# THE EFFECTS OF VARIOUS HORMONE REPLACEMENT THERAPY REGIMENS ON BONE MINERAL DENSITY AFTER 2 YEARS OF TREATMENT

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## ABSTRACT

**Objective:** The effects of various hormone replacement therapies on bone mineral density after 2 years of treatment were evaluated in this study.

**Methods:** A total of 138 patients treated with either conjugated equine estrogen or transdermal 17-β estradiol alone or in combination with medroxyprogesterone acetate or dydrogesterone had bone mineral density measurements of the first four lumbar vertebrae by using a Dual X-ray Hologic 1000 quantitative digital radiography densitometer.

**Results:** After 2 years of treatment, a significant increase in spinal bone mineral density was found in all groups. No significant differences were found among 6 treatment groups.

**Conclusion:** There were no differences between estrogen replacement therapies and combined hormone replacement therapies. Progesterone did not have any additional effect on bone mineral density.

**Key Words:** Menopause, Osteoporosis, Bone mineral density, Hormone replacement therapy, Conjugated equine estrogen, Transdermal estradiol, Dydrogesterone, Medroxyprogesterone acetate

## INTRODUCTION

The efficacy of hormone replacement therapy (HRT) in preventing bone loss and osteoporotic fractures is now well established (1-4). In previous studies, estrogen has been shown to decrease osteoporosis in both cortical and trabecular bones by approximately 50-60%. However, the effects of progestrone on bone mineral density (BMD) are controversial.

In the literature, the efficacy of oral and transdermal administration of estrogens in cyclic combination with several progestogens has been demonstrated. However no data, comparing the effects of oral estrogen and transdermal estrogen (TDE2) applied alone or in continuous combination with progestogens on BMD, are available in the literature.

This 2 year prospective study was carried out to assess and to compare the changes in spinal BMD in postmenopausal women treated with conjugated equine estrogen (CEE) or transdermal 17-β estradiol either applied alone or in continuous combination with medroxyprogesterone acetate (MPA) or dydrogesterone (DD).

## MATERIALS AND METHODS

**Patients:** This study was carried out prospectively in menopause department at Dr. Zekai Tahir Burak Women's Hospital. A total of 180 healthy women who had entered menopause 1 to 12 years ago requested hormone replacement therapy (HRT) were recruited among symptomatic patients. Patients gave their informed consent to the study before admission. Postmenopausal status was confirmed by high levels of gonadotropins. All women were within 20% of ideal body weight. Systemic and pelvic examination were done at admittance. None of the patients was taking drugs or suffering from medical disorders known to affect bone metabolism. Women with excessive cigarette consumption (5/day) were excluded. Of 180

patients, 50 who had had hysterectomy in perimenopausal years were divided into 2 different hormone replacement therapy with only estrogen, and patients who had intact uterus received one of the cobined hormone replacement therapies listed below. Patient selection for each group was done randomly, but it was not blinded neither to the physicians nor to the patients.

**Drugs:** Patients were divided into 6 treatment groups as follows:
1) CEE 0.625 mg/day and MPA 2.5 mg/day (n= 33),
2) CEE 0.625 mg/day and DD 10 mg/day (n= 32),
3) Transdermal 17-β estradiol 0.05. mg/day and MPA 2.5 mg/day (n= 32),
4) Transdermal 17-β estradiol 0.05. mg/day and DD 10 mg/day (n= 33),
5) Transdermal 17-β estradiol 0.05 mg/day (n= 25),
6) CEE 0.625 mg/day (n= 25),

**Trial compliance:**
Of 180 women, 138 completed the study. Ninety-eight women were recruited to 4 groups of combined HRT, while 40 patients who had hysterectomy were recruited to 2 groups of estrogen replacement therapy (ERT). All dropouts took place in the second year of the study. Twenty-four women left the study due to socioeconomical reasons. Eighteen left because of side effects.

**Methods:**
Clinical history, height, weight and body mass index (BMI) were recorded at the beginning of the study. Physical and gynecological examinations, including cytological and histopathological tests, and the examination of breast were done. Mammography, bone mineral densitometry, ultrasonography were obtained as a part of initial examination. Routine hematological and biochemical tests (Complete blood count, urine analysis, serum calcium, phosphate, creatinine, liver and kidney function parameters) were done to exclude medical disorders. patients were followed at 3 or 6 month intervals, but only the initial and 2 year treatment values of bone mineral density (BMD) were included into the study.

