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The Effect of 25-mg Percutaneous Estradiol Implants on the Bone Mass of Postmenopausal Women

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Objective: **To determine whether the lowest available dose of percutaneous implant, 25 mg estradiol (E2), is effective for the prevention of postmenopausal bone loss.**

Methods: **Eighteen healthy postmenopausal women were treated with 25-mg percutaneous E2 implants for 1 year. Dual energy x-ray absorptiometry was performed at the lumbar spine and proximal hip using a quantitative digital radiography densitometer before treatment and after 1 year. Estradiol and FSH were also measured before and after 1 year of treatment. The changes in bone mineral density were compared with a matched reference group of 18 women who did not wish treatment.**

Results: **The median percentage changes in the treated group after 1 year were 5.65% at the lumbar spine, 3.38% at the femoral neck, and 3.36% total hip. At 1 year, there was a significant increase in bone mineral density from baseline at all sites measured except Ward triangle. The median post-treatment E2 level was 320 pmol/L (range 114–813), and FSH was 28 IU/L (range 2–66).**

Conclusion: **This study demonstrates that 25-mg percutaneous E2 implants significantly increase bone mineral density at the spine and hip in postmenopausal women. This dose is effective to prevent postmenopausal bone loss.** ***(Obstet Gynecol 1994;83:43–6)***

Estrogen replacement therapy prevents the loss of bone that occurs with the cessation of ovarian function,[1,2] and epidemiologic data have confirmed that it reduces the incidence of osteoporotic fractures.[3,4] It also alleviates menopausal symptoms and reduces deaths from myocardial infarctions[5] and cerebrovascular accidents.[6]

It is advisable to administer the lowest dose necessary of any drug to provide an adequate response in a patient. The lowest available implant dose, 25 mg estradiol (E2), controls menopausal symptoms and results in a physiologic profile of circulating estrogens.[7] We investigated the effect of this dose on the bone mineral density of postmenopausal women.

Materials and Methods

From previous experience, we expected changes of about 1 standard deviation or greater (about 4%) following treatment with this dose of percutaneous E2. This would require a trial involving 16 patients in each study limb to have a power of 80% of demonstrating a difference with a significance level of 5%.

We recruited 18 healthy postmenopausal women requesting estrogen replacement therapy. All had plasma FSH levels above 15 IU/L. The four who had previously undergone hysterectomy were considered to be menopausal from the time of onset of climacteric symptoms. None of the patients suffered from medical disorders or used any medication known to affect bone metabolism. Women with excessive tobacco use (more than ten cigarettes per day) or alcohol consumption (more than 14 units/week) were excluded.

All subjects received 25-mg percutaneous E2 implants (Organon Laboratories Ltd., Cambridge, UK) for 1 year. These were inserted under the skin of the anterior abdominal wall every 6 months.[8] None received testosterone. The 14 women with uteri were given cyclic medroxyprogesterone acetate, 5 mg (Upjohn Ltd., Crawley, UK) for the first 10 days of each calendar month to protect the endometrium against hyperplasia.

The bone density at the hip and the lumbar spine was measured before treatment and at 1 year using a dual x-ray Hologic 1000 quantitative digital radiogra-

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Table 1. Baseline Demographic Data

	Reference (n = 18)	Treatment (n = 18)
Age (y)	58.3 ± 7.5	55.3 ± 6.6
Menopausal age (y)	9.1 ± 8.9	8.4 ± 6.6
Height (cm)	160.7 ± 7.1	164.9 ± 8.0
Weight (kg)	61.5 ± 8.1	61.7 ± 11.5
Body mass index (kg/m^2)	24.1 ± 3.0	25.3 ± 4.1

Data are presented as mean ± standard deviation.

phy densitometer (Hologic Inc., Waltham, MA). The coefficient of variation, calculated by using a spinal phantom daily, was 0.67% during the course of the study. Precision in vivo was determined by serial scans in ten healthy premenopausal volunteers. The mean coefficients of variation were 0.98% at the lumbar spine, 1.03% at the femoral neck, 1.22% in the trochanteric region, 1.32% in the intertrochanteric region, 1.21% total hip, and 1.83% at Ward triangle. Serum assays of FSH and E2 were performed before therapy and at 1 year.

Placebo-controlled randomization was considered unethical for this study. Therefore, we used as controls a reference group of 18 postmenopausal women matched for age, menopausal age, height, weight, body mass index, and initial bone mineral density who did not wish estrogen replacement therapy.

Two-tailed Student t test and Mann-Whitney U test were used where appropriate to compare the patient groups. The percentage bone density changes at 1 year were compared using Wilcoxon tests.

Results

Table 1 shows the baseline demographic data and Table 2 the initial bone mineral densities for the two groups. There was no significant difference between the groups for age, menopausal age, height, weight, body mass index, and bone mineral density.

