REVIEW ARTICLES

Osteoporosis in men

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Osteoporosis is one of the most common metabolic bone diseases, and its prevalence will rise as our population grows older. Although osteoporosis is less common in men than in women its morbidity and mortality seem to be even greater. Furthermore the incidence of osteoporosis in men may well be underestimated, since men are far less likely than women to have a bone density scan.

Epidemiological studies suggest that, in the USA, about 1.5 million men over 65 years of age have osteoporosis and another 8–13 million have osteopenia[1]. The calculated lifetime risk of fracture for men is 13.5% at the age of 50 years and 25.6% at the age of 60[1].

The prevalence in men of fractures of the spine or hip is about one-third that in women[2]. There seems to be a lag period such that an exponential increase in fracture incidence begins 10 years later in men than in women[3], coinciding with the phase of accelerated bone loss after the age of 70[4].

Although women have a higher overall prevalence of fracture, the increase in fracture risk for each standard deviation decrease in bone mineral density (BMD) seems to be higher in men. Moreover, mortality associated with hip fracture is two to three times higher in men than in women[5–8]. Strict criteria for the diagnosis of osteoporosis in men are still lacking: the World Health Organization definition, based on a T score greater than −2.5, relates to Caucasian women. The underlying mechanisms, risk factors and natural history of osteoporosis in men are now attracting much research attention.

CAUSES OF OSTEOPOROSIS IN MEN

Addressing the determinants of bone density in older men, Orwoll and colleagues found the following associated with low BMD: age, previous fracture, gastrectomy, peptic ulcer, rheumatoid arthritis, glucocorticoid use, hypertension, previous hyperthyroidism, chronic lung disease and smoking[9]. High BMD in the same study was positively associated with bodyweight, moderate alcohol intake, osteoarthritis and thiazide use. A study of healthy men over the age of 70 years indicated that measures of body composition such as weight and lean mass were the main predictors of their bone mass[10]. Men with low femoral neck BMD for age had significantly lower weight and lean mass; those with low spine BMD for age also had significantly lower fat mass[10].

Causes of osteoporosis can be identified in some 40–60% of men with osteoporotic fractures[11,12]. The most common are hypogonadism and glucocorticoid therapy. In addition, gastrointestinal disease, vitamin D deficiency, excessive alcohol intake or chronic anticonvulsant use are present in a substantial proportion. Lately, transplantation has emerged as an important cause of osteoporosis in both men and women[13].

Overt hypogonadism has long been recognized as a cause of osteopenia or osteoporosis. Using dual energy X-ray absorptiometry (DEXA) Finkelstein *et al.*[14,15] found that men with a history of delayed puberty had a significantly lower spinal bone density than age-matched healthy controls. Although there was extensive overlap with normal men, many of those with delayed puberty had osteopenia or osteoporosis. Pubertal delay also results in a reduced anteroposterior diameter of vertebral bodies, causing an apparent reduction in bone density (g/cm^2), whereas volumetric bone density (g/cm^2) may be normal[16]. This observation is disputed[17]; in any case, reduced vertebral size itself seems to be associated with increased fracture risk. A history of delayed puberty is elicited in some 2–3% of men with so-called idiopathic osteoporosis. These findings indicate that timing of puberty is an important determinant of peak bone mass, which in turn is a major determinant of bone density in later life (as it is in women).

The observation that young men with hypogonadotropic hypogonadism have osteoporosis even before epiphyseal closure suggests that the problem lies in defective bone accretion[18]. When hypogonadism is acquired during adult life, osteoporosis seems to result largely from accelerated bone loss[14].

In addition to inducing bone loss directly, corticosteroids may act indirectly by causing hypogonadism. A dose-dependent decrease in serum testosterone[19] is thought to result from both suppression of hypothalamic gonadotropin-releasing hormone secretion and direct effects on testicular testosterone production.

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Whereas moderate alcohol consumption seems to be associated with raised BMD, excessive alcohol is associated with osteopenia/osteoporosis and osteoporotic fractures[11]. Why excessive alcohol should adversely affect BMD is not known but a possible mechanism is decreased bone formation via a direct effect on osteoblast function[20]. Additional factors are vitamin D insufficiency/deficiency and the low serum testosterone often found in alcoholics.

When all possible causes are excluded a considerable proportion of men with osteoporosis (almost 50%) come into the category idiopathic. Some studies have pointed to diminished osteoblastic function[21] in this group. Increased bone resorption has also been suggested but the data are not convincing. Insulin-like growth factor-1 (IGF-1) concentration was found to correlate positively with BMD in men but not in women[22], and low IGF-1 and IGFBP-3 have been reported in men with idiopathic osteoporosis[23]. Neither the clinical relevance nor the mechanism of this observation is clear. Relative or partial oestrogen deficiency has also been suggested as a possible mechanism in idiopathic osteoporosis. Another hypothesis is that, in some men with idiopathic osteoporosis, bone cells respond poorly to normal oestrogen levels because of defective oestrogen receptor expression[24].

