

Brief Report

INCREASED BONE MASS AS A RESULT OF ESTROGEN THERAPY IN A MAN WITH AROMATASE DEFICIENCY

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DURING childhood and young adulthood, the skeleton accrues virtually all the bone mineral it will ever have.¹ Since the aging process is associated with bone loss, the more bone mass one gains in the formative years, the less likely it is that increased bone resorption and decreased bone formation will result in osteoporosis. Hence, the failure to achieve optimal peak bone mass is a pathogenetic mechanism in osteoporosis. The sex steroids are critically important in helping to establish peak bone mass for both sexes. Girls with estrogen deficiency do not achieve optimal peak bone mass.²⁻⁴ Similarly, achievement of peak bone mass is compromised in boys with hypogonadism and those in whom puberty is delayed.^{5,6}

Two rare genetic disorders associated with estrogen resistance or estrogen deficiency suggest that androgens are not solely responsible for the establishment of peak bone mass in males. Smith et al.⁷ described a man with estrogen resistance because of a point mutation in the estrogen-receptor gene. Morishima et al.⁸ and Carani et al.⁹ each described a man with a point mutation in exon 9 of the aromatase gene and an associated inability to convert androgen to estrogen (the man described by Morishima et al. is the patient discussed here). In these two genetic disorders associated with estrogen resistance or estrogen deficiency, osteoporosis was present.

To demonstrate clearly the importance of estrogens in establishing peak bone mass in growing males, it is important to show that replacement of estrogen, in the setting of lifelong estrogen deficiency, leads to restoration of bone mass. We now report the results of such a study, in which a young man with severe aromatase deficiency was treated with conjugated estrogen for three years.

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CASE REPORT

The patient was 24 years old. His 27-year-old sister, the propositus, was evaluated at birth because of ambiguous genitalia. Both the patient and his sister have been reported previously⁸ to have a homozygous point mutation in exon 9 of the aromatase gene, leading to a single-base-pair change at position 1123 and no enzyme activity. The parents were of Italian descent and were consanguineous. They were phenotypically normal, and each had a single copy of the mutant gene. The mother was 165 cm in height, and the father was 190 cm in height. The patient was 204 cm in height, with a eunuchoid appearance. He was heterosexual and sexually active. Macroorchidism was present, with an estimated total testicular volume of 34 ml. Bone age was 14.5 years; only the proximal femoral epiphyses were fused. The ratio of the upper segment to the lower segment was 0.84. Serum androgen concentrations were all markedly elevated, but serum estrone and estradiol concentrations were undetectable. Serum concentrations of follicle-stimulating hormone and luteinizing hormone were elevated (Table 1). Semen analysis was not done.

Bone mass was reduced at all sites. The reductions in standard deviations from the mean for age- and sex-matched normal subjects (z scores) were 1.68 at the lumbar spine, 0.53 at the femoral neck, and 4.65 at the left radius (one third the distance from the wrist to the elbow). Determinations of bone mass by dual-energy x-ray absorptiometry, which assesses two-dimensional area density, are subject to an artifact of size relative to volumetric density¹⁰⁻¹² according to the following equations: the apparent bone mineral density of the lumbar spine = bone mineral content ÷ $A_p^{3/2}$; the apparent bone mineral density of the femoral neck and radius = bone mineral content ÷ A_p^2 , where A_p denotes projected area. Thus, the patient's apparent bone mineral density was even more impressively reduced than his area density. The calculated apparent bone mineral density was lower than the measured area density by 19 percent in the lumbar spine (-1.99 SD), by 75 percent in the femoral neck (-2.12 SD), and by 60 percent in the radius (-7.75 SD). This report presents standard two-dimensional area units because this method of presentation of bone mineral density by dual-energy x-ray absorptiometry is more familiar.

