

## REVIEW

# Osteoporosis in men: a cellular endocrine perspective of an increasingly common clinical problem

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### Abstract

Although it has been accepted that osteoporosis is common in women, only recently have we become aware that it is also widespread in men; one in twelve men in the UK have osteoporosis. In many cases, there are recognisable causes for their osteoporosis, but a significant proportion (approximately one third) of these men have idiopathic disease. A major problem is that these cases are difficult to treat. An important therapeutic strategy would be to identify men at risk from osteoporosis sufficiently early, so that they can begin preventative measures. Moreover, development of novel means of treating these men would be an important clinical advance. With the emphasis on osteoporosis in women, however, the cellular and molecular basis for male idiopathic osteoporosis (MIO) is still poorly understood. Nevertheless, there are some aspects of skeletal regulation which may be specific for men and which could form the basis for addressing these problems. Thus, the importance of oestrogen in maintaining the adult skeleton in men as well as women implies that bone

cells in men can respond to low levels of the hormone. Both oestrogen receptor (ER)  $\alpha$  and  $\beta$  are expressed in bone *in vivo*, which may be important for oestrogen action on bone in men. Furthermore, in osteoporosis generally, there is increasing evidence for defective osteoblast differentiation such that there is a surfeit of adipocytes over osteoblasts. A low peak bone mass is a powerful risk factor for osteoporosis in later life; bone formation and, by implication, osteoblast differentiation, is key to the mechanism by which it is accrued. GH and IGFs are important for regulating osteoblast differentiation. Evidence now suggests that they are associated with bone mineral density, particularly in men. The genes for ERs, GH and IGF-I might be useful candidates with which we can begin to detect men at risk from osteoporosis. Furthermore, the mechanisms by which oestrogen, GH and IGF-I regulate the male skeleton could provide the basis for developing novel means of treating MIO.

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### Features of male osteoporosis

Osteoporosis affects approximately one third of women in the United Kingdom, and this has overshadowed the disease in men. It is now recognised that one in twelve men in Western countries have osteoporosis; 30% of all hip fractures are in men (Eastell *et al.* 1998) and it accounts for at least one quarter of the total £1 billion burden of osteoporosis on the National Health Service in the United Kingdom. Moreover, recent observations of Ismail *et al.* (2000) indicate that the effects of the disease in men are at least as severe as in women. There are well-recognised risk factors for men; for example, treatment with anti-inflammatory steroids, tobacco and alcohol consumption, and hypogonadism. At least a third of men with osteoporosis, however, have idiopathic disease. Why certain men have male idiopathic osteoporosis (MIO) and whether

suitable treatment can be developed for them are major questions. Due to the emphasis on osteoporosis in women, however, the cellular and molecular basis for MIO is still poorly understood. In this article, we wish to review some of the fundamental mechanisms of skeletal regulation in order to ascertain if there are aspects of them which are specific to men, and which might form the basis for detecting men at risk from the disease and to review suitable treatments for MIO patients.

The standard World Health Organisation definition of osteoporosis in women is of a bone mineral density which is 2.5 standard deviations below that of a healthy normal control. Evidence suggests that the same definition can be applied to men, if based on gender-specific T scores (Selby *et al.* 2000). A typical clinical presentation is often that of long bone fracture following a non-traumatic event, or crush fractures of the vertebrae. In both men and women,

bone mass adaptation to mechanical loading or deformation is thought crucial to preservation of skeletal structure and there is evidence that this may be hormone sensitive (Notelovitz *et al.* 1991). Intrinsic to maintenance of bone mineral density and structural integrity of the skeleton is the mechanism of bone remodelling. A major purpose of this process is replacement of old bone and it depends upon a balance between bone resorption, by osteoclasts, and bone formation through osteoblast activity. Osteoporotic bone loss is due to an imbalance in bone remodelling; either increased bone resorption, decreased bone formation or a combination of the two. Following the menopause, this bone loss is emphasised further through the increased initiation rate of bone remodelling cycles. Although raised osteoclasts has been regarded as a classic feature of postmenopausal bone loss in women (Cohen-Solal *et al.* 1995, Eriksen *et al.* 1999), histomorphometric classification of bone biopsies from over 140 women with postmenopausal osteoporosis demonstrates a minimum of five different combinations of osteoblast and osteoclast dysfunction (Rehman *et al.* 1995), involving changes in cell number with or without altered cell activity. Similar investigations of osteoporosis in men have been less extensive, but indications are that, although bone turnover may be increased, reduced trabecular number or size is a common feature of men with osteoporosis (Francis *et al.* 1989, Mosekilde 1989).

