal females, which results in different T-scores (0.5 to 1.0 SD units lower when normal male data are used) and therefore different frequencies of "osteoporosis" (defined as a T-score less than −2.5). Using the normal, young male value, 3% to 6% of men over 50 have osteoporosis, compared with a 22% gender-specific prevalence in women. However, the female prevalence rises steeply with age from less than 10% at 50 to 59 years of age to over 60% at over 80 years. In older women who develop an incident hip fracture during follow-up, between 64%[5] and 28%[6] of these fractures have been attributed to osteoporosis, based on T-scores at the femoral neck or the total hip respectively. The study that attributed 64% of incident hip fractures to osteoporosis also included men, of whom only 39% of those with hip fractures would have been classified as osteoporotic using a gender-specific comparator. This might suggest that more men than women fracture bones that are not "osteoporotic." More importantly, as has been repeatedly emphasized, a large proportion of individuals who suffer fragility fractures do not have osteoporosis by bone density criteria. This has been one of the major reasons for developing better instruments for predicting absolute fracture risk, such as the FRAX (fracture risk assessment) and the 2010 CAROC tool launched by the Canadian Association of Radiologists and Osteoporosis Canada.

In addition to bone quantity (as reflected in bone density), bone quality[7] and the extent of trauma are important determinants of fracture. Bone quality depends on the macrostructure or geometry of bones (e.g., the length and diameter of the femoral neck) as well as the microstructure, which includes the thickness and porosity of the outer cortex,[8] and the interconnections between, and number of trabeculae. The rate of bone turnover is an additional determinant of bone strength. Newer technologies, especially quantitative computerized tomography (QCT) and high-resolution peripheral CT (HRpQCT) are beginning to shed light on some of these characteristics, but at present these are mainly research tools.[8-10]

Pathogenesis of bone loss in men

Bone loss in men has many causes, and often the same patient is affected by several of these. As in women, it is useful to distinguish between primary and secondary osteoporosis. Primary includes age-dependent and idiopathic osteoporosis. The chief causes of secondary osteoporosis in men are excessive alcohol use, treatment with glucocorticoids, and hypogonadism, including that experienced by men receiving androgen deprivation therapy (ADT) for prostate cancer.[11]

Men lose trabecular bone from about age 40 onwards,[1] but they do not have the accelerated loss in midlife that occurs in women, and hence their trabecular bone is better preserved in old age. Furthermore, men tend to preserve their trabeculae (which become thinner), whereas women lose trabeculae as well as their interconnections, which results in a greater loss of bone strength.[6] The loss of cortical bone begins later,[1,8] and is also less marked in men than women. With aging, there is periosteal addition of bone, together with expansion of the marrow cavity, so that the bone diameter enlarges, which to some extent provides a compensatory increase in bone strength.

There is great interest in the role of sex steroids in contributing to osteoporosis in older men, even in the absence of overt hypogonadism.[12] Both testosterone and estradiol are present in the blood; most of the estradiol (85%) is derived from testosterone by peripheral aromatization. Sex hormone binding globulin (SHBG) increases with age, necessitating measurement of bioavailable levels of testosterone and estradiol. For some time we've known that bone density, rate of bone loss, and fracture incidence all correlate more closely with estradiol than with testosterone levels.[2] Furthermore, increased bone turnover was shown to be suppressed by estradiol and not by testosterone in older men in very elegant studies.[13] Interestingly, the threshold level of bioavailable estradiol below which bone turnover and bone loss are accelerated appears to be similar in men and women, at around 40 pmol/L.

Other potential endocrine contributors to bone loss in aging men include parathyroid hormone (PTH), in part secondary to vitamin D deficiency (as in women), growth hormone, and insulin-like growth factors (IGF-1).

Nutritional factors potentially contributing to osteoporosis include

deficiencies of vitamin D, calcium, and protein. Vitamin D deficiency was found in 26% of osteoporotic males, and "insufficiency" in 72%[14] in MrOs, the very large multicentre study of male osteoporosis in the US. Vitamin D deficiency is best assessed by measuring the serum level of 25hydroxyvitamin D using a precise method, preferably mass spectrometry. The indications for measurement of the 25hydroxyvitaminD level are controversial; it should be considered in certain patient groups known to be predisposed to vitamin D deficiency, such as those with malabsorption, dark skin pigmentation, or obesity. Osteoporosis Canada has recommended that 25hydroxyvitamin D be measured in all patients receiving antiresorptive treatment for osteoporosis, preferably after they have been taking the recommended vitamin D supplement for at least 3 months. Calcium deficiency should be avoided by ensuring a total intake from diet and supplements of 1000 to 1200 mg per day, and recognizing that calcium may be more important in achieving a good peak bone mass during earlier life than for treating osteoporosis in later life. Dietary protein deficiency may be a problem in the very elderly. Both vitamin D and protein deficiency can contribute to muscle weakness and therefore to falls and fractures.[15]

