Osteoporosis and hypogonadism in men

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It is estimated that almost 1 in 10 men will suffer a fracture caused by osteoporosis after the age of 50 years. Among those are a considerable number of men who will fracture their hip. A number of therapies have demonstrated efficacy in improving bone density in men, and the issue of which therapy and when to institute it is addressed in this article.

The current diagnostic criteria for osteoporosis were developed in relation to post-menopausal women, and rely on the use of dual X-ray absorptiometry (DXA) measurements of bone mineral density (BMD) to allow clinicians to identify both men and women with osteoporosis. A DXA measurement of BMD that is <2.5 standard deviations (SD) below the young adult reference (i.e. a T score of –2.5 SD or less) in both men and women is consistent with osteoporosis and increased risk of fracture in both men and women (Kanis, 2000; Selby et al, 2000). It is estimated that about 7% of white males over age 50 years have osteoporosis, and up to 1 in 5 men will suffer an osteoporotic fracture after the age of 50 years. As in women, there is an age-related increase in both vertebral and hip fractures, particularly in the eighth decade onwards, which leads to the inevitable age bias observed in those individuals who sustain a hip fracture.

AETIOLOGY

The main risk factor for the development of osteoporosis in women is post-menopausal bone loss as a result of a lack of oestrogen following the menopause. In men, there is no discrete event equivalent to the menopause, and the factors resulting in age-related declines in BMD are less clear. As a result, in 50% of cases or more, the osteoporosis is considered secondary to another pathological process (Orwoll and Klein, 2001). Principal among these secondary causes of osteoporosis in men are corticosteroid usage and hypogonadism, with each accounting for about 20% of the total incidence of osteoporosis. In addition, low bone mass has been documented in a number of other conditions, although it is unclear whether the principal diagnosis is directly responsible for the low measured BMD.

While the management of osteoporosis in patients undergoing corticosteroid treatment has been addressed with its own national guideline (Royal College of Physicians of London, 2002), male hypogonadism has had relatively little attention in relation to its role in the development of osteoporosis, nor have the effects of testosterone replacement on bone density or fracture risk reduction been subjected to the same rigorous testing that other agents have.

Osteoporosis is a genuine medical condition worthy of discussion at the highest level. The link between osteoporosis and fractures, with their associated morbidity and mortality, has reached the level of government action. The report, *Falling Short: Delivering Integrated Falls and Osteoporosis Services in England*, was published in 2004 to tackle the problem. A principal driver behind this action is the current cost of osteoporosis to the NHS: £1.7 billion per annum. This cost is estimated to rise to £2.1 billion by 2010. While the emphasis rightly focuses on post-menopausal women, the group who carry the highest risk, are more numerous and use up the majority of resources, men are also at risk of osteoporosis and associated fractures, and the aetiology, epidemiology and risk of osteoporosis in men deserve attention.

MALE HYPOGONADISM

Testosterone and oestrogen both play significant parts in the development and maintenance of bone mass in both men and women. Men have a higher peak bone mass than women, and do not suffer the rapid decline in bone mass observed at the menopause. On average men lose 5–15% of cortical and 15–40% of trabecular bone with ageing, compared with losses of 25–30% of