### Importance of oestrogens for maintaining bone in men and women

It is well recognised that oestrogens are important for maintaining bone mineral density and skeletal structure in women; falling oestrogen levels in women during the menopause causes bone loss leading to osteoporosis. Likewise, androgens were thought to exert a similar effect on the male skeleton (Orwoll 1996). Indeed, hypogonadism and lowered testosterone levels are an important cause of osteoporosis in men. Our understanding of gonadal steroid action on bone has now altered radically, largely due to reports describing men either with a null mutation of oestrogen receptor (ER) (Smith *et al.* 1994) or aromatase genes (Morishima *et al.* 1995, 1997, Bilezikian *et al.* 1998). In both situations, although testosterone was synthesised and the androgen receptor (AR) unaffected, there was abnormal skeletal development and marked osteopenia. Furthermore, although there are reports that testosterone treatment improved bone mineral density in hypogonadal men (Behre *et al.* 1997), osteoporotic patients with Klinefelter's disease did not respond to this treatment (Wong *et al.* 1993), nor was it effective in treating males with aromatase deficiency (Carani *et al.* 1997). They, however, responded to oestrogen. A key question is the identity of androgen target cells in the adult male skeleton. Although AR expression has been reported in bone cells

*in vitro* (Colvard *et al.* 1989) and in the growth plate of adolescents (Abu *et al.* 1997), it is low *in vivo* in mature bone cells of adult men and women (Braidman *et al.* 2000a), in agreement with previous reports that AR expression is age and site dependent (Kasperk *et al.* 1997). Androstenedione treatment, however, reduces loss of cancellous bone in ovariectomised rats, even when aromatase activity was inhibited (Lea *et al.* 1998), but it is not known if this is relevant to the skeleton in adult men. Whether testosterone *per se* has a direct action on the adult male skeleton is still unclear, and it may be that it influences bone indirectly, either through muscle or changes in calcium regulation. The possibility remains that a major function of testosterone in the maintenance of adult bone, even in men, is to be the source of oestrogen. Indeed, it has now been proposed that bone loss in ageing men and women is associated with falling oestrogen levels (Khosla *et al.* 1998, Riggs *et al.* 1998). Further, in men, bone mineral density (Slemenda *et al.* 1997) and indices of bone formation (Anderson *et al.* 1998) are correlated positively with oestrogen levels. This was observed even when eugonadal men with osteoporosis were treated with testosterone. Moreover, in these patients there was no correlation between bone formation and testosterone levels (Anderson *et al.* 1997). A weaker association was reported between oestrogen and bone resorption (Slemenda *et al.* 1997). Although it has been suggested that, in postmenopausal women, high doses of oestrogen stimulate osteoblast function (Tobias & Compston 1999), overall, the evidence reviewed above for the importance of oestrogen to bone formation in men, implies that osteoblasts may also be sensitive to lower circulating levels of male oestrogen.

