

Osteoporosis in men

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Osteoporosis was once thought inappropriately to be an inevitable consequence of aging. This disease has assumed increasing importance, especially in women, because of the morbidity and mortality associated with fractures and the burgeoning public health burden that this represents. However, more recently, it has been recognized that men also lose bone density with advancing age and are subject to osteoporotic fractures. One in 8 men beyond the age of 50 will have an osteoporotic fracture and some 30% of hip fractures – representing the greatest health care burden – occur in men. Moreover, the mortality following a hip fracture is greater in men than women. Until recently, osteoporotic fractures in men have been a neglected health problem, but this area has now become the subject of renewed interest and investigation.

Epidemiology of osteoporosis and fractures in men

Much less is known about the epidemiology of osteoporosis and osteoporotic fractures in men than in women. As well, not much is known about male osteoporosis in different populations and ethnic groups. Interestingly, men have more fractures than women early in life, probably as a result of trauma. However, around the age of 50 to 60, this pattern is reversed with fragility fractures of the vertebrae, wrist/arm, humerus and elsewhere being more common in women. In the Rochester Epidemiology Project in Minnesota and the Dubbo Epidemiology Project in Australia, lifetime fracture risks beyond the age of 50 and 60, respectively, were estimated (Table 1). Of the approximately 1.7 million hip fractures worldwide in 1990, about one-third occurred in men and the mortality associated with hip fracture in elderly men >75 years of age was 30% versus 9% for women. It is thought that a greater number of co-morbid conditions at the time of fracture contribute to the increased mortality risk.

Vertebral fractures were considered uncommon in men and most were thought to be related to trauma earlier in life. However, recent information suggests that the incidence of clinically apparent vertebral fractures is about half that of women. In fact, in persons over 65 years of age in the Dubbo study, the prevalence of spine fractures was similar for men and women (between 10%-20%). In the European Vertebral Osteoporosis Study (EVOS), similar data were obtained



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Table 1: Osteoporosis in men

	Risk (%)
Rochester Epidemiology Project*	
Estimated lifetime fracture risk at age 50 years	
Proximal femur	6.0
Clinical vertebral	5.0
Distal forearm	2.5
Any of the above	13.1
Dubbo Osteoporosis Epidemiology Study†	
Lifetime atraumatic fracture risk	
60 years of age	25.6
70 years of age	20.6
80 years of age	9

* Data from reference 10

† Data from reference 9

when the age standardized prevalence of vertebral deformity was estimated for men and women (around 12%-20%).

In summary, by age 80, 1 in 10 men have had a fracture. Hip, spine, and humerus fractures increase with age and there is a 5-fold increase in multiple fractures in men >75 years of age compared to those in their early 60s. Recent updated estimates for men suggest an 11% prevalence of hip fractures compared to 23% for women, and an associated 3.2-fold increase in mortality in men versus a 2.2-fold increase in women. For vertebral fractures, there is a similar prevalence in men and women between the ages of 50 and 80. Very recent data have suggested a 2.4-fold increase in mortality with vertebral fractures and this all-cause mortality is higher in men than in women (relative 5-year survival is 0.84 in women and 0.72 in men).

Etiology and pathogenesis

Osteoporosis in men is not a homogenous entity with a single causative factor; rather, it is the result of genetic and environmental interactions influencing, among other things, peak bone mass, bone size, and micro architecture.

According to Seeman, bone in men is less fragile compared to women because there is :

- a higher peak bone mass and size (cross-sectional area)
- less bone loss as a percentage of the peak bone mass in men
- trabecular thinning, secondary to reduced bone formation, rather than trabecular plate perforation and loss of connectivity (giving rise to increased weakness) as occurs in women
- less cortical bone thinning due to a reduced extent of endocortical resorption and in men greater periosteal bone formation, and
- less intracortical porosity in men.

All of these features give rise to the gender differences in fragility between men and women. Moreover, longitudinal studies have shown that although men do not have an accelerated phase of bone loss that is equivalent to the one experienced by women at menopause, there is an increase in bone loss with age that is greater in trabecular bone than in cortical bone. This loss can reach about 1% per year in older men.

Interestingly, bone loss in men is primary through diminished bone formation. While endocortical bone resorption occurs in both men and women (greater in women than men), subperiosteal bone formation is greater in men than women. This increases the outer diameter of the axial and appendicular skeleton. The net result is a relative maintenance of cortical thickness in men compared to women and, in addition, an increase in the diameter of male long bones that helps prevent fracture by conferring an additional mechanical advantage and increased strength to the bone.

