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Editoral

Sex Hormones and Osteoporosis in Men

F. H. Anderson,[1] R. M. Francis,[2] P. L. Selby,[3] C. Cooper[4]

[1]University Department of Geriatric Medicine, Level E Centre Block (807), Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK
[2]University of Newcastle upon Tyne, Freeman Hospital, Newcastle upon Tyne, UK
[3]University of Manchester, Manchester Royal Infirmary, Manchester, UK
[4]MRC Environmental Epidemiology Unit, Southampton General Hospital, Southampton, UK

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Osteoporosis in men is a common disorder, the incidence of which is increasing. Bone is lost with advancing age in men as well as in women, leading to an increased risk of fracture after minimal trauma. Recent epidemiological data from North America suggests a lifetime risk of fracture of the hip, spine, or forearm of 13.1% in white men aged 50 [1]. Despite the considerable public health burden attributable to these fractures, our understanding of their pathogenesis is incomplete and there is no established treatment for osteoporosis in men.

Androgen deficiency is thought to play an important role in many cases of male osteoporosis. Biochemical evidence of hypogonadism is found in about 20% of men with vertebral fractures [2] and up to 50% of men with hip fractures [3, 4], often without other clinical features of gonadal failure. In cell culture studies using human osteoblast-like cells from both men and women [5–7], specific androgen receptors can be identified by nuclear and cytosolic binding assays (Table 1). Similarly, osteoblasts obtained from fresh femoral bone specimens can also metabolize the circulating androgen androstenedione to testosterone and 5α-dihydrotestosterone (DHT) in both men and women [8] at rates dependent mainly on androstenedione concentration. Cells of osteoclast lineage may also have these properties, though this is less well established. Androgen receptors have also been directly demonstrated in osteoblasts and osteocytes around the growth plate [9]. Androgens may promote proliferation and differentiation of osteoblasts, inhibit osteoclast recruitment or affect osteoblast-to-osteoclast signaling.

Animal studies have mostly been performed in orchiectomized (orch) male rats, though there are reservations about the appropriateness of this model because the rat skeleton grows throughout life. Replacement therapy with either testosterone or 5α-DHT results in enhanced bone mass, though this remains lower than in control rats [10].

In male humans, androgens have a marked effect on bone growth and peak bone mass via the growth hormone/IGF-I axis; accordingly, androgen deficiency before puberty leads to lower bone mineral density (BMD) in both cortical and trabecular bone. Loss of androgens in later life is associated with increased bone resorption and loss of trabecular bone, but cortical bone mass is not greatly affected [11, 12]. In a study of 12 men who had undergone judicial castration for ''sexual delinquency'' [13], bone turnover was increased and lumbar spine BMD fell significantly, with evidence of the most rapid loss in the first 5 years after castration. Rates of bone loss were as high as 7% per year, comparable to loss rates seen in early postmenopausal women. In this study, calcitonin therapy was effective in reducing bone loss, and low calcitonin levels have been reported in another group of young hypogonadal men who had not undergone surgery [14]. Others have found low plasma 1,25 dihydroxyvitamin D levels and impaired calcium absorption in hypogonadal men [15].

This combination of clinical and experimental evidence has led to the current prevailing view that gonadal androgens are the principal bone-active steroid hormones in males. However, recent evidence from several directions suggests that there is a significant effect of estrogens, and the role of adrenal androgens has also attracted interest.

Estradiol is detectable in the serum of healthy men at levels comparable to those in postmenopausal women; this is a result of peripheral conversion of testosterone by the enzyme aromatase, a member of the microsomal cytochrome P450 group [Fig. 1]. Because these levels are rather low, they were not regarded as physiologically important until epidemiological research into heart disease risk suggested a protective effect of endogenous estrogens in men [16]. This is partly explained by the fact that a lower proportion of circulating estradiol is bound to sex hormone binding globulin (SHBG) in men than in women due to competition with the higher levels of androgens [17]. In subsequent prospective controlled trials, Bagatell et al. [18] treated men receiving GnRH agonist and testosterone replacement therapy with an aromatase inhibitor, and showed that the estrogen-deficient men had a significant 8% fall in HDL cholesterol compared with the other study group or normal controls, demonstrating that the levels of estradiol normally found in men are sufficient to alter lipid profiles favorably. Separately, Zmuda et al. [19] showed that adding

Correspondence to: F. H. Anderson

Table 1. Detection of receptors for androgens and estrogens in osteoblast-type cell lines of human origin (after Vanderschueren [20])

Cell type/cell line	Binding assay	Androgen receptors/cell	Estrogen receptors/cell	Ref
Osteoblast	Nuclear	821	1537	[5]
Sarcoma				
SaOS3	Cytosol	1277	Not detected	[6]
U2-OS		1605	Not detected	
Sarcoma				
TE85	Cytosol	2800	—	[7]
Osteoblast	Cytosol	—	2400	[21]

