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Osteoporosis in Men

New Insights into Aetiology, Pathogenesis, Prevention and Management

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Abstract

Osteoporosis is increasingly recognised in men. Low bone mass, risk factors for falling and factors causing fractures in women are likely to cause fractures in men. Bone mass is largely genetically determined, but environmental factors also contribute. Greater muscle strength and physical activity are associated with higher bone mass, while radial bone loss is greater in cigarette smokers or those with a moderate alcohol intake.

Sex hormones have important effects on bone physiology. In men, there is no abrupt cessation of testicular function or 'andropause' comparable with the menopause in women; however, both total and free testosterone levels decline with age. A common secondary cause of osteoporosis in men is hypogonadism. There is increasing evidence that estrogens are important in skeletal maintenance in men as well as women. Peripheral aromatisation of androgens to estrogens occurs and osteoblast-like cells can aromatise androgens into estrogens. Human models exist for the effects of estrogens on the male skeleton. In men aged >65 years, there is a positive association between bone mineral density (BMD) and greater serum estradiol levels at all skeletal sites and a negative association between BMD and testosterone at some sites.

It is crucial to exclude pathological causes of osteoporosis, because 30 to 60% of men with vertebral fractures have another illness contributing to bone disease. Glucocorticoid excess (predominantly exogenous) is common. Gastrointestinal disease predisposes patients to bone disease as a result of intestinal malabsorption of calcium and colecalciferol (vitamin D). Hypercalciuria and nephrolithiasis, anticonvulsant drug use, thyrotoxicosis, immobilisation, liver and renal disease, multiple myeloma and systemic mastocytosis have all been associated with osteoporosis in men.

It is possible that low-dose estrogen therapy or specific estrogen receptor–modulating drugs might increase BMD in men as well as in women. In the future, parathyroid hormone peptides may be an effective treatment for osteoporosis, particularly in patients in whom other treatments, such as bisphosphonates, have failed. Men with idiopathic osteoporosis have low circulating insulin-like growth factor-1 (IGF-1; somatomedin-1) concentrations, and IGF-1 administration to these men increases bone formation markers more than resorption markers. Studies of changes in BMD with IGF-1 treatment in osteoporotic men and women are underway.

Osteoporosis in men will become an increasing worldwide public health problem over the next 20 years, so it is vital that safe and effective therapies for this disabling condition become available. Effective public health measures also need to be established and targeted to men at risk of developing the disease.

Osteoporosis is increasingly being recognised in men.[1] In the next 20 years it is likely to emerge as an important public health problem both in the West and in the developing world, as numbers of elderly men increase and the age-specific incidence of hip fractures in men also increases. It is projected that, over the next 15 years, ≈30% of hip fractures will occur in men.[2] Recent epidemiological data show the incidence of vertebral fractures in men to be 0.73 per 1000 person-years, which is half the incidence seen in women,[3] but is not 10%, as previously reported.[4] However, even this is likely to be a conservative estimate because only ≈30% of vertebral fractures are symptomatic and come to clinical attention.

Recent data show that vertebral fracture rates are as great in men as in women but, because women live longer, the lifetime risk of a vertebral fracture from age 50 onward is 16% in White women and only 5% in White men.[5] In Australian men aged 60 years, the lifetime risk of an osteoporotic fracture is 29%, about half that in women. In men aged 60 to 80 years, these will be predominantly non-hip fractures.[6] Depending on age, between 60 and 90% of hip and vertebral fractures in White men aged >45 years can be attributed to osteoporosis.[7]

It is also important to recognise that there is likely to be increased morbidity and mortality following hip fractures in men compared with women.[8] One month after hip fracture, the mortality rate in men was 16%. 55% of men with hip fractures were discharged to nursing homes. Only 41% of survivors recovered their prefracture level of functioning. Age and deterioration in postoperative mental state increased the risk of early death. The prevalence of both moderate and severe vertebral deformities increases with age in men and severe vertebral deformities are associated with a greater functional impairment in men than in women.[9]

Cost estimates for these fragility fractures in Australian men range between $AU70 to 230 million per year.[4,10] Geographical variation in fracture rates also occurs in men; their hip fracture risk is higher than that of women in Singapore and fracture rates for men in some parts of the US and Europe continue to increase while those for women have probably stabilised.[6] Thus, osteoporosis in

men is already a public health problem and its economic and personal burden will increase unless public health strategies are initiated to prevent the disease or effective therapeutic options for established disease are identified.

