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Review

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Management of male osteoporosis: report of the UK Consensus Group

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Summary

Although osteoporosis is generally regarded as a disease of women, up to 30% of hip fractures and 20% of vertebral fractures occur in men. Risk factors for osteoporotic fractures in men include low body mass index, smoking, high alcohol consumption, corticosteroid therapy, physical inactivity, diseases that predispose to low bone mass, and conditions increasing the risk of falls. The key drugs and diseases that definitely produce a decrease in bone mineral density (BMD) and/or an increase in fracture rate in men are long-term corticosteroid use, hypogonadism, alcoholism and transplantation. Age-related bone loss may be a result of declining renal function, vitamin D deficiency, increased parathyroid hormone levels, low serum testosterone levels, low calcium intake and absorption. Osteoporosis can be diagnosed on the basis of radiological assessments of bone mass, or clinically when it becomes symptomatic. Various biochemical markers have been related to bone loss in healthy and osteoporotic men. Their use as diagnostic tools, however, needs further investigation. A practical approach would be to consider a bone density more than one SD below the age-matched mean value ($Z < -1$) as an indication for therapy. The treatment options for men with osteoporosis include agents to influence bone resorption or formation and specific therapy for any underlying pathological condition. Testosterone treatment increases BMD in hypogonadal men, and is most effective in those whose epiphyses have not closed completely. Bisphosphonates are the treatment of choice in idiopathic osteoporosis, with sodium fluoride and anabolic steroids to be used as alternatives.

Introduction

Osteoporosis is generally regarded as a disease of women, related to the decline in oestrogen levels that occurs at the menopause. The enormity of the problem in women and the potential role of hormone replacement therapy in the prevention and treatment of osteoporosis has led to neglect of the problem of osteoporotic fractures in men. Epidemiological studies, however, reveal that about 30% of all hip

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fractures occur in men,[1] and vertebral fractures are more common in men than was previously thought.[2] A major review published in 1995[3] observed that guidelines for the diagnosis of osteoporosis in men or women are poorly validated, and that therapy for male osteoporosis is largely unexplored. Few therapeutic trials have been performed specifically in men, though men with osteoporosis have been included in mixed populations treated with a variety of agents. The aim of this meeting was to review the field, to identify the risk factors for the development of osteoporosis in men, and to attempt to draw up some diagnostic and management guidance for male osteoporosis.

The scope of the problem

In 1990, about 30% of 1.66 million hip fractures worldwide occurred in men, and this figure is projected to rise to 6.26 million by 2050.[1] In the UK, 9417 of 43 220 hip fractures (22%) in 1985 occurred in men.[4] Although vertebral fractures are regarded as being uncommon in men, over a 40-year period, men accounted for 20% of vertebral fractures due to moderate trauma in those aged 35–69 years,[2] and in those over 80 years old, the prevalence of vertebral fractures in men is nearly half that in women.[5] More recent studies have suggested that the prevalence of vertebral deformity in older men may be as great as in women, and the degree of deformity greater.[6] The incidence of forearm fractures in men remains at a low level throughout life.[7]

Of those limb fractures in men and women attributed to underlying bone pathology, osteoporosis alone is responsible for more than two-thirds of such fractures, and represents a very large number of cases.[8] The lifetime risk from the age of 50 years of sustaining an osteoporotic fracture of the hip, spine (clinically diagnosed), or wrist is about 5% for men and 15% for women (Table 1),[1,9] and up to 17% of men could experience a hip fracture by the age of 90 years.[10] This means that a typical UK general practice of 2000 patients would each year see about two osteoporotic fractures in men: on average, one wrist fracture each year and one hip and vertebral fracture every 2 years. In a recent prospective European study, the overall prevalence of vertebral deformity was similar for men and women across all age groups from 55 years to 74 years, but was higher in men younger than 55 years and in women over 75 years.[11] When the prevalence was adjusted for spinal BMD, however, men showed a slightly greater prevalence of asymptomatic vertebral fractures over most age ranges, including the over-75 age group.[12]

Table 1 Lifetime risk of an osteoporotic fracture from age 50 years

Type of fracture	Lifetime risk (%)			
	UK		USA	
	Men	Women	Men	Women
Hip	3	14	6	18
Vertebral (clinical)	2	11	5	16
Wrist	2	13	3	16

The incidence of limb fractures in men is biphasic, with a peak in adolescence and early adulthood, related to trauma, and a later rise after the age of about 70 years due to osteoporosis.[8] In Black populations, the incidence of osteoporotic fractures in men is closer to that in women than it is in Caucasian populations.[13] The incidence of hip fractures among Japanese men, however, appears to be only about half that of Caucasian men, though the reasons for this are not clear.[14] Environmental factors appear to play some part, however, as Black American men suffer more hip fractures than Black South African men.[13] In addition, men suffer more vertebral deformities as a result of severe trauma than women, who tend to acquire fractures after mild or moderate trauma.[15]

A secular trend has been noted in the incidence of hip fractures, with a linear increase from 1930 onwards,[16] and a greater increase between 1968 and 1985.[17] The incidence rates for vertebral fractures in men rose between the 1950s and the 1980s, particularly in those aged over 80 years.[5]

Several risk factors for osteoporotic fractures in men have been described, many of which are similar for men and for women. The risk factors for hip and vertebral fractures include a low body mass index, smoking, high alcohol consumption, corticosteroid therapy, and physical inactivity.[18–24] Diseases that predispose to bone loss and neuromuscular instability appear to increase the risk of fractures, either by association with secondary osteoporosis or by increasing the tendency to fall. These include thyroidectomy, cirrhosis of the liver, pernicious anaemia, chronic bronchitis, Parkinson's disease, vertigo and blindness,[25] hypogonadism,[26] and possibly reduced calcium intake[20] for hip fractures, and tuberculosis and peptic ulcer for vertebral fractures.[27] Exercise may not have as great a protective effect against vertebral fracture as against hip fractures.[28]

Although the incidence of hip fractures has been rising over recent years, mortality from this cause appears to be decreasing in Europe.[29] The mortality rate of hip fracture overall is about 18% in the UK, but men have a nearly three-fold higher chance of death after hip fractures than women.[30] This is

Table 2 The scope of the problem of male osteoporosis

Although osteoporosis is generally regarded as a disease of women, up to 30% of hip fractures and 20% of vertebral fractures occur in men.
Of those limb fractures in men and women attributed to underlying bone pathology, osteoporosis alone is responsible for more than two-thirds.
Asymptomatic vertebral fractures may be present in 25% of men by the age of 70–79 years.
The risk factors for osteoporotic fractures in men include:
* low body mass index
* smoking
* high alcohol consumption
* corticosteroid therapy
* physical inactivity
* diseases that predispose to low bone mass and neuromuscular dysfunction.

The economic costs of fractures in men in the UK are projected to rise to over £100 million per annum by 2011.

Table 3 The pathogenesis of primary osteoporosis in men

The determinants of peak bone mass in men include:
* race
* genetic factors
* hormonal factors
* diet
* exercise.

Bone loss with age in normal men is a result of increased bone turnover and decreased bone formation.
Age-related bone loss may be a result of:
* declining renal function
* vitamin D deficiency
* increased parathyroid hormone levels
* low serum testosterone levels
* low calcium intake and absorption
* physical inactivity.

reflected in the female : male ratio for death from femoral neck fracture of about 1.5 : 1 in many elderly European populations.[29] In older men, there is a large excess of observed over expected deaths from hip fracture.[31]

In 1976, fractures and dislocations in the USA accounted for 32% of days of restricted activity from injuries of all types, equivalent to over 6 days of restricted activity for each 10 persons.[32] The direct costs alone of hip fractures have been estimated as £288 million for the period 1991–1992 in the UK.[33] As the age structure of the population increases, this figure is projected to rise to over £100 million by the year 2011 for male osteoporosis alone, unless treatment patterns change or the age-specific incidence falls.[33] Although fewer hip fractures occur overall in men, they tend to stay longer in hospital and account for about 25% of these costs.[33]

Table 2 summarizes the scope of the problem of male osteoporosis.

