A Cross-Sectional Study of the Effects of Long-Term Percutaneous Hormone Replacement Therapy on Bone Density

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The effect of hormone implants on the bone density of postmenopausal women was studied in 110 patients (mean age 54.7 years; mean menopausal age 8.6 years, range 2–30) who had received hormone replacement in the form of estradiol (50–75 mg) and testosterone (100 mg) pellets at 6-month intervals for 2–24 years (mean 5.2). They were compared with 254 untreated women (mean age 55.0 years; mean menopausal age 6.8 years, range 1–37). The bone density at the spine, measured by quantitative digital radiography, was 1.123 grams hydroxyapatite (gHa)/cm^2 in the treated group and 0.951 gHa/cm^2 in the controls ($P < .0001$). The total bone density at the proximal femur was 1.002 gHa/cm^2 in the treated group, compared with 0.914 gHa/cm^2 in the controls ($P < .0001$). There were significant differences in the density of the trochanteric, intertrochanteric, and neck areas of the proximal femur as well as the Ward triangle (all $P < .0001$). These differences became significant from the age of 55 at the neck of the femur, Ward triangle, and lumbar spine, and from age 60 for all other values. Subcutaneous estradiol and testosterone prevent postmenopausal osteoporosis and maintain normal bone density for as long as treatment is continued. ***(Obstet Gynecol 78:1002, 1991)***

Osteoporosis has long been recognized as a major cause of death and disability and a considerable burden to health care expenditure. It is now widely accepted that estrogens prevent postmenopausal osteoporosis, and the established view that lost bone substance cannot be replaced is being questioned.[1]

Bone mass increases throughout adult life and peaks toward the end of the fourth decade, after which there is an age-related loss in both sexes.[2] In women, however, there is a marked acceleration in bone loss starting before menopause and lasting for 5–10 years, after which the age-related loss continues.[3] By the age of 70 a woman will have lost nearly 50% of her bone mass, whereas a man will lose just 25% by the age of 90.[4]

Previous studies have evaluated the administration of oral estrogens at the time of menopause in order to prevent the rapid loss of bone that occurs at the climacteric.[5,6] The effects of long-term administration of hormone implants on bone have been studied in less detail, although there is some evidence that implants may be more effective.[7] We have reported an 8% increase in vertebral bone density with hormone implants, which was directly related to estradiol (E2) levels achieved after 1 year of therapy.[8] However, such annual increases cannot be maintained. To determine the effects of long-term administration of hormone replacement, we investigated the hormone profiles and bone density of 110 patients who had received implants of E2 and testosterone at 6-month intervals for 2–24 years (mean 5.2). They were compared with a control group of postmenopausal women of similar age who had not received estrogen therapy.

Materials and Methods

The bone densities of a group of 254 untreated postmenopausal women were compared with those of 110 postmenopausal women who had received long-term hormone replacement with E2 and testosterone implants (Table 1). The untreated subjects were of mean age 55.0 years (range 33–79), and mean 6.8 years past menopause (range 1–37). They were of confirmed postmenopausal status with a serum FSH of 15 IU/L or more (mean 54.3, range 15–99), and had a mean serum E2 of 122 pmol/L (range 37–225).

The treated group received percutaneous E2 and testosterone implants, with the dose varying between 50–75 mg E2 in each patient to achieve adequate symptom control, along with 100 mg testosterone at

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Table 1. Characteristics of the 364 Subjects

	Control (N = 254)	Treated (N = 110)
Age (y)	55.0 (33–79)	54.7 (35–74)
Weight (kg)	65.4 (45–99)	64.56 (46–97)
Menopausal age (y)	6.8 (1–37)	8.6 (2–30)
Duration of treatment (y)		5.2 (2–24)

Data are presented as mean (range).

Table 2. Plasma Hormone Profiles and Bone Density at the Spine and Proximal Femur in Postmenopausal Women

	Control (N = 254)	Treated* (N = 110)
Hormone		
FSH (IU/L)	54.3 (15–99)	3.0 (0.9–56)†
E2 (pmol/L)	122 (37–525)	926 (74–2540)†
Testosterone (nmol/L)	0.91 (0.3–4.6)	1.51 (0.4–5.9)†
Bone density (gHa/cm^2)		
Spine (L_2, L_3 mean)	0.951 (0.54–1.467)	1.123 (0.76–1.574)†
Total femur	0.914 (0.480–1.319)	1.002 (0.764–1.417)†
Trochanter	0.649 (0.315–0.951)	0.726 (0.229–1.076)†
Intertrochanteric region	1.059 (0.527–1.519)	1.151 (0.771–1.675)†
Ward triangle	0.550 (0.234–1.069)	0.641 (0.397–1.102)†
Femoral neck	0.754 (0.394–1.304)	0.846 (0.580–1.345)†

E2 = estradiol; Ha = hydroxyapatite.
Data are presented as mean (range).
* Long-term estradiol and testosterone implants.
† $P < .0001$.