### ER expression in the skeleton

It has been known for some time that osteoblasts express ER and respond to oestrogen *in vitro*, with respect to synthesis of bone matrix proteins (Eriksen *et al.* 1988, Komm *et al.* 1988, Benz *et al.* 1991), growth factors and markers of osteoblast differentiation (Ernst & Rodan 1991, Bodine *et al.* 1997, Kassem *et al.* 1998, Oursler 1998, Tau *et al.* 1998). Human cells across the osteoblast lineage express 'classic' ER $\alpha$  protein and mRNA *in vivo* and *in vitro* (Braidman *et al.* 1995, Hoyland *et al.* 1997, 1999, Kusec *et al.* 1998, Oreffo *et al.* 1999a). *In vitro* transfection studies (Ernst *et al.* 1991, Harris *et al.* 1995) demonstrate that the receptor may be responsible for many effects of oestrogen on osteoblast-like cells. The open epiphyses and marked bone loss in the adult man with a null mutation in ER $\alpha$  (Smith *et al.* 1994) are further indications of its importance to the male skeleton. Nevertheless, although there is some reduction in bone mineral density of ER $\alpha$  knockout mice, ovariectomy of these animals produced a more profound bone loss (Pan *et al.* 1997). One possibility is that other receptors may be important for oestrogen

action on the mouse skeleton. A second ER (ER $\beta$ ) is now recognised (Kuiper *et al.* 1996) and there is evidence for its expression in rat bone (Onoe *et al.* 1997, Windahl *et al.* 2000). Skeletal abnormalities in ER $\beta$  knockout mice, however, are surprisingly subtle, in that the bone mineral content of the cortices is increased only in adult females; males and immature animals remain unaffected (Windahl *et al.* 1999). ER $\beta$ , however, is expressed in transformed fetal human cells of osteoblast lineage *in vitro* (Arts *et al.* 1997) and in the growth plate of adolescent boys and girls (Vidal *et al.* 1999). The role of ER $\beta$  in oestrogen action on the adult human skeleton is unclear and is a matter for current debate. Investigations conducted in our laboratory (Braidman *et al.* 2001) demonstrate that it is clearly expressed in osteoblasts and some osteocytes equally well in both adult men and women, although it is uncertain, at present, whether the same cells express both ER $\alpha$  and ER $\beta$ .

Whether or not oestrogens act directly on osteoclasts is less clear; there is evidence which suggests that the hormone may influence bone-resorbing cells indirectly in the mouse, via cells of osteoblast lineage (Jilka *et al.* 1992). Studies with avian osteoclasts, however, demonstrate that oestrogens can act on these cells directly (Oursler *et al.* 1991, 1993, Robinson *et al.* 1996) and there are some indications for a similar action with osteoclasts of human origin (Mano *et al.* 1996, Kameda *et al.* 1997). Expression of ER $\alpha$  in mammalian osteoclasts, however, is controversial; some groups report receptor expression, either of mRNA or protein, in mature cells (Mano *et al.* 1996, Hoyland *et al.* 1997, Pederson *et al.* 1997) but others demonstrate its expression only in immature osteoclasts (Huang *et al.* 1998, Kusec *et al.* 1998, Oreffo *et al.* 1999b). In contrast, our own observations (Braidman *et al.* 2001) demonstrate clear ER $\beta$  expression in human osteoclasts *in vivo*, in both adult men and women, and show that the receptor is relatively abundant in these cells. This might provide a mechanism by which oestrogens may act on osteoclasts directly.

Overall, although receptor expression early in the osteoblast lineage is still unclear, the evidence suggests that ER $\alpha$  and ER $\beta$  are both expressed in the later stages of differentiation. This could be of considerable importance to men, as their bone must respond to relatively low constant oestrogen levels, compared with large variations in circulating concentrations of the hormone experienced by pre-menopausal women. The presence of the two receptor isoforms provides a means of amplifying the effects of the small oestrogen concentrations in men. If the same cells express both receptors, this could be achieved through heterodimerisation (Cowley *et al.* 1997, Ogawa *et al.* 1998). Alternatively, if ER $\alpha$  and ER $\beta$  are similarly expressed in different cells of the osteoblast lineage, even low oestrogen concentrations could influence a wide spectrum of gene expression and thereby a variety of biological effects. A similar situation has been discussed for

neural tissue (Kuiper *et al.* 1998). Such mechanisms as these may be the basis for the strong correlation between oestrogen levels in men with both bone mineral density and bone formation (Slemenda *et al.* 1997, Anderson *et al.* 1998, Khosla *et al.* 1998, Riggs *et al.* 1998).

