EFFECT OF ADDING ALENDRONATE TO HORMONE REPLACEMENT THERAPY ON BONE MINERAL DENSITY IN ESTABLISHED POSTMENOPAUSAL OSTEOPOROSIS

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ABSTRACT

Objective: The purpose of this prospective randomized study was to evaluate the impact of adding alendronate to hormone replacement therapy (HRT) in established postmenopausal osteoporosis.

Patients: Forty patients were randomly assigned to receive either 0,625 mg. conjugated estrogen with 2,5 mg. medroxyprogesterone acetate (HRT) alone or HRT combined with 10 mg. alendronate daily for one year. Both groups received a daily supplement of 500 mg. of elemental calcium. Bone mineral density of lumbar spine and femur neck were measured prior to treatment and at the end of one year by dual energy X-ray absorptiometry.

Results: Nineteen patients from alendronate and HRT group, 18 patients from HRT group completed the study. HRT group had an increase in bone mineral density of 7,5±0,02% at lumbar spine ($p<0.01$) and 11,6±0,04% at femur neck ($p<0,001$). Whereas alendronate and HRT group had a mean increase in bone mineral density of 7,8±0,02% at lumbar spine ($p<0.01$) and 17,8±0,02% at femur neck ($p<0.01$). Both treatments were well tolerated.

Conclusions: Both HRT alone and HRT combined with alendronate treatments in postmenopausal osteoporosis appears to increase bone mineral density at spine and femur neck. There is a greater increase in bone mineral density at femur with HRT alendronate combination treatment which did not achieve significance.

Key Words: Alendronate, Hormone replacement therapy, Bone density

INTRODUCTION

Postmenopausal osteoporosis is a common disorder characterized by an increase in bone resorption relative to bone formation with an increased rate of bone turnover (1). It is a common and important cause of morbidity and mortality among postmenopausal women, affecting approximately 28 million individuals in the United States (2). The incidence of hip fractures increases with age, rising from 0.3/1000 to 20/1000 from 45 to 85 years (3). White women have approximately 16% lifetime risk of having hip fracture. Hip fractures alone occur in more than 300.000 women per year in the United States with a mortality of 40.000 women annually and an associated cost of billions of dollars (3).

Postmenopausal hormone therapy has a beneficial impact on the risk of cardiovascular disease, cognitive function, atrophic changes as well as prevention and treatment of osteoporosis

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(4-6). Postmenopausal Estrogen Progestin Interventions (PEPI) (6) trial demonstrated that hormone replacement therapy had a gain of 5% in bone mineral density in spine and 2% in the femur neck compared with a 2% loss in placebo group at the end of three years.

Bisphosphonates are effective in preventing bone loss by inhibiting bone resorption, increasing bone density in both the spine and the hip in normal postmenopausal women (7-11). In women with osteoporosis, alendronate reduced the risk of nonvertebral fractures by 30% and vertebral fractures 90% in the first 3 years of treatment (7). There are numerous studies demonstrating the effectiveness of both HRT and alendronate in the treatment of osteoporosis individually (5-9). However, the literature on the impact of combining alendronate to HRT in the treatment of postmenopausal osteoporosis is very scarce. The purpose of this prospective study was to evaluate the impact of adding alendronate to hormone replacement therapy in established osteoporosis.

METHODS

Forty women at least 3 years postmenopausal and with established osteoporosis (defined as a bone mineral density of the lumbar spine and femur at least 2,5 standard deviation below the mean value in premenopausal women) presented to the Marmara University Hospital, Menopause Clinic were included in this study. Informed consent was obtained from all subjects, and the study was approved by the Institutional Review Board of the Marmara University School of Medicine. None of these patients smoked and there was no history of prior treatment of bisphosphonates, calcitonin or hormone replacement therapy. Women with vitamin D deficiency, Paget's disease, hyperparathyroidism, who were treated with glucocorticoids, who had systemic disease and abnormal renal or hepatic function were excluded from the study.

Subjects were randomly assigned according to 1/1 ratio to receive either 0.625 mg conjugated estrogen with 2.5 mg medroxyprogesterone acetate (Premelle, Wyeth-Ayerst, USA) (HRT) alone or HRT combined with 10 mg alendronate (Fosamax, Merck Sharp&Dohme, New Jersey, USA) daily for one year. Both groups received a daily supplement of 500 mg of elemental calcium. Height and weight of all patients were recorded initially. Patients were recalled at first, third and sixth month to assess drug compliance.