METHODS

Biochemical Determinations

Serum 5 α -dihydrotestosterone, androstenedione, and testosterone were measured by Mayo Medical Laboratories (Rochester, Minn.). Serum estrone, estradiol, follicle-stimulating hormone, luteinizing hormone, osteocalcin, and bone-specific alkaline phosphatase activity were measured by SmithKline Beecham Laboratories (Syosset, N.Y.). Urinary deoxypyridinoline, pyridinoline, and creatinine were measured with the use of Corning Nichols Institute (San Juan Capistrano, Calif.). Urinary calcium was measured with the use of atomic absorption spectroscopy.

Bone Densitometry

Sequential bone densitometry was performed over the three-year period on the same machine, a QDR 1000W densitometer (Hologic, Waltham, Mass.). In our hands, the precision was 0.68 percent at the lumbar spine, 1.36 percent at the femoral neck, and 0.70 percent at the distal radius.

RESULTS

With his informed consent, the patient was treated with conjugated estrogens (Premarin). The initial daily dose of 0.3 mg was gradually increased during the first 12 months to 0.75 mg, which is the dose he is still taking. Shortly after the initiation of estrogen treatment, linear growth, which had been continuous, ceased. All epiphyses of the hand and wrist were completely fused within six months (Fig. 1). Serum

TABLE 1. HORMONAL, BONE-TURNOVER, AND METABOLIC INDEXES BEFORE AND AFTER THREE YEARS OF ESTROGEN THERAPY.*

INDEX	BEFORE ESTROGEN THERAPY	AFTER ESTROGEN THERAPY	NORMAL VALUE
Hormonal and bone turnover			
Serum estradiol (pg/ml)	<7	64	10–50
Serum estrone (pg/ml)	<7	49	10–50
Serum androstenedione (ng/dl)	335	217	30–263
Serum testosterone (ng/dl)	2015	990	200–1200
Serum 5 α -dihydrotestosterone (ng/dl)	125	79	30–85
Serum luteinizing hormone (mIU/ml)	28.3	11.3	2.0–9.9
Serum follicle-stimulating hormone (mIU/ml)	28.3	12.7	5.0–9.9
Serum alkaline phosphatase activity (IU/liter)	241	136	39–117
Serum osteocalcin (ng/ml)	19.8	14.4	3–13
Urinary calcium (mg/g of creatinine)	94	61	50–250
Urinary pyridinoline (nmol/mmol of creatinine)	102	51.0	20–61
Urinary deoxypyridinoline (nmol/mmol of creatinine)	25.3	8.9	4–19
Metabolic (fasting values)			
Plasma glucose (mg/dl)	70	101	70–105
Serum insulin (μ U/ml)	52	15	5–25
Serum cholesterol (mg/dl)			
Total	238	234	<200
HDL	36	46	36–54
LDL	139	123	<130
Serum triglycerides (mg/dl)	317	176	30–200

*To convert values for estradiol to picomoles per liter, multiply by 3.67; to convert values for estrone to picomoles per liter, multiply by 3.70; to convert values for androstenedione to nanomoles per liter, multiply by 0.035; to convert values for testosterone to nanomoles per liter, multiply by 0.035; to convert values for 5 α -dihydrotestosterone to nanomoles per liter, multiply by 0.034; to convert values for calcium to millimoles per liter, multiply by 0.25; to convert values for glucose to millimoles per liter, multiply by 0.056; to convert values for cholesterol to millimoles per liter, multiply by 0.026; and to convert values for triglycerides to millimoles per liter, multiply by 0.011. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

estrone and estradiol concentrations rose into the normal range for men within the first three months and remained at or slightly above normal thereafter (Table 1). The increase in serum estrogen concentrations was accompanied by a gradual reduction in serum testosterone and 5 α -dihydrotestosterone concentrations. The patient's serum luteinizing hormone and follicle-stimulating hormone concentrations decreased to levels that were slightly higher than normal (Table 1). The estimated testicular volume decreased from 34 to 28 ml.

Markers of bone turnover gradually approached normal values (Table 1). Within 18 months, urinary concentrations of calcium, pyridinoline, and deoxypyridinoline were normal. In contrast, serum alkaline phosphatase activity did not begin to fall until after 18 months of therapy. Even after 36 months of therapy, serum alkaline phosphatase activity was 136 IU per liter, which was still above the normal range of 39 to 117 IU per liter.