6-month intervals for a minimum of 2 years (mean 5.2 years, range 2–24). This group had a mean age of 54.7 years and were a mean of 8.6 years past menopause (range 2–30). The mean serum FSH was 3.07 IU/L (range 0.9–56.0) and mean E2 was 926 pmol/L (range 74–2540). The two groups of women did not differ significantly in age, weight, menopausal age, or parity, or in the incidence of smoking, alcohol consumption, or exercise. All had undergone natural menopause and initially attended the clinic because of postmenopausal symptoms rather than concern about developing osteoporosis. Testosterone was given routinely as an adjunct to estrogen therapy in these patients.

All women received oral cyclic norethisterone 5 mg/day for the first 7–10 days of each calendar month to prevent endometrial hyperplasia.[9] Hormone implants were inserted into the subcutaneous fat of the anterior abdominal wall or thigh under local anesthesia.[10]

Bone density at the lumbar spine and proximal femur was measured by quantitative digital radiography (Hologic, Waltham, MA). The results given are those for the mean values of L_2 and L_3 at the spine and the femoral neck, trochanteric region, intertrochanteric region, Ward triangle, and the total at the proximal femur. The equipment was standardized daily using a spine phantom containing a known equivalent of hydroxyapatite, and the results were expressed in grams hydroxyapatite per projected square centimeter of bone (gHa/cm^2). The coefficient of variation for the phantom was 0.87% in our clinic. Precision in vivo was determined by performing two measurements 1 month apart for 12 months in ten volunteers. Precision was 0.98% at the lumbar spine, 1.03% at the femoral neck, 1.22% at the trochanteric region, 1.32% at the intertrochanteric region, and 1.83% at Ward triangle.

Data on bone density, age, and weight of the two groups were normally distributed and therefore compared using the unpaired Student t test. All other values were analyzed using the Mann-Whitney U test.

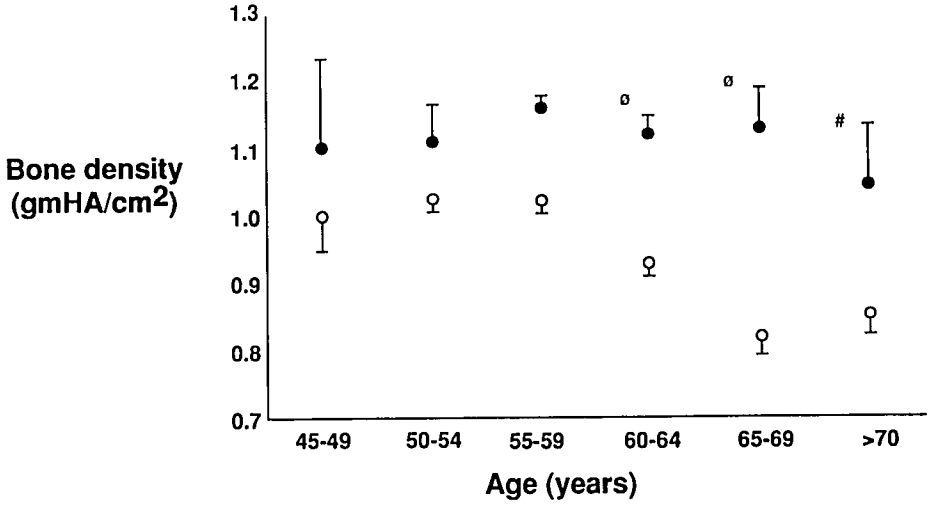

Figure 1. Bone density of L_2 and L_3 in untreated women (*open circles*) and women treated with hormone implants (*closed circles*), expressed in quinquennia from ages 45–70. ø = $P < .05$; # = $P < .005$. gmHA = grams of hydroxyapatite.