Pathogenesis of primary male osteoporosis

Factors contributing to the pathogenesis of primary osteoporosis in men are summarized in Table 3.

Determinants of peak bone mass in normal men

Although comparatively little attention has been paid over the years to the determinants of peak bone mass in men, race, genetic factors,[34] hormonal factors, diet[35] and exercise[36] have all been shown to have an influence. As in women, genetic factors account for a substantial amount of the variation in peak bone mass, but the precise genes involved remain to be elucidated.

The most obvious influence on peak bone mass is hormonal, and this is accounted for by the differences in pubertal development in males and females. Women exhibit a dramatic increase in bone mass during puberty, which is almost complete when puberty ends.[37] Similar changes occur in men, but at a slightly later time corresponding to the later onset of puberty, and peak bone mass is consequently achieved at a later age. The greater peak bone mass in men is largely related to body size rather than to bone mineral density (BMD)[3] except at certain sites such as the radius.[38] Indeed, although bone mineral content (BMC) at the age of 18 years is higher in males than in females, BMD at the lumbar spine and femoral neck may actually be lower.[39] The age of pubertal onset may be important in determining peak bone mass, and it has been shown that males with constitutional delay of puberty have substantially lower spine and forearm BMD than those with a normal onset of puberty, despite matching the two groups for length of post-pubertal exposure to testosterone.[40] After reaching peak bone mass, men maintain a stable bone density during middle age, but then lose bone at an accelerating rate into old age.[41]

Age-related bone loss in normal men

Bone loss occurs with ageing in men as in women, and longitudinal studies suggest that this loss may reach 5–10%/decade,[42] which is greater than estimated from cross-sectional studies.[43] Overall loss of peak bone mass from 20 years to advanced old age may reach 5–15% for cortical bone and 15–45% for trabecular bone.[44,45] This bone loss is associated

with histomorphometric evidence of decreased bone formation, with decreased osteoid seam width and trabecular width.[44,46] Trabecular number may also be decreased (as in women), and trabecular connectivity reduced,[47] while bone turnover may be increased in elderly men.[48]

Up to 40% of men with severe osteoporosis have no identifiable medical condition or risk factor associated with bone loss[44,49] and in such men with primary osteoporosis the pathogenesis of age-related bone loss is far from clear. Although genetic factors partly determine peak bone mass, they do not appear to be important in age-related bone loss in men.[50] There have been some reports that men with osteoporotic fractures have hypercalciuria,[51,52] but it is unclear whether this is due to increased bone resorption or renal leakage of calcium. It has been suggested that a combination of declining renal function and vitamin D deficiency during normal ageing may produce secondary hyperparathyroidism and consequent loss of bone.[53] Increasing levels of serum parathyroid hormone with age have been implicated in age-related bone loss in men,[53] as have decreasing serum growth hormone levels.[54]

A variety of other factors may influence age-related bone loss, including low vitamin D levels,[53] low serum testosterone levels,[35,52,55,56] and low calcium intake[35] and absorption.[44] Other studies, however, have shown little if any correlation between BMD at various sites and free testosterone levels[57] or dietary calcium intake.[58] Both smoking and very high alcohol consumption increase the rate of bone loss and the risk of vertebral fractures.[7,52]

Conditions associated with secondary osteoporosis

In addition to the bone loss associated with normal ageing, over 50% of men with symptomatic vertebral crush fractures have secondary causes of osteoporosis,[23,44,49] compared with about 35% in women. The most prominent of these are long-term use of corticosteroids, hypogonadism, alcoholism, and gastrointestinal and thyroid/parathyroid disorders. Recently, however, transplantation has been reported as an important cause of secondary osteoporosis. The available information on secondary causes of osteoporosis in men is summarized in Table 4.

Table 4 Secondary causes of osteoporosis in men

The key drugs and diseases that definitely produce a decrease in BMD and/or an increase in fracture rate in men are:
* long-term corticosteroid use
* hypogonadism
* alcoholism
* transplantation.
The incidence of vertebral and other fractures is increased about twofold in men using long-term corticosteroids.
Bone mass is reduced by oral corticosteroids, and to a lesser extent by inhaled corticosteroids, possibly partly as a result of decreased testosterone levels.
Case reports of men with Cushing's syndrome suggest that corticosteroid-induced osteoporosis may be partially reversed by early discontinuation of therapy.
Hypogonadism before puberty markedly decreases cortical bone development, is a common cause of secondary osteoporosis, and is reversible with adequate replacement therapy.
Alcohol abuse significantly reduces spinal BMD and increases fracture risk by 2.8-fold at the hip, mainly because of the increased tendency to fall, but also possibly as a result of poor nutrition, magnesium and calcium imbalance, and secondary hypogonadism.
Bone loss after organ transplantation amounts to about 8% at the lumbar spine and 10% at the femoral neck. Over 90% of this bone loss occurs within the first few months and is probably mainly a result of the large doses of corticosteroids used for immunosuppression. Fracture rates post-transplant may be as high as 50% over the first year.
There is some evidence for other minor causes of secondary osteoporosis in men, but few studies have been performed and these conditions warrant further investigation. They include:
* gastrointestinal disorders
* hyperparathyroidism/hypercalciuria
* thyrotoxicosis
* immobilization
* anticonvulsant drugs.

Corticosteroid therapy

Although most studies have included both men and women, corticosteroid excess is one of the most prominent causes of osteoporosis in men, accounting for about 16% of patients with vertebral crush fractures.[18,44] Although the risk of fractures associated with long-term corticosteroid use is greater in women than in men, it is nevertheless increased two-fold in men, even when adjusted for the influence of rheumatoid arthritis.[59] In rheumatoid arthritis patients using corticosteroids for more than 5 years, the risk of fracture increases to about 33%.[60] Other variables associated with fracture (older age, high disability index, disease duration, prior osteoporosis, lack of physical activity and impaired grip strength) emphasize the need for caution in prescribing long-term corticosteroids in older patients with long-term disease.[60] Even low-dose oral or inhaled corticosteroids have been reported to increase the rate of bone loss in the calcaneus and distal and proximal radius

2–3-fold in elderly men and women compared with control subjects.[61]

The effects of corticosteroids are often difficult to separate from those of the underlying disease. In rheumatoid arthritis, total body calcium was decreased in men to a similar extent as in women due to the disease and was further decreased by treatment with corticosteroids in both sexes, but only significantly so in women.[62] Corticosteroid treatment also significantly lowered BMD in the anteroposterior spine in men with rheumatoid arthritis compared with those receiving non-steroidal anti-inflammatory drugs alone or control subjects.[63] BMD in the lateral spine, femoral neck, Ward's triangle and trochanter was significantly lower in both users and non-users of corticosteroids than in the control patients, but the two groups were not significantly different from each other (Figure 1). In contrast, total body calcium was not reduced in asthmatic men treated with oral or inhaled corticosteroids,[64] and although in a separate study men with asthma had consistently lower lumbar spine BMD than women, irrespective of the duration of prednisolone treatment or the cumulative dose of inhaled corticosteroid,[65] these data are confounded by the use of hormone replacement therapy in most of the women studied.