## Oestrogen and MIO

The notion that falling oestrogen levels in ageing men are responsible for bone loss, analogous to the situation in postmenopausal women (Slemenda *et al.* 1997, Khosla *et al.* 1998) has been developed further to provide an explanation for MIO (Riggs *et al.* 1998). Whether this is true for all MIO cases is, however, open to debate. In a small group of younger MIO patients, oestrogen levels (both total and free) were significantly lower than in the matched control group (Gillberg *et al.* 1999), although it is important to note that levels of the hormone in all the subjects were within the normal range. A similar study of older men with idiopathic osteoporosis (Resch *et al.* 1992) demonstrated that although oestrogen levels in patients were lower than in controls, there was no significant difference between them. Examination of the data from both these studies indicates that there may be a group of MIO patients with significantly lower oestrogen levels than their normal counterparts. That these hormone levels are within the normal range, however, attests to the sensitivity with which the skeleton in men may respond to oestrogen, as discussed previously in this article. Thus, a small decrease in circulating oestrogen levels may be sufficient to cause a fall in bone mineral density and, thereby, risk of osteoporosis. Other patients, in both these studies, had oestrogen levels identical to age-matched controls. Observations from our own laboratory (Anderson *et al.* 1998) demonstrate this in a larger group of men with idiopathic osteoporosis who were relatively young (<55 years of age). We hypothesised that in some of these MIO patients with normal oestrogen levels, responses of bone cells to oestrogen might be impaired, possibly through defective ER expression. We therefore investigated the expression of ER $\alpha$  protein in sections of bone biopsies from a group of younger men (<56 years of age) with MIO. There was a marked loss of receptor protein expression in their osteoblasts and osteocytes, although receptor mRNA was still expressed (Braidman *et al.* 2000a,b). Whether or not all MIO patients with normal oestrogen levels have defective expression of ER $\alpha$  is not known. Loss of ER $\beta$  expression in bone cells may also be associated with MIO, and this requires further investigation.

In all three studies (Resch *et al.* 1992, Anderson *et al.* 1998, Gillberg *et al.* 1999), there were men with normal bone mineral density but relatively low oestrogen levels; likewise, in many older men, oestrogen levels fall but they do not proceed to develop osteoporosis. Clearly, there are

other factors important in the aetiology of MIO; for example, there are reports of decreased circulating insulin-like growth factors (IGF) in some men with idiopathic disease (Kurland *et al.* 1997, 1998). This is of particular interest, as IGF-I levels correlate positively with bone mineral density in men but not in women (Janssen *et al.* 1998) and introduces the possibility that some aspects of the underlying mechanisms for osteoporosis are gender specific. Whether these features protect bone in men from the effect of, for example, falling oestrogen levels, is a question of considerable importance and may depend upon their role in bone formation and osteoblast differentiation.

### Osteoblast differentiation and osteoporosis

Osteoblast differentiation from the stromal stem cell pool is essential to development and maintenance of the normal skeleton. The high proportion of osteoporotic cases in which there is reduced osteoblast number and activity, irrespective of whether osteoclasts is raised (Rehman *et al.* 1995), indicates that, in many cases, defective osteoblastogenesis is important to the aetiology of the disease. Marrow stromal pluripotent stem cells are the common progenitors of the osteoblast, chondroblast, fibroblast and adipocyte differentiation pathways, (Bab *et al.* 1985, 1986, Owen & Friedenstien 1988), which are controlled by complex interactions between growth factors and cytokines (Locklin *et al.* 1995, Kuznetsov *et al.* 1997). The transforming growth factor- $\beta$  (TGF $\beta$ ) superfamily, which includes the bone morphogenic proteins (BMPs), is important in this regard; BMP-2 and BMP-7 stimulate osteoblast differentiation *in vitro* from stromal stem cell progenitors by acting on osteoblast-specific transcription factors (Yeh *et al.* 1998, Gori *et al.* 1999). Furthermore, growth hormone (GH) stimulates osteoblast differentiation *in vivo* (Kroger *et al.* 1997) and in cultured stromal osteoblast progenitors, in the absence or presence of IGF-I and -II (Langdahl *et al.* 1998a), although there is some suggestion that the IGFs and the IGF-binding proteins (IGFBP) may be more important in later stages of osteoblast differentiation (Thomas *et al.* 1999a). The exact involvement of oestrogen in osteoblast differentiation is still uncertain; there are indications that GH may be important for early commitment to the osteoblast lineage, whereas oestrogen may act only on the later stages (Loveridge *et al.* 1996).

