Osteoporosis and low-trauma fracture in men

Given that about 20% of all individuals with osteoporosis defined on WHO criteria are men, awareness of the risk factors and appropriate management strategies for such patients is essential.

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Osteoporotic fractures are more common in women than men, and consequently there has been a tendency for the intellectual focus, research effort, treatment strategies and public health message to concentrate on addressing the problem in women. However, osteoporosis in men is a common and preventable condition that also deserves attention.

Osteoporosis and fracture risk

Osteoporosis is a disease of bone characterised by low bone mass and microarchitectural deterioration of bone tissue that leads to increased susceptibility to fracture (Figure 1). It is usually diagnosed by measuring bone mineral density (BMD) using dual energy x-ray absorptiometry (DXA). The WHO has arbitrarily defined osteoporosis as BMD at any site at least 2.5 standard deviation units below the mean of a gender-matched, young adult population (i.e. a T score of –2.5 or less). In women, a T score of –2.5 corresponds with an eightfold increased risk of fracture compared with a T score greater than zero.

Although BMD is a powerful predictor of fracture in women, the relation between BMD and fracture risk is not the same in men. Fracture rates are lower in men, but fractures tend to occur at higher BMD. For this reason, some experts have argued that the threshold for defining osteoporosis in men be either lowered (to match the absolute fracture risk of women) or raised (to reflect the same relative risk, with respect to non-osteoporotic men). At present, it seems appropriate to use the WHO definition (i.e. a T score of –2.5 or less, with respect to the mean of a young normal male population), while recognising that fracture occurs at a higher absolute BMD and absolute fracture rates at the cutoff level are lower in men than in women.

IN SUMMARY

- **Osteoporosis is a significant clinical problem in men.**
- **Roughly 400,000 men in Australia have osteoporosis. About 27% of men aged 60 years will have an osteoporotic fracture during their remaining life.**
- **Mortality and morbidity following osteoporotic fracture may be greater in men than in women.**
- **Secondary causes play a significant role in the development of osteoporosis in men.**
- **Management includes identifying and treating secondary causes of osteoporosis and encouraging adequate calcium and vitamin D intake and regular weightbearing exercise.**
- **Testosterone replacement therapy is recommended for patients with established hypogonadism, but testosterone supplementation of normal ageing men remains controversial.**
- **Pharmacological interventions of proven benefit include bisphosphonates and, in selected patients, teriparatide.**

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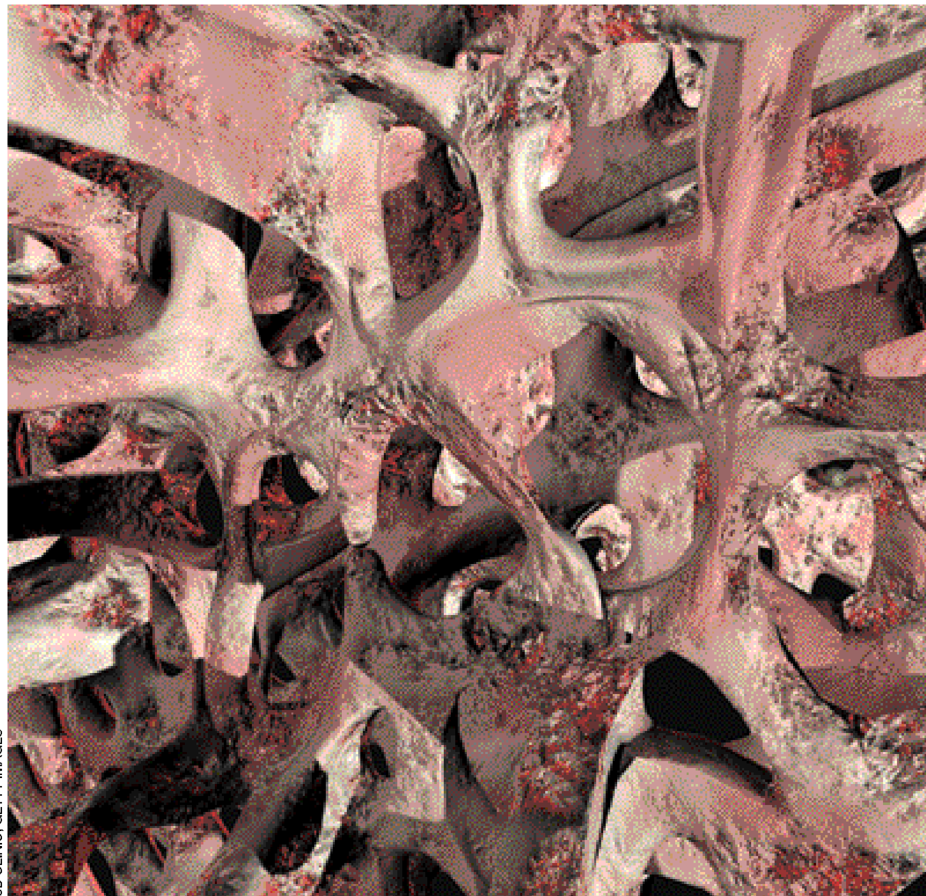