Bone mass increased dramatically at all sites. At one year, bone mass in the lumbar spine, femoral neck, and distal radius had increased by 7.7 percent, 9.8 percent, and 6.8 percent, respectively. Increases in bone mass continued, and by three years, the increase was 20.7 percent in the lumbar spine, 15.7 percent in the femoral neck, and 12.9 percent in the

distal radius (Fig. 2). These percentage increases correspond to the following increases in grams per square centimeter: lumbar spine, from 0.931 to 1.123; femoral neck, 0.920 to 1.060; and distal radius, 0.570 to 0.643. When these results were expressed as improvements in T scores (standard deviations from the mean in normal young men), the bone mass increased from -1.96 to $+0.08$ in the lumbar spine, from -0.36 to $+0.96$ in the femoral neck, and from -4.65 to -3.28 in the distal radius.

There were no changes in serum concentrations of calcium, phosphorus, parathyroid hormone, 25-hydroxyvitamin D, or 1,25-dihydroxyvitamin D, all of which were normal. The base-line serum insulin concentration was elevated (52 μ U per milliliter) when the plasma fasting glucose concentration was normal, indicating a state of insulin resistance (Table 1). The serum insulin concentrations gradually became normal during therapy without any changes in the fasting plasma glucose or glycosylated hemoglobin values. Similarly, the initially elevated serum concentrations of triglycerides and low-density lipoprotein cholesterol became normal. The changes in serum concentrations of insulin, low-density lipoprotein cholesterol, and triglycerides provide further evidence of the importance of estrogen in carbohydrate and lipid metabolism.¹³⁻¹⁷ Correction of the

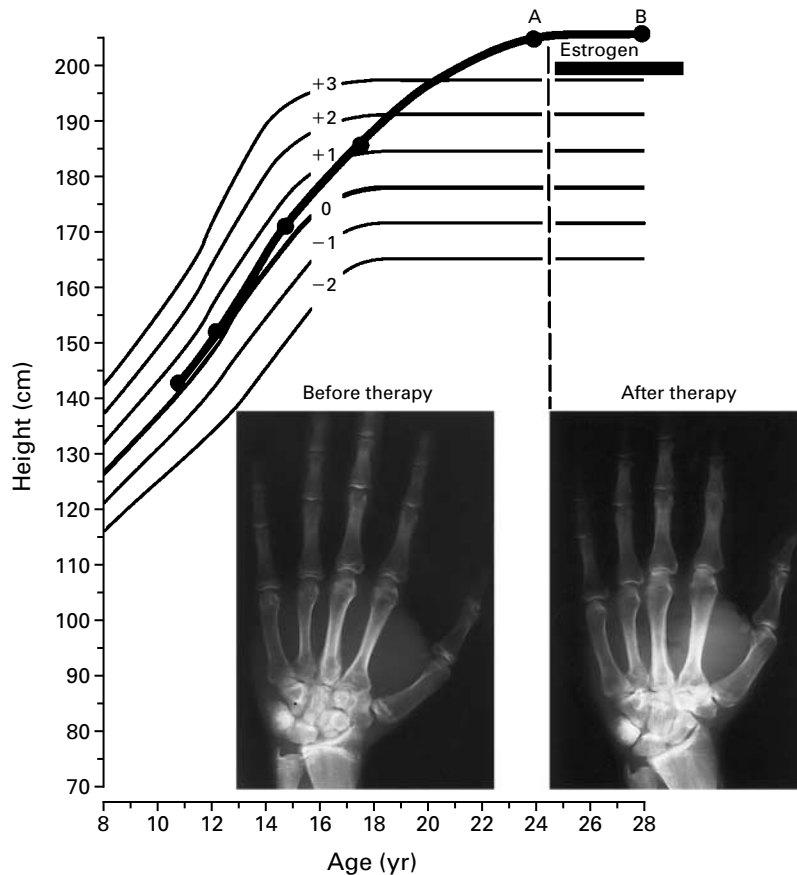


Figure 1. Growth Curve and Bone Age before and after Three Years of Estrogen Therapy.