There is a close inverse association between differentiation from the stromal stem pool of osteoblasts with that of adipocytes (Bennett *et al.* 1991, Beresford *et al.* 1992). The current view is that there may be a plasticity between the two lineages or that they are derived from common precursors. Certainly factors like the BMPs, which stimulate osteoblastogenesis, concomitantly repress adipocyte differentiation from stromal stem cell populations *in vitro* (Gori *et al.* 1999). The observation that in osteoporosis

there is an increase of bone marrow adipocytes, at the expense of osteoblasts (Burkhardt *et al.* 1987), therefore suggests a defect on osteoblast differentiation from the stromal stem cells, which favours adipogenesis. To investigate this further, we compared the ratio of adipose tissue to haematopoietic/stromal tissue in trabecular bone of osteoporotic patients with that in normal controls, and found that it was increased significantly in the patients. Evaluation of the histomorphometric indices of osteoblast activity indicates that the increased volume of adipose tissue is associated with reduced bone formation. Moreover, if adipocytic/haematopoietic ratio is used as a proxy in assessing the amount of stromal tissue present, then there is a strong association between variability in this parameter and trabecular bone apposition. Overall, this supports the hypothesis that osteoporosis results from a clonal switch in differentiation of early stromal cells to the adipocytic pathway. Such a switch would also result in a decrease in the number of osteoblasts in osteoporotic bone, a finding we have previously demonstrated (Rehman *et al.* 1995).

Such impairment in osteoblast differentiation could prevent bone formation from matching raised bone turnover, resulting, for example, from lowered oestrogen levels in either men or women, or through defective responses of bone cells to oestrogen, as may be the case in some MIO patients. This further suggests that whatever the cause of the increased bone turnover, either lowered oestrogen levels or other factors, only those individuals with sufficiently impaired osteoblast differentiation would present with osteoporosis. From this perspective, it could be argued that lowered oestrogen levels may not always result in the disease, and implies that understanding the defects in osteoblast differentiation may lead to a means of predicting those at risk from osteoporosis.

Reports of increased osteogenesis in animal models, in which there is over-expression of *cfos* and the related Fra-1 transactivation factors, demonstrate the importance of these local factors in the regulation of osteoblast differentiation (Jochum *et al.* 2000). Over-expression of a naturally occurring truncated transcription factor, delta FosB, however, stimulated osteoblastogenesis but reduced adipogenesis (Sabatakos *et al.* 2000). Adipogenesis may further influence osteoblastogenesis through the action of the body mass regulator, leptin. In addition to its central role in controlling metabolism, body weight and gonadal function, it has been shown to inhibit bone formation, in experimental animals, through the central nervous system (Ducy *et al.* 2000). Studies on human marrow stromal cells *in vitro*, however, indicate that it can act directly on them to enhance osteoblast differentiation, and decrease adipogenesis (Thomas *et al.* 1999b). Whether expression of *cfos*, FosB or leptin is altered in osteoporosis in general, or specifically in male osteoporosis, is yet to be determined. Another possibility is that decreased synthesis or function of BMPs may also be important in osteoporosis but for

men, specifically, lowered IGF-I levels or activity may be of especial relevance (Janssen *et al.* 1998, Kurland *et al.* 1997, 1998), since this might lead to reduced osteoblast differentiation. This further suggests that there are aspects of adipocyte and osteoblast differentiation which may be specific to understanding osteoporosis in men.