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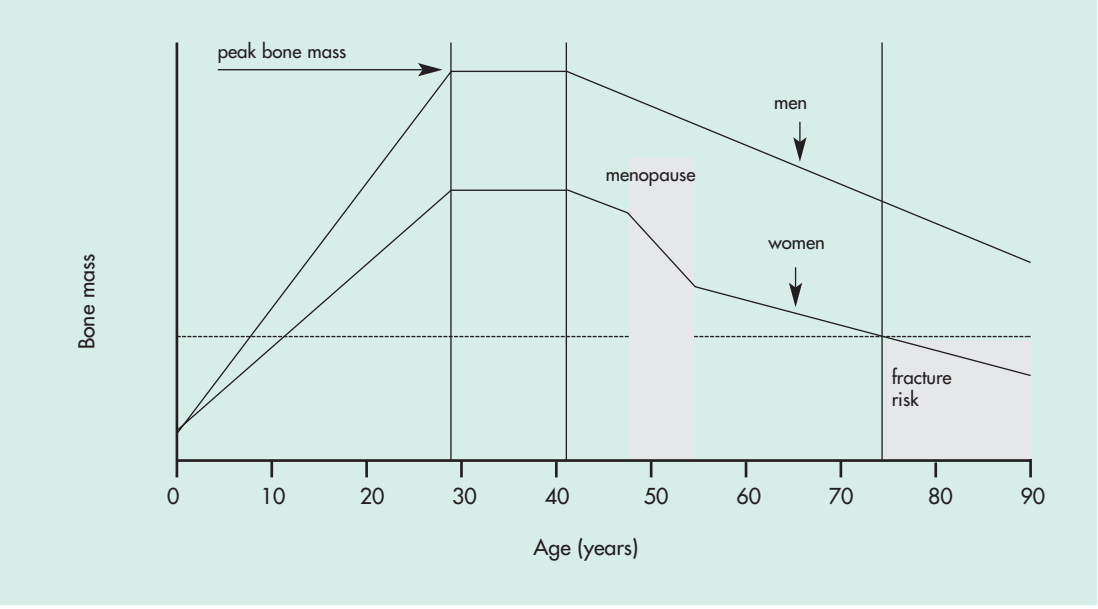

Figure 1. Variation in bone mass in men and women. The higher attained peak bone mass and slower loss of bone in men helps to explain the reduced fracture risk seen in men until their 70's and onwards.

cortical and 35–50% of trabecular bone in women (National Osteoporosis Society, 2000) (*Figure 1*).

There are numerous causes of male testosterone deficiency, and the principal defect may lie in the testes or distant from them (*Table 1*). In many of these conditions, the development of testosterone deficiency is gradual and by the time a diagnosis of testosterone deficiency is made on clinical grounds, the man has evidence of significantly reduced testosterone secretion, either in the form of low total or free testosterone measurements.

TABLE 1.
Some common causes of osteoporosis in men

Idiopathic causes
Senility
Secondary causes
Hypogonadism*
Glucocorticoid excess
Alcohol excess
Gastrointestinal disease, e.g. coeliac disease, chronic liver disease
Thytotoxicosis
Anticonvulsant use
Homocystinuria
Rheumatoid disease
Immobilization
Osteogenesis imperfecta
Primary hyperparathyroidism

* May result from testicular damage, e.g. mumps, torsion, bilateral orchiectomy, drugs, e.g. luteinizing hormone releasing hormone (LHRH) agonists, ciproterone acetate, diethinyl stilboestrol, pituitary disease, inborn errors of steroid synthesis or action.

However, a group of older men may experience a slow and poorly defined age-related decline in testicular function—the so-called 'andropause'—who may be at risk of future fractures owing to prolonged modest testosterone deficiency. This is controversial and is beset with difficulties in defining what constitutes abnormal testosterone concentrations in men above 65 years of age and which treatments are best to prevent any fracture risk in these men (Handelsman and Liu, 2005). Estimates of the frequency of testosterone deficiency in older men vary, and are made more problematic by the difficulty in defining the level of circulating testosterone at which the diagnosis is established and at which treatment should be initiated.

CURRENT TREATMENTS FOR MALE OSTEOPOROSIS

The management of osteoporosis in men is based on the same principles as those in women: the appropriate use of non-pharmacological and pharmacological measures to prevent fractures, especially of the hip and spine. The World Health Organization (WHO) definition of osteoporosis (Who Study Group, 1994) is based on DXA measurement of BMD at the hip and lumbar spine, the patient's age and previous fracture history. On the basis of the WHO definition treatments can be directed to patients with the highest fracture risk and the greatest chance of subsequent benefit. Advice from the National

Institute for Clinical Excellence (NICE) (2005) and the Scottish Intercollegiate Guidelines Network (SIGN) (2003) relate treatment guidance to women with prior fragility fracture. This guidance is less helpful when treating men and is hindered by the poor quality of evidence available to influence clinical decision making because the majority of randomized controlled trials have been conducted on post-menopausal women.

