MALE OSTEOPOROSIS – APPENDIX 4

Osteoporosis has only recently been recognized as a significant health problem in ageing men. With greater recognition of the problem and the wide availability of DEXA scans, it has become clear that it can also affect younger men. Although the rate of fractures in men is increasing, the causes and treatment of male osteoporosis are not well researched. Strategies similar to those aimed at preventing fractures in postmenopausal women may need to be introduced in men.

EPIDEMIOLOGY

Hip Fracture

The incidence of hip fracture in men is increasing in all countries and is higher with urbanization. In Hong Kong, where hip fractures were once rare, the age-specific incidence in men over the age of 80 tripled between 1966 and 1989. This contrasted with that in women, which did not quite double over the same period. Elderly men who sustain hip fractures are an average of five years older than their female counterparts and have a higher rate of co-morbidities, leading to greater morbidity and mortality.

A study from the Mayo clinic found a mortality rate of 16% 30 days after a hip fracture in men. Extrapolating a recent Geelong analysis, the number of hip fractures in elderly Australian men is expected to double by the year 2026 and quadruple by 2051, whereas in North America and Europe the number is expected to plateau by 2026.

Vertebral fractures

Until recently the rate of vertebral fractures in elderly men in comparison to women was unclear and was thought to be significantly lower.

Work based on the Dubbo osteoporosis study has suggested that the frequency of vertebral fracture is higher in older men than in older women. A recent study of vertebral fractures in men and women has demonstrated that crush, wedge and biconcave deformities occur in both sexes and are all associated with back pain. Wedge deformities are the most common, the lower thoracic spine being the most frequent site. All types of fractures are associated with height loss.

Lifetime fracture risk

The Dubbo study provided an estimate that the residual lifetime fracture risk for an individual at age 60 with average life expectancy was 29% for males and 56%for females. The overall fracture incidence was 2685 per 100,000 person years. Non-hip fractures, although common in 60 to 80-year-olds, were frequently ignored as a public health problem. The median cost per hospital-treated fracture in 1992 was $10,511.

PATHOPHYSIOLOGY OF BONE LOSS AND FRACTURE IN MEN

It is not known shy osteoporosis is becoming more prevalent in men. The cause is not identified in about 45% of cases.

Hypogonadism is responsible for about 20%, excessive alcohol intake 5% and other health problems 10% of cases. A careful and detailed assessment of possible causes should be undertaken (Table). A fasting metabolic bone study may need to be considered (details available on request).

Compared with abstainers, men who drink at least 28 drinks a week have a slightly higher risk of hip fracture and those who drink 70 or more have a five times higher risk. The risk differs according to the type of alcohol preferred: beer drinkers have a higher risk than those who prefer other alcoholic beverages.

Both androgens and oestrogens are important in men for maintenance of bone mass. Abrupt loss of androgens, such as that associated with the use of potent anti-androgens in the treatment of advanced prostate cancer, can lead to a rapid bone loss and an increased rate of osteoporotic fracture, which accelerates significantly after five years of use. Total and free testosterone levels decline with age and also with corticosteroids. Rapid bone loss from hypogonadism in men, like that from early oestrogen loss in women, is most significant in trabecular bone (the spine, hip, distal forearm and ribs).

The importance of oestrogens in men has been demonstrated by ‘experiments of nature’. One report describes severe osteoporosis and failure of epiphyseal closure in a man with oestrogen resistance due to a mutation of the oestrogen receptor gene. Another describes the reversal of severe osteoporosis by oestrogen treatment in a man with an aromatase defect.

In a recent Garvan Institute analysis, low oestrogen, high sex hormone binding globulin (SHBG), high PTH and low free testosterone levels were found to be common determinants of low BMD in elderly men.

Risk factors associated with fracture in older men include low femoral neck BMD, quadriceps weakness, high body sway, falls in the preceding 12 months, history of fractures in the previous five years, lower body weight and shorter current height. Use of thiazide diuretics, increased physical activity and moderate alcohol intake were shown to protect against fracture.

DIAGNOSIS

Any man with a minimally traumatic fracture or history of a secondary cause of osteoporosis (Table) should have a DEXA assessment. The initial assessment is carried out to establish the presence and degree of osteoporosis, whether the process is generalized (i.e., affecting all skeletal sites – spine and hip and forearm) and a baseline to follow the response to the disease process or treatment. If significant degenerative lumbar spine disease exists or multiple lumbar vertebral fractures have occurred, the forearm or total body should be examined instead of the lumbar spine.

Osteoporosis is diagnosed in men with a history of minimally traumatic fractures, even if the DEXA scan does not show a T score of <2.5 at any one site. Minimally traumatic fractures commonly occur in people on corticosteroids, who can sustain fractures in the osteopenic range (T score between –1 and –2.5).

Ultrasound of the calcaneum has not yet shown to be sensitive enough to identify men with osteopenia or osteoporosis and cannot be recommended as an alternative to a DEXA assessment.