Bone mineral density (BMD) and risk factors for osteoporosis and fracture

The definition of osteoporosis proposed by the World Health Organization Expert Panel in 1994 was based on data from post-menopausal white women. Whether these same criteria can be used for defining osteoporosis in men is a moot point.

Real bone mineral density, as determined by DEXA, is higher in men than women, but volumetric density (as identified by QCT) is similar. Analysis of fracture risk has been complicated by these differences in men and women. Cross-sectional studies have shown lower bone density in men with fractures compared to those without. Yet, men fracture at a higher bone density than women. After adjusting for bone size, however, men and women seem to fracture at similar bone density values and gender-specific T-scores of bone density. Because we still have few studies that have attempted to relate bone density changes to eventual fracture risk, one cannot be certain about the implications of bone density levels or the definition of a fracture threshold. Nevertheless, the probability of fracture decreases as the bone density increases. BMD does seem to predict fracture in men, and males and females have equivalent risks of fracture for equivalent BMD levels. For the present, the bone mineral density *modus operandi* is to use a similar approach for men and women applying the -1 and -2.5 standard deviation thresholds (“T-scores” based on the density levels in young normal males) to identify osteopenia and osteoporosis.

As with women, the etiology of male osteoporosis can be divided into primary or idiopathic, accounting for 40-50% of cases and secondary causes. The most common secondary causes are glucocorticoid usage, hypogonadism, and excess alcohol intake. The risk factors for osteoporosis and fractures are multi-factorial (Table 2). The sex hormones, both androgens and estrogens, are important for normal bone development and retain this importance throughout life. Several interesting experiments of nature have emphasized the importance of both testosterone and estrogen in the development of the male skeleton and its lifelong maintenance. Some men were identified with mutations in the gene for the aromatase enzyme which converts testosterone to estrogen, while other men were found to have genetic mutations leading to the absence of the estrogen receptor. As

Table 2: Some risk factors for osteoporotic fractures in men

• ↓ BMD	• Co-morbidity
• ↓ BMI	• Hypogonadism (testosterone deficiency)
• Previous fracture	• Alcohol abuse
• Height loss	• Smoking
• Physical inactivity	• Corticosteroid use
• Muscle weakness (especially quadriceps)	• Psychotropic drugs
• Higher body sway	• ↓ vitamin D
• Falls	• COL 1A-1 gene polymorphism

expected, in men with the aromatase enzyme defect, estrogen treatment (but not testosterone) resulted in improvement in bone density. There was no such improvement among men with mutations in the estrogen receptor when given estrogen. It appears that both estrogen and androgen are necessary for peak bone mass development in the male skeleton and both are required for optimal skeletal growth. Moreover, it seems that testosterone is necessary for the periosteal bone growth that occurs with age, giving rise to greater cortical width and bones of larger diameter. Interestingly, however, in older men, cross-sectional studies have not been able to show a consistent association between testosterone levels and bone density, whereas low estradiol levels are strongly associated with low bone mass. In addition, in some studies of testosterone therapy in older men with osteoporosis, bone density increase was better correlated with changes in estradiol than changes in testosterone.

Although the data are still somewhat confusing and more studies are required, sex hormone deficiency is an important cause of bone loss in men. Testosterone does fall with age for a number of reasons, although there is no abrupt loss similar to the fall in estrogen at menopause in women. However, no studies have reliably identified the level of serum testosterone (or estradiol for that matter) that may be regarded as “hypogonadal” for the male in the context of skeletal health. Much more study is required to define the level of these

sex steroids and the level at which bone balance becomes negative, thus allowing one to predict the development of low bone density.

Other important hormonal factors undergoing intensive investigation include growth hormone and insulin-like growth factors (IGF-1). Both have been shown to decrease with advancing age and there is speculation concerning their role in the age-related decrease in bone density. IGF-1, and one of its important binding proteins IGFBP-3, are positively associated with bone density. IGF-1 levels may be reduced among men with fractures. Moreover, there are important associations between the sex hormones, growth hormone, and different growth factors. Nevertheless, growth hormone treatment does not appear to have a conspicuous effect on bone density, and there have not been any fracture studies.

