Geriatrics Grand Rounds: Eve’s Rib, or a Revisionist View of Osteoporosis in Men

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It is widely accepted that estrogen withdrawal following menopause predisposes women to accelerated bone loss and increased risk of developing osteoporosis. Although osteoporosis is a significant public health problem for aging men as well as women, the cause of osteoporosis in men remains largely unknown. A substantial number of men with osteoporosis present with bone loss secondary to conditions associated with reduced gonadal steroid hormone levels. Although hypogonadism is related to bone loss in men, and androgen levels decline with age in men, it is not at all clear that reduced androgen levels are related to bone loss in older men. What, then, is the role of gonadal steroids in osteoporosis in men? This review focuses on recent research—including clinical investigations of men with genetic disorders of estrogen action, basic biomedical studies of estrogen receptor “knockout” mice, and population-based comparisons of bone density with gonadal steroids in older men—leading to the surprising conclusion that estrogen plays a vital role in maintenance of bone in men as well as in women. Possible mechanisms whereby reduced estrogen levels might result in bone loss in both sexes are also reviewed, as are potential therapeutic implications of a role for estrogen in osteoporosis in men.

O VER the past several years a profound change in our understanding of osteoporosis in men has emerged. Recent clinical and basic science research in bone biology supports what might otherwise be deemed a radical view of bone loss in aging men. This view can aptly, if obliquely, be introduced with a passage recounting the creation of the first man and woman. In Genesis 2 (1, pp. 2–3),

. . . the Lord God formed man from the dust of the ground and breathed into his nostrils the breath of life, and man became a living being. . . . The Lord God said, “It is not good for the man to be alone. I will make a helper suitable for him.” . . . But for Adam no suitable helper was found. So the Lord caused the man to fall into a deep sleep, and while he was sleeping, he took one of the man’s ribs and closed up the place with flesh. Then the Lord God made a woman from the rib he had taken out of the man, and he brought her to the man. The man said, “This is now bone of my bones and flesh of my flesh; she shall be called ‘woman,’ for she was taken out of man.”

The scriptural text clearly traces the origin of bone—in both men and women—to the first man. It is, then, an irony that most of our understanding of how bone loss occurs during aging and leads to osteoporosis has come from studies of the recipients of Adam’s rib. Yet, the recent biomedical literature is beginning to suggest that what we have learned about Eve’s rib (or more precisely Eve’s vertebra) is, perhaps surprisingly, also applicable to men and the process by which they lose bone with age. The care of older women and men with reduced bone mass and osteoporotic fracture is increasingly managed by clinical geriatricians. The pose of this article is to review for the practicing geriatrician an evolving area of investigation in which osteoporosis in women is providing fundamental insights into the pathogenesis and, ultimately, the treatment of osteoporotic fractures in older men.

**Bone Loss and Osteoporosis in Aging Women and Men: General Considerations**

In a now classic study published in 1978, Lindsay and colleagues (2) reported that following oophorectomy, women sustained a dramatic loss of bone mineral content, which was prevented by administration of estrogen. When estrogen treatment was withdrawn, bone content diminished rapidly and ultimately achieved the same low levels observed in ovariectomized women who had never received estrogen replacement. From data such as these, it is now widely accepted that women are predisposed to accelerated bone loss and increased risk of developing osteoporosis in association with estrogen withdrawal following menopause. Recognition that estrogen plays an essential role in maintaining bone mass in women has, in fact, transcended the medical literature and been incorporated into our cultural knowledge base.

Changes in bone mass of women and men over the entire life span are characterized by differences, as well as important similarities, between the two sexes (Figure 1) (3). In both women and men, bone mass increases to a peak by about age 30 and then declines. The rate of decline in women is accelerated at the time of menopause, but subsequently is roughly parallel to the rate of bone loss occurring in aging men. Reduction of bone mass in both women and men may ultimately reach a critical fracture threshold that defines osteoporosis. However, because of the accelerated early phase of postmenopausal bone loss in women and also
a lower peak bone mass in women than in men, bone mass in women is likely to fall to a fracture threshold at an earlier age than in men.

Despite a greater likelihood of osteoporotic fracture in women than in men, the risk of osteoporosis in men is also substantial. In an analysis of lifetime fracture risk in 50-year-old white men and women, Melton and colleagues (4) estimated that men are about one third as likely as women to sustain a fracture of the hip or spine; distal forearm fracture risk in men was about one sixth of that in women. Put another way, if the lifetime risk of any of the three fractures in 50-year-old white women is 40%, then a full 13% of all 50-year-old white men are also likely to sustain a fracture over their lifetime. The importance of race and ethnicity as variables in osteoporotic risk should be emphasized, insofar as Caucasians are at higher risk than blacks, Hispanics, or Asians. In terms of medical costs, a staggering $13.8 billion was spent for the treatment of osteoporotic fractures in the United States in 1995. Twenty percent of this amount, or $2.7 billion, was expended for the treatment of fractures in women. For both men and women, most of the expense was for fractures of the hip in older individuals greater than or equal to 65 years of age (5). Interestingly, mortality of older (>65 years old) hip fracture patients has been reported to be higher for men than women (6). Thus, osteoporosis is clearly a significant public health problem in aging men as well as in women.