Figure 1. Osteoporosis: atrophy of bony trabeculae.

Epidemiology

About 20% of all individuals with osteoporosis defined on WHO BMD criteria are men. In 2001, roughly 400,000 Australian men were affected, and this figure is predicted to rise to 600,000 by 2021.[1] The lower prevalence in men, compared with that in women, can be attributed to their greater accrual of bone mass during growth and the lack of a dramatic loss of sex steroids (as occurs in women during menopause). Men also have shorter life expectancy, which reduces their prevalence of all age-related diseases.

Useful Australian data on the prevalence of osteoporotic fractures are available from epidemiological studies recently conducted in Geelong, Victoria, and Dubbo, NSW.[2,3] From these, we can determine that fracture rates in men are about one-half of those in women. In men, fracture rates increase with age (but less steeply than in women). The rates in men over 60 years of age are only 50% higher than in those under 55 years, whereas the rates in women over 60 years are 600% higher than in those under 55 years. A man aged 60 years has a 27% likelihood of sustaining a fracture in his remaining lifetime, whereas a woman at the same age has a likelihood that exceeds 50%.

Traumatic fractures are more common in men, and this is reflected in the higher incidence of fractures in young men than in young women. The most common osteoporosis related fractures in both men and women affect the hip, vertebrae, wrist (Colles' fracture) and humerus, which account for 63% of all fractures in women and only 32% in men. The difference suggests that fractures are more widely distributed across anatomical sites in men than in women and that a smaller proportion of the total fracture burden in men is attributable to osteoporosis.

Before the age of 65 years, men have a higher prevalence of vertebral deformities on x-ray than women; after this age, women have an incidence that increases and overtakes that in men. Clinical vertebral fractures are more common in women, but there is a suggestion that the pain and morbidity associated with such fractures may be greater in men. In both men and women, vertebral fractures are a risk factor for subsequent fracture and increased morbidity and mortality.[4]

The incidence of hip fracture increases exponentially in women after age 65 years; this pattern of increase is also seen in men, but it occurs about 10 years later. Hip fracture is associated with similar levels of postfracture debility: age-matched institutionalisation rates of 14% and complication rates of 30% are similar for men and women. Mortality, however, is higher in men than in women (14% *v.* 6%).[5]

Risk factors

The clinical risk factors for osteoporosis and low-trauma fracture in men differ from those in women, and their presence should prompt the clinician to arrange a DXA scan to further define fracture risk. Major risk factors for low bone mass and osteoporosis in men include:

- age greater than 70 years
- cigarette smoking
- alcohol dependence
- low dietary calcium
- vitamin D deficiency
- low body weight
- family history of osteoporosis
- Caucasian race.

Most women with osteoporosis have no risk factors other than their age and postmenopausal status. Men, however, have identifiable secondary causes at presentation in up to 60% of cases (see Table). Hypogonadism, either primary or secondary to pituitary disease or therapy with GnRH agonists (for prostate cancer), may be present. Endocrine disorders such as hyperthyroidism, hyperparathyroidism and Cushing's syndrome and treatment with glucocorticoids, anticonvulsants

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Table. Important secondary causes of osteoporosis in men

Hypogonadism
Vitamin D deficiency
Glucocorticoid excess (iatrogenic and endogenous)
Gastrointestinal disease and gastrectomy (including coeliac disease)
Idiopathic hypercalciuria
Hyperthyroidism
Hyperparathyroidism
Monoclonal gammopathy of uncertain significance
Multiple myeloma and other lytic metastases
Anticonvulsant and chronic heparin therapy
Mastocytosis
Chronic renal failure
Chronic liver disease

and long term heparin may also cause osteoporosis. Multiple myeloma, gastrointestinal disease (including coeliac disease) and idiopathic hypercalciuria are sometimes implicated. A thorough screen for secondary causes is mandatory and may often lead to useful interventions for improving skeletal health.