Osteoporosis in males younger than 60 in the absence of obvious causes (idiopathic male osteoporosis) may have genetic causes such as adult forms of osteogenesis imperfecta. In other patients there may be abnormalities of SHBG, IGF-1, or of aromatization of testosterone to estradiol. In another group of osteoporotic men, often identified because they also have renal calculi, urinary calcium is increased (so-called idiopathic hypercalciuria). As a group, men with renal stones, most of whom have idiopathic hypercalciuria, have reduced bone densities[16] and an increased frequency of fractures.[17] Smoking is also a risk factor for osteoporosis, and for fractures, and is included when using the FRAX tool to calculate absolute fracture risk.

In the US, the National Osteoporosis Foundation recommends that pharmacological treatment for osteoporosis be considered if the T-score at any site is −2.5 or below, or if the 10-year risk of major osteoporotic fracture exceeds 20%, or if the 10-year risk of hip fracture exceeds 3%.

Case-finding and diagnosis of osteoporosis in men

The guidelines for evaluating osteoporosis in men are not well validated. Some organizations have recommended routine bone mineral density (BMD) screening of men by dual X-ray absorptiometry (DXA) at age 65[18] or at age 70 or 75, but a recent study suggested that it may not be cost-effective before age 80.[19] Qualitative ultrasound and CT bone screening are not standardized. Bone density measurement by DXA clearly has predictive value for fractures at a population level. As in women, a gender-specific T-score of less than −2.5 (as provided on the DXA printout) has been used to define osteoporosis in men over 50. The presence of an unequivocal fragility fracture is also diagnostic of osteoporosis. Estimation of absolute fracture risk, using assessment instruments such as the CAROC tool or the FRAX tool, is clearly an improvement over the use of DXA alone. Both tools have been thoroughly validated in Canadian populations.[20,21]

FRAX calculates absolute fracture risk using age, weight, presence or absence of prior fragility fracture, parental history of hip fracture, current smoking, glucocorticoid use (ever), rheumatoid arthritis, and use of three or more units of alcohol per day. If available, a density measurement of the femoral neck bone obtained by DXA can also be included in the calculation. The output is the 10-year risk of major osteoporotic fracture (including wrist, humerus, vertebra, and hip) and the 10-year risk of hip fracture alone. In the US, the National Osteoporosis Foundation recommends that pharmacological treatment for osteoporosis be considered if the T-score at any site is −2.5 or below, or if the 10-year risk of major osteoporotic fracture exceeds 20%, or if the 10-year risk of hip fracture exceeds 3%. In some jurisdictions, FRAX without a DXA bone density measurement is being used, or proposed,[22] to assign patients to one of three groups: "low fracture risk (<10% 10-year risk of any major osteoporotic fracture)," requiring only lifestyle advice; "intermediate risk (10% to 20%," requiring further refining of fracture risk,

perhaps with the help of BMD testing; and "high fracture risk (>20%)," requiring consideration of pharmacological treatment without need for BMD testing. Individuals with positive risk factors should have a fracture risk assessment, with or without a DXA study. It should be emphasized that the FRAX tool is a useful guide, but it is not prescriptive—the physician's judgment remains important, together with the patient's own choice. Like FRAX, the 2010 version of CAROC also uses the femoral neck BMD, together with age, sex, and history of fragility fracture or glucocorticoid use, to categorize patients as low, intermediate, or high risk of major osteoporotic fractures. There is excellent concordance between FRAX and CAROC.

The 2010 Osteoporosis Canada Guidelines[18] provide clear indications when to consider BMD testing in patients younger than 50, and in the 50 to 64 age group, and recommend BMD testing in all men (and women) 65 or older. BMD testing then allows fracture risk assessment using FRAX or CAROC. As with the "FRAX without DXA" approach described above, patients who are categorized as low risk (<10% 10-year risk for any osteoporotic fracture) should receive lifestyle advice only, and those categorized as high risk (>20%) should be considered for pharmacotherapy, usually a bisphosphonate. In the intermediate risk group (10% to 20% 10-year fracture risk), particular attention should be directed toward identifying vertebral fragility fractures (which, like other fragility fractures, imply high risk). Several other factors should also be considered, including rapid bone loss, ADT, a disproportionately low spinal BMD, and recurrent falls, since these may indicate that more aggressive treatment (pharmacotherapy) is required.

Most drugs shown to be effective in postmenopausal women—either in improving bone density, or preferably in reducing fracture risk—are similarly effective in men. Exceptions, of course, are estrogens and selective estrogen receptor modulators.