One mechanism for the effect of corticosteroid treatment on bone is suppression of testosterone levels,[66,67] possibly as a result of alterations in hypothalamic function.[67–69] In men with chronic obstructive airways disease, the decrease in testosterone level may be more than 50% when therapy is given for at least 1 month,[68] though neither low-dose nor high-dose inhaled corticosteroids have been associated with significantly reduced testosterone levels.[70] Men with rheumatoid arthritis, however, may have reduced testosterone levels even without corticosteroid treatment.[69]

The reversibility of corticosteroid-induced osteoporosis has been studied in patients with Cushing's syndrome. Case reports have shown that surgical treatment can produce a 20% increase in lumbar spine BMD, with a smaller increase in femoral neck BMD, accompanied by a significant rise in serum osteocalcin.[71] Recovery of osteoporotic changes (vertebral compression fractures) within 2 years after cure of Cushing's syndrome has also been reported.[72] The improvement may not be sufficient, however, to prevent continued fractures.[73]

It thus seems that vertebral and other fractures are increased in prevalence in men using oral corticosteroids. Bone mass is reduced, and serum osteocalcin levels are suppressed. Inhaled corticosteroids may have similar but milder effects in men as in women. The effect of corticosteroids in lowering testosterone levels may be partly responsible for reduced bone formation, but other mechanisms are probably also involved. Lastly, the evidence from case reports in Cushing's syndrome suggests that corticosteroid-induced osteoporosis may be partially reversed by early discontinuation of corticosteroids.

Hypogonadism

The causes of primary (testicular failure) and secondary (defective gonadotrophin elaboration and secretion) hypogonadism are shown in Table 5.[55,67,74–78] The common denominator of all these conditions is low testosterone production. Androgens influence osteoblast proliferation,[79] growth factor and cytokine

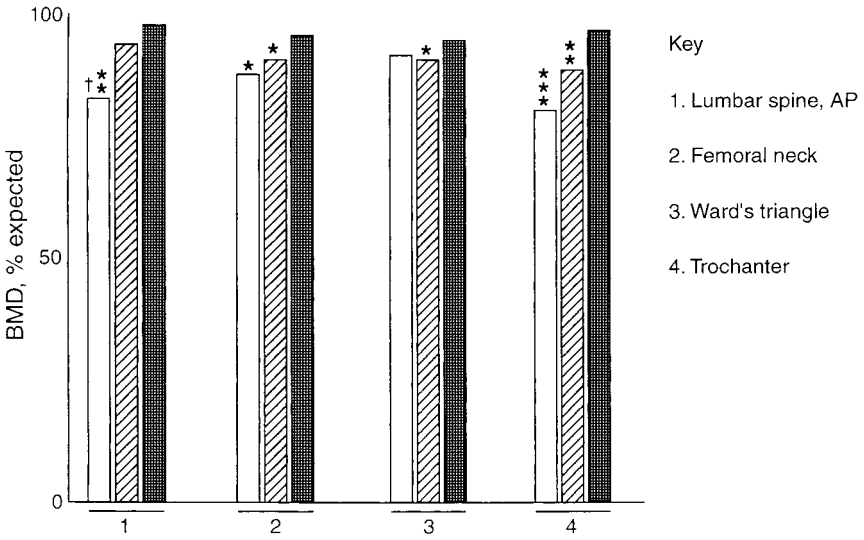

Figure 1. BMD in 20 healthy men (solid columns), 20 men with rheumatoid arthritis without (hatched columns) or 20 with (open columns) corticosteroid therapy (average 7.5 mg/day). Men with rheumatoid arthritis had lower BMD and those taking corticosteroids even lower BMD at the spine. Drawn from Table 4 in Garton and Reid.[63] *$p<0.05$, **$p<0.01$, ***$p<0.001$ compared with controls. †$p<0.01$ compared with men with rheumatoid arthritis not taking corticosteroids.

Table 5 Causes of primary and secondary hypogonadism in men

Primary	Secondary
Castration	Pituitary tumours and infiltrations
Hyperprolactinaemia	Haemochromatosis
Klinefelter's syndrome	Use of gonadotrophin releasing hormone agonists (prostatic carcinoma)
	Glucocorticoids
	Kallman's syndrome

production[80] and bone-matrix protein production[81] via the androgen receptors that are found on osteoblasts.[82–84]

At puberty, androgens particularly increase cortical thickness through both periosteal and endosteal growth, and they also increase trabecular bone formation at epiphyseal sites.[78,85] Hypogonadism before puberty has a very marked effect on cortical bone development, which can be alleviated by testosterone treatment; BMD can be increased by 26% and BMC by 41% over 1 year by treating boys with constitutional delay of puberty, compared with 0.5% and 5% increases in untreated controls.[86] Low-dose oestrogen may play a role when looking at growth hormone responses to insulin-induced hyperglycaemia, as it may improve sensitivity to growth hormone. There is one case report of an oestrogen receptor defect in a prepubertal boy whose epiphysis did not fuse.[87]

Long-standing hypogonadism in adult men is associated with reduced bone remodelling and low serum 1,25-dihydroxy vitamin D levels[88] and with decreased bone formation,[89,90] although in some studies there is biochemical and histological evidence of increased remodelling,[55] which is reversible with adequate replacement therapy.[91] Cortical area in men with Klinefelter's syndrome is positively correlated with serum testosterone levels (Figure 2),[92] however, and in those who are only mildly hypogonadal, BMD is only slightly reduced below normal.[93] Haemochromatosis is often associated with low spinal BMD, and the principal mechanism for osteoporotic change in this disease also appears to be testosterone deficiency.[76]

Alcoholism

Although moderate alcohol consumption may be associated with an increase in BMD, at least at the greater trochanter,[94] many studies have suggested that alcohol abuse is associated with osteoporosis, and in particular with an increased fracture risk.[18,95–99] Bilateral or multiple rib fractures are significantly associated with alcoholic liver disease.[100] Alcohol abuse significantly lowers spinal BMD compared with age-matched controls, and reduces trabecular bone volume in the iliac crest.[101] Axial BMD decreases in parallel with the duration of drinking history.[102] One of the principal reasons for the increased fracture risk is the greater propensity to fall, but poor nutrition, increased renal excretion of calcium and magnesium, malabsorption of calcium and secondary hypogonadism may also contribute.[103]

Although alcohol has a direct acute effect on osteoblast function,[101,104] as evidenced by decreased osteocalcin production, there is no evidence of osteomalacia, disordered vitamin D metabolism, or increased remodelling due to hyperparathyroidism. Changes appear to arise as a result of a reduced osteoid seam width and osteoblast numbers, with a prolonged mineralization lag time, indicating that alcohol has detrimental effects on bone formation and less pronounced suppressive effects on bone resorption.[101] Alcohol withdrawal reverses the effects on bone to some extent. Thus, after 2 years of alcohol withdrawal in 30 men, both lumbar spine and femoral neck BMD increased by about 3%.[105] Serum osteocalcin levels are rapidly normalized by alcohol withdrawal.[102,105,106]

In a recent study, alcoholism was associated with a 2.8-fold increase in the risk of hip fracture and cirrhosis with a 3.5-fold increase.[25] Neither cirrhosis nor low testosterone levels, however, are prerequisites for vertebral fractures in alcoholic men. In a group of 76 men who had on average consumed 27 units of alcohol/day for 24 years, serum testosterone levels were unchanged compared with control subjects and only 17 subjects had histological changes in the liver.[23] Lumbar spine BMD was slightly but significantly lower than in the control subjects, and 30% of the alcoholics had vertebral compression fractures, though only 4% were symptomatic.