Factors that increase the risk of fracture in men independently of BMD include a low BMI, physical inactivity, cognitive and neuromuscular dysfunction, and a previous history of falls. As in women, the most potent predictors of fracture risk are age and previous fracture history. An exception in men appears to be the isolated vertebral deformity – the incidence of this sort of deformity does not increase with age or predict low BMD. Unlike in women, the presence of an isolated vertebral deformity does not appear to herald the presence of osteoporosis or increased risk of fracture and is probably related to the increased loads on the male skeleton during manual work or sport. Multiple vertebral deformities in men are, however, associated with lower BMD and predicted by glucocorticoid use, prior fracture and low BMI, suggesting that this is a phenomenon related to increased skeletal fragility.

The development of osteoporosis in men is described in the box on page 43.

Management

The first step in managing any man with osteoporosis is to screen fully for secondary causes and treat these as appropriate. All preventive strategies for osteoporosis should be implemented – these involve avoidance of excessive alcohol intake, smoking cessation and regular weight-bearing exercise. Strategies for falls prevention should be implemented and, in cases where falling remains a significant risk, hip padding should be considered.

Calcium intake should be 1500 mg per day. Preferably, calcium should be obtained from food sources but if this proves impossible (as it often does) then calcium supplements should be administered, preferably in the evening. Vitamin D intake should exceed 200 IU per day in men under 50 years, 400 IU for men 51 to 70 years, and 600 IU per day in men over 70 years; specific replacement therapy should be implemented if the measured 25(OH)-vitamin D_3 level is below 50 nmol/L. In the case of vitamin D insufficiency (20 to 50 nmol/L) or deficiency (<20 nmol/L), stores should be replenished with larger doses of vitamin D, 3000 to 5000 IU per day over one to three months).

Testosterone replacement

Studies of testosterone replacement in hypogonadal men have shown normalisation of testosterone and oestrogen levels. There is an increase in BMD (more at the spine than at peripheral sites) and lowering of bone formation markers, suggesting that the effect of testosterone in these settings is primarily antiresorptive. In some studies, bone formation markers have been transiently elevated, suggesting a small anabolic effect.[10] If the onset of hypogonadism is prior to puberty then testosterone therapy may not be able to fully restore BMD.[11]

Testosterone levels decline with age, and this has led to speculation that testosterone replacement in normal ageing men without clearly defined hypogonadism may have a range of health benefits, such as improving bone mass and reducing bone loss. A variety of clinical trials have been performed, with varying inclusion criteria and differing testosterone replacement regimens; some show a BMD benefit whereas others do not. Most studies show an improvement in lean body mass that might have other benefits with respect to postural stability and reduced falls.

No study to date has provided evidence for fracture reduction with testosterone treatment of men with true hypogonadism or age-related relative testosterone deficiency.

Bisphosphonates

Bisphosphonates are pyrophosphate analogues that bind to bone surfaces and inhibit osteoclastic bone resorption, and several have been shown to reduce bone turnover and increase bone density in different clinical circumstances. Alendronate (Fosamax) and risedronate (Actonel) are orally active agents that have proven antifracture efficacy in postmenopausal women, and these have become the mainstay of treatment for osteoporosis in this group.

A randomised, placebo controlled trial of alendronate for treating osteoporosis in men was published in 2001.[12] Investigators enrolled 241 men aged between about 30 and 90 years with low BMD, approximately one-third of whom had vertebral fracture, and randomised them to receive alendronate 10 mg or placebo daily; all participants received calcium and vitamin D supplements. After two years, an increase in BMD was noted at the lumbar spine and hip and for the total body in men who were treated with alendronate. The magnitude of the BMD increase was the same as that

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seen with alendronate in postmenopausal women and similar in men with hypogonadism who entered the trial. There was also a significant reduction in the incidence of radiological vertebral deformities, but not of nonvertebral fractures.

