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## The relationship between plasma estradiol and the increase in bone density in postmenopausal women after treatment with subcutaneous hormone implants

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Twenty-three postmenopausal women with a median of 2 years past menopause (range, 1 to 12 years) and a median age of 52 years (range, 39 to 62 years) were recruited to participate in a longitudinal study designed to investigate the factors that influence the increase in bone density with subcutaneous estradiol and testosterone implants. All women received 75 mg of estradiol with 100 mg testosterone subcutaneously. Bone density was measured at the spine and hip by dual-photon absorptiometry before therapy and after 1 year of subcutaneous hormonal therapy. The mean pretreatment bone density at the lumbar vertebrae and neck of the femur was 0.84 grams of hydroxyapatite per square centimeter (SD, 0.11) and 0.73 grams of hydroxyapatite per square centimeter (SD, 0.10), respectively. The bone density at both sites increased with values of 0.91 grams of hydroxyapatite per square centimeter (SD, 0.11) and 0.75 grams of hydroxyapatite per square centimeter (SD, 0.11), respectively. These values represent an increase of 8.3% ( $p < 0.0001$ ) at the spine and 2.8% ( $p < 0.01$ ) at the neck of the femur. The plasma estradiol level increased from a median of 80.5 pmol/L to 453 pmol/L ( $p < 0.001$ ). The percentage increase of vertebral bone density was not related to age, number of years past the menopause, pretreatment bone density, or serum testosterone levels, but a significant correlation was found between the percentage increase in bone density at the spine and the serum estradiol level ( $p < 0.02$ ,  $r = 0.45$ ). (AM J OBSTET GYNECOL 1990;163:1474-9.)

**Key words:** Osteoporosis, menopause, estradiol

After Albright's<sup>1</sup> observation that estrogen therapy can reduce urinary calcium excretion in postmenopausal women a number of prospective studies confirmed the values of estrogen replacement therapy in the prevention of postmenopausal osteoporosis.<sup>2-4</sup> Epidemiologic studies<sup>5, 6</sup> also showed a reduction in the incidence of osteoporotic fractures with such therapy.

Most studies used oral estrogen therapy, which although effective in the suppression of climacteric symptoms usually results in plasma estradiol and follicle-stimulating hormone (FSH) levels that are still in the postmenopausal range.<sup>7</sup> Although it has been claimed that the minimum dose of oral estrogen required to prevent postmenopausal osteoporosis is 0.625 mg conjugated equine estrogen<sup>8</sup> the optimal dose and route

of estrogen necessary to achieve an increase in bone density is not known.

The percutaneous route of administration avoids the enterohepatic circulation and is associated with physiologic plasma levels of estradiol and estrone. This is in contrast to the low levels of estradiol and high levels of estrone found after oral therapy with both conjugated equine estrogens or estradiol valerate.<sup>9, 10</sup> Subcutaneous implants of estradiol and testosterone are effective in the alleviation of climacteric symptoms,<sup>11</sup> and a cross-sectional study<sup>12</sup> showed an apparent superiority of implant therapy over oral therapy in the therapeutic effect on bone density. The suggestion was made in this study that the greater bone density after implant therapy was a result of the greater plasma estradiol levels achieved with this route when compared with oral estrogen therapy.

We present the results of a prospective study of estradiol and testosterone implants on the bone density and plasma hormone levels in postmenopausal women over 1 year of therapy.

### Patients and methods

A total of 23 postmenopausal women with a median age of 52 years (range, 39 to 62) were recruited into

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Table I. Mean values of bone density at lumbar spine and neck of femur, body weight, blood pressure, and plasma hormone values before therapy and after 1 year of estradiol and testosterone implants

Treatment	Pretreatment	1 Year after treatment
Mean bone density at spine gHa/cm <sup>2</sup> (SD)	0.84 (0.11)	0.91 (0.11)*
Mean bone density at femur gHa/cm <sup>2</sup> (SD)	0.73 (0.10)	0.75 (0.11)†
FSH (IU/L) median (range)	71 (28-100)	12 (1-62)‡
Estradiol (pmol/L) median (range)	80.5 (30-580)	453 (204-883)‡
Testosterone (nmol/L) median (range)	0.6 (0.3-1.8)	0.9 (0.4-2.4)§
Mean weight in kg (SD)	67.3 (7.7)	66.7 (7.0)
Mean blood pressure (mm Hg) (SD)	120 (37)/73 (12)	125 (21)/75 (13)

\**p* < 0.0001, Student's paired *t* test.

†*p* < 0.01, Student's paired *t* test.

‡*p* < 0.001, Wilcoxon matched-pair signed-rank test.