After the institution of estrogen therapy (bar), linear growth ceased immediately, and height remained at 204 cm. The epiphyses closed within six months (insets). At a chronologic age of 24.5 years, the patient's bone age was 14.5 years (A). His bone age matured with closure of epiphyses after therapy (B). The numbered curves represent the mean and standard deviations in normal young men.

lipid abnormalities could also have been due, in part, to normalization of the high serum androgen concentrations.^{18,19}

The patient reported no side effects from estrogen therapy. He did not gain weight, develop gynecomastia, or have mood disturbances. He had no change in libido or sexual orientation.

DISCUSSION

The case we describe illustrates the essential role of estrogens in skeletal development in males. Reports of osteoporosis in humans and animals with gene defects in the estrogen receptor^{7,20,21} and in patients with aromatase deficiency have called attention to the importance of estrogens in skeletal growth. But it remained to be shown that correction of the specific estrogen deficit with estrogen could restore bone mass. The hypothesis that estrogen replacement would be beneficial could not be tested in the patient described by Smith et al.⁷ because of a defective estrogen receptor.

In a male patient with aromatase deficiency studied by Carani et al.,⁹ estrogen was administered for only six months, and skeletal measurement was restricted to the lumbar spine. In addition, that patient's aromatase deficiency was complicated by a hypothalamic-pituitary-gonadal disorder. In the only study of an affected female for whom bone densitometric data are available, Mullis et al.²² reported changes in a three-year-old girl, but over an even shorter period of time. No data on bone mineral density in other girls with aromatase deficiency have been reported.²³⁻²⁸ In the patient we describe, conjugated estrogens were given continuously for three years, with beneficial results at the lumbar spine, hip region, and distal radius.

Previous notions that the male skeleton accrues more mass than the female skeleton because of its greater exposure to androgens must now be reconsidered. It appears that both androgens and estrogens are important and that, together, they are the critical determinants of peak mass in the male skeleton. This