In the past, the problem of osteoporosis in women has overshadowed research into osteoporosis in men, so little is known of the factors causing low bone mass or increased bone loss in men. Although few prospective studies of fragility fractures in men have been made, low bone mass, risk factors for falling and other factors important in the aetiology of fractures in women are likely to be associated with fragility fractures in men.

A recent prospective study has shown that men and women have the same risk of vertebral fracture for the same absolute calcaneal bone mass;[11] however, it is uncertain if the same relationships exist for spinal and proximal femur bone mineral density (BMD). The Dubbo Epidemiology Study demonstrated that increased body sway and decreased quadriceps strength in addition to low femoral neck BMD were associated with an increased risk of hip fractures in men.[12] In a large case-control study from Rochester, conditions linked with an increased risk of falling were also associated with a 7-fold increase in hip fracture risk, while diseases linked with secondary osteoporosis doubled the fracture risk.[13] Overall, these factors accounted for ≈72% of hip fractures in men. In a smaller case-control study that examined risk factors including serum free testosterone levels, hypogonadism was associated with a 4.6-fold increase in hip fracture rates after adjusting for race.[14] In men with rheumatoid arthritis, the risk of hip fracture was doubled; corticosteroid use also independently increased hip fracture risk by 2.6-fold.[15]

1. Bone Mass and Rates of Bone Loss in Men

Bone mass is thought to be largely genetically determined. Studies in twins have shown that genetic factors account for ≈60% of the variance in bone mass in both men and women.[16,17] Nevertheless, environmental factors also make an important contribution to bone mass. Greater muscle strength and physical activity are associated with greater bone mass in men.[18] Recent prospective studies of radial bone loss in older men show that cigarette smoking and moderate alcohol consumption contribute to bone loss, as they do in women.[19] Bone loss from the femoral neck occurred at a rate of 0.82% per year in men, a slightly lower rate than that in women.[20] No bone loss occurred at the spine; however, the rate of loss from the hip increased with aging. Overall, prospective studies of bone loss in men have been limited, partly because age-related bone loss occurs at a relatively slow rate and also because, given the precision of current methods for measuring bone mass, accurate estimates of rates of bone loss, particularly at the femoral neck, require long periods of follow-up.

Peak bone mass is greater in men than women (fig. 1) predominantly because they have larger bones.[22] This difference is possibly androgen-dependent. In tubular bones, total width is greater and cortical thickness is increased with reduced cortical porosity.[23] Vertebral cross-sectional area is 25% greater in men than women; this is due to an increase in vertebral width and depth (but not height). Age-related vertebral bone loss is less in men than in women because the vertebrae increase in cross-sectional area by 25 to 30% with aging in men as a result of subperiosteal apposition of new bone.[24] This also occurs in the long bones, with the girth of long bones increasing more in men than in women.[25] Hip axis length may also be different in men than in women, creating another anatomical advantage in reducing propensity to fracture.

Although age-related rates of bone loss at predominantly trabecular sites (distal radius, vertebrae and calcaneus) are similar in men and women, the pattern of loss is not. In men this is the result of generalised trabecular thinning, but in women there is a more marked loss of trabecular elements.[24]

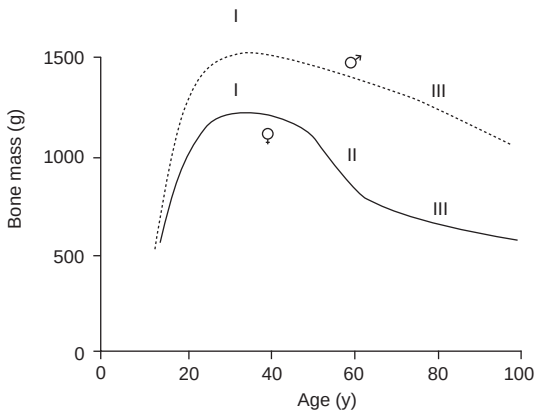

Fig. 1. Changes in bone mass with age in men and women (reproduced from Riggs et al.,[21] with permission). **I** = peak bone mass; **II** = postmenopausal bone loss; **III** = age-related bone loss.