If osteoporosis in women, at least the form associated with the early accelerated phase of bone loss after menopause, is related to estrogen withdrawal, then what is the cause of osteoporosis in men? When we look in the textbooks and review articles for an answer, we are disappointed to find that in the numerous series reported, many or even most of the cases (between about 40% and 70%) are of unknown cause (7). The terms used to describe osteoporosis in men without conditions known to reduce bone mass are “idiopathic” and “primary.” Of note, osteoporosis occurring in men or women of advanced age (i.e., 70 years old), has been termed type II osteoporosis, to distinguish it from postmenopausal, or type I, osteoporosis. The relationship between idiopathic osteoporosis, which occurs over a broad age range, and type II osteoporosis in older men remains to be clarified (7).

In a large percentage of male patients (between about 30% and 60%), osteoporosis is thought to be secondary to other conditions that cause bone loss. The most prominent secondary causes are reported to be hypogonadism (present in 5%–33% of cases), glucocorticoid excess (perhaps most often in association with steroid treatment of a variety of diseases), alcoholism, and other disorders, with cigarette smoking also listed as a major risk factor (7). Interestingly, a number of these conditions, in addition to hypogonadism, are at least potentially related to reduced gonadal steroid levels. Certainly, excess glucocorticoids and alcoholism can lower testosterone levels by a variety of mechanisms. Moreover, smoking—at least in women—can reduce estrogen levels, although epidemiologic studies relating smoking and testosterone levels in men have yielded discrepant results (7,8). If a substantial fraction of “secondary” osteoporosis is related to conditions that can reduce gonadal steroid levels, is it possible that changes in gonadal function might also play a role in otherwise idiopathic osteoporosis in men—perhaps even in analogy with estrogen withdrawal–induced bone loss in women? Put simply, what is the role of gonadal steroids in osteoporosis in men?

CASE PRESENTATION

The question of whether gonadal steroids play a role in osteoporosis in men may be illustrated with the following case of a 71-year-old man with osteoporosis and low serum testosterone. He was a Mexican American man admitted in September 1998 to the inpatient service of the South Texas Veterans Health Care System for compression fractures of the spine and severe pain. Onset of atraumatic back pain had been about 6 weeks prior to admission, when a T10 compression fracture was diagnosed radiologically. He had been treated successfully for pain with morphine but had a sudden recurrence 2 to 3 days before admission. His past history included a left hip fracture 6 years prior to admission and chronic obstructive pulmonary disease requiring inhaled and occasionally systemic glucocorticoids. He had a long history of smoking but no alcohol intake. On physical examination, the patient was in severe pain in the area of his thoracic spine and had diminished deep tendon reflexes in his lower extremities; testes were of normal size and consistency.

Initial x-rays were deferred because of the patient’s severe pain; but subsequent radiological studies revealed, in addition to diffuse osteopenia, the previously noted T10 compression fracture and a new compression fracture at T8 (presumably the cause of the patient’s renewed pain). Figure 2 shows two of the patient’s x-rays for comparison. First, in a lateral chest x-ray taken almost 9 years prior to admission, the height of the vertebral bodies is generally maintained, with perhaps minimal end plate deformity. Second, the most recent lateral chest film (taken in February of 1999) shows diffuse loss of height of T10, nearly complete collapse of T8, and severe kyphosis.

Laboratory evaluation on admission revealed a normal serum calcium (9.0 mg/dl) and phosphorus (3.1 mg/dl), an elevated alkaline phosphatase (161–213 U/l; normal, 39–
(117) consistent with increased osteoblast activity following compression fracture, essentially normal serum protein electrophoresis, and also normal prostate-specific antigen (0.7 ng/ml; normal, 100-250). Among hormone measurements, serum intact parathyroid hormone (PTH) level was normal (26 pg/ml; normal, 10-65). Serum 25-hydroxyvitamin D level, which was not measured initially, would nevertheless have been an appropriate test for evidence of osteomalacia. (Serum 25-hydroxyvitamin D measured after the patient’s hospitalization was normal [26.2 ng/ml; normal, 8.9-46.7].) Urinary free cortisol (21-33 μg/24 h; normal, ≤ 50) and thyroid function tests (total thyroxine, 5.6-6.0 μg/dl; T3 resin uptake, 37%-40%; free thyroxine, 1.1 ng/ml; thyrotropin, 0.8-1.2 IU/ml) were also normal.

