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HORMONE REPLACEMENT THERAPY INCREASES TRABECULAR AND CORTICAL BONE DENSITY IN OSTEOPOROTIC WOMEN

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Summary Twenty five postmenopausal Caucasian women with established osteoporosis or severe osteopenia were treated with continuous combined estrogen/progesterone (2 mg 17 β estradiol and 5 mg medroxiprogesterone) and 1000 mg of calcium daily. The mean age of the patients was 57 ± 6 years (range 44 to 69 years), and the average postmenopausal interval was of 10.7 ± 4.2 years. The bone mineral density (BMD) of the lumbar spine and proximal femur was determined using DXA densitometer at baseline, 12 and 24 months of treatment. Serum and urine measurements were done at baseline and 12 months. After 24 months of treatment bone mineral density increased at the trochanter 10.2% $p < 0.001$, lumbar spine 9.6% $p < 0.001$, Ward's triangle 8.6% $p < 0.005$ and femoral neck 5.7% $p < 0.001$ in comparison to basal levels. In the first year of treatment serum alkaline phosphatase and urinary hydroxiproline diminished significantly in comparison to basal levels ($p < 0.001$, for both). In conclusion, this study indicates that continuous combined estrogen progesterone therapy decreases bone turnover and increases BMD of the spine, femoral neck and trochanter in established osteoporosis.

Key words: estrogen, osteoporosis, bone mineral density

Estrogen administration prevents postmenopausal bone loss in early menopause and it has been observed to be also effective in women up to 70 years of age[1-5] Thus, the effect of estrogen therapy in osteoporosis prevention has been well-documented, and their use has increased substantially over the past decade[6], but there are few studies in patients with established osteoporosis.[7-10] The doses and therapeutic regimes of these studies were different and in only three reports the patients received a continuous estrogen/progesterone treatment[8-10]

The objective of this study was to determine the effect of continuous administration of estradiol and progestine on the bone mineral density (BMD) of the lumbar spine and proximal femur during treatment and biochemical bone turnover parameters in patients with established osteoporosis.

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Material and Methods

Patients

Twenty five postmenopausal Caucasian women with osteoporosis or severe osteopenia were recruited for the study. Patients with secondary osteoporosis or other significant medical conditions that contraindicate the use of estrogens were excluded.

We considered: 1) osteoporosis: patients with atraumatic vertebral or hip fractures. 2) severe osteopenia: patients with BMD below the fracture threshold established at the 90th percentile of vertebral osteoporotic patients (see below).

The mean age of the patients was 57 ± 6 years (range 44 to 69 years), average postmenopausal interval was 10.7 ± 4.2 years, the mean weight was of 62 ± 7 kg, the mean height was 156 ± 6 cm and the body mass index (BMI) was 26 ± 3. The average age at the beginning of menopause was 46 ± 6 years (range 32 to 55 years). Nine

of the 25 patients had their menopause before or at 45 years of age.

Eleven patients of the seventeen that completed one year of treatment had vertebral fractures, 3 hip fractures and 3 patients had severe osteopenia. Thirteen patients completed two years of treatment: 8 patients had vertebral fractures, 2 patients had hip fractures and 3 had severe osteopenia.

After the initial evaluation all the patients started the treatment with the administration of 1 pill containing 2 mg of 17 β estradiol and 5 mg of medroxiprogesterone. They also received 1000 mg of calcium (Calcio Sandoz Fortísimo) orally during 2 years. Patients consent were obtained orally.

Throughout the study the patients were seen every two months. Weight, height and tolerance of treatment were evaluated. All the patients were followed at regular intervals by their own gynecologists.

Compliance to trial

Of the 25 women who entered the trial, 17 (68%) completed 12 months and 13 (52%) completed 24 months of the study.

Eight women discontinued treatment in the first year: one because a breast tumour (benign) was discovered in the first month of treatment, two because of bleeding during 30 or more days, one because of gastrointestinal intolerance, one had an hemoptysis with no relationship to estrogen treatment and three of them for personal reasons. In the second year, four women discontinued treatment for personal reasons.