2. Osteoporosis in Men

2.1 Possible Factors Affecting Age-Related Bone Loss

A number of explanations for excessive bone loss may coexist in the individual man with osteoporosis. Age-related bone loss alone can cause an increased risk of fracture. This may be related to a decline in bone formation with aging,[26,27] although some recent studies have also demonstrated an increase in bone turnover with aging in men.[28] However, newer bone resorption markers do not consistently increase with age.[29,30] In most studies of healthy men, higher levels of bone turnover markers have been associated with lower BMD of the proximal femur[27,28,30] and, less commonly, with lower spinal BMD.[27,29]

Changes in growth factors or cytokines may contribute to age-related bone loss, as do nutritional deficiencies, inactivity and loss of gonadal function. Dietary calcium deficiency is common in men, >50% of whom ingest less than the recommended daily allowance. Aging has also been associated with increased parathyroid hormone (PTH) levels,[31] decreased calcifediol (25-hydroxy vitamin D) levels[32] and, in some studies, decreased calcitriol (1,25-dihydroxy vitamin D_3) levels.[33,34] Intestinal resistance to calcitriol occurs in women with osteoporosis and it may also exist in men. This intestinal resistance may be receptor mediated or caused by post-receptor events.[35,36] There is growing evidence that the decrease in calcium absorption with aging is related to both reduced renal 1α-hydroxylase activity and reduced levels of calcitriol, as well as intestinal resistance to calcitriol. It is unlikely that the abnormal alleles of the vitamin D receptor (VDR) gene associated with low bone density[37] have a functional effect on reducing calcium absorption. Nevertheless, calcium supplementation has a greater effect on increasing bone density in women with the abnormal (BB) VDR allele.[38]

Although several reports have linked dietary calcium intake to bone density in men, the evidence is inconclusive. Some studies have found an effect of calcium intake on axial but not radial bone density.[39,40] Studies of relationships between calcium nutrition and hip fracture in men are suggestive of a beneficial effect but remain speculative.[41] A recent study examined the effects of dietary calcium supplementation on fragility fractures in non-institutionalised men and women aged >65 years. Men had only 2 fragility fractures in the placebo group. Rates of bone loss at the spine and femoral neck were reduced by ≈1% in the first year of calcium treatment, but not during the subsequent 2 years of the study, whereas total body bone loss was unaffected in the first year but reduced by a similar amount in the subsequent 2 years.[42]

Bodyweight and mechanical force have strong effects on bone density. Decreases in physical activity and muscle strength with aging may also contribute to age-related bone loss by reducing mechanical forces on skeletal tissues. The relationship between changes in sex hormone levels with aging and age-related bone loss are discussed in more detail in section 3.

2.2 Secondary Pathological Causes of Osteoporosis

30 to 60% of men evaluated for vertebral fractures have another illness contributing to the pres-

ence of bone disease.[1] Glucocorticoid excess (predominantly exogenous) is the most common secondary cause, accounting for 16 to 18% of cases.[43] The pathophysiology of glucocorticoid-induced osteoporosis is similar in women and men and the most important mechanism is a direct inhibition of osteoblast activity and decreased osteoblast recruitment. However, muscle weakness, immobility, impaired intestinal calcium absorption, hypercalciuria and a reduction in serum testosterone levels also all contribute to glucocorticoid-associated bone loss.[44]

The link between alcohol (ethanol) abuse and bone diseases has been well established by epidemiological studies;[4] however, the mechanism of alcohol-related bone loss is unclear. Osteoblast function is decreased by alcohol as assessed by bone histomorphometric studies[45] and this also may be secondary to a direct toxic effect of alcohol on osteoblasts. Colecalciferol deficiency and reduced free serum testosterone concentrations in alcohol-induced bone disease may contribute to bone loss.[46]

Tobacco use is associated with decreased bone mass in women.[47] In a study in men, the relative risk of vertebral fracture in smokers was 2.3.[48] This risk was independent of alcohol consumption. The mechanism of this effect is unknown, but may relate to decreased bodyweight and decreased calcium absorption. However, another larger study did not support such a strong influence of tobacco on fracture risk.[12]

Gastrointestinal disease predisposes men to bone disease, as a result of intestinal malabsorption of calcium and colecalciferol. In particular, gastrectomy is a common association of vertebral osteoporosis in men. Other gastrointestinal diseases (coeliac disease, Crohn's disease, small intestinal resection) cause bone disease equally in men and women.[1] Hypercalciuria and nephrolithiasis in men are associated with osteopenia and this may be related to secondary hyperparathyroidism, increased calcitriol levels and increased bone turnover rates.