In contrast to other hormone determinations, measurements of the pituitary-gonadal axis revealed distinct abnormalities. Serum testosterone was extremely low (71 ng/dl; normal, 241-827), as were serum gonadotropins luteinizing hormone (LH, 1.5 mIU/ml; normal, 3.1-34.6 for men >70 years) and follicle-stimulating hormone (FSH, 2.9 mIU/ml; normal, 2.8-55.5 for men >70 years)—a picture consistent with secondary, or hypogonadotropic, hypogonadism. This patient’s subsequent hormone evaluation will be discussed later. Of note, his acute hospital course was marked primarily by treatment with morphine and the bone resorption inhibitor calcitonin.

This patient’s presentation, then, serves to highlight the question at hand: What is the role of gonadal steroids in the pathogenesis of osteoporosis in men?

**RELATIONSHIPS AMONG HYPOGONADISM, TESTOSTERONE, AGING, AND BONE LOSS IN MEN**

The question of whether reduced gonadal steroid levels contribute to osteoporosis in aging men can initially be broken down into three sequential questions:

1. Is there, in fact, a relationship between hypogonadism and osteoporosis in men?
2. Do androgen levels decline with age in men?
3. Are (presumably reduced) testosterone levels associated with bone loss in aging men?

With respect to the first question, as has already been noted, hypogonadism is present in a significant percentage of men evaluated for osteoporosis. In addition, many forms of hypogonadism are, in turn, associated with reduction of bone mass (7). For example, lumbar bone mineral density (BMD) has been found to decline progressively as a function of time following orchidectomy in young men castrated because of sexual delinquency (9). A similar decrease in lumbar bone density over time has been demonstrated in older men made hypogonadal by gonadotropin-releasing hormone agonist treatment for benign prostatic hyperplasia (10). There is also evidence that bone loss occurring in hypogonadal men reaches osteoporotic levels. For example, two case-control studies in the early 1990s concluded that hypogonadal elderly men are at increased risk for minimal trauma hip fracture (11,12). In a more recent study, hypogonadism was identified as a risk factor for bone loss and fracture in a majority of male nursing home residents with a history of hip fracture (13). Finally, although not hypogonadal...
per se, adult men with a history of constitutionally delayed puberty have also been reported to have decreased spinal and radial BMD (14).

In answer to the first question, then: Yes, there is a relationship between hypogonadism and osteoporosis in men. The second question—do androgen levels decline with age in men—has been investigated and debated over many years. Results of numerous studies have differed, depending largely on the populations of subjects examined and the conditions of blood sampling (15,16).

In discussing androgen levels in aging men, we must first recall that the vast majority of circulating testosterone is bound to plasma proteins. Of the total testosterone in plasma, under normal conditions about 44% is not biologically active, because it is tightly bound to sex hormone-binding globulin (SHBG), also termed testosterone-binding globulin. The so-called “bioavailable” fraction consists of the unbound, or “free,” testosterone (a minimal 2% of the total) plus the approximately 54% that is weakly bound to albumin and other proteins (17). Total, free, and bioavailable fractions are all measurable, but the bioavailable fraction, which has ready access to target tissues, is often considered perhaps the most physiologically relevant measure. It should be noted that SHBG also binds estrogen, and the relationships between SHBG-bound and bioavailable fractions of estrogen are similar to those described for testosterone.

There is now general agreement that, as in the representative study of healthy aging men illustrated in Figure 3, serum total testosterone decreases quite modestly with age, but because of an age-related increase in SHBG binding capacity, the bioavailable testosterone decreases with age to a greater extent than the total testosterone (18). In another study of healthy ambulatory subjects, total testosterone levels in 75-year-old men were found to be about one third less than in 25-year-old men, whereas the bioavailable fraction at the older age was reduced by half (15). Most studies demonstrating age-related changes in testosterone (total and bioavailable) and SHBG have been cross-sectional in design (15,16,18). However, a longitudinal decline of total testosterone together with an increase of SHBG during aging has also been observed in healthy older men (19). The reasons for the decline in testosterone levels with age are subtle and complex; evidence for functional changes at multiple levels of the hypothalamic-pituitary-testicular axis in aging men has been reviewed previously (15,20).

These data provide an answer to the second question: Yes, androgen levels do decline with age in men. Thus, if hypogonadism and osteoporosis are related in men, and androgen levels are decreased in older men, we can now proceed to our third question: Are testosterone levels associated with bone loss in aging men? Here, the role of gonadal steroids in osteoporosis in men begins to appear uncertain, because the many correlative studies conducted in this area have failed to show a clear-cut association between testosterone (total or otherwise) and BMD in aging men. A review of the literature over the past 12 years reveals eight studies focusing on the relationship between male gonadal function and BMD, measured by currently established methods, in healthy aging men. Of these eight studies, which varied considerably in numerous aspects of study design, five found no correlation of testosterone with BMD (21–25); only three of the eight studies reported limited correlations and even then only in selected skeletal sites (26–28). It is important to keep in mind that testosterone does not generally decline to frankly hypogonadal levels during aging, and the men participating in these correlative studies had testosterone levels that, for the most part, would be considered to be in the eugonadal range.

