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Effects of Combination Therapy of Alendronate and Hormonal Therapy on Bone Mineral Density in Postmenopausal Korean Women: Multicenter, Randomized Controlled Clinical Trial

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This study evaluated the effects of combination treatment with alendronate (ALEN) and hormone therapy (HT) on bone mineral density (BMD) in postmenopausal Korean women. This multicenter, randomized, controlled clinical trial enrolled 344 postmenopausal women with low BMD. The women received HT (0.625 mg/day of conjugated equine estrogen and 2.5 mg/day of medroxyprogesterone acetate) alone or in combination with ALEN (10 mg/day) for 1 year. Changes in BMD and biochemical markers of bone turnover were evaluated. Data from 203 women (HT alone, 99; combination treatment, 104) who completed this study were analyzed. BMD at the lumbar spine and total hip increased significantly in both treatment groups after 1 year. There were no significant differences between HT alone vs. the combination of ALEN and HT in mean BMD increase at the lumbar spine (6.9% vs. 7.9%) and total hip (3.7% vs. 3.8%). Combined therapy suppressed serum osteocalcin and urinary deoxypyridinoline to a greater extent than HT alone. In conclusion, compared to HT alone, combination treatment with ALEN and HT for 1 year did not offer a benefit in BMD in postmenopausal Korean women with low BMD.

Keywords: Osteoporosis; Bone Mineral Density; Combination Therapy; Alendronate; Hormone Therapy

INTRODUCTION

Estrogen insufficiency is the main cause of involutional osteoporosis in women. Increased bone turnover and an imbalance between bone resorption and formation results in accelerated loss of bone mass in early postmenopausal women. The ensuing secondary hyperparathyroidism and decrease in bone formation are also associated with estrogen deficiency (1).

Hormone therapy (HT) prevents bone loss, improves bone mineral density (BMD) (2,3), and reduces the incidence of vertebral and non-vertebral fractures in both osteopenic and osteoporotic women (4-6). HT is an established treatment for osteoporosis in postmenopausal women. Bisphosphonate, which inhibits osteoclast activity and decreases bone turnover at sites of bone resorption, is another established treatment for osteoporosis (7,8). However, the mechanisms of actions for bone health are somewhat different; whereas bisphosphonate predominantly acts on osteoclasts (9), estrogen also has effects on osteoblasts and osteocytes (10). It has been suggested that estrogen might have an anabolic effect on bone (11,12), and also has favorable effects on bone quality (13).

Suboptimal or no response to treatment is an important issue in clinical practice that may result from poor adherence to treatment, co-morbidities, insufficient calcium and vitamin D, malabsorption, erroneous dose or interval, or lack of drug efficacy (14). Indeed, 20%–30% of postmenopausal women may experience bone loss even with HT (15). Therefore, in some situations, such as severe osteoporosis or failure to achieve an optimal response to either HT or bisphosphonate alone, additional benefit from a combination of the 2 treatments might be expected because of their different mechanisms

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of action. Indeed, the combination of HT and bisphosphonate produced a greater increase in BMD over either treatment alone in several studies (16-19). However, data on the effect of combination therapy are mixed (16-23). Moreover, the efficacy of the combined therapy for fracture prevention has not yet been proven.

Ethnic differences in treatment response might exist. As Asians usually have lower BMD than Caucasians, mainly due to their smaller bone size (19), osteoporosis treatment could produce stronger effects on BMD in Asian women than in Caucasians. To date, few randomized studies combining bisphosphonate with HT have been reported in Asian countries (24). In a recent study, no difference in BMD gain was reported by the addition of alendronate (ALEN) for 1 year to ongoing HT before ALEN use in Korean women (25). The current study was conducted to evaluate the effects of combining ALEN with HT in postmenopausal Korean women who had low BMD.

MATERIALS AND METHODS

Study participants

A total of 344 postmenopausal women (mean age, 59.1 years) participated in this multicenter clinical trial conducted at 5 university hospitals from September 1999 to June2003. Women were considered postmenopausal if duration of amenorrhea was ≥ 12 months or if the serum level of follicle stimulating hormone was > 40 IU/L.