Bone mineral density measurement

Bone mineral density of the lumbar spine and proximal femur was determined using a DXA densitometer (Lunar DPX-L) at baseline, 12 and 24 months of treatment.

The coefficient of variation in vitro was determined with an anthropometric standard (Hologic) and it was 0.6% for the anteroposterior lumbar spine. The reproducibility was determined in healthy subjects (20 years old) surveyed on 10 different days. The coefficients of variations were the following: lumbar spine 1.5% and femoral neck 1.5%.

The fracture threshold is represented by the 90th percentile of the BMD of osteoporotic women with vertebral fractures (0.895 g/cm^2) or hip fractures (0.690 g/cm^2) studied previously[11].

Biochemical parameters

Serum and urine biochemical measurements were done at the beginning of the study and 12 months afterwards. The biochemical methods for the different determinations were the following: serum and urinary total calcium were measured by atomic absorption spectrophotometry[12], phosphorus by the colorimetric method of Taussky and Schorr[13] and creatinine by the colorimetric method of Taussky[14]. The alkaline phosphatase was measured by the method of King Armstrong[15] and total urinary hydroxiproline excretion was measured by the colorimetric method of Kivirikko et al.[16]

Statistical analysis

Means and standard deviations were estimated for bone mineral density of the spine and proximal femur, age, weight, height, menopausal age and number of years since menopause. The significance of differences were estimated using Student's t test. The results of the bone mineral density were expressed as Z scores and as for paired samples a percentual increment. The Z score was obtained by dividing the difference between the observed value of the bone mineral density and the mean normal value of the age matched control by the standard deviation about the mean normal value.

Results

Table 1 shows the biochemical results (basal and 12 months). In the first year of treatment serum alkaline phosphatase and urinary hydroxyproline excretion diminished significantly compared to basal levels ($p < 0.001$). Serum calcium, serum phosphorus and urinary calcium did not change during treatment.

Table 2 shows the Z score and the BMD of the spine and proximal femur (neck, Ward's triangle and trochanter). The Z score and the BMD of the spine and trochanter increased significantly during the first year of treatment. In the second year all areas studied increased significantly.

The percentage of increases of BMD in the first year were the following: 6.2% in trochanter, 5.5% in lumbar spine, 2.9% in Ward's triangle and 2.2% in femoral neck. Thirteen patients continued treatment during the second year. The percentages of increase during the second year were the following: 5.9% in Ward's triangle, 4.3% in trochanter, 3.7% in lumbar spine and 3.6% in femoral neck (Figure 1). The mean percentage of changes over the two years of treatment were the following: 10,2% in trochanter, 9.6% in lumbar spine, 8.6% in Ward's triangle and 5.7% in femoral neck.

The adverse effects of the treatment were the following: 6/25 patients experiencied slight uterine

TABLE 1.— *Biochemical parameters ($\bar{X}$ ± 1SD) basal and after 12 months of hormone therapy*

	Calcium (mg/dl)	Phosphorus (mg/dl)	Alkaline Phosphatase (UKA)	Urine Calcium (mg/24hs)	Urine Hydroxyproline (mg/24hs)
Basal	9.5 ± 0.4	3.7 ± 0.4	14.6 ± 4.0	122 ± 44	26.3 ± 9.2
12 months	9.3 ± 0.4	3.4 ± 0.5	10.1 ± 2.8*	154 ± 118	13.5 ± 5.5*
Reference values	8.9 - 10.4	2.6 - 4.4	5 - 16	80 - 250	15 - 40

* $p < 0.001$ compared to basal levels.