Transplantation

Little is known about bone disease following organ transplantation in either men or women, but as survival improves with new surgical and immunosuppressive treatments, it is becoming increasingly important, and is often a cause of serious morbidity. Three main types of post-transplantation bone disease occur: avascular necrosis, osteoporosis, and osteomyelitis. Post-transplant osteoporosis appears to affect trabecular (cancellous) bone more than cortical bone, as evidenced by the greater incidence of spinal fractures.[107] Although most information is available for male cardiac transplant patients, up to 70% of renal and 40% of liver transplant patients may also suffer moderate to severe osteoporosis.[108,109]

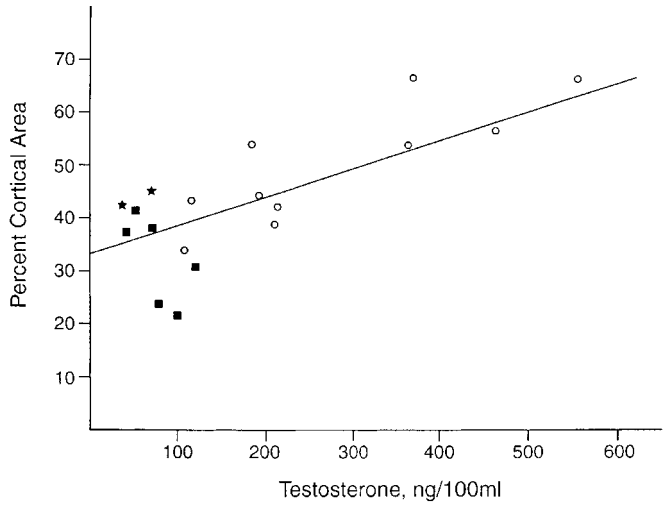

Figure 2. Bone mineral content (BMC) correlated with serum testosterone ($r=0.71$, $p<0.001$) in men with hypogonadism due to Klinefelter's syndrome (circles), hypogonadotrophic hypogonadism (squares), and traumatic castration (stars). BMC was expressed as the percentage cortical area of the second phalanx of the left index finger and the left metacarpal. From Foresta *et al.*[92]

Three recent studies have documented losses of lumbar spine BMD of about 8% in the 12 months following cardiac transplantation,[110–112] and femoral neck BMD losses of about 10%.[112] Total body loss of BMD, however, only amounted to 1% over 12 months.[112] Over 90% of the spinal bone loss during the 12 months after transplantation occurred within the first 3–6 months following transplantation,[111,113] and less than 1% additional loss of BMD occurred in the second year after transplantation.[112] Between 2 and 3 years, spinal BMD started to increase.[112]

Men awaiting cardiac transplantation have a slightly reduced BMD at both the spine and femoral neck compared with age-matched controls. Both Z scores and T scores are decreased,[110] and decrease further following transplantation (Figure 3).[110,114] The lower T scores in particular indicate that post-transplant patients are at increased risk of osteoporotic fractures. The reported fractures rates following cardiac transplantation range from 8% to 50%, depending on the length of follow-up, size of the study, and whether radiographs were obtained for all patients or only those with symptomatic fractures.[110,112,115–117] The fracture incidence (spinal and non-spinal) during the first year after liver transplantation is about 20%.[118]

The possible causes of post-transplant osteoporosis include immunosuppressive therapy, pre-existing bone disease, vitamin D deficiency, immobilization, and sex hormone deficiency, of which the major contributor is probably immunosuppressive therapy. Many patients are given very large doses of corticosteroids immediately post-transplant, followed by repeated large doses if rejection occurs. High doses of corticosteroids cause metabolic effects within a few days or weeks,[119] and lumbar spine and total body BMD are negatively correlated with the dose of prednisolone given.[109] Although the effects of cyclosporin in humans are complex, animal experiments suggest it induces a high bone turnover state with increased resorption,[120] partly effected by a rise in plasma PTH levels.[121] Serum osteocalcin levels rise after transplantation,[112,122] indicating increased bone turnover. This is confirmed by an increase in histomorphometric indices,[123] and an increase in activation frequency and erosion depth[124] over 3 months post-transplant. The mechanism of post-transplant bone loss thus appears to be a primary depression of bone formation within 3 months, followed by an increase in bone turnover with increased osteoclastic activity and erosion depth.

Other causes of secondary osteoporosis

A number of other conditions may contribute to the development of male osteoporosis,[44] though only post-gastrectomy bone disease shows a male preponderance. Disturbances of calcium homoeostasis and vitamin D metabolism were originally thought to contribute to the bone loss often found in these conditions, but current evidence suggests that these make only a minor contribution.

Gastrointestinal disease

Traditionally, gastrointestinal diseases were thought to cause osteoporosis because of decreased intake or malabsorption of calcium and vitamin D.[125] In a recent case-controlled study, however, ionized calcium and parathyroid hormone levels were normal, and vitamin D levels only slightly lower, in men

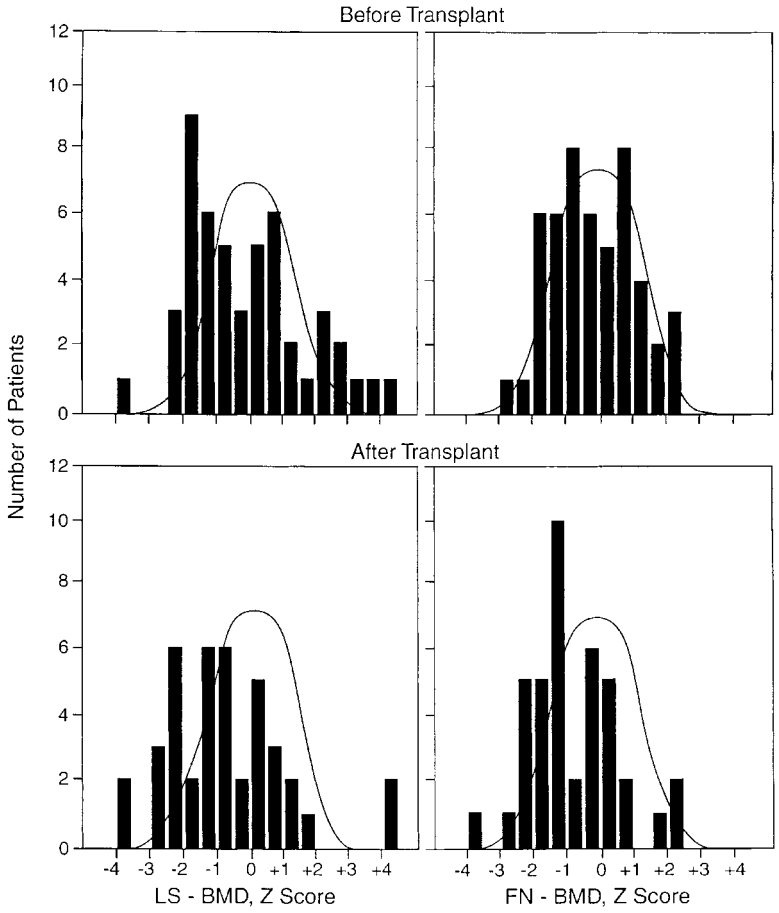

Figure 3. BMD of the lumbar spine (LS-BMD) and femoral neck (FN-BMD) in men (30) and women (10) before (upper) and after (lower) cardiac transplantation (mean 28 months). BMD at both sites was normal before and low after transplantation. The results are expressed as Z scores, SD units from the expected value for age and sex. The standard normal curve is shown. From Shane *et al.*[114]

who had undergone partial gastrectomy, though significantly more had vertebral fractures.[126] The major differences from the control subjects were a significantly greater prevalence of smoking and low body mass index (BMI), which appeared to be major risk factors for low BMD in these patients (Figure 4), as in another group of elderly men with vertebral fractures.[18] Smoking lowered vitamin D levels significantly in the gastrectomy patients, but not in control subjects.[126]

Hyperparathyroidism

Although over 50% of patients with hyperparathyroidism are asymptomatic, about 20% have hypercalciuria and 10% have osteoporosis.[127] Bone loss appears to occur early in the course of the disease and then stabilizes at the normal rate; parathyroidectomy only partially reverses this bone loss.[128,129] Although some studies have shown that the risk of all fractures is increased in women with primary hyperparathyroidism,[130] the balance of evidence suggests that fracture rate is not increased.[128,131]