Prevention and treatment of male osteoporosis

Since there is, at present, little evidence-based data from clinical trials with fracture endpoints in men, many recommendations have been extrapolated from guidelines developed for women. It is clear that prevention of low bone density and the risk for fracture requires measures to achieve peak bone mass, as well as to prevent bone loss and skeletal trauma (ie, falls). Those at high risk for osteoporosis and fractures because of secondary conditions or high risk lifestyle activities (eg, smoking, excessive alcohol consumption, etc.) should be identified. Patients should be counseled about lifestyle modifications and prudent appropriate exercise should be recommended. While the data concerning calcium and vitamin D supplementation are not definitive, most studies point to a benefit from calcium supplementation to slow down bone loss. Moreover, an adequate calcium intake early in life is necessary

to achieve optimal peak bone density. Although there is no absolute consensus concerning optimal calcium and vitamin D intake, a reasonable approach is to suggest at least 1000-1500 mg of elemental calcium per day and 800-1000 units of vitamin D. It is thought that these amounts of calcium and vitamin D will be of potential benefit in all elderly individuals, particularly to decrease the development of secondary hyperparathyroidism and osteomalacia.

Testosterone deficiency plays a central role in the development of osteoporosis, both alone and through its aromatization to estrogen. Hypogonadism is present in some 20% of men > 60 years and increases significantly with age. About 50% of men with spine and hip fractures have hypogonadism. Thus, it is important to exclude hypogonadism in all men presenting with osteoporosis and consider treatment, especially among those with spine and hip fractures where the prevalence is even higher. There have been a paucity of prospective randomized controlled trials to guide treatment recommendations, but what studies exist, show that testosterone therapy can significantly increase both trabecular and cortical bone density in hypogonadal men (and possibly even eugonadal men) with vertebral crush fractures. Clearly more studies are required, particularly with fracture endpoints. However, among men with hypogonadism, testosterone therapy should be offered alone or as adjunctive therapy. The usual contraindications to androgen therapy apply.

Bisphosphonate therapy has been a cornerstone of osteoporosis treatment in women. Although there have been no large randomized anti-fracture trials with bisphosphonates in men, a bone density endpoint trial was recently reported by Orwoll confirming the efficacy of alendronate in improving bone density at the spine and the hip. Moreover, in a

sub-analysis there was a statistically significant reduction in morphometric vertebral fractures. From this trial and data with other potent bisphosphonates, such as risedronate, the bisphosphonates should be regarded as appropriate treatments for men with either primary or secondary osteoporosis and fractures.

Most of the treatments in current usage are bone resorption inhibition therapies. On the horizon are exciting possibilities with bone formation stimulating treatments, including parathyroid hormone and possibly other growth factors (eg, growth hormone, analogues of IGF, bone morphogenetic proteins) still in the early stages of development.

Conclusion

The importance of osteoporosis in men and the consequences of fragility fractures is now being appreciated as a significant, hitherto relatively neglected, public health concern. While osteoporosis in men and women have many similarities, there are some interesting differences. Bone loss is clearly the result of a bone remodeling imbalance over time that is not so much due to increased bone resorption, as reduced bone formation. Our therapies, while not entirely empirical, have been guided by studies in women, and carefully controlled, randomized, anti-fracture clinical trials in men are required. It is clear that hypogonadism is an important causative factor in the development of bone fragility. It should be investigated and treated. While all risk factors should be identified, it is particularly important to correct the most common of these, (ie, alcohol excess, tobacco use, glucocorticoid therapy).

This rapidly emerging, worldwide problem needs urgent attention and large clinical fracture endpoint studies to guide evidence-based recommendations for prevention and treatment.

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Abstracts of Interest

Recombinant Human Parathyroid Hormone (1-34) therapy reduces incidence of moderate/severe vertebral fractures in men with low bone density.

ORWOLL E, SCHEELE WH, CLANCY AD ET AL. PORTLAND OR

Recombinant human parathyroid hormone (1-34) [rhPTH(1-34)], given once daily increased vertebral bone mineral density (BMD) and reduced vertebral fractures by 65%- 69% in postmenopausal woman with osteoporosis (19-month median PTH exposure). Osteoporosis is common in men but there have been few large trials of therapies to prevent fractures in men. Thus, we performed a randomized, double-blind, placebo-controlled, clinical trial of the effects of rhPTH(1-34) on bone mineral density in 437 men (mean age 59 yr) with spine or hip BMD > 2 SD below male young adult mean. Men were randomly assigned to receive placebo (n=147), PTH 20 µg/day (n=151) or PTH 40 µg/day (n=139) by once-daily subcutaneous injections. The median study drug exposure was 11 months. After stopping therapy, 81% (355) of the men volunteered for an 18-month observation study of subsequent effects on BMD (data not shown) and fractures. During the treatment and observation periods, all subjects received daily calcium and vitamin D supplements. Other osteoporosis treatment use was reported by 22% (79/355) of the men (placebo, 29%; PTH20, 16%; PTH40, 22%) during the observation period. Vertebral fracture incidence was assessed from lateral spinal radiographs using a semi-quantitative grading score in 269 men with radiographs at both the original study baseline and 18 months after