Thus, the third question can be answered only with the statement that it is not at all clear whether lower testosterone is related to bone loss in older men. If this is the case, then what is the role of gonadal steroids in osteoporosis in men? Have we perhaps been focusing on the wrong gonadal steroid?

THE ROLE OF GONADAL STEROIDS IN OSTEOPOROSIS IN MEN: THE CASE FOR ESTROGEN

New and surprising insights linking osteoporosis in men to reduced levels of gonadal steroids are emerging from
three areas of research: first, clinical investigations of male patients whose genetic disorders represent truly extraordinary experiments of nature; second, basic biomedical studies of transgenic mice; and third, population-based research into the clinical epidemiology of osteoporosis in older men. In this section, we will review findings obtained recently from two remarkable patients, a transgenic mouse model, and populations of aging men.

**Genetic Disorders of Estrogen Action in Men**

**Patient 1.**—Patient 1, who was described in 1994 (29), was a 28-year-old white man with tall stature, a history of progressive “knock knees,” and unfused epiphyses on x-ray. His parents were second cousins. He had undergone normal early growth and development, including acquisition of normal secondary sexual characteristics, but did not experience a growth spurt and continued to grow slowly after adolescence. A diagnosis of Osgood-Schlatter disease (tibial tubercle osteochondritis) had been made when the patient was 20 years old, and he had been treated with rest. On physical examination, he was quite tall (6 ft, 8 in) and was healthy in appearance, but with prominent genu valgum. He had unusually long legs, with an upper-to-lower-body ratio of 0.88 (average for men, 0.96). His feet were 13 inches in length, but he had no acromegalic features. He had a full beard, no gynecomastia, and normal male genitalia and prostate.

The patient’s growth chart was remarkable chiefly for failure to stop growing after adolescence, which is consistent with a bone age of only 15 years on a left hand x-ray and open epiphyses on left knee films. Because his bones appeared demineralized on x-ray, bone densitometry was performed and revealed a remarkable reduction in bone density (see Table 1 for values of BMD and other laboratory determinations described later). His karyotype was 46,XY, and semen analysis revealed normal sperm density with reduced viability.

The clue to this patient’s diagnosis came from measurements of his sex steroids. Whereas serum testosterone was normal, estradiol was more than twice the normal upper limits for a man, yet, the gonadotropins LH and FSH were both elevated. These findings are indicative of a classic hormone-resistance syndrome, with increased levels of hormone—in this case, estrogen—but elevated gonadotropins in the absence of perceived negative feedback at the level of the hypothalamus.

Table 1. Two Male Patients With Genetic Disorders of Estrogen Action: Laboratory Determinations at Baseline and After Estrogen Treatment

<table>
<thead>
<tr>
<th>Biochemical Measurements</th>
<th>Patient 1</th>
<th>After Estrogen Treatment</th>
<th>Normal Range</th>
<th>Patient 2</th>
<th>After Estrogen Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum estradiol, ng/ml</td>
<td>119</td>
<td>250</td>
<td>10–50</td>
<td>&lt;7</td>
<td>64</td>
</tr>
<tr>
<td>Serum testosterone, ng/dl</td>
<td>445</td>
<td>—</td>
<td>265–800/200–1200</td>
<td>2015</td>
<td>990</td>
</tr>
<tr>
<td>Serum LH, mIU/ml</td>
<td>37</td>
<td>34</td>
<td>2–20/2.0–9.9</td>
<td>26.1</td>
<td>11.3</td>
</tr>
<tr>
<td>Serum FSH, mIU/ml</td>
<td>33</td>
<td>30</td>
<td>2–15/5.0–9.9</td>
<td>28.3</td>
<td>12.7</td>
</tr>
<tr>
<td>Binding proteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum SHBG, nmol/l</td>
<td>6.0</td>
<td>7.0</td>
<td>6–44</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Serum TBG, mg/dl</td>
<td>2.8</td>
<td>2.5</td>
<td>1.7–3.6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Serum CBG, mg/l</td>
<td>24</td>
<td>27</td>
<td>19–45</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bone turnover</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum osteocalcin, ng/ml</td>
<td>18.7</td>
<td>19.4</td>
<td>3–13</td>
<td>19.8</td>
<td>14.4</td>
</tr>
<tr>
<td>Serum bone-specific alkaline phosphatase, ng/ml</td>
<td>34.2</td>
<td>33.3</td>
<td>4.3–19.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Serum alkaline phosphatase, IU/l</td>
<td>—</td>
<td>—</td>
<td>39–117</td>
<td>241</td>
<td>136</td>
</tr>
<tr>
<td>Urine pyridinoline, nmol/mmol creatinine</td>
<td>110</td>
<td>116</td>
<td>20–61</td>
<td>102</td>
<td>51</td>
</tr>
<tr>
<td>Urine deoxypyridinoline, nmol/mmol creatinine</td>
<td>32</td>
<td>34</td>
<td>4–19</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>Urine telopeptide, nmol BCE/mmol creatinine</td>
<td>248</td>
<td>239</td>
<td>23–10</td>
<td>20.7)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

**Notes:** LH = luteinizing hormone, FSH = follicle-stimulating hormone, SHBG = sex hormone-binding globulin, TBG = thyroxine-binding globulin, CBG = corticosteroid-binding globulin, BCE = bone-collagen equivalent.