Hypercalciuria

Absorptive and resorptive hypercalciuria[132] are both associated with an absolute increase in serum concentration of, or enhanced sensitivity to, vitamin D, leading to more pronounced trabecular rather than cortical bone loss.[51,133] Renal hypercalciuria, in contrast, is associated with increased levels of parathyroid hormone and more cortical relative to trabecular bone loss; this may be exacerbated by a low dietary calcium intake.[134] Vertebral bone loss in hypercalciuric men is modest compared with that in normal subjects.[133]

Thyroid disease

Hyperthyroidism is ten times less common in men than in women, but in both sexes leads to an increase in bone resorption with variable changes in BMD, which seem to affect cortical rather than trabecular bone.[135] Symptomatic osteoporosis in hyperthyroidism is rare and may be an indication that other conditions are affecting the skeleton.[136] For example, correction of hypothyroidism with low-

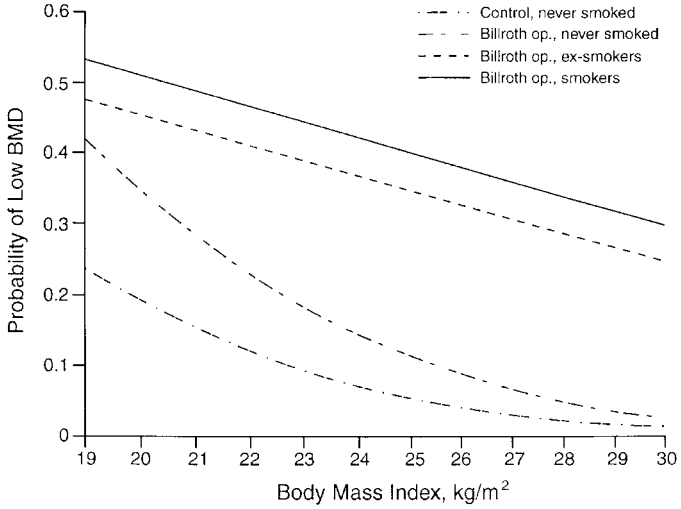

Figure 4. Probability of low BMD of the calcaneum (less than mean −1 SD of young normal) in 129 men after partial gastrectomy (Billroth I or II) related to smoking habits and Body Mass Index. Smokers were particularly likely to have low BMD. From Mellstrom *et al.*[126]

dose, chronic thyroxine replacement therapy may amplify focal imbalance due to alcoholism, increasing bone turnover and causing a preponderance of trabecular bone loss. In men at least, thyrotoxicosis is probably not an important cause of osteoporosis, unless it is complicated by other factors, such as smoking and alcohol abuse. Historically, more bone disease used to be seen in both sexes in association with hyperthyroidism, indicating that the lack of an association between hyperthyroidism and osteoporosis now may be the result of more rapid diagnosis in recent years.

Anticonvulsant and other drugs

These compounds have been clearly associated with alterations of vitamin D metabolism, but poor dietary intake and lack of exposure to sunlight may also contribute to the osteomalacia seen in older patients.[137,138] In children taking valproate, lumbar spine and radial BMD was significantly decreased, while carbamazepine also caused a similar but less marked reduction in BMD.[139] The decrease in BMD was proportional to the duration of valproate therapy, but the mechanism of bone loss with anticonvulsant therapy was not clear. Increased bone resorption has been implicated,[140,141] but the development of a reversible Fanconi's syndrome[142] may implicate renal calcium loss as a factor. Warfarin has also been demonstrated to be associated with a significant reduction in spine and forearm trabecular bone in a case-control study of men on long-term therapy.[143] Sedatives of any kind, if they lead to reduced physical activity, are likely to lead to reduced BMD in children.[144]

Immobilization

Immobilization for up to 3 weeks increases bone resorption and decreases bone formation, which over the course of 6 months can produce trabecular bone losses of up to 33%.[145] During the period between 6 and 12 months after immobilization, bone turnover returns to normal and BMD stabilizes. Intervention will only be effective, therefore, during the early months after immobilization, and thereafter will have no effect.

Diagnosis of male osteoporosis

An individual's bone mass is usually related to the normal range by means of standard deviations (SDs), usually expressed as either a T score or a Z score. The T score expresses BMD as the number of SDs by which the given value differs from the mean peak bone mass of a young, sex-matched reference group. A T score provides an indication of the risk of developing pathological fractures, and this risk increases exponentially with decreasing T scores.[110] In contrast, a Z score, which expresses BMD as the number of SDs by which the given value differs from the BMD of an age-matched and sex-matched reference group, places the patient in relation to the normal population of the same age and sex. Z scores are calculated as the difference between the individual BMD and the reference group divided by the SD for the reference group:

$$Z\ \text{score} = (\text{BMD} - \text{BMDage}) \div \text{SDage}$$

where BMD is the measured BMD, BMDage is the

mean BMD for age-matched normal subjects, SDage is the SD for age-matched normal subjects.

A modest change in this SD value can alter the Z score from an abnormal to a normal value.

The WHO criteria[146] for osteopenia and osteoporosis in women are as follows: (i) low bone mass (osteopenia), a value for BMD or BMC more than 1 SD below the young adult mean but less than 2.5 SD below this value; (ii) osteoporosis, a value for BMD or BMC 2.5 SD or more below the young adult mean.

Reference ranges

It is essential that appropriate reference ranges are established for BMD in men, as the WHO criteria for the diagnosis of osteoporosis relate specifically to Caucasian women. The reference ranges currently used are generally those supplied by instrument manufacturers, and often relate to a smaller study population than those obtained for women. This may lead to inaccuracy in the reference ranges for men. If the normal range is set within narrow limits and the mean bone mass is defined at too high a level, a large proportion of normal individuals may wrongly be assessed as abnormal, as seems to be the case with the WHO definition of osteopenia in women. The data available from the National Health and Nutrition Examination Surveys III data (NHANES III) indicate that in a sample of 1676 non-Hispanic white men, femoral neck BMD was 3–5% lower than the reference range recommended by the densitometer manufacturer and the SDs were 26–30% higher.[147]

Several studies have related BMD in men to the risk of fracture. In a group of 654 men in the Malmo area in whom BMD was assessed by single-photon absorptiometry, those in the lowest quintile of BMD had a 6–13-fold increase in the risk of fracture over the following 11 years.[148] In general, low BMD at the spine or the hip is associated with a greater risk of fracture.[149–155] Based on the available European data, the fracture risk increases by about two-fold for every reduction of 1 SD below the normal age-matched mean BMD, which is similar to the risk increase found in women.[12] The risk of vertebral fracture is nearly 7-fold greater in white North American men with a BMD more than 1 SD below the population mean, compared with those with BMD more than 1 SD above the mean.[156]

It seems, therefore, that although BMD can be accurately measured and a low BMD predicts fracture risk, current reference ranges for men still need to be validated in clinical practice. The use of BMD as a basis for therapy in men is not yet established, nor whether treatment based on BMD influences fracture risk, though measurement of BMD has been recommended in men with vertebral abnormalities or radiographic evidence of osteopenia, in those on long-term corticosteroid treatment, and in those with asymptomatic hyperparathyroidism.[157,158]

Radiological assessment

Vertebral deformity identified radiologically is negatively correlated with vertebral BMD.[12,156] The incidence/prevalence of vertebral deformity has generally been assessed in single-country studies,[2,27,156,159] and has sometimes been a secondary measure in a trial designed to investigate another endpoint. Large or multicentre studies require protocols that can be used reliably by different radiologists or radiological technicians. In principle, use of vertebral height ratios avoids the problems of different magnifications in different centres, provided that if the spine is imaged on two films, both are taken at the same magnification. These height ratios can be used to identify three types of vertebral deformity: biconcavities, wedge fractures, and crush fractures.[160,161] Although a 15% or 20% reduction of anterior, posterior, or central height is a commonly accepted radiological definition of vertebral compression fracture,[162] the normal ranges of vertebral height vary between centres.[163] The presence of osteoporosis is thus better defined by the number of SDs an individual's vertebral height differs from the population mean vertebral height: a threshold value of -3 SDs was chosen in the EVOS study for both the Eastell-Melton and the McCloskey-Kanis algorithms, though data for -4 SDs was also presented (Eastell-Melton algorithm) for three populations.[163] Wedge fractures are the most common deformity in both men and women, accounting for about 55% of all vertebral deformities.[11]