Bone mineral density of L_2 - L_4 lumbar spine and left femur neck were measured by dual energy X ray absorptiometry with use of DPX (Lunar, Madison WI, USA) densitometer prior to treatment and at the end of one year. Technicians who measured bone density were blind to treatment regimes. Coefficients of variation for the densitometer were 1% for the spine and 2.2% for the proximal femur in vivo. Scans were analysed with 1.3 version software.

For statistical analysis, paired t test is used for within group comparisons and Mann Whitney test is used for between group comparisons. P values are two sided.

RESULTS

The baseline characteristics of forty women between the ages of 45 and 67 years are shown in Table I. The treatment groups did not differ significantly in age, years since menopause, body mass index, bone mineral density of spine and femur. Nineteen patients from HRT and alendronate group, 18 patients from HRT group completed the study.

There were significant increases in bone mineral density of the spine and femur neck at 12 months in both HRT and HRT with alendronate group. At the end of one year HRT and alendronate group had increased their bone density 7.8±0.02 percent at lumbar spine ($p<0.01$) and 17.8±0.02 percent at femur neck ($p<0.01$). HRT group had a mean increase in bone mineral density of 7.5±0.02 percent at lumbar spine ($p<0.01$) and 11.6±0.04 percent at femur neck ($p<0.01$) (Figs. I and II). Alendronate and HRT combination treatment produced greater increase in bone mineral density, especially at femur, than HRT alone, but the differences were not statistically significant.

Both alendronate and HRT were well tolerated. Two patients in HRT and alendronate group experienced mild stomach pain. One patient from

HRT group and two patients from HRT with alendronate group complained of breast tenderness, which disappeared within a few months. Five patients (25%) from HRT and 6 patients (30%) from HRT with alendronate group had breakthrough bleeding. Nevertheless only 2 of them, one from each group, discontinued therapy within 3 months due to breakthrough bleeding. One patient from HRT group dropped out because of social reasons.

Table I. Baseline Characteristics of the Study Participants

Chracteristics	HRT and Alendronate Mean	HRT Mean	p
Age	55,6±5,3	54,7±5	NS
Years since menopause	9,1±1,1	10,1±1,2	NS
BMI	24,2±2.8	25±3	NS
Bone mineral density (g/cm2)			
Lumbar spine	0,875±0,08	0,875±0,1	NS
Femur	0,770±0,1	0,767±0,08	NS

* Values are means ± SD
** NS: Non - Significant

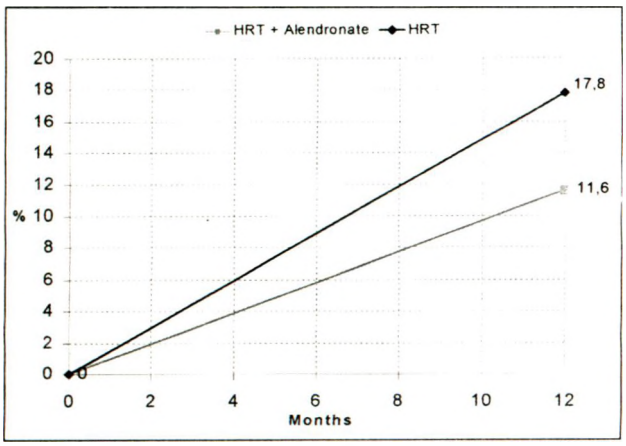

Fig.1.: The percent of change in bone mineral density in femur in both HRT and HRT with alendronate group at the end of one year.

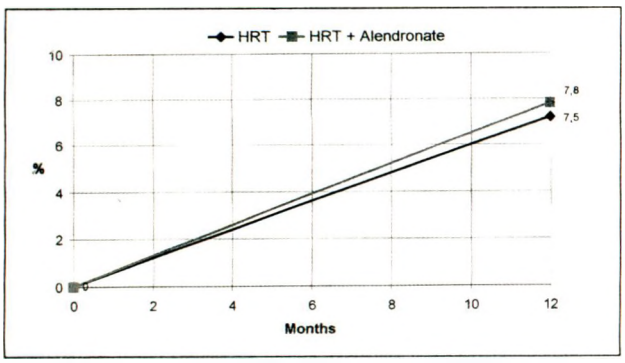

Fig.2.: The percent of change in bone mineral density in spine in both HRT an HRT with alendronate group at the end of one year.