§*p* < 0.01, Wilcoxon matched-pair signed-rank test.

this prospective study. The median number of years past the menopause was 2 (range, 1 to 12). Menopausal status was defined as amenorrhea >1 year's duration with a serum FSH level >20 IU/L.

All women received hormone replacement therapy by subcutaneous implants of 75 mg estradiol and 100 mg testosterone. A further implant of the same dose of estradiol and testosterone was given after 6 months and again at 1 year.

Assays of FSH, estradiol, and testosterone were performed before treatment and at 1 year. The bone density was estimated in the spine of L2-4 and in the neck of the right femur with a Novo 22A BMC-LAB with gadolinium 153 as the source of radiation. The absorptiometer was standardized with a solution radiologically equivalent to hydroxyapatite, and the results were expressed as grams of hydroxyapatite per unit projected area of bone in square centimeters (gHa/cm<sup>2</sup>). The precision of the machine with the use of the phantom was 0.69% and short-term precision for normal subjects was 2.04%. Measurements were made before insertion of the hormone implant and at 12 months after therapy within 1 week of the insertion of the third implant.

**Statistical analysis.** The bone density values before and after treatment approximated to a normal distribution and the increase was therefore analyzed with the paired Student *t* test. The hormonal parameters could not be regarded as normally distributed and the changes were analyzed with the Wilcoxon matched-pairs signed-rank test. The Spearman correlation coefficient was calculated to express the relationship be-

tween the changes in bone density and the serum estradiol levels, serum testosterone levels, age, number of years past the menopause, and pretreatment bone density.

### Results

Of the 23 patients studied 22 patients showed an increase in the bone density after 1 year of therapy (Table I). The mean bone density at the lumbar spine before therapy was 0.84 gHa/cm<sup>2</sup> (SD 0.11), which increased to 0.91 gHa/cm<sup>2</sup> (SD, 0.11) after 1 year (*p* < 0.0001). The value for the proximal femur was 0.73 gHa/cm<sup>2</sup> (SD, 0.10), which increased to 0.75 gHa/cm<sup>2</sup> (SD, 0.11, *p* < 0.01). The mean increase in the lumbar spine was 0.07 gHa/cm<sup>2</sup> (95% confidence interval, 0.06 to 0.08 gHa/cm<sup>2</sup>). The mean increase at the femur was 0.02 gHa/cm<sup>2</sup> (95% confidence interval, 0.01 to 0.04 gHa/cm<sup>2</sup>). These values represent a mean increase in the bone density of 8.3% at the spine and 2.8% at the neck of the femur after 1 year.

The median serum FSH level before therapy was 71 IU/L (range, 28 to 100 IU/L) with a median serum estradiol level of 80.5 pmol/L (range, 30 to 580 pmol/L) and a serum testosterone level of 0.6 nmol/L (range, 0.3 to 1.8). After 1 year of therapy the serum FSH level significantly reduced to 12 IU/L (range, 1 to 62; *p* < 0.001), the serum estradiol level increased to 453 pmol/L (range, 204 to 883; *p* < 0.001), and the serum testosterone level increased to 0.9 nmol/L (range, 0.4 to 2.4; *p* < 0.01).

A significant correlation was found between the percentage increase of vertebral bone density and the

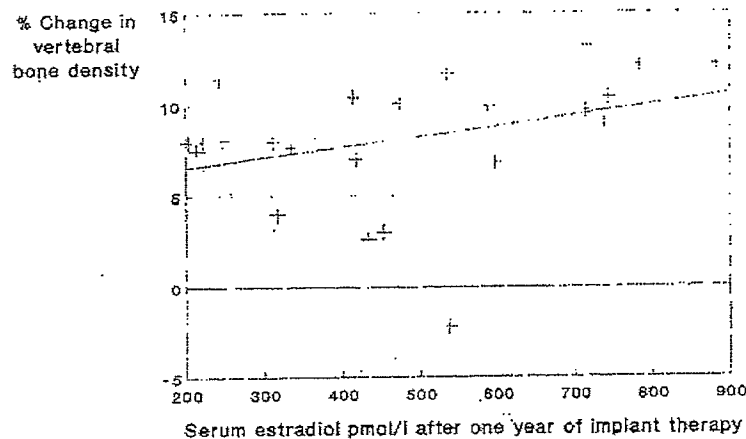


Fig. 1. Correlation between percentage increase in vertebral bone density with plasma estradiol levels after 1 year of therapy with estradiol and testosterone implants.