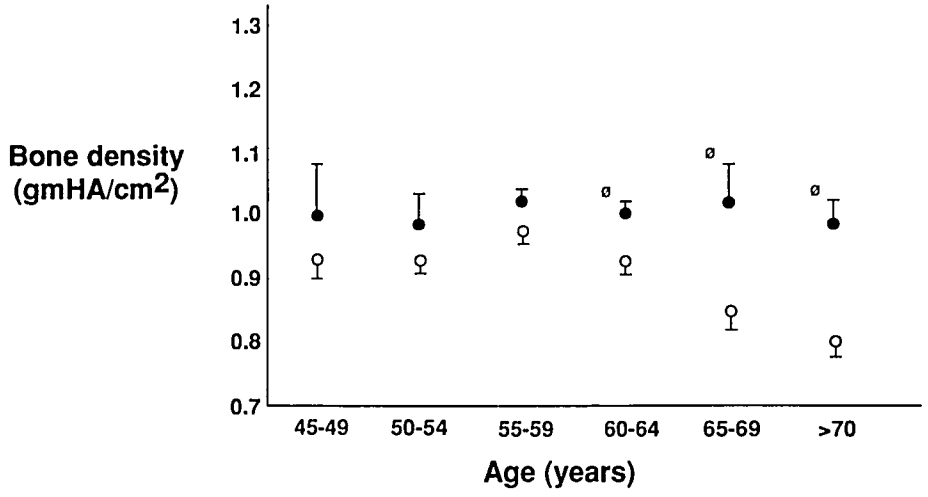

Figure 2. Bone density of the hip in untreated women (*open circles*) and women treated with hormone implants (*closed circles*), expressed in quinquennia from ages 45–70. Ø = $P < .05$. gmHA = grams of hydroxyapatite.

Results

The mean bone density at the spine was 1.123 gHa/cm^2 in the treated group and 0.951 gHa/cm^2 in the controls ($P < .0001$). The mean value for bone density at the proximal femur was 1.002 gHa/cm^2 in the treated patients, compared with 0.914 gHa/cm^2 in the controls ($P < .0001$) (Table 2).

The cross-sectional results in quinquennia demonstrated that age-related bone loss in an untreated postmenopausal population occurred at a rate of approximately 1.5% per year at the spine and 1% at the proximal femur, whereas bone density was preserved at both sites in the treated women (Figures 1 and 2). There was a significant difference between treated and untreated subjects at all sites from the age of 60 (Table 3). However, at the femoral neck, Ward triangle, and lumbar spine, this difference was significant from the age of 55 ($P < .05$). Bone density apparently increased with duration of therapy for up to 8 years (Figure 3).

At the spine, the bone density showed a significant correlation with plasma E2 levels ($r = 0.27$, $P < .01$). There was no correlation between bone density at the proximal femur and plasma E2 levels ($r = 0.09$).

In the treated group the mean serum E2 concentration was 926 pmol/L, compared with 122 pmol/L in the controls ($P < .0001$). With increasing duration of therapy, E2 levels rose to reach a state of equilibrium after 8 years (Figure 4). The mean serum FSH concentration was 3.0 IU/L in the treated group, compared with 54.3 IU/L in the control population ($P < .0001$). There was a significant rise in testosterone levels, from 0.91 to 1.51 nmol/L ($P < .0001$).

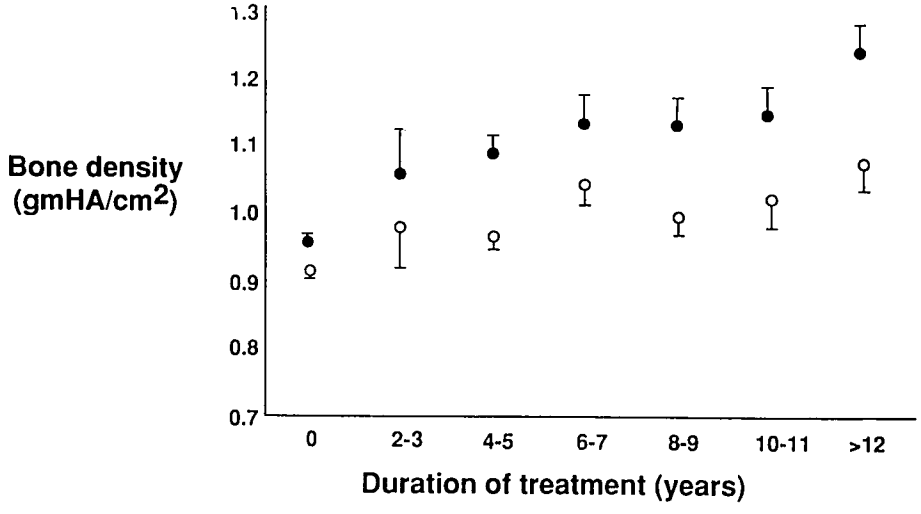

Figure 3. Bone density of the spine (*closed circles*) and hip (*open circles*) in 110 patients related to duration of therapy with hormone implants. gmHA = grams of hydroxyapatite.