SEX STEROIDS AND BONE METABOLISM IN MEN

Testosterone deficiency was found in 71% of elderly men with hip fracture compared with 32% of controls[25]. Cross-sectional studies, however, did not reveal an association between serum testosterone and BMD[26,27]. The importance of androgens is illustrated by findings in men who have undergone orchiectomy for carcinoma of the prostate. Daniell reported a 14% incidence of osteoporotic fracture compared to 1% in those who did not have orchiectomy[28]. 5-year follow-up showed that 38% of men with orchiectomy had experienced a non-traumatic fracture. Their hip BMD was 20% lower than in non-orchiectomized men.

In contrast to data showing no correlation between testosterone concentration and BMD, oestradiol concentrations were positively associated with BMD independent of androgen concentration[29,30]. Therefore, age-related bone loss could be due to inefficiency in the conversion of testosterone into oestrogen[31,32]. In a recent study, age-related decrease in bioavailable oestradiol correlated with bone loss in elderly men[33]. The role of oestradiol in men is probably best illustrated by examples of gross osteoporosis in men with oestrogen resistance due to loss-of-function mutations in the ERα gene and in the aromatase gene[35]. By contrast, women with complete androgen insensitivity have low bone density despite normal serum testosterone concentrations[36,37].

The detection and functional characterization of androgen receptors in bone cells has implicated bone tissue as a potential target tissue for androgens. These receptors are expressed in osteoblasts (the bone-forming cells)[38] and functional androgen receptors have also been detected on osteoclasts[39]. Androgens directly regulate various aspects of osteoblastic lineage cells including proliferation, differentiation, mineralization and gene expression[40]. Therefore testosterone might stimulate bone formation directly. In addition to the effect on bone mass, androgens have beneficial effects on muscle mass and muscle strength—which is important for fracture prevention.

Some of the effects of androgen on bone may be mediated by regulation of autocrine and paracrine factors in bone such as transforming growth factor beta, IGF-1 (and differential regulation of IGF-binding proteins) and interleukin-6[40,41]. The mediation of the skeletal effects of androgens is therefore still unclear. It may be directly via androgen receptors or indirectly via oestrogen receptors after aromatization to oestrogen. Probably both pathways are important for bone health. Indeed, a recent study which investigated bone turnover markers in elderly men being given oestrogen alone, androgen alone or both after suppression of their endogenous sex steroids with a gonadotropin-releasing hormone agonist, provided some important information[42]. It seems that oestradiol is essential in regulation of bone resorption whereas both oestradiol and testosterone are important in maintaining bone formation[42].

Another working hypothesis is that direct androgen binding to androgen receptors in bone is most important in early skeletal development whereas bone remodelling, crucial to maintenance of healthy bones throughout life, is primarily stimulated by oestrogen.

MANAGEMENT OF OSTEOPOROSIS IN MEN

Androgen replacement

Testosterone replacement in men with hypogonadism is the most common clinical approach to management. However, this therapy seems to be of limited efficacy; reliable data on fracture reduction with testosterone replacement do not exist and therapy has to be individually balanced against potential risks.

Although testosterone therapy increases BMD in hypogonadal men irrespective of age[43], their response to testosterone replacement in terms of change in BMD is variable. Previously untreated men with the lowest BMD, particularly those with open epiphyses, have been noted to benefit the most[43,44]. Timing of the start of testosterone replacement in men with hypogonadotropic hypogonadism seems to be crucial for bone mineral accretion. If androgen replacement is initiated after the age of 20 neither cortical

nor trabecular bone reaches the normal range. The degree of osteopenia/osteoporosis is proportionate to the delay in initiation of androgen replacement[45].

Of older men with low testosterone, only those who had pretreatment testosterone less than 6.9 nmol/L had a significant increase in BMD with testosterone replacement[46]. In eugonadal men some modest improvement in spine BMD has been achieved with testosterone therapy[47,48] but in this group the potential risks of such therapy demand extreme caution.

Bisphosphonates

Orwoll and colleagues have reported excellent results with alendronate, given for 2 years to men with osteoporosis[49]. Those who received the drug showed not only a 7.1% increase of spine BMD but also a lower incidence of vertebral fracture. The response to alendronate seemed unrelated to baseline free testosterone or oestradiol concentrations—that is to say, those with low serum testosterone benefited to the same extent as those with normal testosterone and oestradiol. Bisphosphonate therefore appears to be the treatment of choice for eugonadal men and for men with hypogonadism in whom testosterone therapy is contraindicated.

Future therapies

One promising strategy is to give parathyroid hormone intermittently. Kurland *et al*. have reported an impressive increase in spine BMD over 18 months with this treatment[50].

Since low IGF-1 concentrations have been implicated in the pathogenesis of idiopathic osteoporosis in men, treatment with IGF-1 might also be beneficial. *In vitro* and animal studies indicate a clear role for IGF-1 in bone metabolism and maintenance[51,52]. The usefulness of growth hormone is controversial. A small study in elderly men who had been recruited for growth hormone treatment on the basis of low IGF-1 concentration showed very modest increase in spine BMD of 1.6% over 6 months. Existing data offer no justification for treatment of osteoporosis with growth hormone unless the person is growth hormone deficient.

A particular need is for a selective androgen receptor modulator that acts on bone and muscle tissue while avoiding adverse effects on the prostate and lipids—ideally with a companion oestrogen receptor modulator with its oestrogen agonist effects confined to bone.

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