TABLE 2.— *Bone mineral density ($\bar{X}$ ± 1SD) and Z score at baseline, 12 and 24 months of hormone therapy.*

	Spine L2 L4 (g/cm^2)	Femoral neck (g/cm^2)	Ward's triangle (g/cm^2)	Trochanter (g/cm^2)
Basal	0.848 ± 0.108	0.741 ± 0.091	0.592 ± 0.097	0.625 ± 0.083
Z SCORE	- 1.8	- 1.2	- 1.4	- 1.1
12 months	0.903* ± 0.104	0.758 ± 0.086	0.610 ± 0.098	0.666* ± 0.079
Z SCORE	- 1.2*	- 1.0	- 1.2	- 0.7*
24 months	0.938+++ ± 0.121	0.786+++ ± 0.092	0.648++ ± 0.096	0.696+++ ± 0.090
ZSCORE	- 0.8+++	- 0.6+++	- 0.7+	- 0.4+++

* $p < 0.001$ 12 months vs basal
+++ $p < 0.001$ ++ $p < 0.005$ +$p < 0.01$ 24 months vs basal

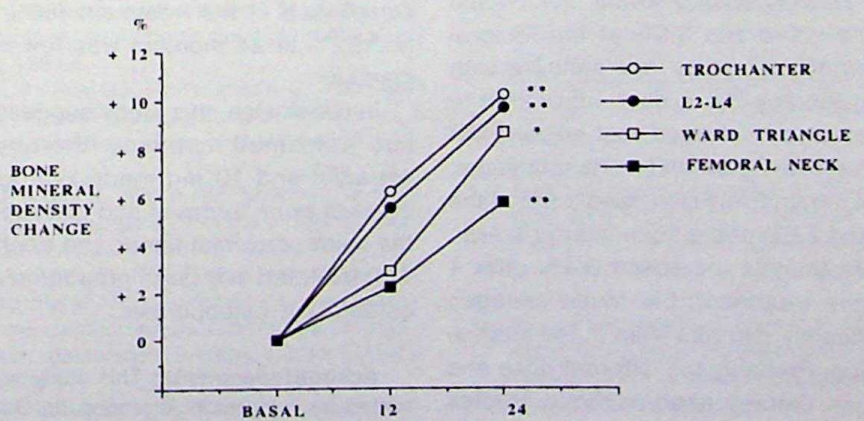

Fig.1.— Percentage of change of the BMD at different skeletal areas during the first and second year of combined estrogen/progesterone therapy. (* $p < 0.005$, ** $p < 0.001$, 24 months versus basal)

bleeding during two or three days in the first months, 11/25 patients developed breast tenderness, 5/25 patients reported hypogastric pain, 1/25 patients weakness and 1/25 patients ankle edema. Body weight increased significantly during treatment (62 ± 6 kg vs 65 ± 8 kg, $p < 0.04$).

Discussion

The results of this study show that two years of treatment with continuous estrogen progestin therapy increased bone mineral density of the lumbar spine and proximal femur in post menopausal osteoporotic women significantly. There are several papers that studied postmenopausal normal woman under hormonal treatment by few studies in women with established osteoporosis.

The present study shows a major gain of bone mass induced by the therapy and it is more evident at the spine and trochanter (predominantly trabecular) and less in the femoral neck (predominantly cortical), although the trend is similar at both sites. Similar results were obtained in few following studies. Civitelli et al[7] showed a net gain of 8,3% at the spine and 2.6% at the femoral mid shaft BMD after one year of hormone replacement therapy. The femoral shaft did not respond as good to estrogen therapy as the lumbar spine did, although in that study the authors used twice the dose of estrogen as we used in our study. Christiansen and Riis[8] observed an increase of 12% at the spine BMD in two years, 8-10% at the ultradistal forearm and 3.5% at the mid shaft forearm and total body after one year of treatment with estrogen therapy identical to the one used in the present study. Lindsay et al [9] showed an increase of 10.6% at the spine and 5.5% at the femoral neck BMD, during two years of treatment with other estrogen therapy but a dose equivalent to our study. Grey et al.[10] showed that spinal BMD increment of 7.1% at 1 year and 8.9% at 2 years. In the proximal femur, BMD increased 2.9% at the femoral neck and 2.5% at the trochanter at 1 year. BMD at Ward's triangle increased 3.4% after 1 year of hormone treatment, but these changes were not significantly different from those seen in the control group. Probably the different dose and type of estrogen therapy used in these studies might account for some difference in the results obtained, but eventually all the treatments increased trabecular and cortical bone.