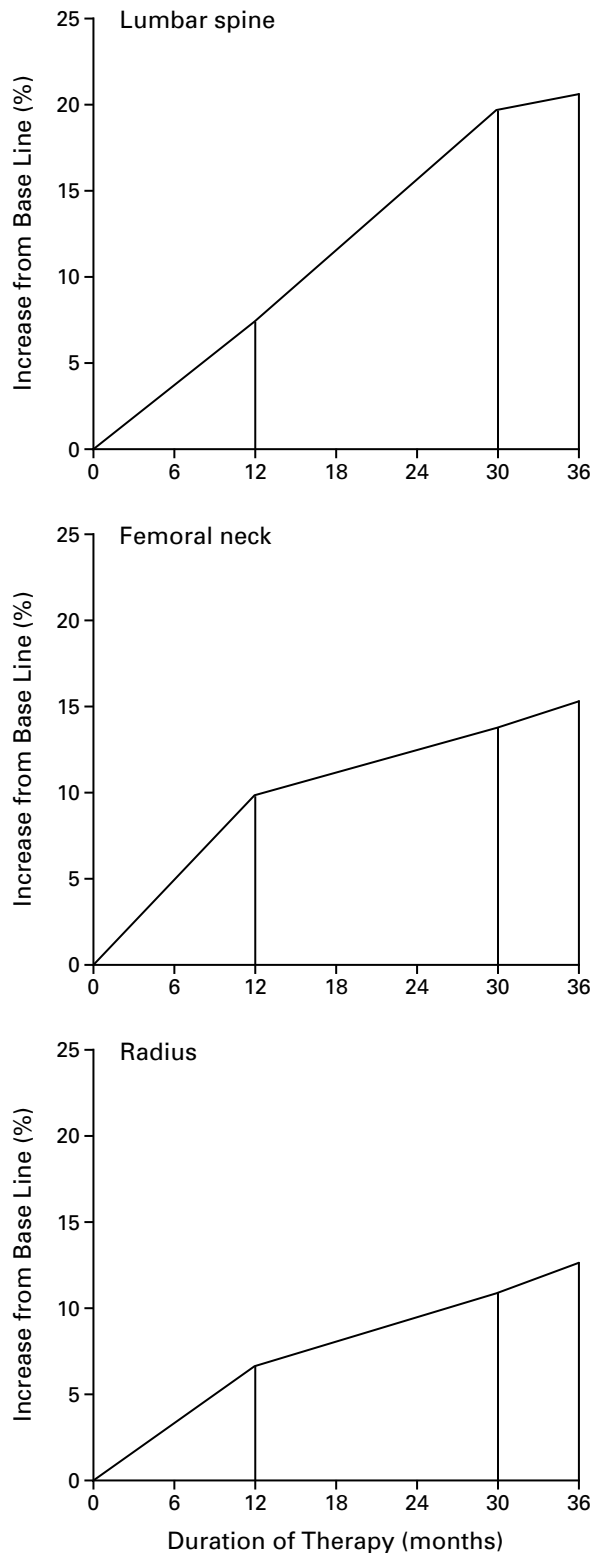


Figure 2. Changes in Bone Density during Estrogen Therapy. The percentage increase from base-line values is shown for each site. After the base-line determination, specific measurements were made at 12, 30, and 36 months.

conclusion is supported by the finding of Vander-schueren et al.²⁹ that male rats require both androgens and estrogens for optimal skeletal growth. Similarly, for optimal peak bone mass in women, androgens and estrogens are important.^{30,31} The results of the present study document that in males both androgens and estrogens are required for optimal peak bone mass.

The gain in bone mass was due to a true net anabolic effect, because after estrogen therapy was instituted, the patient immediately stopped growing and, as in the patient described by Carani et al.,⁹ all epiphyses fused. Furthermore, there were no substantial increases in bone size after the epiphyses closed. Thus, gains in bone mass accurately reflect accrual of bone mineral rather than a mixture of growth effects on the skeleton. This is especially important to note because the results of dual-energy x-ray absorptiometry are subject to changes due to increments in two-dimensional skeletal size that do not necessarily reflect a true change in volumetric density.¹⁰⁻¹² The mechanisms of bone accrual are likely to be due both to the antiresorptive effects of estrogens³² and to direct anabolic effects. A direct anabolic effect is inferred because it is difficult to account for the remarkable increase in bone mass by an exclusive antiresorptive effect, given the moderate elevations in bone turnover before therapy and the interval over which the improvement occurred.³³

Improvements in bone mass in this patient are particularly remarkable, considering the fact that estrogen therapy also reduced androgen concentrations to normal levels. The explanation for the elevated androgen concentrations is twofold. First, because of the complete absence of aromatase activity, no testosterone was metabolized by conversion to estrogen. Second, the elevated serum concentrations of luteinizing hormone stimulated the Leydig cells to overproduce androgen. The elevation in serum concentrations of luteinizing hormone and follicle-stimulating hormone suggests that estrogen, in addition to testosterone and inhibin, has an important role in regulating the secretion of both gonadotropins.³⁴⁻³⁶ When estrogen was deficient, the gonadotropin concentrations were elevated; with estrogen replacement, they became normal. The fact that bone mass increased when the androgen concentrations were declining strengthens the case for a specific anabolic effect of estrogen on the skeleton in males.

We conclude that 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. Several recent studies have provided evidence of the latter point. Slemenda et al.³⁷ and others³⁸⁻⁴¹ have shown that the slow, age-related decline in bone mass in men is more directly related to declining estrogen concentrations than to declining androgen concentrations. It is also possible that the therapeutic effects of androgens in men with osteoporosis are

due in part to their conversion to estrogens.⁴² With regard to the developing skeleton in males, the results of our study demonstrate the importance of estrogen sufficiency in the establishment of peak bone mass.

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