### Peak bone mass as a determinant of osteoporosis

Many of the basic mechanisms by which bone mass is accrued, and the factors which determine bone loss in osteoporosis, are similar in both men and women. Bone mass in an adult, at a specific time-point, is the net result of subsequent bone loss from his or her peak bone mass. There is complex interplay between environmental and genetic factors, which affect either bone formation or bone loss. This has been studied extensively in this context, but mostly in women. Of the few studies with men, investigations of elderly male twins demonstrated that environmental and lifestyle factors were more important than inheritance in determining bone loss (Christian *et al.* 1989, Slemenda *et al.* 1992). Even in elderly women it has been suggested that the contribution of genetic factors to bone turnover and bone loss is likely to be small (Garnero *et al.* 1996). In any event, a high rate of bone loss may not necessarily lead to osteoporosis, if it is offset against a relatively high peak bone mass. Indeed, it is peak bone mass which is recognised as an important determinant for osteoporosis in later life (Johnston & Slemenda 1993, 1994, Teegarden *et al.* 1995).

Peak bone mass is accrued between 20 and 35 years of age. Although some environmental and lifestyle factors, particularly physical fitness and exercise, may be important influences on bone mass in young adult males (Casez *et al.* 1995), in contrast with bone loss in later life, a major component of peak bone mass in men is determined by genetic factors (Ettinger *et al.* 1997). Thus, the high bone mass in black Americans, compared with their counterparts, is reflected more by ethnic differences in peak bone mass than in bone turnover (Ettinger *et al.* 1997, Bikle *et al.* 1999). Genetic determinants of peak bone mass, therefore, be predictors for later osteoporosis (Johnston & Slemenda 1994, Kelly & Harris 1995, Deng *et al.* 1999a).

Specific genes and their polymorphisms have been investigated for association with bone mass, e.g. Sp1 binding site of the collagen gene (Grant *et al.* 1996, Langdahl *et al.* 1998b, Uitterlinden *et al.* 1998), the receptor for 1,25 dihydroxy vitamin D<sub>3</sub>, (Morrison *et al.* 1994, Riggs *et al.* 1995, Eccleshall *et al.* 1998), interleukin 6 (Murray *et al.* 1997), interleukin 1 receptor (Keen *et al.* 1998), TGFβ (Bertoldo *et al.* 2000) and parathyroid hormone receptor type 1 (Duncan *et al.* 1999). The studies were all carried out in either women or populations of older subjects of an age when accretion of bone mass has ceased and bone loss has begun. It is therefore uncertain

whether these gene polymorphisms are associated with peak bone mass, or if they are relevant specifically to men. Polymorphisms of the gene for ERα, however, may be of interest in view of the potential sensitivity of the male skeleton to oestrogen, and the importance of ERα expression to some men with idiopathic osteoporosis, discussed earlier in this article. Moreover, ERα polymorphisms have been associated with bone mineral density in normal men (Ongphiphadhanakul *et al.* 1998a), although this study was with men of all ages. Furthermore, there is evidence that ERα polymorphisms are associated with bone mineral density in women, although this is dependent on the site of measurement, age and ethnicity of the population (Deng *et al.* 1999b, Mizunuma *et al.* 1997, Ongphiphadhanakul *et al.* 1998b, Vandevyver *et al.* 1999). It is still unclear whether this is also true for polymorphisms of this gene and peak bone mass in men.