Table 3. Plasma Hormone Profiles and Bone Density in Quinquennia From Age 45 to 70 and Over

	45–49 y			50–54 y			55–59 y			60–64 y			65–69 y			≥70 y		
	Control (N = 17)	Treated (N = 5)	P	Control (N = 44)	Treated (N = 14)	P	Control (N = 71)	Treated (N = 34)	P	Control (N = 60)	Treated (N = 35)	P	Control (N = 29)	Treated (N = 14)	P	Control (N = 33)	Treated (N = 8)	P
Hormone																		
FSH (IU/L)	39	2.4	<.001	50	2.4	<.001	54	3.9	<.001	61	2.3	<.001	53	2.5	<.001	57	2	<.001
E2 (pmol/L)	161	674	<.01	206	934	<.0001	164	926	<.0001	101	933	<.0001	98	991	<.0001	98	829	<.0001
Bone density (gHa/cm^2)																		
Femoral neck	0.804	0.811	NS	0.781	0.829	NS	0.804	0.854	<.05	0.742	0.838	<.0001	0.681	0.865	<.0001	0.639	0.850	<.0001
Trochanter	0.673	0.695	NS	0.622	0.710	NS	0.695	0.747	NS	0.642	0.717	<.005	0.586	0.734	<.005	0.569	0.710	<.001
Intertrochanteric region	1.091	1.140	NS	1.066	1.136	NS	1.124	1.165	NS	1.072	1.142	<.05	0.989	1.180	<.05	0.928	1.138	<.005
Total femur	0.945	0.992	NS	0.927	0.989	NS	0.971	1.017	NS	0.924	0.977	<.01	0.846	1.018	<.05	0.797	0.972	<.005
Ward triangle	0.625	0.741	NS	0.598	0.643	NS	0.603	0.650	<.05	0.544	0.618	<.01	0.471	0.642	<.005	0.437	0.658	<.005
Spine (L_2, L_3 mean)	1.016	1.091	NS	1.025	1.117	NS	1.021	1.154	<.001	0.936	1.114	<.0001	0.825	1.129	<.0001	0.855	1.047	<.05

E2 = estradiol; NS = not significant; Ha = hydroxyapatite.

Discussion

This study confirms the value of long-term hormone replacement for the prevention of postmenopausal bone loss. Bone density at both the spine and femoral neck was significantly greater in those who had received continuous hormone implants for 2 years or more compared with the control group, although the two groups did not differ in either chronological or menopausal age. Even women over the age of 70 failed to show an age-related loss of bone if they were treated with estrogens. The difference in bone density between the groups became significant from age 60 for all values measured. However, at the lumbar spine, femoral neck, and Ward triangle (the weakest point of the hip), this difference occurred 5 years earlier. This latter observation confirms the findings of a 1-year prospective controlled study of implants in which these three sites showed the greatest increase in bone density. This increase was significantly correlated with serum E2 levels and may have reflected the greater proportion of metabolically active trabecular bone at these sites.[11]

Several investigators have documented an increase in bone density on commencing hormone replacement therapy, but this has usually been dismissed as a transient effect and the result of "hole filling."[5,6] However, the higher bone density in patients on long-term therapy indicates that bone density may increase significantly with extended therapy. This has important consequences for the treatment of women with established osteoporosis, who may have a significant increase in bone density, and demonstrates the value of prolonged hormone replacement therapy in women many years past menopause.

We have previously shown a greater bone density after 8 years of percutaneous estrogen therapy compared with the bone density achieved after 8 years of oral therapy, and believe this to be a result of the higher E2 levels achieved by percutaneous implants.[7] This cross-sectional study also shows a correlation between spine bone density and serum E2 levels in spite of different chronological ages, menopausal ages, and bone density at the commencement of therapy, and differing durations of therapy.