Back pain

Although back pain is a common clinical presentation of atraumatic vertebral fractures,[164] the diagnostic importance of back pain for osteoporosis is currently unclear. In a study of 63 men with vertebral fractures, scores for all six domains of the Nottingham Health Profile were worse than in age-matched or elderly control groups, and this difference was particularly marked for pain, energy and mobility.[164] In an analysis of cases from 13 European centres, fewer cases than control subjects had ever experienced back pain, but a significantly higher percentage of cases than control subjects currently had back pain; however, there were no differences in severity, duration or occurrence of an episode during the previous year.[165] In a series of 30 patients (mainly women) with acute painful vertebral compression fractures, only 43% were correctly diagnosed at the

first visit.[166] Because vertebral osteoporosis is a diagnosis that is less often considered in men, the diagnostic accuracy of clinicians for male vertebral fractures at the first visit is unlikely to be better. In a Swedish series comparing cases of hip fracture with control subjects, the incidence of back pain in the control group was twice that in the hip fracture patients, though vertebral fractures were shown radiologically in twice as many hip fracture patients as in control subjects; the authors concluded that the major reason for back pain in the elderly did not appear to be related to spinal osteoporosis.[167]

Bone turnover and markers

As with other aspects of male osteoporosis, fewer biochemical measurements have been made in men than in women. A variety of biochemical indicators have been related to bone loss in healthy men, including increases in urinary calcium, osteocalcin, serum parathyroid hormone and vitamin D levels.[168] Most biochemical studies in normal men suggest that bone formation increases with age, in contrast to the histomorphometric evidence of decreasing bone formation with age. In men with osteoporosis, urinary calcium and hydroxyproline excretion and serum alkaline phosphatase levels are increased, indicating increased bone turnover.[169] Serum osteocalcin levels are also increased and vitamin D levels decreased, indicating increased bone formation.[170]

In both normal men and women, urinary excretion of pyridinium cross-links increases with age,[171] indicating increased bone resorption. The clinical relevance of the reported sex-related differences in urinary cross-link concentration[172] is not yet clear. In a recent study of normal men, total body BMC decreased steadily with age, most notably in the sixth and eighth decades,[173] and largely as result of the decrease in hip BMC. Bone-specific alkaline phosphatase, serum osteocalcin and pyridinoline crosslink, however, all showed a decrease to about age 50 years, followed by an increase, more pronounced with some markers than with others (Figure 5).

The conclusions of the group relating to the diagnosis of male osteoporosis are summarized in Table 6.

Prevention and treatment options

Therapy of male osteoporosis has seldom been investigated, and few therapeutic trials have been performed in solely male populations, though some men with osteoporosis have been included in mixed populations in trials of various agents. It cannot be assumed that agents that are effective in women will be effective in men, as the pathogenesis of male osteoporosis differs from that of postmenopausal osteoporosis. In the USA, there are no approved pharmacological therapies for male osteoporosis.[3] Agents that influence bone resorption or formation may be useful, as in women, but specific treatment of the underlying pathological condition may also stabilize or improve bone mass in men with osteoporosis.

The prevention and treatment options for male osteoporosis are summarized in Table 7.

Testosterone treatment

Low testosterone levels are often found in men with a variety of causes of osteoporosis, and up to 16% of men with vertebral crush fractures exhibit hypo-

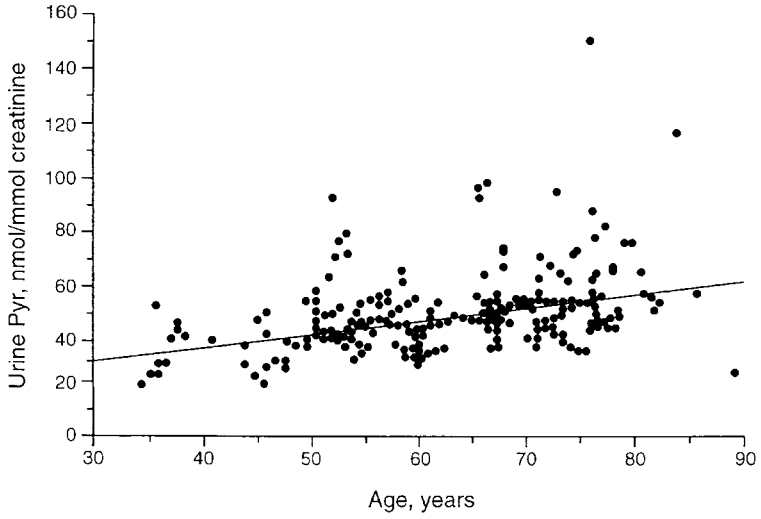

Figure 5. The effect of age on bone resorption in men. There was an increase in free pyridinoline excretion (measured by ELISA and expressed as a ratio to creatinine) with age ($r=0.31$, $p<0.001$) in 236 men. From Delmas *et al.*[171]

Table 6 Diagnosis of osteoporosis in men

Osteoporosis can be diagnosed on the basis of radiological assessments of bone mass or clinically when it becomes symptomatic.
BMD can be related to the peak adult mean (T score) or to the sex-matched, age-matched mean (Z score).
Although general reference ranges can be useful, reliable reference ranges have not yet been established for men of different ethnic origins.
The use of BMD as a basis for therapy is not yet established, nor whether treatment based on BMD influences fracture risk. However, vertebral deformity identified radiologically correlates negatively with vertebral BMD.
A practical approach would be to consider a Z score of less than −1 as an indication for therapy.
The diagnostic importance of back pain is currently unclear, and the major reason for back pain in the elderly may not be osteoporosis.
Various biochemical markers have been related to bone loss in healthy and osteoporotic men. Their use as diagnostic tools, however, needs further investigation.

Table 7 Prevention and treatment options for male osteoporosis

The treatment options for men with osteoporosis include agents to influence bone resorption or formation and specific therapy for any underlying pathological condition.
Testosterone treatment increases BMD in hypogonadal men and is most effective in those whose epiphyses have not closed completely.
Eugonadal men with idiopathic osteoporosis may also benefit from testosterone treatment, with significant increases in spinal bone mass.
Confirmation is required that the increase in BMD produced with testosterone ultimately reduces fracture risk.
Intermittent cyclical etidronate significantly increases spinal and possible femoral BMD over 2 years in men with osteoporosis, irrespective of the underlying cause.
Pamidronate may have similar beneficial effects, but is not currently licensed for use in osteoporosis.
Although there is some evidence that calcitonin may be effective in increasing BMD, few of the studies are well designed, and calcitonin is too expensive and too inconvenient for routine use.
The efficacy of vitamin D supplementation is doubtful.
The use of anabolic agents remains investigational at the present time.
Bisphosphonates are the treatment of choice, whilst sodium fluoride and anabolic steroids should be considered in the case of treatment failure.

gonadism.[49] Testosterone treatment in hypogonadal men rapidly increases 1,25-dihydroxy vitamin D levels and corrects calcium malabsorption, leading to an improvement in calcium balance and an increase in bone formation.[88] Testosterone treatment of hypogonadal men significantly increased forearm bone density, but the effect was greater in men whose epiphyses had not completely closed.[174,175] Testosterone also significantly increased spinal BMC/BMD in hypogonadal men over periods of 3 months to at least 1 year,[175,176] but again the effect was greater in men with open than with closed epiphyses.[175] A histomorphometric case study suggests that relative osteoid volume, total osteoid surface, linear bone formation and bone mineralization are all increased by testosterone treatment of hypogonadism.[90]