A number of agents are a available for treating osteoporosis in men (*Table 2*). At present bisphosphonates are regarded as first-line therapy for improving bone density in men with osteoporosis. Patients receiving these drugs should be assessed to ensure they are replete in calcium and vitamin D. If there are concerns about the possibility of poor dietary intake, a supplement containing calcium ≥1000 mg and vitamin D ≥800 iu administered with the bisphosphonate preparation.

While bisphosphonates are the drugs of first choice they are not without their drawbacks. In particular, the need to fast before and after oral administration, the need to remain upright for 30 or more minutes and the risk of upper gastrointestinal discomfort, mean that they are often discontinued prematurely. Another potential caveat in their use relates to the duration for which they should be administered continuously. Initial advice was to stop treatment after 5 years and advocate a 'drug holiday' with subsequent assessment of bone turnover with bone markers. However, more recent data suggest that 10 years of continuous use of alendronate is not harmful to the underlying bone, and more prolonged treatment may be safe (Bone, 2004).

A number of studies (Stevenson, 2005) have addressed the role of oral and intravenous bisphosphonates in treating men with osteoporosis, and have shown that both routes provide adequate means of improving bone density in men using the commonly prescribed doses of the drugs. In clinical practice a once-weekly bisphosphonate such as alendronate 70 mg is commonly the initial choice. As yet there are no data to show that fracture event rates are reduced by bisphosphonate treatment, but the improvements in BMD experienced by men treated with these agents are similar to those observed in women, who experience reductions in fracture events of up to 50% (SIGN, 2003).

In addition to bisphosphonates, other bone active agents such as parathyroid hormone (rhPTH 1-34), strontium ranelate and calcitonin have been used to improve bone density and reduce fracture rates in women with osteoporosis. There is no reason to suspect these will have similar efficacy in men with osteoporosis, but formal studies are not available as yet in many cases. However, strontium ranelate does not have a licence for use in men.

At present the evidence for using testosterone to prevent fractures in men with osteoporosis is weakened by the absence of large good quality studies in men with osteoporosis and testosterone deficiency. A number of studies have demonstrated positive effects of testosterone replacement on bone mineral density in androgen-deficient males, although none have been powered or designed to demonstrate reductions in fractures. Similarly, the combination of testosterone—to render hypogonadal males testosterone replete—with bisphosphonates has been

TABLE 2.
Therapies available for use in treating hypogonadal men with osteoporosis

Agent	Drug class	Trade names	Recommended dose	Licensed in men
Alendronate	Bisphosphonate	Fosamax	70 mg once weekly or 10 mg once daily	Yes
Risedronate	Bisphosphonate	Actonel	35 mg once weekly or 5 mg once daily	Treatment of glucocorticoid-induced osteoporosis only
Cyclic etidronate/ Calcium citrate	Bisphosphonate			Yes
Teriparatide	Parathyroid hormone	Forsteo		No
Strontium ranelate	Mixed anabolic/ antiresorptive	Protelos	2 g once daily	No
Calcium plus vitamin D			Calcium 1000 mg plus vitamin D 800 iu daily	Yes
Testosterone	Sex steroid	Nebido	Variable depending on preparation	Yes

Note: The list* does not include treatments that may have been used in men but are not routinely used in clinical practice in the NHS in Great Britain.

demonstrated to have positive effects on BMD (Orwoll et al, 2000).

In men with testosterone deficiency, replacement with testosterone, either by injection or transcutaneous patch, is the favoured method. Decisions on which testosterone preparation to use will be guided by experience and the patient's preference. Depot testosterone injections are the likely first choices. Available options are testosterone enanthate 250 mg, administered every 4 weeks or testosterone undecanoate 1000 mg, given every 3 months. The newly available four-times a year preparation, testosterone undecanoate, has been shown to adequately maintain testosterone levels in hypogonadal men and may allow for a more tolerable treatment regimen compared with more frequent injections (von Eckhardstein and Nieschlag, 2002).