**BMD**
The BMD at the lumbar spine was measured by using a Dual X-ray Hologic 1000 quantitative digital radiography densitometer (Hologic Inc. U.S.A.). The coefficient of variation calculated by using a spinal phantom daily was 0.5% during the course of the study. BMD values were obtained in the first four lumbar vertebrae and expressed in gm/cm2.

**Statistical analyses**
SPSS for Windows, version 4.01 (SPSS Inc, Michigan, USA) was used for statistical calculations. BMD were evaluated as percentage changes from baseline. Since the distributions were not normal and the number of patients in each group was small, Friedman test was used to evaluate whether the groups differed in respect to longitudinal changes in BMD. Wilcoxon test was used to evaluate the difference in BMD levels between, before and after the treatment in each group. The percent change in BMD was calculated according to the formula: (BMD initial-BMD 2nd year)/BMD initial.

Kruskall-Wallis analysis was used to compare differences between groups in terms of percent change in BMD, age, the duration of menopause and BMI. Values were given as mean±standard deviation. A limit of 5% was accepted as the significance level.

## RESULTS

Baseline demographic data were given in Table I. These 6 groups were found similar in regard to age, menopausal duration and BMI ($p>0.05$). The initial and the second year treatment BMD values were shown in Table II. The initial BMD values were found to be similar in 6 treatment groups ($p>0.05$). After 2 years of treatment, significant increases in spinal BMD were observed in all 6 groups (Wilcoxon test). The percent changes in bone density measurements after 2 years of treatment were shown in Table II and no statistically significant difference were found among 6 treatment groups. The combined and the single estrogen treatment regimens were observed to be equally effective in protecting bone mineral density.

## DISCUSSION

Estrogen effects bone metabolism directly by its receptors on the osteoblasts (5) or indirectly by some factors like vitamin D, IGF-I, GH, TGF. Likewise, progesterone has been shown to decrease bone resorption via its receptors on the bone cells or by acting as a glucocorticoid antagonist (6,7)

In several studies, the minimum dose to prevent spinal and femoral bone mineral content has been reported as 0.625 mg/day and 0.05 mg/day for CEE and TDE2 respectively (8,9) CEE and TDE2, applied in these indicated dosages, showed a significant increase in BMD by 3-5% per year, compared with a 2-4% per year decrease in the control group (10,11). In addition to this, the efficacy of CEE and TDE2 on spinal and femur bone has been found to be similar (11). In this study, the increase over baseline BMD measurements at the end of 2 years of treatment with CEE and TDE2 was observed as 3.4% and 3.8%, ($p>0.05$) respectively, which were consistent with other reports.

In the literature, the efficacy of several combined hormone regimens were investigated. It has been reported that oral estrogen or transdermal estrogen, administered in a cyclic fashion combined with MPA, showed a significant increase in BMD in a range between 0.88% and 5.3% (7,12). In our series, continuous application of MPA and DD, combined with CEE or TDE2, showed a significant increase in BMD that ranged between 3.6% and 5.1%.

In recent years, the addition of progestogens to estrogens and the difference in efficacy have been vigorously investigated. However, the data are controversial. In some reports, the addition of progesterone by its anti-resorptive effect (13) was expected to act synergistically. Progesterone also has been reported to be effective only on cortical bone loss. (7,8). The combination regimen had been reported to be different from estrogen alone. The addition of MPA to CEE resulted in a 26% increase in BMD in 12 months compared with CEE applied alone (14). In contrast, in the other reports (15,16), the efficacy of progesterone for maintenance of BMD had been demonstrated to be unimportant. In our series, no differences were found between combined hormone and estrogen therapy groups in terms of preventing spinal bone loss.

In conclusion, the results of this study confirmed that hormone replacement therapy had a significant preventive effect on postmenopausal osteoporosis. The efficacy of estrogen and progesterone on BMD was observed to be independent of estrogen and progesterone types and therapeutic modalities. Moreover, we did not observe any difference between combined hormonal treatment and estrogen replacement treatment.

**Table I :** Demographic data of 6 different hormone replacement therapy groups.

| | Age* (years) | Duration* (range) (years) | BMI* ($gr/cm^2$) |
|---|---|---|---|
| **Group 1 (n=33)** | 48.25 ± 6.46 | 4.28 ± 3.34 (3-11) | 26.25 ± 3.00 |
| **Group 2 (n=20)** | 51.15 ± 6.05 | 3.22 ± 2.46 (3-9) | 26.49 ± 3.21 |
| **Group 3 (n=23)** | 49.31 ± 5.45 | 3.04 ± 2.36 (2-10) | 26.46 ± 2.97 |
| **Group 4 (n=22)** | 48.27 ± 5.14 | 2.73 ± 2.23 (2-8) | 26.91 ± 3.48 |
| **Group 5 (n=22)** | 48.00 ± 6.39 | 3.91 ± 3.11 (3-10) | 27.02 ± 4.48 |
| **Group 6 (n=18)** | 48.44 ± 6.27 | 4.33 ± 3.16 (3-9) | 27.32 ± 3.57 |