Anticonvulsant drug use (phenobarbital, phenytoin), thyrotoxicosis, immobilisation, liver and renal disease, multiple myeloma and systemic mastocytosis have all been associated with osteoporosis in both men and women.[1]

2.3 Idiopathic Osteoporosis

In ≈45% of men with symptomatic vertebral fractures, no known cause of bone disease could be identified.[49] The wide age range of men with idiopathic osteoporosis (23 to 86 years) suggests that in some men there may be a premature onset of age-related osteoporosis; however, the pathogenesis may differ in younger men. Importantly, the structural bone defect is similar to that in adult male hypogonadism with reduced trabecular numbers, rather than reduced trabecular thickness. Nevertheless, there are no consistent features of idiopathic osteoporosis in men. In one study, intestinal calcium absorption was reduced and calcitriol levels were decreased.[49] Calcium balance was also negative in 16 men with idiopathic osteoporosis because net calcium absorption was insufficient to offset urinary calcium losses.[49]

Although a defect in osteoblastic function has been identified in idiopathic male osteoporosis, it is not a consistent finding.[50-52] The age of the individual may be important in this regard, with young men having reduced histomorphometric indices of bone formation, while older men had similar bone formation rates to age-matched controls, but evidence of slightly increased bone resorption.[53] Unfortunately, there are no data concerning the levels of currently available biochemical bone markers in osteoporotic men. As in hypogonadism, the structural bone defect is a reduction in trabecular number rather than a decline in trabecular thickness; however trabecular connectivity has not been formally addressed in any study.

3. Sex Hormone Effects on Bone in Men

3.1 Androgen Effects

Although there is no abrupt cessation of testicular function or 'andropause' comparable with the menopause in women, both total and free testoster-

one concentrations decline with age in men. The age-related reduction in total testosterone is accompanied by a proportionately greater increase in sex hormone binding globulin, resulting in a larger decline in free testosterone with age in men.[54] Age-related decreases in adrenal androgens are greater than for testosterone and may have more impact on age-related bone loss.[55] A limited correlation exists between free testosterone levels with bone density at some, but not all, skeletal sites and these findings have been inconsistent between studies.[40]

One of the most common secondary causes of osteoporosis in men is hypogonadism. This is associated with a phase of rapid bone loss and increases in biochemical markers of bone turnover, as it is in women. This is followed by a phase of bone loss associated with low bone turnover. The role of androgens in bone accretion and skeletal maintenance in men has been poorly studied.

In addition, it is uncertain whether testosterone therapy of eugonadal men results in significant increases in bone density. One nonrandomised study of parenteral testosterone therapy of eugonadal men detected increases in spinal but not proximal femur bone mass.[56] However, a double blind, placebo-controlled trial of transdermal testosterone showed no effect.[57] Nevertheless, hypogonadism is present in as many as 30% of men with osteoporotic vertebral fracture,[1] and low testosterone concentrations are also common in men with hip fractures.

As previously noted, androgens are important in both attainment of peak bone mass and in the maintenance of bone mass in adult men. In prepubertal hypogonadism, the bone deficit is more marked in cortical compartments than that in adult-onset hypogonadism, where trabecular bone loss occurs with a reduction in trabecular numbers. Histomorphometric studies have also shown that bone formation rates are reduced in hypogonadism;[58] however, bone turnover increases acutely following orchidectomy.[59] Testosterone replacement in hypogonadal men increased spinal and distal radius BMD by ≈6% per year, although cortical deficits are not replaced.[60,61] Body fat and biochemical bone turnover markers decreased, while lean muscle mass increased with testosterone therapy.

In European hypogonadal males with fractures, calcitriol levels were decreased. Both bone formation parameters and plasma calcitriol levels increased following testosterone treatment.[50] In contrast, US studies have not demonstrated reduced bone formation rates, but a slight increase in mean remodelling rate comparable with postmenopausal estrogen deficiency in women.[58] Thus, nutritional colecalciferol deficiency may have contributed to the European study findings.

3.2 The Androgen Receptor as a Transcription Factor

Overall, there are relatively low concentrations of androgen and estrogen receptors in osteoblasts in men. Androgens and estrogens affect bone cells by indirect as well as direct mechanisms secondary to changes in concentrations of systemic and local factors. Several of these effects, including proliferation, growth factor and cytokine production, and bone matrix protein production (type I collagen, osteocalcin, osteopontin), are mediated by the androgen receptor (AR). The AR is a member of the steroid hormone/nuclear receptor superfamily. The AR is a ligand-dependent transcription factor, and comprises 3 functional domains: the steroid-binding domain, DNA-binding domain and amino-terminal domain.