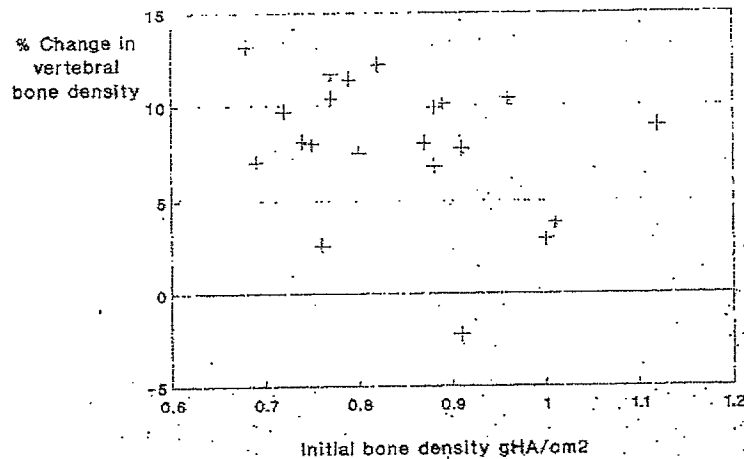


Fig. 2. Effect of pretreatment bone density on percentage increase in bone density with estradiol and testosterone implants.

plasma estradiol levels achieved after 1 year of therapy (Fig. 1,  $r = 0.45$ ;  $p < 0.02$ ). There was no significant correlation between the increase in bone density and the initial bone density (Fig. 2), age (Fig. 3), the number of years past the menopause (Fig. 4), and the serum testosterone level (Fig. 5).

#### Comment

These data show an increase of 8.8% in the bone density at the spine and 2.8% at the hip after 1 year of therapy with subcutaneous estradiol and testosterone implants. Evidence from our cross-sectional study with the use of the same method of bone densitometry reporting the vertebral bone density of 1.02 gHa/cm<sup>2</sup> and proximal femur values of 0.80 gHa/cm<sup>2</sup> after 8 years of such therapy<sup>12</sup> strongly suggest that this increase is not transient and will be maintained over the years.

Christiansen et al.<sup>13</sup> reported that the use of a combined preparation of oral estradiol, estriol, and norethindrone within 3 years of menopause resulted in an increase in bone density of 3% after 3 years of therapy. Lindsay et al.<sup>14</sup> (1984) found an increase of 2% to 4% over 5 years when mestranol 25  $\mu$ g was prescribed within 3 years of menopause but this dose only maintained bone density if it was started more than 3 years after menopause. More recently Munk-Jensen et al.<sup>15</sup> reported an increase of 6.4% in the vertebral bone density of women treated within 2 years of menopause with continuous oral estradiol and norethindrone for 1 year. None of these authors reported the estradiol levels obtained with the therapy. In our study we were able to show an increase in bone mass even 10 years after menopause. This increase was the same as found in the younger postmenopausal woman and was also inde-

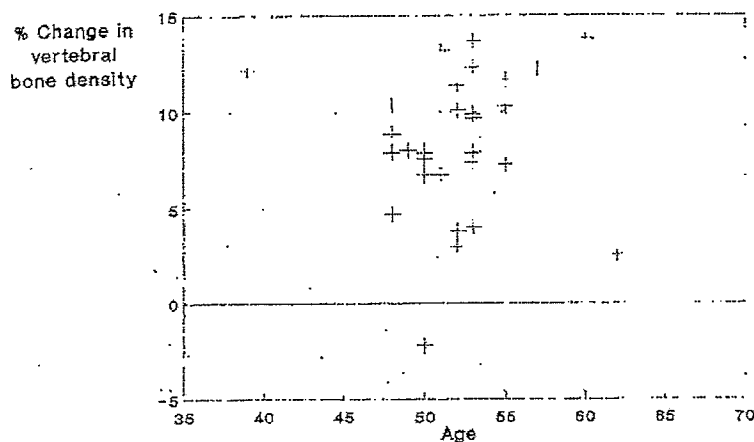


Fig. 3. Effect of age on percentage increase in bone density with estradiol and testosterone implants.

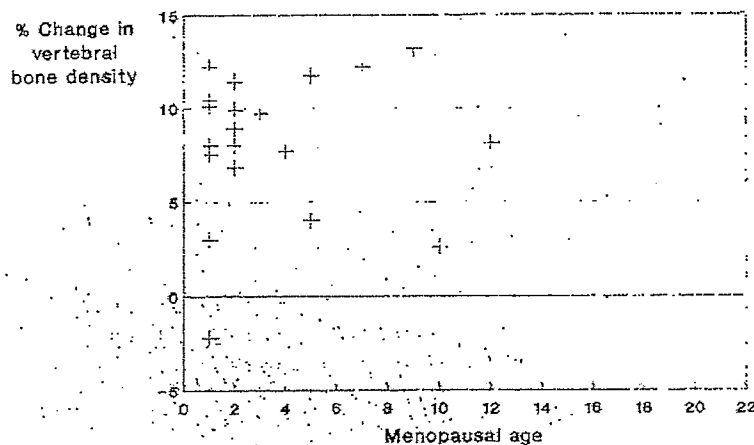


Fig. 4. Effect of number of years past menopause on percentage increase in bone density with estradiol and testosterone implants.