Laboratory evaluation[18] is mainly directed at identifying secondary causes of osteoporosis, and usually includes serum protein electrophoresis and testing for CBC, serum calcium and albumin (for calcium correction), alkaline phosphatase, creatinine, TSH, and perhaps 25hydroxyvitamin D. In addition, tests to exclude specific disorders may be considered if indicated: PTH, 24-hour urine calcium, serology for celiac disease, testosterone, and luteinizing hormone. Although estradiol is clearly of great importance in the pathophysiology of male osteoporosis,[12] the accurate measurement of bioavailable estradiol involves complex technology and is not yet routinely available. It is likely to become an important part of the investigation of male osteoporosis in the future, when these technical problems are resolved and when it is translated into new and effective treatments for male osteoporosis. Markers of bone formation and resorption are only occasionally useful in the individual patient, but are widely used for investigative purposes.

Treatment

Much less information is available regarding the pharmacological treatment of osteoporosis in men compared with women. However, the available data suggest that most drugs shown to be effective in postmenopausal women—either in improving bone density, or preferably in reducing fracture risk—are similarly effective in men. Exceptions, of course, are estrogens and selective estrogen receptor modulators (SERMs such as raloxifene), which are not used in men because of their feminizing effects.

Among the bisphosphonates, alendronate, risedronate, and zoledronate have positive effects on BMD and vertebral fracture risk. Bisphosphonates are equally effective in improving bone density in men with normal or low testosterone levels, and the decision to use androgens should be made independently of the decision to use a bisphosphonate.

Parathyroid hormone (teriparatide) improves bone density in men as it does in women, but has not yet been proven to reduce fractures in men.

Thiazide diuretics may have a positive effect on bone. Both improved BMD[23] and a reduction in hip fractures[24] have been reported with thiazide treatment, and a few men with idiopathic hypercalciuria and osteoporosis have shown a rapid recovery

in bone mass when treated with hydrochlorothiazide.[25] Whether this is a result of the thiazide-induced reduction in urinary calcium excretion, or possibly due to a direct effect of thiazide on bone, is not known.

Strontium ranelate (available in Europe but not North America) and calcitonin have not been well studied in men.

Denosumab (Prolia), the newly released monoclonal antibody to RANKL (receptor activator of nuclear factor kappa-B ligand), acts as an osteoclast suppressor. In men receiving ADT for prostate cancer, denosumab (given twice yearly by subcutaneous injection) caused an increase in BMD at all sites, and decreased vertebral fractures.[26]

Sex steroid therapy requires further study. In symptomatic hypogonadism, testosterone is appropriate, and improves bone density as well as increasing muscle mass and strength. How much of the bone effect is due to aromatization to estradiol is not known. More controversial is the use of testosterone (administered by injection or transdermal gel or patch) in older asymptomatic males with low testosterone levels. There has been some concern about potential adverse effects on the prostate and on lipid levels, as well as an increased risk of cardiac events.[27] Both PTH and bisphosphonates are as effective in improving bone density in hypogonadal as in eugonadal males. Testosterone has also been recommended in various forms of secondary osteoporosis, such as that due to glucocorticoid treatment, and may help, even if mainly by improving muscle mass and strength.

In view of the demonstrated role of estradiol, estrogen might be expected to help the osteoporosis of hypogonadal males, but its feminizing action precludes long-term use. Similarly, raloxifene has been shown to reduce bone resorption in men in short-term studies.

Calcium, vitamin D, and exercise recommendations for men are similar to those for women. It seems prudent to ensure a total daily vitamin D intake from food and supplements of 1000 to 2000 units. An insufficient intake of calcium (less than 1000 mg per day) should be avoided, preferably by consuming adequate high-calcium foods, but if necessary by taking calcium supplements. Inactivity can contribute to bone loss, and appropriate strategies can reduce the risk of falling,[28] particularly exercises designed to improve balance, such as tai chi.

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Summary

Osteoporosis in men is an important and inadequately appreciated problem. This is partly a result of the earlier disproportionate emphasis on osteoporosis in women, especially following menopause. Both primary care physicians and members of the public need to maintain an awareness of male osteoporosis so that patients who are at risk for fractures are appropriately assessed and treated. Among important risk factors are a prior fragility fracture (including an asymptomatic vertebral fracture), glucocorticoid use or heavy alcohol consumption, a family history of osteoporosis, and frequent falls. The new tools for assessment of absolute fracture risk, FRAX and CAROC, are useful in guiding the treatment of osteoporosis. Bisphosphonates are effective in improving bone density in men with normal or low testosterone levels, and appropriate exercise and fall-reduction programs can help to reduce injuries. The identification and treatment of persons at risk for fragility fractures aims to reduce the substantial morbidity, mortality, and costs that result from osteoporosis-related fractures.

Competing interests

Dr Dian has received funding from Novartis, Amgen, Merck, and Lilly for his involvement in research and CME events related to the treatment of osteoporosis.

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