The amino-terminal domain of the AR is involved in the modulation of transcription activation (transactivation).[62] Different transactivation regions within the amino-terminal domain of the AR may be active in regulating different genes, allowing cell-specific and gene-specific regulation of expression. Within the amino-terminal domain are 2 polymorphic regions: a stretch of glutamine (Gln) residues, encoded by CAG repeats, with the number of Glns normally varying between 11 and 31, and with most individuals having between 18 and 25 repeats;[63,64] and a stretch of GGN repeats that ranges in size between 16 and 24 Gly repeats.[65]

Studies on the AR suggest that the poly Gln stretch in the amino-terminal domain acts as a repressor of transcription activation. Deletion of the Gln repeats in the amino-terminal domain causes increased transactivation from androgen responsive promoters. Studies have shown that changes in the CAG/Gln length can alter transcription activation of AR responsive genes in a promoter-dependent manner.[66] However, these studies have been limited to investigating AR with either normal (n = 20) versus greatly increased or decreased numbers of CAG repeats.

3.3 Androgen-Responsive Genes

Androgen-responsive genes include the 2 androgen-dependent kallikrein-like genes, prostate specific antigen (PSA) and human glandular kallikrein 1. PSA can specifically cleave insulin-like growth factor binding protein-3 (IGFBP-3; somatomedin binding protein-3), increasing the amount of locally bioavailable insulin-like growth factor-1 (IGF-1; somatomedin-1).[67] Epidermal growth factor receptor expression and transforming growth factor-α (TGFα) secretion are upregulated by androgens.[68,69] Androgens may also directly reduce IGF-3 expression, suggesting that one target for androgenic regulation of cell growth may be through IGF-3 regulation.[70] Castration causes an increase in *c-myc* gene expression in the ventral rat prostate; an effect reversible by androgen treatment;[69] thus, *c-myc* may also mediate androgenic effects.

Type I collagen is a sex hormone-responsive protein produced during osteoblast proliferation. Type I procollagen propeptide (PICP) is a bone formation marker. Serum PICP levels decrease in men but increase in women with aging,[26] as well as increasing during IGF-1 treatment.[71] Low serum levels of IGF-1 have been reported in men with idiopathic osteoporosis and may thus be partly responsible for the low bone formation rates observed in some men with this condition.[72] A defect in the type I collagen gene has also been identified in a family with osteoporosis affecting both male and female members.[73] Recently, a polymorphism in the Sp1 transcriptional control region of the collagen type I α1 gene has been shown to be over-represented in postmenopausal osteoporotic women and associated with low BMD.[74] No studies of Sp1 polymorphisms or their relationship to AR alleles have been performed in men.

3.4 Estrogen Effects

There is increasing evidence that estrogens have an important role in skeletal maintenance in men as well as in women (fig. 2). Peripheral aromatisation of androgens to estrogens occurs in men as well as in women. In addition, osteoblast-like cells can aromatise androgens into estrogens. Aged male rats treated with an aromatase inhibitor had similar bone loss to orchidectomised rats, indicating aromatisation of androgens into estrogen may partially explain the effects of androgens on bone.[75] Human models also exist for the effects of estrogens on the skeleton. A man with a stop mutation in the estrogen receptor gene and high circulating estradiol levels had failure of epiphyseal fusion and continued skeletal growth and severe osteoporosis.[76] Similarly, an aromatase-deficient man developed tall stature and osteoporosis, and low-dose

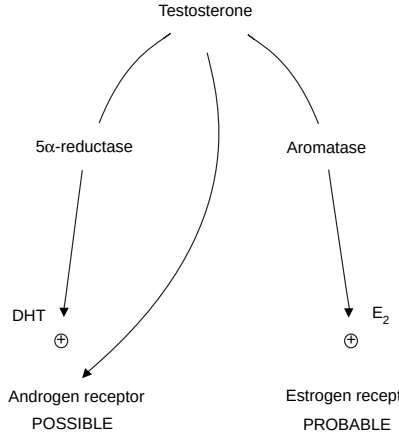

Fig. 2. Direct and indirect effects of androgens on skeletal maintenance (reproduced from Vanderscheueren et al.,[75] with permission). **DHT** = dihydrotestosterone; **E_2** = estradiol.

estrogen therapy resulted in a large increase in bone density.[77,78]

A recent study has shown that bone density at all skeletal sites was significantly positively associated with greater serum estradiol levels in men aged >65 years.[79] There were also negative associations between serum testosterone and bone density at the spine and hip, and sex-hormone binding globulin was negatively associated with bone density only at the greater trochanter. Bodyweight, age and serum sex steroids accounted for 30% of the variability of bone density in men with consistent positive associations between bone density and serum estradiol levels in men. Importantly, within the normal range, lower serum testosterone levels were not associated with low bone density in men.