1Values for patient 1 from (29).
2Values for patient 2 from (34).
3Patient 1 treated with high-dose transdermal ethinyl estradiol for 6 mo (maintenance dose fourteen 100-μg patches/wk); patient 2 treated with conjugated estrogens (Premarin) for 3 y (maintenance dose 0.75 mg/d).
4Two different normal ranges reported for measurements in patient 1 (to left of diagonal) and patient 2 (to right of diagonal).
5Value for lumbar spine bone mineral density 3.1 SD < mean for age-matched normal women; >2 SD < mean for 15-year-old boys.
6Values in parentheses denote % change in g/cm² from baseline after estrogen treatment.
7T scores denote SDs from mean in normal young men.
the pituitary. At the time this patient was investigated, estrogen resistance, presumably caused by a mutation of the estrogen receptor, had never been described before and was thought to be lethal if it did exist. Nonetheless, those studying this patient hypothesized that primary estrogen resistance might explain the elevated estrogen and gonadotropin concentrations, and—most strikingly for our discussion—might also account for the failure of epiphyseal fusion and bone demineralization.

If this man’s phenotype were caused by estrogen resistance, then he should not respond to estrogen replacement. In fact, the patient was treated with high-dose transdermal ethinyl estradiol for a 6-month period, at the end of which time his estradiol level increased even further; but his high gonadotropin levels still did not fall. Also, the concentrations of several normally estrogen sensitive proteins (SHBG, thyroxine-binding globulin, and corticosteroid-binding globulin) did not change with estrogen treatment, and clinically, he did not exhibit any signs of feminization.

Bone turnover measurements included biochemical markers of bone formation (serum osteocalcin and bone-specific alkaline phosphatase) and bone resorption (in the form of urinary excretion of several collagen cross-link products of resorption). In the baseline state, all measures of bone turnover were elevated, suggesting that the patient’s decrease in bone mineralization was the result of increased bone remodeling. The indicators of bone turnover did not change after 6 months of high-dose estrogen. Estrogen treatment also had no effect on the patient’s diminished BMD and delayed bone age.

In view of the patient’s clinical resistance to estrogen, peripheral blood was obtained to study his estrogen receptor gene. Conformation analysis suggested a homozygous mutation of exon 2 of the estrogen receptor gene (i.e., the classic estrogen receptor, now termed estrogen receptor α; see later). Direct sequencing of exon 2 revealed a substitution of thymine for cytosine at codon 157, resulting in the replacement of an arginine codon, or CGA, with a premature stop codon, or TGA. The translated protein would be severely truncated, lacking DNA- and hormone-binding domains, and, thus, functionally inactive. Interestingly, the patient’s parents were found to be heterozygous carriers of this mutation.

This remarkable patient was reported by Smith and colleagues in their 1994 New England Journal of Medicine (29) article, “Estrogen Resistance Caused by a Mutation in the Estrogen-Receptor Gene in a Man.” The extraordinary conclusion of the article was as follows: “...that androgen alone is not sufficient to promote skeletal maturation and retain bone mass and that estrogen has a pivotal role in the mineralization of the skeleton in males as well as females” (italics added) (29, p. 1059). The authors also concluded that elevated gonadotropin levels in their patient suggest a role for estrogen in the feedback inhibition of gonadotropin secretion in men. An editorial accompanying the article by Smith and colleagues (30) acknowledged the scientific, and even aesthetic, significance of this case report with the comment, “once again the alert scrutiny of an error of nature has revealed a new elegance in the way things are” (p. 1089).

Patient 2.—The second patient is as instructive as the first, inasmuch as the findings in the two patients provide complementary, and equally fundamental, insights into the role of estrogen in maintenance of bone mass in men. Patient 2, who was first described in 1995 (31), was a 24-year-old man brought to medical attention because of his sister, who was being evaluated for virilization. His presentation is very similar to that of Patient 1. There was a history of parental consanguinity. The patient underwent normal early growth and development, and developed normal male secondary sexual characteristics. Like Patient 1, he continued to grow after puberty and was still growing at the time of evaluation. His sexual orientation, libido, and function were essentially normal. On physical examination, he was tall (6 ft, 8 in) and had relatively long limbs, with an upper-to-lower-body segment ratio of 0.84. He had no acromegalic features and normal male genitalia.

The patient’s growth chart documented that he had ranged near the mean value for height for boys, but then had continued to grow after adolescence. Bone age was 14 years at a chronological age of 24 3/12 years. In addition to a delayed bone age, x-rays revealed epiphyseal fusion only at the proximal femur and evidence of osteopenia. Bone densitometry at three sites revealed diffuse reductions in mineral density relative to mean values for age- and sex-matched controls (see Table 1 for values of BMD and other laboratory determinations described later).