The role of testosterone treatment in management of eugonadal men with idiopathic osteoporosis is currently under investigation. In an open pilot study, 23 men presenting with vertebral fractures were given testosterone for 6 months.[177] Although no changes in femoral neck BMD were seen at 6 months, spinal BMD increased significantly by 5% over this period (Figure 6). Surprisingly, markers of both bone formation and resorption were reduced, suggesting that at least in the short term, testosterone treatment of eugonadal men increases BMD by decreasing bone resorption.[178] This conclusion is supported by the finding that those patients with the greatest increases in spinal BMD also showed the greatest decrease in urine *N*-telopeptide excretion.[178] The safety profile for testosterone treatment was generally good, with decreases in systolic and diastolic blood pressures and a significant decrease in plasma triglyceride levels, though high-density lipoprotein-cholesterol levels fell.[177] No mood or aggression changes were noted. In a longer term uncontrolled study, testosterone treatment produced a consistent increase in lumbar spine BMD, amounting to 6% over 3 years.[179] A recent controlled study of testosterone treatment in men with steroid-induced osteoporosis, some of whom were hypogonadal, also showed a significant increase in spinal BMD.[180]

It thus appears that testosterone treatment may be beneficial in both hypogonadal and eugonadal men with osteoporosis, but confirmation is required that the benefit in terms of BMD ultimately reduces fracture risk without causing adverse effects in the longer term.

Bisphosphonates

Data in men are available for the bisphosphonates etidronate and pamidronate, but only five of the 12 trials published enrolled only men. In a small, uncontrolled study of men with idiopathic osteoporosis manifested as vertebral fractures, intermittent cyclical etidronate significantly increased spinal

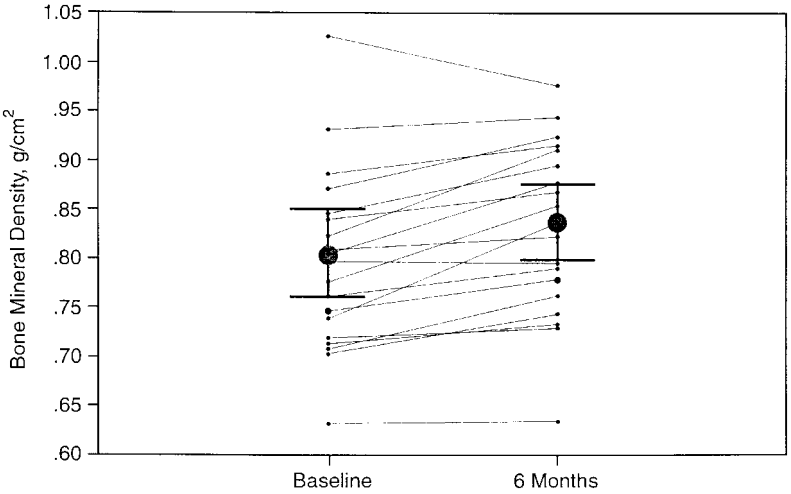

Figure 6. Changes in lumbar spine BMD in 23 eugonadal men with vertebral fractures treated with testosterone esters given intramuscularly for 6 months. Error bars show mean with 95% confidence intervals. There was a significant increase in BMD ($p<0.001$). From Anderson *et al.*[177]

BMD by an average annual rate of change of 3.2% versus baseline values over 2 years, with a small but non-significant improvement in femoral neck BMD (Figure 7).[181] A significant increase in spinal BMD of 6% over 2 years was obtained with intermittent cyclical etidronate in a study of 44 men with idiopathic or secondary osteoporosis, though no changes in femoral neck or forearm BMD were noted.[182] In contrast, Selby *et al.*[183] reported that in addition to a significant increase in spinal BMD of about 6%, intermittent cyclical etidronate produced an increase of about 10% in proximal femoral BMD, although it did not prevent continuing bone loss at the forearm in this group of 36 men with idiopathic or secondary osteoporosis. Significant increases in spinal BMD, but not in femoral neck BMD, over 2.5 years have also been reported in a small uncontrolled study of intermittent cyclical etidronate in men with osteoporosis.[184] In the most recent study in 23 men with radiological evidence of osteoporosis, the mean increase in lumbar BMD was 9.2% after 3 years of intermittent cyclical etidronate; after 4–5 years the mean increase in lumbar BMD in 11 patients was 7.9%.[185] There was no significant increase in femoral neck BMD, nor was there any bone loss. A retrospective study by Orme *et al.*[186] noted a 9% increase in lumbar BMD in 10 patients at 12 months.

In a randomized, controlled study enrolling about 50% men with corticosteroid-induced osteoporosis, intermittent cyclical etidronate increased both spinal and hip BMD in the total group by about 6% over 1 year, compared with a decrease of about 4% on calcium supplementation alone. This was equivalent to an increase in Z score of 0.34 at both sites.[187] Subgroup analysis, however, suggested that the increase in bone mass was greater in the women than in the men, though this difference may have been exaggerated by the postmenopausal status of the women. In a study in liver transplant patients, intermittent cyclical etidronate produced an increase in vertebral BMD over 1 year of 8.2% in the subgroup of patients (16 men, 7 women) with osteoporosis, compared with a bone loss of 3.4% over 1 year in the untreated patients.[188]

Three uncontrolled studies of pamidronate in men and women with osteoporosis have reported spinal BMD increases of about 8% over 3 years with intravenous pamidronate either alone or combined with fluoride[189] and of about 3% over 2 years with oral pamidronate.[190,191] In a small randomized, placebo-controlled study that enrolled equal numbers of women and men with corticosteroid-induced osteoporosis, oral pamidronate produced a significant

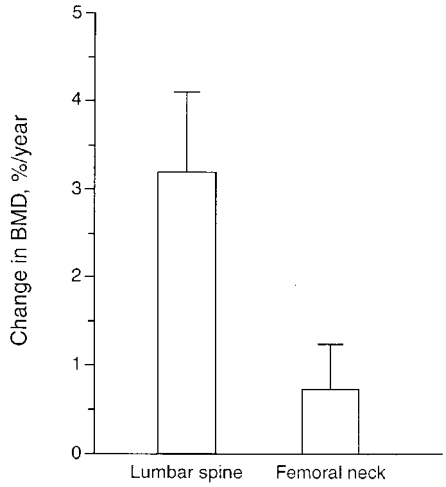

Figure 7. Mean annual increase in lumbar spine and femoral neck BMD in 42 men with vertebral fractures treated with cyclical etidronate for 24 months. From Anderson *et al.*[181]

19.6% increase in vertebral BMD compared with a non-significant 8.8% decrease in the placebo group.[192]

In conclusion, therefore, the bisphosphonates intermittent cyclical etidronate and pamidronate appear to improve BMD in men with osteoporosis, but randomized controlled trials enrolling only men are needed to confirm the preliminary reports.

Calcitonin and calcium/vitamin D

Very little information is available on the efficacy of calcitonin and calcium/vitamin D in men with osteoporosis. In a study in which 41% of the patients were men, calcitonin stabilized BMD over 2 years, leading to only a 1% fall compared with a 15% decrease in a retrospective control group.[193] In a small randomized study in men with osteoporosis, calcitonin treatment for 2 years produced a decrease in vertebral fracture incidence compared with calcium or multivitamin treatment.[194] In a group of patients with osteoporosis as a result of liver transplantation (10 men, 7 women), intramuscular calcitonin produced an increase in vertebral BMD over 1 year of 6.4%, similar to the 8.2% increase obtained with intermittent etidronate.[188] Studies of fracture incidence have provided equivocal results, but many of these studies are flawed.[195]

There is little evidence that vitamin D supplementation can influence bone loss. In a 3-year randomized study of normal men, calcium/vitamin D did not alter the rate of bone loss at either the wrist or the spine.[42]

Recently, Dawson-Hughes *et al.*[196] reported a decrease in non-vertebral fractures after treatment for 3 years of 389 men and women over 65 years with a supplement of calcium (500 mg/day) and vitamin D (700 IU/day). This decrease in fracture rate was surprising as the increases in BMD at the lumbar spine (0.9%), femoral neck (1.2%), total body (1.2%) were so small. The effect in the men was at least as great as the effect in the women.