TREATMENT

There is a lack of data on the efficacy of various drugs in preventing fractures in men. It is reasonable, however, to adopt the principles of treatment that we currently apply to women.

Androgen supplementation
Men who are clearly androgen deficient should receive androgen supplementation. The simplest way of doing this is with a testosterone implant, replaced every 4-6 months. Alternatively testosterone decanoate 250mg can be given every 2-3 weeks intramuscularly.

Exercise and diet
Men with osteopenia or osteoporosis should aim for dietary calcium intakes of 1000-1500mg a day (one portion of dairy products = 300mg Ca). Calcium supplementation may be necessary.

Recommended daily dietary vitamin D intakes are 200 IU in men younger than 50, 400 IU in men aged 50-70 and 600IU in those over 70. The major source of dietary vitamin D is tinned fish, eaten with the oil. Atlantic herring is particularly rich in vitamin D. An increase in weight-bearing exercise should be encouraged in all age groups. Prevention of falls in elderly men may also reduce fracture rates.

Future treatment
There is a pressing need for treatment studies in men with idiopathic osteoporosis using fractures as the primary end-point. It is possible that the male skeleton responds to drugs in a similar manner as the female skeleton, but this cannot be assumed.

Bisphosphonates
Studies using various regimens of Etidronate and calcium in men with idiopathic osteoporosis or vertebral crush fractures have shown significant increases in spine BMD. In one study the treatment effect was comparable to that seen in women with postmenopausal osteoporosis.

A study looking at the effects of alendronate with calcium and vitamin D supplements in men with osteoporotic fractures or low femoral neck T scores showed an increase in lumbar spine BMD and femoral neck BMD. Height loss was less in the alendronate group. A recent New England Journal of Medicine article reported a reduction in vertebral fractures in men with pre-existing vertebral fractures who were treated with alendronate 10mg daily.

Calcitriol
In an Australian study, calcitriol 0.25mg twice daily was shown to be associated with more new fractures than calcium 500 mg bd in men with idiopathic osteoporosis over a period of two years.

BMDs in the spine and hip did not change in either group. These results could reflect the lack of calcium supplements in the calcitriol group.

Oestrogen
Oestrogen treatment, although an interesting option for men, is not likely to be accepted because of its effects on libido and the increased risk of thromboembolism. Selective oestrogen modulators may be an appealing alternative but are likely to increase the risk of thromboembolism and have unknown effects on the male skeleton.

PTH
Currently under trial in postmenopausal women, PTH and its related analogues can lead to impressive increases in spinal and femoral neck bone mass, particularly in combination with oestrogen. It remains to be seen whether these new treatments will become commercially available, as they are expensive and require injection. It is not known whether they are effective in osteoporotic men or can be combined with other agents such as bisphosphonates.

REFERENCES: these are available on request.

Table: Secondary Causes of Osteoporosis

Causes of osteoporosis	**Diagnostic assessment**
Smoking	History
Alcohol intake	History (>27 standard drinks/week associated with hip fracture in men)
Hypogonadism	History, examination, serum total testosterone. LH
Corticosteroids	History, examination, 24 hour urinary free cortisol
Hyperthyroidism	Rarely clinically relevant to osteoporosis; FT4 and TSH.
Hyperparathyroidism	Corrected total serum calcium, or ionised calcium + PTH. May be biochemically subtle, with only elevated serum ionised calcium and inappropriately high PTH
Diabetes mellitus	BSL, Hb Alc (both IDDM and NIDDM)
Oestrogen deficiency or Receptor abnormality	Specialist referral
Vitamin D deficiency	Serum vitamin D level (low level is often unexpected, should always be excluded)
Calcium deficiency	Diet history. Exclude calcium malabsorption secondary to underlying disease (gastric or small bowel resection, Crohn's disease, vitamin D deficiency or a lack of 1.25 $(OH)_2$ Vit D, celiac disease, familial, drugs, e.g. corticosteroids, anti-epileptic medications)
Chronic liver disease	LFTs, abdominal ultrasound
Renal impairment	Serum creatinine
Hypercalciuria	24 hour urinary calcium
Rheumatoid arthritis	History, examination
Ankylosing spondylitis	History, examination, AP pelvic X-ray, spine X-rays, HLA B27
Multiple myeloma	QEPP[2] and urinary TEP[2]
Sideroblastic/macrocytic Anaemia, thalassaemia	FBC, Hb electrophoresis
Mastocytosis	24 hour urinary histamine, 5-hydroxyhistamine, bone biopsy
Post-transplantation	BMD and biochemical screening
Idiopathic	Fasting metabolic bone study[3], bone biopsy

1. Ankylosing spondylitis or inflammatory spondyloarthropathy (may be undifferentiated or associated with Reiter's disease, psoriasis or IBD)
2. QEPP = Quantitative electrophoresis of plasma proteins IEP = immunoelectrophoresis.
3. Details available on request.