However, the effects of testosterone on bone in men with normal or near minor reductions in testosterone production are less well defined. At present there are few data to support the use of testosterone treatment to reduce fracture rates in men without proven hypogonadism, and other agents should be used to improve BMD in men at risk of fracture but without hypogonadism.

Other considerations with regard to the use of testosterone in eugonadal men centre round the risk of polycythemia, hypertension and possible risk of prostate cancer. The latter is of greatest concern and while a number of small studies have suggested there is no increased risk of prostate cancer, the results of larger studies to assess the risk fully are awaited. Before such definitive advice is available, careful selection of patients should include an assessment of the prostate and consideration of repeated PSA measurements (Rhoden and Morgentaler, 2004).

KEY POINTS

- It is estimated that about 7% of white males over age 50 years have osteoporosis, and up to 1 in 5 men will suffer an osteoporotic fracture after the age of 50years.
- Testosterone and oestrogen both play significant parts in the development and maintenance of bone mass in both men and women
- At present bisphosphonates are regarded as first-line therapy for improving bone density in men with osteoporosis.
- There have been a number of studies which have demonstrated the positive effects of testosterone replacement on bone mineral density in androgen-deficient males.
- The causes of osteoporosis in men are different from those in women — underlying hypogonadism or glucocorticoid therapy are common culprits.

CONCLUSIONS

Osteoporosis is increasing in both men and women, and the consequences of not treating it, i.e. fractures, are costly. The causes of osteoporosis in men are different from those in women and underlying hypogonadism or glucocorticoid therapy are common culprits, although it may not be initially apparent.

Treatment of male osteoporosis is undertaken to reduce the risk of key fractures, especially hip and vertebrae fractures, and should include the use of calcium, vitamin D, bisphosphonates, testosterone and other agents when clinically relevant. The benefits and risks of the possible treatments need to be considered carefully. HM

Conflict of interest: Both authors are members of the National Osteoporosis Society, and have received honoraria from all of the major pharmaceutical companies involved in the promotion of bone health in men and women

Bone HG, Hosking D, Devogelaer JP et al; Alendronate Phase III Osteoporosis Treatment Study Group (2004). Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* **350**(12): 1189–99

Handelsman DJ, Liu PY (2005) Andropause: invention, prevention, rejuvenation. *Trends Endocrinol Metab* **16**(2): 39–45

Kanis JA, Gluer CC (2000). An update on the diagnosis and assessment of osteoporosis with densitometry. Committee of Scientific Advisors, International Osteoporosis Foundation. *Osteoporos Int* **11**(3): 192–202

National Institutes for Clinical Excellence (2005). Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. *Technology Appraisal* 87. NICE, London. www.nice.org.uk/pdf/TA087guidance.pdf (accessed 22 June 2005)

National Osteoporosis Society (2000) *Osteoporosis: A Guide to its Causes, Treatment and Prevention*. NOS, Bath

Orwoll E, Ettinger M, Weiss S et al (2000) Alendronate for the treatment of osteoporosis in men. *N Engl J Med* **343**: 604–10

Orwoll ES and Klein RF (1995). Osteoporosis in Men. *Endocr Rev* **16**(1): 87–116

Rhoden EL, Morgentaler A (2004) Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med* **350**(5): 482–92

Royal College of Physicians (2002) *Osteoporosis: Clinical Guidelines for the Prevention and Treatment*. Update on pharmacological interventions and an algorithm for management. www.rcplondon.ac.uk/pubs/wp_osteo_update.htm (accessed 22 June 2005)

Scottish Intercollegiate Guidelines Network. (2003) *Management of Osteoporosis. A National Clinical Guideline*. Guideline number 71. www.sign.ac.uk/guidelines/fulltext/71/index.html (accessed 22 June 2005)

Selby PL, Davies M, Adams JE (2000). Do men and women fracture bones at similar bone densities? *Osteoporos Int* **11**(2): 153–7

Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J (2005) A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. *Health Technol Assess* **9**(22): 1–160

von Erckhardstein S and Nieschlag E. (2002) Treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks: a phase II study. *J Androl* **23**: 419–25

WHO Study Group (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. *Technical Report Series* 843. WHO, Geneva