In transsexual men treated with estrogens and antiandrogens, bone density increased, and both bone turnover and serum IGF-1 levels decreased. In contrast, testosterone administration to transsexual women increased bone formation, but this did not result in increased bone density, despite increases in serum IGF-1 levels.[80] Thus, adult bone remodelling may be preferentially regulated via the estrogen receptor (ER), with estrogen playing a pivotal role in skeletal mineralisation in both men and women. In support of this hypothesis, both male and female ER gene knockout mice have BMD that is 20 to 25% lower than wild-type mice.[81] The latter experiment has been difficult to interpret because of the smaller skeletons of the ER gene knockout mice compared with wild type mice. Nevertheless, less severe ER defects could also be responsible for idiopathic osteoporosis in some men.

Recently, *Pvu*II and *Xba*I restriction length polymorphisms of the ER gene have been associated with low bone density in healthy postmenopausal Japanese women.[82] Women with the Px haplotype had lumbar spine and total body BMD 0.47 and 0.64 SDs lower, respectively, than Px haplotype-negative women. No studies of this ER haplotype have been performed in men.

4. Treatment of Osteoporosis in Men

There have been no studies of specific drug therapy for osteoporosis in men with fragility fractures as an end-point. There have been no randomised placebo-controlled trials and few uncontrolled prospective trials of therapies for osteoporosis using BMD as an end-point in men. Therapies for osteoporosis can either inhibit bone resorption (bone density initially increases with infilling of the remodelling space and then remains stable) or stimulate new bone formation (fig. 3). A summary of the published uncontrolled studies that have examined drug efficacy in men with osteoporosis is shown in table I.

To summarise these limited studies, calcitonin resulted in increases in total body calcium but was not different to calcium and/or colecalciferol supplements in this regard.[83] It also reduced biochemical markers of bone turnover in the short-term in castrated men, although effects on bone density were not studied.[59]

Cyclical etidronic acid (disodium etidronate) given in 2 dosage regimens caused increased lumbar spine bone density at 2 years; however, bone density at both the distal and proximal radius decreased over the same time, while proximal femur bone density remained unchanged.[84] This study was controlled, so it is not known whether changes occurring with etidronic acid were different from those expected with placebo or calcium alone. In 42 men with vertebral crush fractures, treated with 3-monthly cycles of disodium etidron-

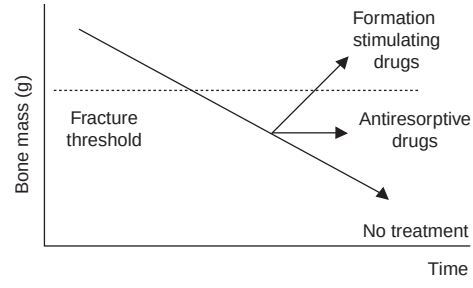

Fig. 3. Effect of treatment on bone mass.

Table I. Studies examining drug efficacy in men with osteoporosis

Agent	Osteoporosis type	Duration	No. of patients	End-point	Control group(s)	Effect	Reference
Calcitonin	Idiopathic	2 years	8	TB BMC	Calcium, colecalciferol	+	83
				Radius BMC	Colecalciferol	0	
	Hypogonadal	3 months	9	BBM	Crossover (self control)	+	59
Etidronic acid	Mixed	2 years	36	LS BMD	Nil	+	84
				FN BMD		0	
				DR BMC		–	
				PR BMC		–	
	Vertebral fractures	2 years	42	LS BMD	Nil	+	85
				FN BMD		0	
	Idiopathic secondary	1 year	10	LS BMD	Nil	+	86
				FN BMD		0	
Testosterone esters	Vertebral fractures	6 months	21	LS BMD	Nil	+	87
				FN BMD		0	
				BBM		+	
Parathyroid hormone and calcitriol (1,25-dihydroxy vitamin D_3)	Idiopathic	1 year	8	Trabecular BMD	Nil	+	88
				DR BMC		0	

BBM = biochemical bone markers; **BMC** = bone mineral content; **BMD** = bone mineral density; **DR** = distal radius; **FN** = proximal femur; **LS** = lumbar spine; **PR** = proximal radius; **TB** = trabecular bone; + = a positive effect of active treatment; **0** = no effect of active treatment; **–** = no effect.