discontinuation of rhPTH(1-34), (placebo, 101; PTH20, 87; PTH40, 81). At baseline, 41% of the men had ≥ 1 prevalent vertebral fractures. During the entire study period (median 30 months), 22 men had at least one new vertebral fracture [placebo=12 (12%) and combined PTH=10 (6%)]. For the combined PTH treatment groups, the relative risk of new vertebral fractures was 0.50 (P=0.086; 95% CI, 0.23-1.12), comparable to that found in women during a similar observation period (RR=0.53; P<0.001; 95% CI, 0.42-0.68). There were fewer men with moderate or severe vertebral fractures in the PTH treatment groups than in placebo [placebo=7 (7%); combined PTH=2 (1%)]; relative risk 0.17 (P=0.029; 95% CI, 0.04-0.81). Therefore, rhPTH(1-34) treatment over 11 months significantly reduced the risk of moderate or severe vertebral fracture during a 30-month period, including 18 months following discontinuation of parathyroid hormone treatment. rhPTH(1-34) is an effective therapy for osteoporosis in men.

J Bone Miner Res 2001;16(suppl 1):S162 Abstract #1104.

Effect of cigarette smoking and alcohol consumption on bone mineral density in men – Data from the Canadian Multicentre Osteoporosis Study (CaMos).

OLSZYNSKI WP, POLISCHUK CO, DRINKWATER DT, DAVISON KS, MURRAY TM, BROWN JP. SASKATOON, SK, TORONTO, ON, QUEBEC, QC
To determine whether there were differences in bone mineral density (BMD) between smokers, non-smokers (n=2468), alcohol drinkers and non-drinkers (n=2583), men, aged 25-96 y, were assessed at the lumbar spine (LS) and femoral neck (FN) using dual energy x-ray absorptiometry. Smoking status was determined from the lifetime equivalent packs of cigarettes smoked. Smokers were divided into NON (0 to < 6 mo ever smoked); LO (> 6 mo smoked, 0 to 5000); MOD (5000 to 10000); HI (10000 to 20000); and VHI 20000+ packs) groups. Drinkers were determined from servings of alcohol consumed per day in the last 12 months. Drinkers were divided into NON (0), LO (>0 to 0.5), MOD (0.5 to 1.0), HI (1.0 to 2.0), and VHI (2.0+ servings) groups. WT and AGE adjusted values (to means of 81.7 kg and 59.3 y) for BMD (g/cm²) at the LS and FN for smokers and alcohol drinkers were:

Group	Smoking Status		Alcohol Status	
	LS	FN	LS	FN
NON (873, 649) ¹	1.050 ± .148 ²	0.820 ± .118	1.025 ± .153	0.798 ± .127
LO (520, 916)	1.052 ± .160	0.820 ± .114	1.039 ± .151	0.810 ± .121
MOD (414, 510)	1.022 ± .163*	0.804 ± .122*	1.035 ± .158	0.816 ± .113 [†]
HI (493, 317)	1.022 ± .155*	0.796 ± .111*	1.059 ± .160 [†]	0.827 ± .125 [†]
VHI (268, 191)	1.040 ± .164	0.803 ± .115*	1.060 ± .166 [†]	0.813 ± .111

¹n, by group for smokers drinkers; ²Mean ± SD, adjusted for WT and AGE; *different from NON-smokers; [†]different from NON-drinkers, P< 0.05 Adjusted LS and FN BMD values for MOD and HI smokers were less than that of NON, but not VHI-smokers. In contrast, LS and FN BMD values were greater in drinkers (LO to HI) than non-drinkers. There was a low (r=0.16, P< 0.01) correlation between smokers and drinkers (n=1289): 14.7% of LO-smokers were LO-drinkers, whereas 16% of HI and VHI smokers were also HI and VNI drinkers. Regression analyses revealed that WT accounted for 7.5% and 10.7% of the explained variance for LS and FN BMD, respectively; and AGE another 0.4% and 5.8%. Alcohol consumption accounted for only 0.3% of the variance for LS BMD, whereas smoking made no additional contribution to LS or FN BMD. When men with medical conditions or taking medications known to affect BMD were excluded, similar trends were found. We conclude that, in men, BMD appears to be negatively affected by smoking whereas alcohol consumption may have a protective effect.

J Bone Miner Res 2001;16(suppl 1):S517 Abstract #M356.

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