Table 3 presents the median percentage bone density changes with 95% confidence intervals for all the sites measured. At 1 year, the treatment group showed a significant increase in bone mineral density from baseline at all sites except Ward triangle. The differences between the patient groups were significant ($P <$ .05) after this time. The median post-treatment serum E2 level was 320 pmol/L (range 114–813), and FSH was 28 IU/L (range 2–66).

Three women in the treated group lost substantial amounts of bone (more than twice the measurement precision) from the lumbar spine, and two lost bone from the femoral neck. Fourteen and 11 women gained a significant amount of bone mass at the lumbar spine and femoral neck, respectively.

Table 2. Baseline Bone Mineral Density Data

Bone density (g/cm^2)	Reference (n = 18)	Treatment (n = 18)
L2–4	0.933 ± 0.168	0.937 ± 0.185
Femoral neck	0.709 ± 0.136	0.707 ± 0.123
Trochanter	0.647 ± 0.107	0.601 ± 0.099
Intertrochanteric region	0.990 ± 0.199	0.967 ± 0.184
Total hip	0.840 ± 0.150	0.823 ± 0.149
Ward triangle	0.508 ± 0.141	0.547 ± 0.138

Data are presented as mean ± standard deviation.

Table 3. Median Percentage Changes in Bone Density

	Reference (n = 18)	Treatment (n = 18)
L2–4	−1.14	5.65*†
	(−3.45, 0.96)	(2.81, 7.57)
Femoral neck	−1.46	3.38*†
	(−3.99, 0.62)	(1.25, 6.46)
Trochanter	−2.94*	4.52*†
	(−4.53, −1.03)	(3.03, 6.63)
Intertrochanteric region	−1.14	2.62*†
	(−3.65, 1.24)	(0.41, 4.88)
Total hip	−2.8*	3.36*†
	(−5.16, −0.52)	(1.24, 5.34)
Ward triangle	−0.88	1.36
	(−4.22, 4.79)	(−3.59, 5.34)

Data are presented as mean (95% confidence interval).
* $P <$ .05 from baseline after 1 year.
† $P <$ .05 between groups after 1 year.

Discussion

Oral preparations are the most commonly prescribed for estrogen administration largely because they are cheap and convenient. Ingested E2 is metabolized by the liver to the less potent estrone, with a reversal of the physiologic ratio.[9] It is claimed that the minimum dose of oral estrogen necessary to maintain bone mass is 0.625 mg conjugated equine estrogens[1] and 1–2 mg of E2.[2] These doses are used widely in clinical practice today. Unfortunately, patient compliance with oral therapy is poor. Less than 30% of women prescribed estrogen replacement pick up their prescription, and of those who do, only one-third continue with the medication for more than 3 months.[10]

The percutaneous route of administration avoids the hepatic first-pass effect, resulting in physiologic premenopausal plasma levels of E2 and estrone.[11] Transdermal patches are effective but are unsightly and expensive, and can cause allergic skin reactions. Conversely, percutaneous implants are not only cheap and convenient, but they also overcome the problem of poor patient compliance. Studd et al[12] demonstrated a

significant correlation between serum E2 levels and the percentage increase in vertebral bone density in postmenopausal women. Estradiol implants may be regarded as the most effective treatment for postmenopausal osteoporosis because of the high E2 level achieved.

The most commonly administered doses of implants are 50, 75, and 100 mg E2, used for premenstrual syndrome,[13] climacteric depression,[14] and osteoporosis.[12] The addition of 100 mg testosterone implant can further enhance the patient's feeling of well-being and improve her sexuality.[15] Although these doses of estrogen may be indicated to treat the patient with severe menopausal problems, depression, or established osteoporosis, they may be unnecessarily large for the early postmenopausal woman with mild climacteric symptoms. These doses are also more likely to be associated with supraphysiologic serum E2 levels in approximately 3% of patients.[16] Although there are no published data demonstrating any ill effects with these high E2 levels, the clinical implications remain uncertain.

In a study of six patients using single-photon absorptiometry, 25-mg implants maintained the postmenopausal skeleton.[17] Our study is the first to demonstrate an increase in bone mineral density with this dose of E2 using the high-precision dual energy x-ray absorptiometry. The increases were comparable to reported data on 1.25 mg conjugated equine estrogens,[18] 2 mg E2,[19] and 50 μg Estraderm TTS[20] (Ciba-Geigy, Summit, NJ) preparations.

Bone mineral density will decrease in some women despite the use of accepted bone-sparing doses of estrogen.[21] In our study, three treated women (16.6%) lost a significant amount of bone density at the spine, and two (12.5%) lost bone from the femoral neck. This emphasizes the necessity for serial bone densitometry to ensure that there is an appropriate response to low-dose therapy. If this measurement is unavailable or a poor skeletal response is evident, then administration of a higher dose of E2 should be considered.[12]

This study confirms that 25-mg E2 implants are an effective preparation for the prevention and treatment of postmenopausal bone loss.