Other trials in men have shown alendronate to be superior to the vitamin D analogue alfacalcidol and calcium and vitamin D alone. The effects of alendronate in women and men have been compared in one study and found to be equivalent. The effect of alendronate 70 mg weekly in men has been shown to be comparable to 10 mg daily.

Risedronate has been found in one clinical trial to increase BMD and reduce vertebral fracture rates.[13] In this open label study, 316 men were randomised to receive risedronate 5 mg daily plus calcium and vitamin D, or calcium and vitamin D, or alfacalcidol and calcium. Compared with the control goups, the risedronate group had a 3.7% increase in lumbar spine BMD over one year and 60% reduction in vertebral fracture rates.

Although the effect of bisphosphonates on skeletal health in women has now been confirmed in many trials and long term data confirming safety are available, no such information is available for men. In addition, the efficacy of these agents for preventing nonvertebral fractures – including hip fractures – can only be assumed by extrapolating from studies conducted in women. Because the number of studies is limited, we cannot confidently predict the efficacy of bisphosphonates in certain subgroups of men, such as those of different ethnic or racial background or those with less severe osteopenia.

Secondary osteoporosis

Bisphosphonates are also effective in treating osteoporosis in men that is associated with a predominant secondary cause. Hypogonadal men treated with alendronate respond in a similar way to eugonadal men. The acute bone loss associated with androgen ablation in the treatment of prostate cancer is prevented by concurrent treatment with intravenous pamidronate (Aredia, Pamisol) or zoledronic acid (Zometa). Men who have glucocorticoid-induced osteoporosis have been studied along with women in randomised trials and, like women, seem to respond with modest increases in BMD and a reduction

How does osteoporosis develop in men?

The role of sex steroids

The main circulating sex steroid in men is testosterone, which is converted by aromatase "to oestrogen in a variety of tissues so the absolute level of oestrogen in men is of the same order of magnitude as that in postmenopausal women. Hypogonadal men become deficient in both testosterone and oestrogen. Studies of men with deficiencies of the oestrogen receptor alfa and of aromatase have underlined the importance of oestrogen in the male skeleton – men with either type of deficiency had osteoporosis with increased bone turnover and unfused epiphyses, despite intact androgen receptors and elevated circulating testosterone.

Important physiological studies in the last six years have helped to define the roles of oestrogen and testosterone in male bone metabolism. In one study, men treated with GnRH agonists and rendered hypogonadal were given replacement therapy, either testosterone in the presence of an aromatase inhibitor, or oestrogen.[6] It appears that oestrogen is responsible for most of the antiresorptive effect of sex steroids, whereas testosterone shares an important anabolic role. During growth, testosterone may drive the anabolic process that results in increased subperiosteal apposition and increased bone size in men.

With increasing age, levels of sex hormone binding globulin in men rise and bioavailable testosterone and oestradiol levels fall (although not to the levels seen in truly hypogonadal men or postmenopausal women); bone resorption is increased and bone formation is reduced, resulting in bone loss.[7] Bioavailable oestradiol levels seem most closely correlated with BMD. Insulin-like growth factor 1 (IGF-1) levels also fall, which may contribute to the high levels of sex hormone binding globulin and have a direct effect on bone formation, particularly periosteal bone apposition.

Genetic factors

In most cases, osteoporosis is considered to be a polygenetic disease with a complex overlay of environmental factors. Many published studies have shown genetic influences on BMD in women by examining polymorphisms in genes coding for sex steroid receptors, calciotropic hormones and their receptors, and bone matrix proteins such as collagen.

Data for men are much more limited. Rare cases have been described in which a single gene defect has led to premature osteoporosis – examples include inactivating mutations of genes coding for oestrogen receptor alfa and aromatase that interfere with oestrogen action and lead to osteoporosis and delayed epiphyseal closure. Recently, polymorphisms in the androgen receptor have been found to be associated with lower BMD in men. Other candidate genes, such as those coding for the vitamin D receptor and for type I collagen, are under investigation.