The axial skeleton is the site where postmenopausal bone loss is more marked and it is a very important area to select in the patients who are at risk for developing osteoporosis[17].

This study demonstrates that estrogen therapy reverses this process by acting at lumbar spine and femoral neck in women with established osteoporosis and for the first time a very significant increment of the femoral great trochanter BMD was observed (see below). The biochemical parameters which assess bone turnover showed a significant decrease during the treatment, similar to that observed by other authors[7-9, 18]

Hip fractures are associated with greater morbidity and mortality. For these reasons the fact that hormone replacement therapy can increase the BMD at the femoral neck and trochanter in established osteoporosis is of particular importance. Of great significance is the 10.2% increment over the trochanter BMD after 2 years of treatment. More than half of the hip fractures occur at the trochanteric level[19]. BMD of the trochanter is significantly diminished in patients with trochanteric fractures compared to controls and in comparison to patients with cervical fractures[20, 21] Thus, presumably the increment of trochanteric BMD might prevent to a significant extent future trochanteric fractures.

The continuous estrogen regime produced few side effects and was generally well tolerated. One of the main concerns of postmenopausal women is weight gain during estrogen/progesterone treatment. This group of patients had a mean increase of 3 kgs during the 24 months of treatment. The compliance of the treatment (68% at 12 months and 52% at 24 months) was lower than in other studies[10].

In conclusion, this study suggests that continuous combined hormone therapy (2 mg 17β estradiol and 10 mg medroxyprogesterone) decreases bone turnover and increases the BMD of the spine, proximal femur and trochanter and it is well tolerated in a large proportion of women with established osteoporosis.

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Resumen

La terapia hormonal de reemplazo aumenta la densidad mineral ósea en mujeres osteoporóticas

Se estudiaron 25 mujeres caucásicas postmenopáusicas con osteoporosis u osteopenia severa. Las mismas recibieron tratamiento continuo con estrógenos y progesterona (2 mg de 17 β estradiol y 5 mg de medroxiprogesterona) y 1000 mg de calcio por día. La edad promedio de la población fue 57 ± 6 años (rango 44 a 69 años), y el promedio del intervalo postmenopausia fue 10,7 ± 4,2 años. La densidad mineral ósea de la columna lumbar y del fémur proximal fue determinada usando un densitómetro DXA. Las mediciones se realizaron antes de iniciar el tratamiento, a los 12 y 24 meses de tratamiento. Las determinaciones bioquímicas séricas y urinarias se realizaron antes de iniciar el tratamiento y a los 12 meses. La densidad mineral ósea se incrementó después de 24 meses de tratamiento en trocánter 10,2% $p < 0,001$, columna lumbar 9,6% $p < 0,001$, triángulo de Ward 8,6% $p < 0,005$ y cuello de fémur 5,7% $p < 0,001$ en comparación con los niveles basales. Durante el primer año de tratamiento la fosfatasa alcalina e hidroxiprolina disminuyeron significativamente en relación a los niveles basales ($p < 0,001$ para ambos). Como conclusión este estudio indica que la terapia continua combinada con estrógenos y progesterona disminuyó el recambio óseo y aumentó la densidad mineral ósea en la columna lumbar, cuello de fémur y trocánter en pacientes con osteoporosis establecida.