References

1. Lindsay R, Hart DM, Clark DM. The minimum effective dose of estrogen for prevention of postmenopausal bone loss. Obstet Gynecol 1984;63:759–63.
2. Christiansen C, Christensen MS, Larsen N-E, Transbol IB. Pathophysiological mechanisms of estrogen effect on bone metabolism. Dose-response relationships in early postmenopausal women. J Clin Endocrinol Metab 1982;55:1124–30.
3. Paganini-Hill A, Ross RK, Gerkins VR, Henderson BE, Arthur M, Mack TM. Menopausal estrogen and hip fractures. Ann Intern Med 1981;95:28–31.
4. Spector TD, Brennan P, Harris PA, Studd JWW, Silman AJ. Do current regimes of hormone replacement therapy protect against subsequent fractures? Osteopor Int 1992;2:219–24.
5. Henderson BE, Paganini-Hill A, Ross RK. Estrogen replacement therapy and myocardial infarction. Am J Obstet Gynecol 1988; 159:312–7.
6. Paganini-Hill A, Ross RK, Henderson BE. Postmenopausal oestrogen therapy and stroke: A prospective study. Br Med J 1988;297:519–22.
7. Owen EJ, Siddle NC, McGarrigle HT, Pugh MA. 25 mg oestradiol implants—the dose of first choice for subcutaneous oestrogen replacement therapy? Br J Obstet Gynaecol 1992;99:671–5.
8. Thom M, Studd JWW. Practical procedures; hormone implants. Br Med J 1980;1:648–50.
9. Powers MS, Schenkel L, Darley PE, Good WR, Balestra JC, Place VA. Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17-beta estradiol: Comparison with conventional oral estrogens used for hormone replacement. Am J Obstet Gynecol 1985;152:1099–106.
10. Nachtigall LE. Enhancing patient compliance with hormone replacement therapy at the menopause. Obstet Gynecol 1990; 75(suppl):77S–80S.
11. Thom M, Collins WP, Studd JWW. Hormonal profiles in postmenopausal women after therapy with subcutaneous implants. Br J Obstet Gynaecol 1981;88:426–33.
12. Studd JWW, Savvas M, Watson N, Fogelman I, Cooper D. The relationship between plasma estradiol and the increase in bone density in postmenopausal women after treatment with subcutaneous hormone implants. Am J Obstet Gynecol 1990;163:1474–9.
13. Magos AL, Brincat M, Studd JWW. Treatment of the premenstrual syndrome by subcutaneous implants and cyclical oral norethisterone: A placebo-controlled study. Br Med J 1986;i:1629–33.
14. Montgomery JC, Appleby L, Brincat M, et al. The effect of oestradiol and testosterone implants on psychological disorders in the climacteric. Lancet 1987;i:297–9.
15. Studd JWW, Collins WP, Chakravati S, Newton JR, Oram D, Parsons A. Oestradiol and testosterone implants in the treatment of psychosexual problems in the postmenopausal woman. Br J Obstet Gynaecol 1977;84:314–6.
16. Garnett T, Studd JWW, Henderson A, Watson N, Savvas M, Leather A. Hormone implants and tachyphylaxis. Br J Obstet Gynaecol 1990;7:917–21.
17. Notelovitz M, Johnson M, Smith S, Kitchens C. Metabolic and hormonal effects of 25 mg and 50 mg 17 beta-estradiol implants in surgically menopausal women. Obstet Gynecol 1987;70:749–54.
18. Civitelli R, Agnusdei D, Nardi P, Zacchei F, Avioli LV, Gennari C. Effects of one-year treatment with estrogens on bone mass, intestinal calcium absorption, and 25-hydroxyvitamin D-1alpha-hydoxylase reserve in postmenopausal osteoporosis. Calcif Tissue Int 1988;42:77–86.
19. Munk-Jensen N, Pors Nielsen S, Obel EB, Bonne Eriksen P. Reversal of postmenopausal vertebral bone loss by oestrogen and progestogen: A double blind placebo controlled study. Br Med J 1988;296:1150–2.
20. Ribot C, Tremollieres F, Pouilles JM, Louvet JP, Peyron R. Preventive effects of transdermal administration of 17 beta-estradiol on postmenopausal bone loss: A 2-year prospective study. Obstet Gynecol 1990;75(suppl):42S–6S.

21. Stevenson JC, Cust MP, Ganger KPF, Hillard TC, Lees B, Whitehead MI. Effects of transdermal versus oral hormone replacement therapy on bone density in spine and proximal femur in postmenopausal women. Lancet 1990;336:265–9.

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