Mutations of the low-density lipoprotein receptor-related protein 5 have been associated with osteoporosis-pseudoglioma syndrome.[8,9] Investigation of polymorphisms within this gene has revealed foci that explain up to 15% of the variance of bone mass in men and are related to bone mass accrual in boys. There is no doubt that a range of genetic polymorphisms contribute to the skeletal phenotype in men and determine the pattern of bone growth and response to ageing.

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Consultant's comment

As the male population enjoys an increased life expectancy, their incidences of diseases related to ageing are increasing. By 2010, one-third of all hip fractures in Australia will occur in men. Paradoxically, most men (and women) with osteoporosis are not being identified or treated. Fragility fractures in men are important to recognise because an underlying cause is likely to be present in most cases – hypogonadism, vitamin D deficiency and glucocorticoid use are the most common secondary causes of osteoporosis. In addition, clinical risk factors, such as smoking, excessive alcohol use or poor calcium intake, can be addressed.

Australia is the second country in the world to provide reimbursement for treating osteoporosis in men, and bisphosphonates are the cornerstone of management for preventing further fragility fractures. In the future, selective oestrogen receptor or androgen receptor modulating drugs may be useful in men, avoiding unwanted side effects of oestrogen or androgens. It is likely that other anabolic therapies will be identified. Currently, however, the most important thing family doctors can do is consider whether their older male patients may be at risk of osteoporosis. This review by Dr Gilfillan is timely and recommended in that it increases awareness among family physicians about the problem of osteoporosis.

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in vertebral fracture rates when treated with bisphosphonates such as etidronate (Didronel), alendronate, risedronate and pamidronate.

Teriparatide

Parathyroid hormone causes increased bone resorption and osteoporosis when administered as a continuous intravenous infusion or when elevated in hyperparathyroidism. It has, however, long been recognised in animal models of intermittent administration that parathyroid hormone has a pronounced anabolic effect on bone. Recently, this effect was demonstrated in postmenopausal women during a randomised controlled trial of teriparatide (Forteo), a synthetic fragment of endogenous human parathyroid hormone.

The data are more limited in men. In a small trial, 23 men with idiopathic osteoporosis who were administered parathyroid

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hormone (400 IU daily) showed improvements in bone density over 18 months. In a larger placebo-controlled trial of 437 men, those who were randomised to teriparatide (either 20 or 40 µg daily) showed BMD increases at the lumbar spine of 5.9 and 9.0% and at the hip of 1.5 and 2.9%, respectively.[14] Subjects with hypogonadism were found to respond to therapy as well as eugonadal men. Histomorphometric analysis of bone biopsy specimens has shown parathyroid hormone to be truly anabolic, with increased trabecular bone volume and endocortical new bone leading to cortical thickening. Bone turnover is increased and cortical porosity may be increased at some sites. Fracture data for treatment with parathyroid hormone are lacking, but a follow up study of the patients treated for 11 months in the larger study mentioned above showed the number of moderate and severe vertebral fractures to be significantly reduced at the end of an 18-month period of observation.

Teriparatide must be given by daily subcutaneous injection and is currently very expensive. Treatment courses are limited to a once-in-a-lifetime period of 18 months because osteosarcomas were found to develop in rats treated for lengthy periods and at high dose, but no osteosarcomas have been described in humans or other species. In view of these issues, teriparatide is limited to treating severe osteoporosis, often after the failure of other therapy and generally under the supervision of a specialist.

Conclusion

With the extended life expectancy that men enjoy and the bulge in the population representing the post-war generation, an epidemic of osteoporosis and low-trauma fracture can be expected in men over the next 20 to 30 years. It is imperative that we come to understand the aetiology and pathogenesis of osteoporosis in men and develop ways of identifying those who are at increased risk so that therapies can be cost effectively directed towards lowering the societal burden of fractures. The available therapies needed to be further tested in men so that their efficacy can be determined and the need to rely on data in women is removed. MT

A list of references is available on request to the editorial office.

DECLARATION OF INTEREST: The author has been a principal investigator in clinical trials involving Merck Sharp and Dohme (alendronate) and Sanofi Aventis (risedronate), and has received honoraria for educational lectures delivered on behalf of Merck Sharp and Dohme, Sanofi Aventis and Eli Lilly (teriparatide).

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