* Kruskal Wallis analysis, no significant difference

**Table II :** The BMD at the initial and at the second year and the percent change in study groups

| | BMD initial ($gr/cm^2$) | BMD* at 2nd year ($gr/cm^2$) | %† change |
|---|---|---|---|
| **Group 1 (n=33)** | 0.894 ± 0.087 | 0.937 ± 0.082 ‡ | 5.07 ± 5.40 |
| **Group 2 (n=20)** | 0.842 ± 0.121 | 0.869 ± 0.109 ‡ | 3.61 ± 3.39 |
| **Group 3 (n=23)** | 0.892 ± 0.097 | 0.927 ± 0.093 ‡ | 4.58 ± 8.64 |
| **Group 4 (n=22)** | 0.907 ± 0.103 | 0.943 ± 0.129 ‡ | 3.98 ± 7.35 |
| **Group 5 (n=22)** | 0.877 ± 0.154 | 0.906 ± 0.135 ‡ | 3.85 ± 5.89 |
| **Group 6 (n=18)** | 0.900 ± 0.128 | 0.925 ± 0.103 ‡ | 3.41 ± 6.85 |

* Friedman test, dependent variables for 3 or more groups, $p>0.05$

† Kruskall Wallis analysis, no significant difference in change of BMD between 6 groups

‡ Wilcoxon $p<0.05$ for all groups

## REFERENCES


1. Lindsay R, Hart DM, Aitken JM, Mac Donald EB, Anderson JB, Clarke AC. Longterm prevention of postmenopausal osteoporosis by oestrogen. Evidence for an increased bone mass after delayed onset of oestrogen treatment Lancet 1976:1 (7968);1038-1041.
2. Lindsay R, Hart DM, Maclean A, Clark AC, Kraszewski A, Garwood J. Bone response to termination of oestrogen treatment. Lancet 1978:1 (8078);1325-1327.
3. Nachtigall LE, Nachtigall RH, Nachtigall RD, Beckman EM. Estrogen replacement therapy I. A 10 year prospective study in relationship to osteoporosis. Obstet Gynecol 1979;53:277-281.
4. Weiss NS, Ure CL, Ballard JH, Williams AR, Daling JR. Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogens. N Eng. J Med 1980;303:1195-1198.
5. Eriksen EF, Colvard DS, Berg NJ, Graham ML, Mann KG, Spelsberg TC, Riggs BL. Evidence of estrogen receptors in normal human osteoblast-like cells. Science 1988;241:84-86.
6. Manolagas SC, Anderson DC. Detection of high affinity glucocorticoid binding in rat bone. J Endocrinol 1978;76:379-380.
7. Gallagher JC, Kable WT, Goldgar D. Effect of progestin therapy on cortical and trabecular bone: Comparison with estrogen. Am J Med 1991;90:171-178.
8. Prior JC. Progesterone as a bone trophic hormone. Endocr Rev 1990;11:386-398.
9. Lindsay R, Hart DM, Clark DM. The minimum effective dose of estrogen for prevention of postmenopausal bone loss. Obstet Gynecol 1984;63:759-763.
10. Adami S, Suppi R, Bertoldo F, Rossini M, Residori M, Maresca V, Lo Cascio V. Transdermal estradiol in the treatment of postmenopausal bone loss. Bone Miner 1989;7:79-86.
11. Stevenson JC, Cust MP, Gangar KF, 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;336:265-269.
12. Lufkin EG, Wahner HW, O'Fallon WM. Hodgson SF, Kotowicz MA, Lane AW, Judd HL, Caplan RH, Riggs BL. Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med 1992;117:1-9.
13. Raisz LG. Local and systemic factors in the pathogenesis of osteoporosis. N Engl J Med 1988;318:818-828.
14. Roof BS. Treatment of postmenopausal osteoporosis. Ann Intern Med 1987;106:780.
15. Riis BJ, Thomsen K, StrfØm V, Christiansen C. The effect of percutaneous estradiol and natural progeterone on postmenopausal bone loss. Am J Obstet Gynecol 1987;156:61-65.
16. Whitehead M, Lobo RA. Consensus Conference: progestogen use in postmenopausal women. Lancet 1988;2 (November 26):1243-1244.