References

1. Al-Azzawi F, Hart DM, Lindsay R. Long term effect of estrogen replacement therapy on bone mass as measurements by dual photon absorptiometry. BMJ 1987; 294: 1261-5.
2. Gotfredsen A, Riis BJ, Christiansen C. Total and local bone mineral during estrogen treatment: a placebo controlled trial. *Bone and Mineral* 1986; 1: 167-9.
3. Prough SG, Aksel S, Wiebe RH, Shepherd J. Continuous estrogen progestin therapy in menopause. *Am J Obstet Gynecol* 1987; 157: 1449-53.
4. Luciano AA, Turksoy RN, Carleo J, Hendrix JW. Clinical and metabolic responses of menopausal women to sequential versus continuous estrogen and progestin replacement therapy. *Obstet Gynecol* 1988; 71: 39-43.
5. Christiansen C, Lindsay R. Estrogens, bone loss and preservation. *Osteoporosis Int* 1990; 1: 7-13.
6. Wysowski D, Golden L, Burke L. Use of menopausal estrogens and medroxiprogesterone in the United States, 1982-1992. *Obstet Gynecol* 1995; 85: 6-10.
7. Civitelli R, Agnusdei D, Nardi P, Zacchei F, Avioli L, Gennari C. Effect of one year treatment with estrogens on bone mass, intestinal calcium absorption, and 25-hydroxyvitamin D-1 hydroxylase reserve in postmenopausal osteoporosis. *Calcif Tissue Int* 1988; 42: 77-86.
8. Christiansen C, Riis BJ. 17 β estradiol and continuous norethisterone: a unique treatment for established osteoporosis in elderly women. *J Clin Endocrinol Metab* 1990; 71: 836-41.
9. Lindsay R, Tohme J. Estrogen treatment of patients with established postmenopausal osteoporosis. *Obstet Gynecol* 1990; 76: 290-5.
10. Grey A, Cundy T, Reid I. Continuous combined oestrogen/progestin therapy is well tolerated and increase bone density at the hip and spine in postmenopausal osteoporosis. *Clin Endocrinol* 1994; 40: 671-7.
11. Vega E, Bagur A, Mautalen C. Densidad mineral ósea en mujeres osteoporóticas y normales de Buenos Aires. *Medicina (Buenos Aires)* 1993; 53: 211-6.
12. Trudeau DL, Freie EF. Determination of calcium in urine and serum by atomic absorptiometry (AAS). *Clin Chem* 1967; 13: 101-4.
13. Taussky HN, Schorr E. Microcolorimetric method for determination of inorganic phosphorus. *J Biol Chem* 1953; 202: 675-85.
14. Taussky HN. A microcolorimetric determination of creatinine in urine by the Jaffe reaction. *J Biol Chem* 1954; 208: 853-60.
15. King E, Armstrong AR. A convenient method for determining serum and bile phosphatase activity. *Can Med Assoc J* 1934; 31: 376-80.
16. Kivirikko KI, Laitinen O, Prockop OJ. Modifications of a specific assay for hydroxyproline in urine. *Ann Biochem* 1967; 19: 249-57.
17. Bagur A, Vega E, Mautalen C, Siseles N, Burucúa A. Densidad mineral ósea en el climaterio. Identificación de pacientes con riesgo de desarrollar osteoporosis. *Medicina (Buenos Aires)* 1990; 50: 30-4.
18. Voetberg G, Netelenbos J, Kenemans P, Peters-Muller E, Weijer P. Estrogen replacement therapy continuously combined with four different dosages of dydrogesterone: Effect on calcium and lipid metabolism. *J Clin Endocrinol Metab* 1994; 79: 1465-9.
19. Greenspan S, Myers E, Maitland L, Kido T, Krasnow M, Hayes W. Trochanteric bone mineral density is associated with type of hip fracture in the elderly. *J Bone Miner Res* 1994; 9: 1889-94.
20. Mautalen C, Vega E. Different characteristics of cervical and trochanteric hip fractures. *Osteoporosis Int* 1993; Suppl. 1: S102-4.
21. Vega E, Mautalen C, Gomez H, Garrido A, Melo L, Sahores A. Bone mineral density in patients with cervical and trochanteric fractures of the proximal femur. *Osteoporosis Int* 1991; 1: 81-6.