pendent of the initial bone density. The correlation between the percentage increase in bone density and the serum estradiol levels supports the hypothesis that the greater effectiveness of this mode of therapy may be a result of the higher serum estradiol levels achieved. Oral estrogen therapy is associated with lower estradiol levels and a less good skeletal response.<sup>12</sup>

The importance of the testosterone component of the treatment is unknown but there was no correlation in this study between plasma testosterone levels and the increase in bone density. Barlow et al.<sup>16</sup> could not show that the addition of testosterone to estrogen therapy improved bone density. However there is some evidence that adrenal androgens may have a role in maintaining the bone mass in postmenopausal women in the study of postmenopausal women with treated Addison's disease.<sup>17</sup> It is thus possible that the anabolic effects of testosterone on the skeleton may partly explain

these results and this component of the therapy is subject to further investigation.

The increase in bone density was greater in the spine than that at the neck of the femur because the more active trabecular bone predominates in the vertebra.<sup>18</sup> There are several models that show such substantial reversal of bone loss, particularly in the vertebra. Treasure et al.<sup>19</sup> showed in a cross-sectional study that the bone loss of anorexia nervosa is reversed when menstruation returns. Greenspan<sup>20</sup> showed that the osteoporosis of hyperprolactinemic men with hypogonadism recovers when the hyperprolactinemia is treated. Matta et al. (1988)<sup>21</sup> reported that the 5.9% loss of bone density after the use of buserelin for 6 months is reversed when it is discontinued. These conditions are all characterized by hypogonadism and the studies indicate

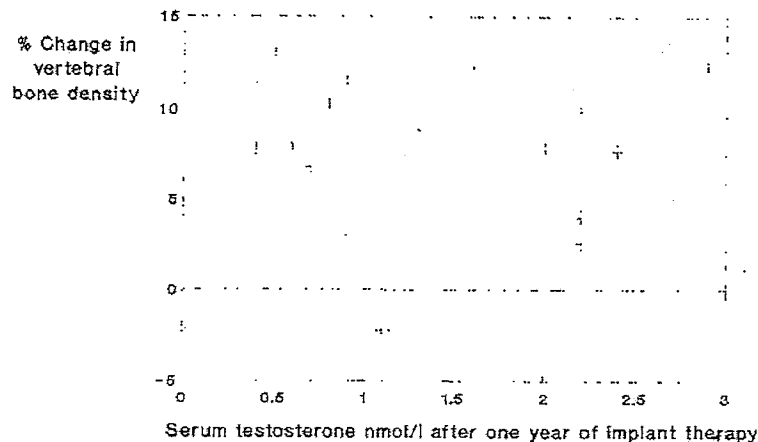


Fig. 5. Effect of serum testosterone after 1 year of therapy on percentage increase in bone density at spine.

that bone can be replaced in both men and women when plasma sex hormones return to normal physiologic levels.

The current recommended oral dosage of estrogens will suppress menopausal symptoms and prevent further bone loss but the serum estradiol and FSH levels achieved often remain in the postmenopausal range.<sup>12</sup> The dosage of orally administered estrogen may be limited by gastrointestinal symptoms and the liver impact on estrogen metabolism. It is probable that the safest way to achieve serum estradiol levels adequate to produce significant increases in bone mass is by the percutaneous route with either transdermal patches or subcutaneous implants.

The mechanism by which estrogen deficiency causes loss of bone remains unclear but the original Albright hypothesis of an association with a generalized loss of collagen including the collagenous matrix of the bone and the collagen of the skin is relevant. The substantial increase in vertebral spine density shown in this study can be compared with the 30% increase in skin collagen and a 25% increase in skin thickness that occurs in postmenopausal women who receive percutaneous estradiol therapy.<sup>23</sup> Only serial histomorphometric studies of bone biopsy specimens in these patients will reveal whether the estrogen-promoted changes in skin collagen are reproduced in the collagenous matrix of postmenopausal women.

It is reassuring from this study that estradiol and testosterone implants may not only prevent osteoporosis but will also be valuable in the older woman who might believe that it is too late to commence estrogen therapy. This therapy is also appropriate for the younger woman with premature ovarian failure who has already suffered substantial bone loss.

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