All cross-sectional studies, even those with well-matched reference groups, have considerable limitations, particularly the lack of baseline data before treatment. Our findings of this substantial increase in bone density must be supported with long-term prospective studies of bone density and histology. These are in progress in this department, and the 1-year data relating to the effects on bone density of percutaneous E2 implants without testosterone are available.[11]

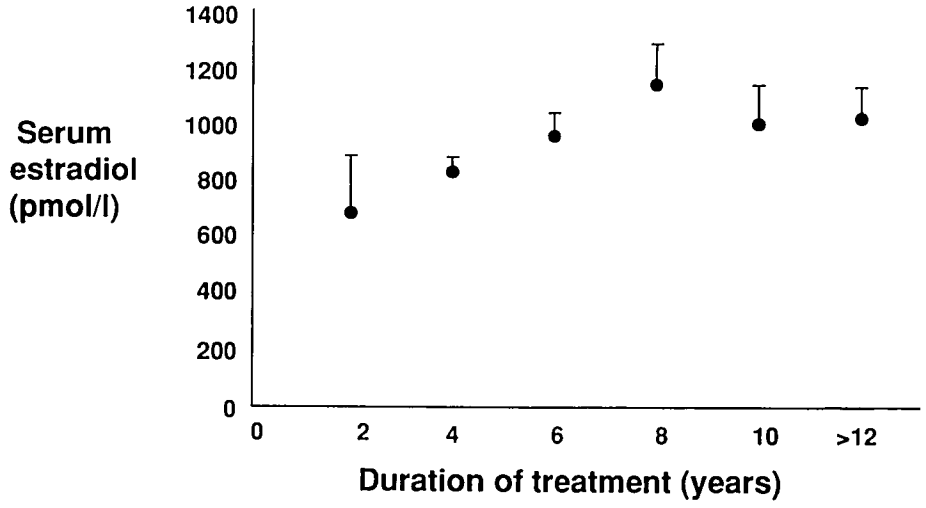

Figure 4. Estradiol levels in 110 patients receiving implant therapy for 2–12 years.

The value of estrogens in preventing osteoporosis was first suggested by Albright et al[12] 50 years ago, and confirmed by many studies since.[13–15] He proposed that the collagen matrix was more important than alterations in calcium metabolism in the etiology of the disease. The generalized atrophy of other collagen-containing tissues such as skin, nails, and pelvic tissues lends circumstantial support to this concept. Work from this clinic has already demonstrated that collagen is lost from the skin after menopause and that this loss cannot only be prevented but reversed with estrogen therapy. Loss of skin collagen occurs at a rate of 1–3% per year immediately after menopause, similar to the rate at which bone is lost.[16,17] Skin collagen (type 1) can be replaced by 25% and skin thickness by 10% in the first year of estrogen therapy. As yet, it is unknown whether the collagen of the bone matrix can be replaced at a similar rate.

All treated women had received testosterone implants along with E2. This was given because of its alleged effect on libido, mood, and depression. Androgens exert an anabolic effect on bone and have been used for this purpose in men. The dose of testosterone given to these patients was only 100 mg every 6 months. Such a dose is thought to be insufficient to have any significant effect on bone density,[18] and controlled prospective data from this clinic support this view.[11]

Cyclic progestogens were given to ensure endometrial protection, at a dose of 5 mg for the first 7–10 days of each calendar month. This regimen is of a shorter duration than is often recommended to achieve endometrial protection yet reduce the frequency of premenstrual syndrome-like symptoms.[9,19]

All treated women had received hormone replacement therapy for at least 2 years and found it an acceptable form of treatment with few side effects. Although breast tenderness can be a problem with all forms of hormone replacement, it is usually dose-dependent and is rare with 50-mg implants. Nausea is not a feature of percutaneous therapy.

Implant therapy avoids the risks of noncompliance in a population already the victims of polypharmacy. Although E2 levels may reach supraphysiologic levels, no harmful effects have been reported on weight, blood pressure, coagulation, or glucose tolerance either in this study or in the literature.[20–23] Implants have the added advantage that the enterohepatic circulation is avoided and an appropriate premenopausal ratio of E2 to estrone is achieved.[24,25] Higher serum E2 levels are attained than with oral estrogen therapy, but in this study only four of 110 patients had hormone levels above the physiologic peak of 1750 μg/L,[26] which is consistent with the prevalence of supraphysiologic levels reported in other studies.[27]

Using quantitative digital radiography, we have shown that long-term estrogen implants are effective in preventing postmenopausal bone loss. This protection is not transient, as the bone density of the spine and proximal femur is over the 90th percentile of age-matched controls in women over age 65, even after only 2 years of estrogens. This suggests that bone density may increase dramatically on the initiation of therapy if adequate levels of estrogen are attained.

Prospective and cross-sectional studies have shown the impressive effects of E2 implants on bone density. These facts taken in concert with the cardioprotective effects of E2 suggest that estrogen implants could be considered the first choice of therapy for the prevention and reversal of postmenopausal osteoporosis.

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Received February 13, 1991.
Received in revised form June 3, 1991.
Accepted June 3, 1991.