ate for over 2 years, spinal BMD increased by 3.2% per year and proximal femur BMD did not change.[85] In a small retrospective study of 10 men with osteoporosis treated with cyclical etidronic acid, the increase in spinal BMD was greater being 9.0% at 1 year.[86]

Testosterone treatment of eugonadal men with vertebral crush fractures for 6 months increased spinal BMD by 5%. During treatment, free androgen and estradiol levels increased by 90 and 45%, respectively,[87] and bone turnover markers decreased. The change in spinal BMD was correlated with the change in estradiol but not testosterone, suggesting that estrogen may decrease bone turnover more effectively than testosterone in men.

Combined with human PTH injections, calcitriol increased trabecular bone density in middle-aged men with idiopathic osteoporosis.[88] However, it is not known whether similar effects would be seen with either PTH or calcitriol treatment alone.

5. Future Options

5.1 Estrogen And Specific Estrogen Receptor-Modulating Drugs (SERMs)

Because estrogen concentrations are important determinants of BMD in men, it is possible that low-dose estrogen therapy might increase BMD in men as well as in women. However, it is unlikely that the majority of men would accept the adverse effects related to estrogen therapy. Of particular concern is the potential for adverse cardiovascular effects in men. While specific estrogen receptor modulating drugs (SERMs) would avoid adverse effects on libido, it is uncertain whether some or all of these drugs would prevent potential cardiovascular adverse effects such as thromboembo-

lism. Because rates of bone loss are low in men, clinical trials of SERMs in men would need to be of at least 3 years' duration and cardiovascular endpoints would also need to be carefully examined in any such study.

5.2 Bone Formation–Stimulating Drugs

5.2.1 Parathyroid Hormone Peptides

As early as 1929, Fuller Albright showed that PTH extract could increase bone density in the rat. These findings have been difficult to translate to the treatment of osteoporosis in humans because of the expense and injectable nature of the peptides, and also because of important species differences in bone and mineral metabolism.

Two controlled studies of teriperatide (hPTH-1-34) and hPTH-1-38 given for 3 years or 1 year, respectively, have examined changes in bone mass in postmenopausal women receiving concurrent hormone replacement therapy.[89,90] Lumbar spine bone mineral content (BMC), that is, bone mass not adjusted for bone area or volume, increased by 11% over 2 years and this increase was maintained following cessation of PTH therapy, albeit after a small but rapid decrease of 2% in bone mass. Total body bone mass increased by 6% while femoral neck BMD decreased by 3.2% over 3 years in both groups. No changes in spinal or total body mass occurred in the control group.

An elegant study of histomorphometric bone turnover indices during PTH therapy has shown that bone formation was initiated on surfaces that would not have had time to be fully excavated by osteoclasts.[91] Later biopsies demonstrated increased wall thickness of completed newborn packets, moderate rather than large increases in bone formation indices and modest changes in bone resorption indices. Enhanced trabecular connectivity as well as increased trabecular thickness may have been responsible for the increased bone volume. An interesting finding in postmenopausal women treated for 1 year with alendronic acid is that nocturnal increases in PTH are associated with decreases in bone turnover and increases in bone density.[92] PTH also prevents bone loss associated with medical oophorectomy for the treatment of endometriosis.[93] PTH combined with calcitriol increases trabecular bone mass in men, as noted in section 4.[88]

As PTH shares the PTH-1 receptor with parathyroid hormone-related protein (PTHrP), it is likely that PTHrP (1-34) analogues will have similar effects on bone to PTH. Such analogues are anabolic for bone in primate models of osteoporosis and have undergone phase I and II clinical trials. However, it is not yet known whether the newly identified PTH-2 receptor contributes to the anabolic effects of PTH/PTHrP. PTHrP, in addition to IGF-1, transforming growth factor-β and prostaglandins may also act as a local modulator of PTH action.

Because of its expense, its injectable mode of administration and the small number of clinical trials, PTH cannot be currently regarded as a suitable first line treatment for osteoporosis. In the future, PTH peptides may be an effective first- or second-line treatment for osteoporosis, particularly in those patients in whom other treatment modalities such as bisphosphonates are perceived to have failed, or in those with very low bone density and presumed trabecular loss.