Although patients with osteoporosis may derive some benefit with calcitonin, clinical experience suggests that it is too expensive and inconvenient for routine use. The efficacy of vitamin D remains doubtful.

Other treatment options

Almost no information is available on the use of fluoride, parathyroid hormone, growth hormone, or other anabolic agents in men with osteoporosis. The use of fluoride for osteoporosis remains controversial, because although dramatic increases in BMD can be achieved, there are doubts about the biomechanical competence of fluoride-treated bone.[197] In a randomized controlled study of 64 males with generalized osteoporosis (but no prevalent vertebral fractures), bone density increased at all measuring sites (spine, femur, radius) in the treatment group on low-dose intermittent fluoride and calcium. In addition, a significant difference in the small number of vertebral and non-vertebral fractures was noted between the monofluorophosphate and calcium versus the calcium alone group.[198] In an uncontrolled study of patients with symptomatic idiopathic osteoporosis, the vertebral fracture rate was reduced from 33% in the first year of fluoride treatment to 11% in the second year in both men and women.[199] Although other studies support this finding, the results in men and women were not analysed separately. The potential of parathyroid hormone treatment in osteoporosis appears to be similar in men and women, and over a period of 6–24 months can produce significant increases in trabecular bone volume.[200] A small study in men with idiopathic osteoporosis confirmed the increase in trabecular bone density over 1 year of treatment with parathyroid hormone plus vitamin D.[201]

Growth hormone treatment can apparently rapidly increase biochemical indices of bone turnover in healthy elderly men and women and in men with idiopathic osteoporosis.[202,203] In a randomized controlled trial of elderly men with low plasma levels of insulin-like growth factor I (IGF-I), treatment for 6 months with growth hormone not only raised IGF-I levels to the normal range for young men, but also resulted in a 1.6% increase in lumbar vertebral BMD, though proximal and distal radial BMD did not change.[204] The use of all these anabolic agents remains experimental at the present time.

Management of the individual

The group considered a number of case histories and the algorithm (Figure 8) summarizes their general approach to the individual male patient with osteoporosis. The indications for BMD measurement reflect conditions commonly associated with low bone mass in men. The measurement of BMD at the spine and hip represents common medical practice in the UK. The choice of a Z score of less than -1 at either the spine or hip will result in the treatment of about 25% of men. The inclusion of the extra criterion of a T score of less than -2.5 ensures that bone loss is treated, but not prevented. In formulating guidelines for postmenopausal osteoporosis, the National Osteoporosis Foundation in the United States proposed that other factors be considered in addition to bone density when making decisions about starting treatment. These factors included current smoking, low weight (73 kg would be the cut-

off for the lower quartile in men), family history of low trauma fracture, and past history of low trauma fracture.[205] Family history of low trauma fracture[206] and a past history of low trauma fracture[207] are risk factors for osteoporosis in men as they are in women. Secondary osteoporosis is common in men and the underlying cause should be treated and BMD measured again. Otherwise, treatment to increase BMD is required.

In the UK the drugs that are currently approved for broad use in osteoporosis include calcium and vitamin D and cyclical etridronate. The drugs that have been approved for postmenopausal osteoporosis to date include alendronate, salmon calcitonin, and anabolic steroids (nandrolone decanoate). The bisphosphonates were considered the drugs of choice, with advantages for cyclical etidronate (low cost), alendronate (greater hip BMD response) and intravenous pamidronate (particularly in men with high bone turnover). Fluoride was considered as an alternative if spine BMD was very low or there was no response to bisphosphonates. Many of these

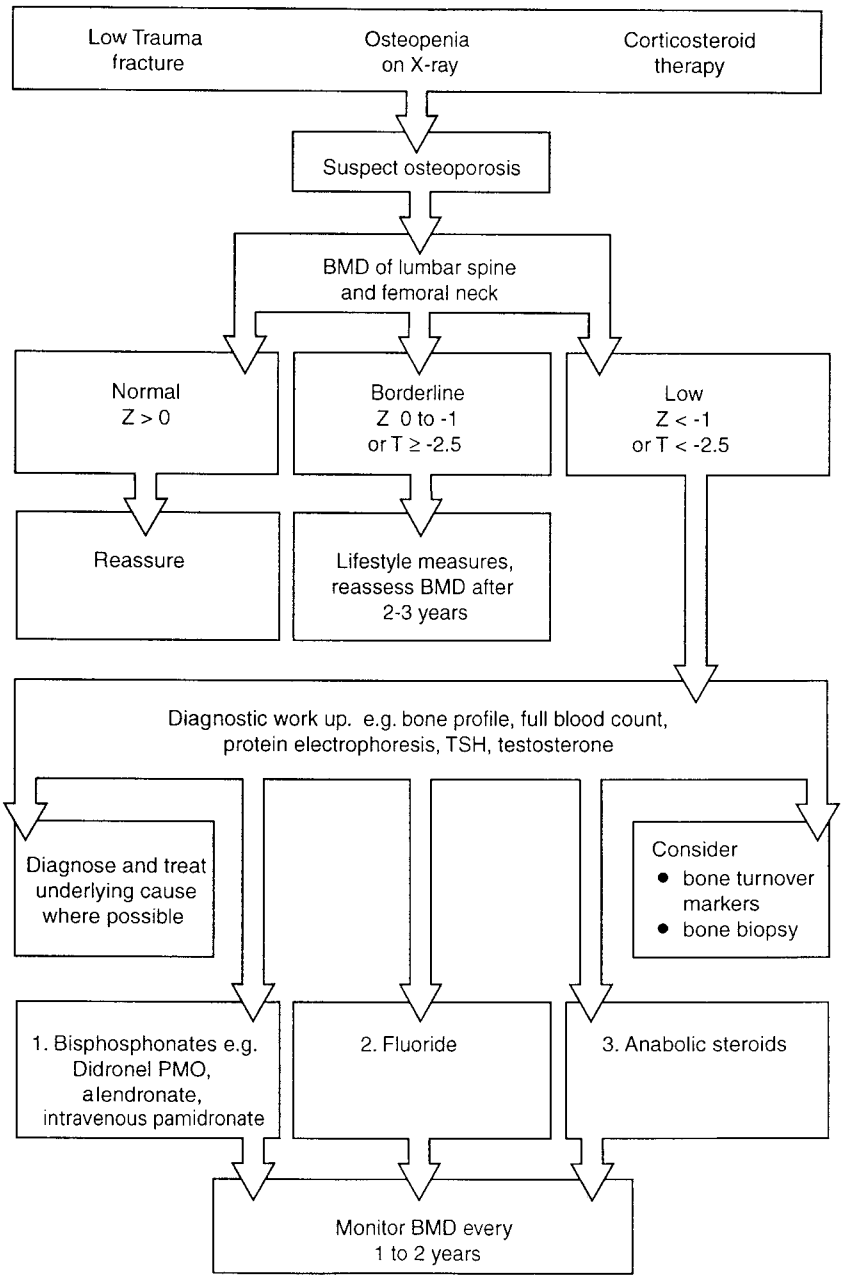

Figure 8. Algorithm for the management of osteoporosis in men. BMD measurements play a central role in the diagnosis and monitoring of treatment. In the UK, the drugs that are currently approved for broad use in osteoporosis include calcium and vitamin D and cyclical etidronate. The drugs that have been approved for postmenopausal osteoporosis to date include alendronate, salmon calcitonin, and anabolic steroids (nandrolone decanoate).

treatments are unproven in men, emphasizing the importance of monitoring the effects of treatment, e.g. repeated spine BMD measurements after 1–2 years.

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