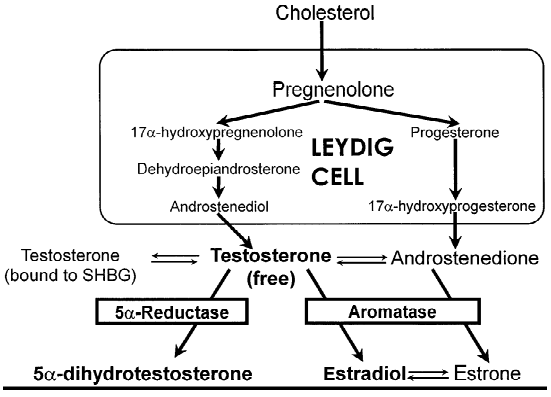

Fig. 1. Sex hormone synthesis in men. Testosterone and androstenedione are produced in the Leydig cells of the testes. Most circulating testosterone is bound by sex hormone-binding globulin (SHBG), in which form it is inactive. Conversion by 5α-reductase or aromatase yields the major active metabolites 5α-DHT and estradiol.

an aromatase inhibitor to supraphysiological testosterone treatment in weightlifters caused a 38% increase in lipoprotein lipase activity with worsening HDL levels. A role for estrogens in skeletal maintenance in the human male is supported by evidence at the cellular level by animal experiments and clinical findings.

Androgen receptors and 5α-reductase are found in osteoblasts at densities consistent with other androgen-sensitive tissues, and with similar binding affinities [6, 7, 20]. However, estrogen receptors are at least equally abundant in cultures of these cell lines [5, 21] and osteoblasts respond metabolically to estrogens *in vitro* [22] and in fresh biopsy samples of male bone [23]. Aromatase activity is present in cultured osteoblast cell lines [22], demonstrating that these cells have the capacity to convert testosterone to estradiol (and vice versa). In orchiectomized rats, estradiol prevents bone loss more effectively than progestogen or 5α-DHT, although a combination of all three is more effective than any single agent [10].

In human males, skeletal estrogen dependency is supported by a number of small studies (mostly published in abstract only) and key case reports describing the effects of interruption of normal estrogen synthesis. In a case-control study, 56 men with vertebral fractures had estradiol levels 30% (SD 5%, $P < 0.0005$) lower than controls [24], a previous smaller study having shown a nonsignificant difference of similar magnitude [25]. In case reports describing genetic mutations, a man with defective aromatase activity [26] and another with nonfunctioning estrogen receptors [27] showed markedly reduced BMD despite normal or raised serum testosterone levels and normal androgen receptors. In both cases, BMD values were similar to those seen in the converse syndrome of genetic males with androgen insensitivity (androgen receptor defect but normal testosterone and estradiol levels) [28]. Perhaps the most convincing evidence is from another case report, in which a 28-year-old man with an inactivating mutation of his aromatase gene presented with infertility and was found to have a eunuchoid habitus with nonclosure of the epiphyses, below-average BMD, and bone age of 15 years. Treatment with regular intramuscular testosterone produced no benefit, but treatment with transdermal estradiol 50 μg twice weekly resulted in skeletal maturation, rapid increase in lumbar spine BMD, and epiphyseal closure [29].

In a cross-sectional study in 37 healthy older men with no history of bone disease (Fig. 2) we found that BMD at the lumbar spine (LS) and hip correlated more closely with serum estradiol ($r = 0.383$, $P < 0.03$) than with testosterone ($r = 0.245$, $P > 0.15$) [30]. In a prospective study of 93 healthy men aged over 65, serum estradiol levels were positively associated with initial BMD values at all sites [31] and were associated with significantly lower rates of bone loss at the radius and hip on twice-yearly BMD measurement over a mean of 2 years ($P < 0.05$, test for trend), whereas testosterone levels were not predictive [32]. In men with vertebral osteoporosis, estradiol levels were found to be positively correlated with BMD at the femoral neck ($r = 0.41$, $P < 0.02$) [33] and spine ($r = 0.29$, $P < 0.03$) [24] and negatively correlated with markers of bone resorption such as hydroxyproline ($r = -0.57$, $P < 0.05$) [34]. Testosterone and estradiol levels were associated with differing and complementary features on bone histomorphometry such as trabecular thickness and trabecular number [34]. In a therapeutic trial of testosterone supplementation in men with osteoporotic vertebral fracture [35], pharmacological doses of testosterone were associated with proportionate rises in estradiol levels, and increases in LS-BMD during testosterone therapy correlated more closely with changes in serum estradiol than with changes in serum testosterone (Fig. 3).