5.2.2 Growth Hormone and Insulin-Like Growth Factor

Both growth hormone (GH) and IGF-1 stimulate osteoblastic differentiation *in vitro*. In animal models, GH and IGF-1 enhance longitudinal growth, bone formation and bone mass; however, responses to GH or IGF-1 are not equivalent and depend on the species, the animal's GH status and the mode of administration. Although rhGH and IGF-1 both enhance trabecular and cortical bone density in GH-deficient patients, rhGH administration to healthy men or women results only in small, inconsistent changes in BMD.[94,95]

Growth hormone treatment of elderly men and women is also associated with a high incidence of unpleasant adverse effects (oedema, glucose intolerance and bilateral carpal tunnel syndrome). Both GH and IGF-1 stimulate bone turnover and activate remodelling osteons. The intriguing possibility ex-

ists that low dose IGF-1 may directly increase osteoblastic function with only a minimal decrease in bone resorption.[71,96] At these doses the adverse effects of higher dose IGF-1 (bloating, oedema, parotid discomfort, tachycardia, orthostatic hypotension) are avoided.[71]

Men with idiopathic osteoporosis have low circulating IGF-1 concentrations. Administration of IGF-1 to these men increases bone formation markers more than resorption markers. Studies of changes in BMD with IGF-1 treatment in osteoporotic men and women are currently underway. A new IGF-1 preparation combines the drug with IGF-3, prolonging the half-life of IGF-1. It has yet to be evaluated in humans. However, because there are no studies of the effects of IGF-1 on bone mass or of the effects of either rhGH or IGF-1 on fracture rates, the results of longer-term clinical trials in men are required before the safety of these agents can be assessed.

6. Effects of Treatment on Healthy Men

In healthy adult men given calcium and colecalciferol supplementation, no effects were seen on rates of bone mineral loss from either the spine or the radius, despite increased urine calcium excretion and suppressed PTH levels.[97] However, men in this study had a high baseline dietary calcium intake (>1100 mg/day). Calcium supplementation in a calcium-deficient population might prove to be more effective, as has been shown in women.[98]

In a recent study of calcium and colecalciferol supplementation to elderly men with calcium 500mg and colecalciferol 700IU daily for 3 years,[42] spinal and femoral neck BMD increased by ≈1% in the first year of treatment only. In contrast, differences of 1% in total body BMC compared with age-matched men occurred in the second to third study years. Non-vertebral fractures were less common in calcium-colecalciferol treatment group in women, but not in men.

Two studies have examined the effects of testosterone replacement in healthy elderly men. One study showed that parenteral testosterone supplementation reduced urinary hydroxyproline excretion and increased spinal BMD.[56] A larger study of transdermal testosterone, however, did not reveal any changes in more up-to-date biochemical bone markers.[57]

Rudman et al.[94] found that in addition to beneficial effects of lean mass, fat mass and skin thickness, vertebral BMD was increased significantly by 1.6% over 6 months with growth hormone administration, but there were no changes in radial and proximal femoral density. Thus, GH is a potential, but unproven, agent in the treatment of osteoporosis; unfortunately, its use is associated with adverse effects and considerable expense.

7. Conclusions

No effective treatment to reduce fracture rates has yet been established for men with osteoporosis. While secondary causes of osteoporosis in men should first be excluded and appropriately treated, there is a need for a treatment to increase bone density and decrease fracture rates where no such cause can be identified in men.

There are no double-blind, placebo-controlled trials of osteoporosis therapies in men. Dietary calcium supplementation in elderly men results in small, but significant increases in bone density at most sites. However, it is likely that both non-sex hormonal antiresorptive drugs (calcitonin, bisphosphonates and calcitriol) and bone formation-stimulating drugs (e.g. PTH) that are efficacious in women will also be effective in men. This is largely because the pathophysiological mechanisms of osteoporosis and the mechanisms of action of these drugs on bone and mineral metabolism are similar in men and women.

Randomised, double-blind, placebo-controlled trials are currently being conducted comparing alendronic acid with calcium; IGF-1 with placebo; PTH with calcium; and calcitriol with calcium in men with idiopathic osteoporosis. These 6-month to 3-year studies will determine whether any of these drugs are effective in increasing lumbar spine, femoral neck and total body bone density in men, as well as examining their effects on bone turnover markers. It is uncertain whether they will

have adequate power to detect differnces in fracture rates.

Osteoporosis in men will become an increasing worldwide public health problem over the next 20 years and for this reason it is vital that safe and efficacious therapies become available to treat men with this disabling condition. Most importantly, effective public health measures also need to be established and targeted to those men at risk of developing the disease.

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