### Osteoblast differentiation and potential predictors of peak bone mass in men

Bone formation is undoubtedly central to the mechanism by which peak bone mass is attained in both men and women. On this basis, factors important in regulating osteoblast differentiation would also be key to attaining peak bone mass. In osteoporosis, there is impaired osteoblast differentiation, which, as discussed earlier, favours adipogenesis at the expense of osteoblastogenesis. If, in some patients, such a defect were to be present throughout life, then it may also be associated with lower peak bone mass. Polymorphisms of genes for factors which are important to the plasticity between adipogenesis and osteoblastogenesis may therefore be suitable candidates for predicting osteoporosis. The question now arises as to whether any of them might be specific for osteoporosis in men. The influence of GH and IGF-I on osteoblast differentiation has already been discussed, so it is especially noteworthy that in men aged between 20 and 40 years bone mass is associated with GH secretion. Moreover, the higher bone mineral density in Afro-Americans is associated with levels of this hormone in men but not in women (Wright *et al.* 1995, 1996). Furthermore, GH-dependent IGFBP is an important determinant of bone mass in healthy men (Johansson *et al.* 1994) and the positive correlation between IGF-I and bone mineral density, which is specific to men (Janssen *et al.* 1998), has been discussed earlier in this article. As oestrogens influence GH and IGF levels, the importance of interactions between these hormones cannot be discounted in this context (Holmes & Shalet 1996). Factors which regulate lean body mass may also be important; it is correlated with bone mineral density in men aged 19–29 years, i.e. at accretion of peak bone mass (Nutti *et al.* 1995). In women, however, reports of its relationship to bone mineral density have depended on the bone mass parameter used, and fat

body mass may also exert an equally important influence (Khosla *et al.* 1996). Regulation of lean body mass may, therefore, be important to peak bone mass in men specifically.

### Development of suitable treatments for men with idiopathic osteoporosis

Bisphosphonates and hormone replacement therapy are now the most often used treatments for osteoporosis in general. Although oestrogen-based therapy is obviously inappropriate for male osteoporosis, the recent development of selective ER modulators (SERMs) may provide the basis for acceptable treatments. For example, raloxifene may act on ERs in bone and cardiac tissues specifically, thereby obviating the 'female' reproductive effects of oestrogen (Gustafsson 1998). Moreover, although raloxifene binds to ER $\alpha$  in bone (Bryant *et al.* 1999) and thereby transactivates oestrogen-responsive genes, together with other SERMs, it has a more potent effect via ER $\beta$  (Paech *et al.* 1997). Bone, which expresses both ER isoforms, could be particularly sensitive to relatively low doses of raloxifene, which might help avoid any potential side-effects in the treatment of male osteoporosis. Furthermore, there is the possibility that oestrogen may have an anabolic effect on bone under certain conditions (Tobias & Compston 1999) and this may also apply to SERMs. The bisphosphonates were developed as agents which suppressed osteoclastic bone resorption and there is evidence that the latest generations of these drugs acts through the mevalonate pathway of osteoclasts (Russell & Rogers 1999, Rogers *et al.* 2000). Although in some obvious respects they are the most appropriate available treatment for male osteoporosis, the possible importance of defective osteoblastogenesis in some men with idiopathic disease implies that bisphosphonates may be less than satisfactory in some cases. Nevertheless, there are recent reports of significantly increased bone mineral density in a double-blind, placebo-controlled study of alendronate treatment of men with osteoporosis (Orwoll *et al.* 2000). Other approaches have concentrated on development of anabolic therapies for osteoporosis; for example, the analogues of parathyroid hormone (Stewart *et al.* 2000) which may prove to be more suitable. On the basis of the discussion in this article, investigating the mechanism by which GH and IGF-I regulate osteoblast differentiation may provide the basis for treatment which may be especially beneficial for the treatment of MIO. A clearer understanding of the cellular and molecular biology of osteoblastogenesis will undoubtedly reveal novel approaches to treating male osteoporosis.

In conclusion, although many aspects of osteoporosis are common to both men and women, there may, indeed, be some significant features of skeletal regulation of especial relevance to the disease in men. Thus, bone is particularly

sensitive to the low levels of circulating oestrogen in men and evidence suggests that GH and IGF-I are important for accretion of male peak bone mass. Further investigation of osteoblast differentiation and of oestrogen, GH and IGF-I action on bone and bone cells in men will yield some specific determinants of male osteoporosis and could initiate novel therapies for this disease.

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