Of course, the gonads are not the only source of sex hormones. There has been considerable interest in the role of the adrenal androgen dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) in the prevention of age-related diseases such as osteoporosis. Human osteoblasts have been shown to convert DHEA into estrone [36], which is a precursor for both testosterone and estradiol, and DHEA itself acts directly on the androgen receptors of osteoblasts to stimulate proliferation and differentiation [37]. Two cross-sectional studies suggest a positive correlation between

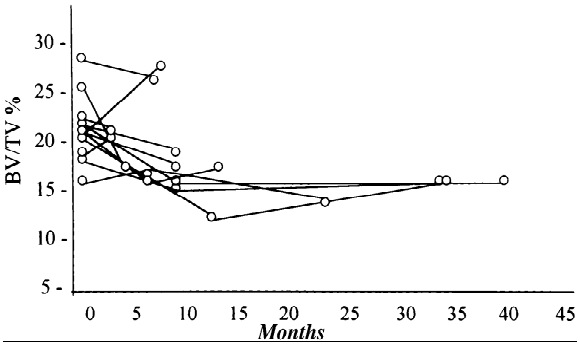

Fig. 2. Relationship between lumbar spine BMD by dual energy X-ray absorptiometry (DXA) and sex hormone levels in 37 healthy older men [30]. **(a)** Serum estradiol—r = 0.38, $P = 0.027$. **(b)**Serum testosterone—r = 0.25, $P = 0.16$.

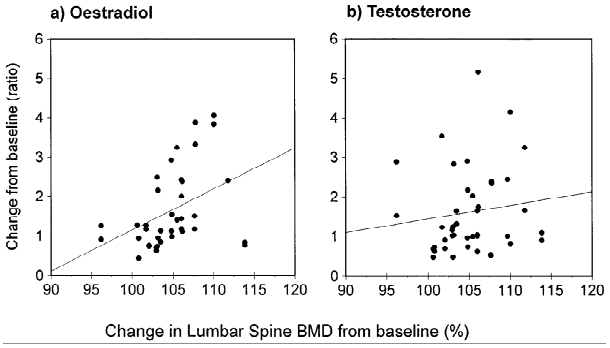

Fig. 3. Relationship between change in lumbar spine BMD, shown as a percentage of baseline value, and change in sex hormone levels, shown as a ratio to baseline value, in 21 men treated with intramuscular testosterone for 6 months [35]. **(a)** Serum estradiol (pmol/liter)—r = 0.40, $P = 0.013$. **(b)** Serum testosterone (nmol/liter)—r = 0.12, $P = 0.45$.

DHEA or DHEAS and BMD in a total of 225 postmenopausal women [36, 38], but a prospective study found no correlation between DHEAS and BMD in either men (n = 260) or women (n = 162) [39]. Further investigation of the role of DHEA/DHEAS in skeletal metabolism, particularly in males, is clearly required.

It seems likely, on the basis of the somewhat limited evidence currently available, that both estrogens and androgens are required for the growth and maintenance of the adult male skeleton. In the presence of low levels of either class of sex hormone during growth there is failure of skeletal maturation and suboptimal peak bone mass [26–29], whereas low levels of hormone activity in later life are associated with rapid skeletal involution and osteoporotic fracture [30–34].

This idea of an interdependence between androgens and estrogens is essentially a hypothesis generated by cross-sectional observation and clinical findings; statistical correlations offer no proof of causality. Nonetheless, such a relationship does help to explain some poorly understood features of androgen action in the male skeleton. One example is the limited usefulness of nonaromatizable anabolic steroids such as nandrolone in men with osteoporosis, where a good initial bone density response is not sustained [40]; after a few months, endogenous testosterone production will have been suppressed and little will be available for conversion to estradiol.

It can be argued that the observation of a relationship between sex hormones and osteoporosis in men is trivial, in that the skeleton is an accepted target organ for these hormones. That much is true, but the important point is the interaction of *both* classes of sex hormone with bone and with each other. Estrogenic activity in men is even less well recognized than androgenic activity in women, and an awareness of the role of aromatase may be of clinical relevance, given the increasing clinical use of aromatase inhibitors. If the relationship is accepted, estrogen assays are a necessary part of the protocol for any study of male osteoporosis where androgens are measured or affected by treatment.

Osteoporosis in men is an important and poorly understood disorder. All treatments for idiopathic male osteoporosis remain experimental, and in view of the known side effects of hormonal therapy many clinicians may prefer to use other agents such as calcitonin, bisphosphonates, or perhaps fluoride [41]. Nevertheless, carefully designed trials of aromatizable androgens or combinations of androgenic and estrogenic drugs offer the prospect of greater understanding of the processes underlying bone turnover and loss in men. Only by increasing our understanding can we act to alleviate the increasing burden of morbidity and mortality associated with osteoporotic fractures, and the huge cost of caring for those—both men and women—who suffer the consequences.

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