Examination of this patient’s sex steroid hormone levels revealed a distinctly different pattern from that of Patient 1; that is, a markedly elevated testosterone level, an estradiol concentration below the level of detection, and, again, elevated gonadotropin levels. What kind of defect might these findings represent? It is useful in this regard to remember that in a variety of peripheral tissues, testosterone serves as a precursor or prohormone for the formation of two types of active metabolites. On the one hand, testosterone can be reduced by the 5α-reductase enzyme to dihydrotestosterone, which, like testosterone, exerts its actions via the androgen receptor. On the other hand, the cytochrome P450 enzyme aromatase converts testosterone to estradiol, which then acts by binding to estrogen receptors (either the classic estrogen receptor α or the more recently discovered estrogen receptor β). A recent Nature editorial (32) calls attention to the dual metabolic paths of testosterone to support the emerging concept that “androgens and oestrogens are the opposite sides of the same coin, and the balance in their actions may determine the biological response of target tissues” (p. 448). In any event, knowing that androgen is converted to estrogen by the aromatase enzyme, the investigators who described patient 2 proposed that low serum estradiol levels on the basis of aromatase deficiency might explain his abnormal serum gonadotropin concentrations, delayed skeletal maturation, and reduced bone mass (31).

Analysis of DNA in lymphoblasts from the patient and his sister indicated a homozygous point mutation in exon 9 of the human aromatase (or CYP19) gene resulting in a cysteine instead of an arginine at position 375. Expression of the mutant cDNA in vitro showed that the mutation had essentially no aromatase activity compared with the wild-type aromatase enzyme. In all, five mutations (four missense
mutations and one splice junction abnormality) have now been described in the human aromatase gene (31,33).

This patient and his sister were first reported together in 1995 by Morishima and colleagues in the Journal of Clinical Endocrinology and Metabolism (31). Unlike the patient with estrogen resistance, this patient, whose defect lay in deficient estrogen production, offered the promise that estrogen therapy might reverse the defect in bone mass. Accordingly, in a follow-up study of Patient 2, measurements of bone turnover and bone density were made before and after 3 years of therapy with conjugated estrogens (Premarin at a maintenance dose of 0.75 mg daily). With estrogen treatment, serum estradiol levels rose, while gonadotropins and testosterone fell essentially to normal levels. The near-normalization of gonadotropin levels confirms a significant role for estrogen in pituitary feedback mechanisms in men. As in Patient 1, serum and urine markers of bone turnover were increased in the baseline state, but, in this case, declined toward normal values during estrogen therapy. In addition, with estrogen treatment, linear growth ceased and all epiphyses of the hand and wrist completely fused. Finally, and perhaps most importantly, bone densities of the lumbar spine, femoral neck, and distal radius all increased dramatically from baseline values over the course of estrogen therapy (34).

The follow-up study of Patient 2, entitled “Increased Bone Mass as a Result of Estrogen Therapy in a Man With Aromatase Deficiency,” was published in 1998 by Bilezikian and colleagues in the New England Journal of Medicine (34). The findings in this report led the authors to restate the conclusion first made in the study of the patient with estrogen resistance: that is, “. . . estrogen is essential for the establishment of peak bone mass in growing boys, as well as for the maintenance of bone mass in adult men” (p. 602). It should be noted here that increased BMD of the lumbar spine has also been reported after estrogen therapy of a male patient with an inactivating aromatase mutation distinct from that found in patient 2 (33).

The Estrogen Receptor Knockout Mouse

Additional insights into the role of estrogen in maintaining bone density in men have also come from experiments in mice. In the early 1990s, Korach and colleagues (35) used the techniques of homologous recombination to disrupt the classic estrogen receptor α gene (in a similar region of the protein as in the human estrogen receptor mutation) and produce a line of transgenic mice possessing the altered gene. Whereas this estrogen receptor knockout (ERKO, also referred to as αERKO) mouse has been the subject of considerable study for its alterations in reproductive function, in at least preliminary experiments, male ERKO mice have also been found to exhibit reduced bone mass. For example, BMD of femurs from adult male ERKO mice has been reported to be about 10% lower than in age-matched wild-type animals (36,37). These early studies of skeletal changes in ERKO mice need to be confirmed and extended, but they do support the human data in implicating a role for estrogen in maintaining bone density in male as in female. Interestingly, in a very recent study of estrogen receptor β knockout (βERKO) mice, male mutants had no demonstrable bone abnormalities in comparison with wild-type mice (38). A comprehensive review of αERKO and βERKO mice describes in detail the phenotypic changes observed thus far in mutant mice of both sexes (39).