DISCUSSION

The present study demonstrated that both HRT alone and HRT combined with alendronate treatments significantly increased bone mineral densities of spine and femur neck in postmenopausal established osteoporosis. The percent of increase in bone mineral density of the spine at one year is similar in both groups (7.8% vs 7.5%). There is a trend towards a greater increase in bone mineral density of femur at one year with alendronate and HRT treatment which did not achieve significance, (17.8% vs 11.6%).

Estrogen therapy has been the mainstay for the prevention and treatment of postmenopausal osteoporosis (1). A large body of data shows that estrogen either maintains bone or slows bone loss and thereby prevents osteoporotic fractures (1). In the PEPI trial at the end of three years, the women receiving hormone treatment had experienced about a 5% gain in bone mineral density in the spine and 2% in the hip compared with approximately a 2% loss in the placebo group (6). In a 10 year follow up study of women receiving estrogen-progestin treatment therapy, the spinal bone density steadily increased, reaching a level of 13% over baseline after 10 years of treatment (12).

Bisphosphonates are effective in preventing bone loss by inhibiting bone resorption. The first generation of bisphophonates also inhibited bone mineralization and therefore intermittent therapy was necessary. The second generation of bisphosphonates allows bone formation to occur while inhibiting bone resorption. A multicenter randomized placebo controlled trial of alendronate 5 or 10 mg/day for 2 years, 20 or 40 mg/day given for 1 year produced a significant increase in the BMD of the lumbar spine of postmenopausal women (13). In this study, the 10 mg/day dosage produced a significantly greater increase in BMD at the total hip than any other dosage. In a 3 years study, Devogelaer et al (14) found that over 92% of patients receiving alendronate had an increase in spine BMD at year 3 compared with baseline. In another study, Tucci et al (15) found that 94.3% of patients receiving alendronate had an increase lumbar spine BMD of ≥4% and none had a decrease, whereas 57.5% of the patients receiving placebo showed a loss of spine BMD. Liberman et al (7)

showed that, there was 8.8% and 5.9% difference in bone mineral density at spine and femur respectively between alendronate and placebo groups at 3 years. The risk of developing new vertebral fractures amounted to 6.2% in the placebo group versus 3.2% in alendronate group with a relative risk of 0.52. In the FIT study (10), 4432 postmenopausal women with low BMD but without any preexisting vertebral fracture, were randomized to receive either alendronate or placebo. Alendronate treatment reduced the risk of vertebral fractures by 51%. Recently in another study, 1499 women who had been postmenopausal for at least 6 months, received alendronate 2.5, 5 mg/day or placebo for 2 years and 110 received estrogen plus progestin therapy (8). Estrogen plus progestin therapy provoked bone gains after 2 years and were slightly lighter than those in patients receiving alendronate 2.5 mg and 5 mg/day. Placebo group lost bone significantly both in spine and at hip. Both treatment regimens were well tolerated. Breakthrough bleeding was observed in 25% and 30% of the patients in HRT and HRT alendronate combination groups respectively. Nevertheless only 5% of the patients discontinued treatment in each group due to bleeding. Mild stomach pain was experienced in only 2 patients in alendronate group.

Estrogen is effective in both prevention and treatment of postmenopausal osteoporosis, however bone loss resumes immediately after discontinuation of treatment (16). Conversely alendronate accumulates in bone and recirculates so accelerated bone loss is not observed when treatment is stopped (10,12).

Both HRT alone or HRT combined with alendronate treatments, showed significant increases in bone mineral densities of spine and femur neck. There is a trend towards a greater increase in bone mineral density especially at femur with alendronate and HRT combination treatment which did not achieve significance. Combination treatment appears to be a reasonable alternative in treatment. The weak point of this study is small sample size, nevertheless future studies with larger groups will enlighten the impact of adding alendronate to HRT in postmenopausal osteoporosis treatment.

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