Population-Based Studies of Aging Men

In the last few years, investigations of bone loss in men and mice with genetic disruption of estrogen action have been complemented by epidemiologic studies evaluating whether endogenous estrogen might, in fact, be better than androgen in predicting bone density in aging men. Bone density was compared to estrogen, as well as androgen, levels in older men in four recent population-based studies: the Indiana University Osteoporosis Study (40), the Rancho Bernardo Heart and Chronic Disease Study (41), the Dubbo Osteoporosis Epidemiology Study (42), and the Rochester Epidemiology Project (43).

These four correlative studies reached several general conclusions. First, total estrogen, but not total testosterone, concentrations are positively associated with BMD in older men. In addition, bioavailable estrogen is a stronger predictor of bone density in older men than is total estrogen. Bioavailable testosterone may also be positively associated with bone density in older men, but less so than is bioavailable estrogen. Overall, then, bone loss in older men is correlated more significantly with reduced estrogen levels than with lower androgen levels. All four epidemiologic studies, therefore, arrived at essentially the same conclusion as was derived from the individual patients with genetic disorders of estrogen action: that is, estrogen plays a vital role in maintenance of bone in men. It is likely that all of these epidemiologic studies deal largely, if not exclusively, with Caucasian populations. Another, recently published, study of aging men in Bangkok, Thailand, arrived at similar conclusions; but the racial composition of subjects in this study was not clarified (44). Of note, very recent data from the Rancho Bernardo Study (45) indicate that reduced levels of total and bioavailable estradiol, but not testosterone, are also associated with increased vertebral fracture risk in older men.

AN INCLUSIVE MODEL OF OSTEOSPOROSIS IN AGING WOMEN AND MEN

Riggs and colleagues (46) recently incorporated the clinical and epidemiologic data relating estrogen to bone loss in men into “A Unitary Model for Involuntary Osteoporosis,” in which estrogen deficiency is proposed to cause both type I and type II osteoporosis in postmenopausal women and contribute to bone loss in aging men. According to this model, the causal role of estrogen deficiency in both postmenopausal osteoporosis and age-related bone loss can be attributed, respectively, to two types of effects of estrogen on the skeleton—direct and indirect. First, estrogen has a direct skeletal effect to restrain bone resorption mediated by cytokines and other factors. Second, there is at least some evidence for indirect effects of estrogen on extraskeletal calcium metabolism that, in turn, affect the skeleton. For example, estrogen may increase calcium absorption from the gut, increase tubular calcium reabsorption in the kidney, and decrease PTH secretion by the parathyroid glands.
Riggs and colleagues (46) have illustrated their proposed model in a schematic depicting bone loss in postmenopausal women and aging men (Figure 4). The model predicts that at the time of menopause in women (Figure 4A), acute estrogen withdrawal releases direct restraints on bone resorption and that the resultant increase in bone resorption leads to accelerated bone loss during the postmenopausal period. The slow phase of bone loss, which eventually becomes predominant with sustained reduction in estrogen levels during aging, is attributed to loss of indirect effects of estrogen on extraskeletal calcium homeostasis leading to net loss of calcium from gut and kidney, increased dietary calcium requirement, secondary hyperparathyroidism, and increased bone turnover. In aging men (Figure 4B), a gradual decline in circulating estrogen, possibly resulting from decreasing levels of testosterone capable of being aromatized to estrogen, would lead to bone loss by the same processes that cause the slow phase of bone loss in aging women. It is interesting in this context that Riggs and colleagues also recently reported that bioavailable estrogen levels decrease by about 50% over the adult life span in men (43). Finally, a reduction in bone formation with age appears to contribute to the slow phase of bone loss in both sexes, but it is unclear whether estrogen deficiency plays a determining role in this aspect of bone loss.

In the May 1998 issue of the Journal of Bone and Mineral Research where Riggs and colleagues proposed their unitary model of osteoporosis, an accompanying editorial (47) pointed out that at least some aspects of this provocative model (e.g., the extraskeletal actions of estrogen, and the transition with increasing age from direct to indirect skeletal consequences of estrogen deficiency) remain incompletely documented. The editorial also cautioned, “It is premature, however, to speculate on how important estrogen is in the processes associated with bone loss in the aging male” (47, p. 776). Despite this healthy skepticism, evidence that estrogen is a determinant of bone mass in older men continues to accumulate. Accordingly, the model by Riggs and colleagues is likely to provide the stimulus for additional experimentation into pathogenetic mechanisms linking estrogen deficiency to osteoporosis in both men and women.

**Gonadal Steroids and Osteoporosis in Men: Implications for Therapy**

What are the therapeutic implications of the emerging view that estrogen does play a role in maintenance of the skeleton in aging men? In this regard, we might return to our earlier question of whether reductions in testosterone have any influence on bone loss in aging men. And, is there a place for testosterone treatment of osteoporosis in men, especially if they are eugonadal? Although this review has focused on evidence for a role of estrogen, in vitro and animal studies provide ample support for direct actions of androgens important to skeletal growth and maintenance in males (48). In humans, however, the role of androgens in maintenance of bone mass remains less clear. For example, human studies of genotypic men with androgen resistance have not yielded convincing evidence of a skeletal phenotype specific to deficient androgen action (49,50).

Even if testosterone is viewed as a prohormone for estrogen, there may still be a place for androgen therapy in eugonadal men. Of interest in this regard is a recent study by Anderson and colleagues (51), in which 21 eugonadal men with osteoporosis were evaluated during 6 months of treatment with testosterone. Although there was no placebo group in this study, BMD of the lumbar spine increased significantly after 6 months of testosterone treatment. Interestingly, the increase in spine BMD correlated with increases in serum estradiol, but not with changes in total (or even bioavailable) testosterone. Testosterone may therefore have exerted a positive effect on bone density only after being aromatized to estradiol (51). In contrast to these results, however, a randomized placebo-controlled trial reported recently by Snyder and colleagues (52) calls into question whether testosterone therapy effectively raises BMD in older eugonadal men. In this latter study, testosterone administered for 36 months to men over 65 years of age increased lumbar spine BMD only in those subjects with relatively low pretreatment values of serum testosterone.

And what about therapy with estrogen itself? In the 1960s and early 1970s, high-dose estrogen therapy was administered to men enrolled in the Coronary Drug Project, a national collaborative trial evaluating the effects of several drug regimens in the secondary prevention of coronary heart disease. The estrogen regimen was discontinued prematurely, not only because no cardiovascular benefits were observed, but also because too many men dropped out of the
study with unacceptable side effects, such as testicular atrophy and gynecomastia (53). More recently, it has been suggested that lower doses of estrogen could conceivably provide useful therapy without adverse side effects for men with osteoporosis. Alternatively, the use of selective estrogen receptor modulators (SERMs) might prevent bone loss in older men without the adverse side effects of estrogen (40). SERMs are pharmacologic agents that bind to estrogen receptors, produce estrogenlike effects in some tissues, but act as estrogen antagonists in others. One of these compounds, the nonsteroidal benzothiophene raloxifene, has been found to preserve bone in postmenopausal women, while decreasing the risk of breast cancer without any adverse estrogenlike effect on the endometrium (54,55). Whether SERMs or low-dose estrogen can provide safe, effective therapy for osteoporosis in men remains to be determined.

**CONCLUDING REMARKS**

Finally, what ever happened to our 71-year-old man (see Case Presentation section) with osteoporosis and low serum testosterone? Calcitonin therapy was continued for more than 1 year and was subsequently changed to the oral bisphosphonate alendronate. Data currently emerging from clinical trials indicate that alendronate is effective in the treatment of osteoporosis in men (56). The patient has sustained no obvious new fractures. But what was the cause of his osteoporosis? Whereas during his hospitalization he had very low serum concentrations of testosterone and gonadotropins (as stated previously), on follow-up studies in the outpatient clinic, when he was no longer acutely ill, his testosterone (335 ng/ml) and gonadotropins (LH, 5.8 mIU/ml; FSH, 7.7 mIU/ml) returned to normal. These changes in pituitary–gonadal hormone values are typical of patients who appear to sustain a transient hypogonadotropic hypogonadism caused by acute illness (57). In this regard, it should be remembered that, while hospitalized, the patient was treated with morphine, which is known to reduce secretion of gonadotropins and testosterone. A serum prolactin level, drawn in the outpatient setting to evaluate the possibility of hyperprolactinemia associated hypogonadism, was also normal (5.8 ng/ml; normal, 2.8–29.9). Interestingly, serum estradiol obtained at the time of the follow-up examination was below the assay’s lower limit of detection (<15 pg/ml; normal, <54 for men). It is perhaps tempting to speculate on the potential relationship between this patient’s osteoporosis and an estrogen level that is undetectable by commercial assay. Clearly, however, our understanding of how estrogen influences bone mass in aging men is currently far too limited to attribute idiopathic osteoporosis to estrogen deficiency in any individual older male patient.

In conclusion, rapidly accumulating evidence suggests that osteoporosis in both women and men is linked to a common critical determinant: estrogen. Three areas of recent investigation—clinical studies of men with genetic disorders of estrogen action, phenotypic characterization of estrogen receptor knockout mice, and epidemiologic research relating bone density with gonadal steroids in aging men—have all led to the conclusion that estrogen plays a vital role in the maintenance of bone in men as well as in women. During the next several years, the relationship between estrogen and bone mass in aging men will likely be explored further in large-scale prospective studies of the causes of osteoporosis in older men and also in clinical trials evaluating the use of SERMs in the treatment of men with osteoporosis. Following preliminary (and somewhat conflicting) reports of associations between estrogen receptor gene polymorphisms and bone mass in men (44,58,59), it is expected that additional research will focus on the identification of estrogen receptor, or possibly aromatase, gene variants as predictors of BMD in aging men. The results of these future studies will enlarge our emerging view of estrogen as an essential element in the pathogenesis and treatment of osteoporosis in men.

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