Only women with BMD at least 2 standard deviations (SD) lower at the lumbar spine or total hip compared with the mean bone mass of normal young Korean women by dual-energy X-ray absorptiometry (DXA) were considered for inclusion. Women were excluded from the study if they had a history of diseases or if they were taking medications (including HT or ALEN) that might affect bone metabolism within 1 year before enrollment. Women were also excluded if they had contraindications for ALEN or HT.

Study design

Patients were randomly assigned to receive either HT alone (173 patients) or HT + ALEN (171 patients) for one year in a 1:1 ratio. The allocation of treatment was based on randomization codes created by SAS program (SAS Institute, Cary, NC, USA) within the same study center. No other specific randomization stratification factor was applied. All women received 0.625 mg/day of conjugated equine estrogen (CEE; Pfizer Inc., Seoul, Korea) and 2.5 mg of medroxyprogesterone acetate (MPA; Pfizer Inc.). In the combination group, 10 mg/day of ALEN (Fosamax; MSD, Seoul, Korea) was given immediately after the patient woke up. Participants were educated to take ALEN with plenty of plain water, and to maintain an upright position for at least 30 minutes afterwards. Calcium supplementation ($CaCO_3$, 500 mg bid) and regular exercise were also encouraged.

The primary end point for efficacy was the change in lumbar spine BMD. The secondary end point was the change in total hip BMD and biochemical markers of bone turnover.

BMD

BMD was measured at the second to fourth vertebrae of the lumbar spine and at the hip by DXA at each hospital. Bone densitometry was performed at study enrollment and after 12 months of treatment using the same device.

Biochemical markers

Samples were collected at 0, 3, 6, and 12 months in the morning after an overnight fast. As a marker of bone formation, serum osteocalcin (OC) was measured using an enzyme-linked immunosorbent assay (ELISA) kit. Urinary deoxypyridinoline (DPD), a marker of bone resorption, was assessed using an ELISA kit and corrected for creatinine level.

Statistical analysis

Statistical analyses were performed using Predictive Analytics SoftWare (PASW) statistics 20 (SPSS Inc., Chicago, IL, USA). At least 224 patients were required to achieve a power of 80% and an alpha of 0.05 to detect a 1.5% difference in the mean change in BMD at the lumbar spine. Considering dropping out of the study, it was initially aimed to enroll a total of 350 participants (70 for each center) into the study.

Data are shown as the mean ± SD or number (percent). T-tests, χ^2 test, or Fisher exact test were used to compare the baseline characteristics, the proportion of participants with no BMD increase, and adverse effects. Changes in BMD within and between the groups were evaluated by paired or Student's t-tests, respectively. In addition, t-tests and repeated-measures analysis of variance were used to evaluate the changes in bone turnover markers within and between the groups. Correlations of changes in BMD between the 2 groups were evaluated using regression analysis after adjusting for age, reproductive history, body mass index (BMI), history of HT, and baseline BMD. A P value < 0.05 was considered statistically significant.

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of Samsung Medical Center (No. 1999-12-04). Informed consent was submitted by all subjects when they were enrolled. This trial was not registered because the registry system was not available when it was investigated.

RESULTS

Characteristics of study participants

Among 344 postmenopausal women who were enrolled, 203 (59%) completed this study including 99 in the HT alone group

(57.2%) and 104 in the HT and ALEN group (60.8%) (Fig. 1). The dropout rate was comparable between groups. The baseline characteristics of the participants are shown in Table 1. There was no statistical difference in any of the variables analyzed between the 2 groups, and the characteristics were not different between women who dropped out and those who completed treatment. We analyzed data for women who completed the study protocol.

BMD changes

BMD at the lumbar spine and total hip increased significantly after 1 year of treatment in both the HT alone and combination group. The 2 groups did not show a statistically significant dif-

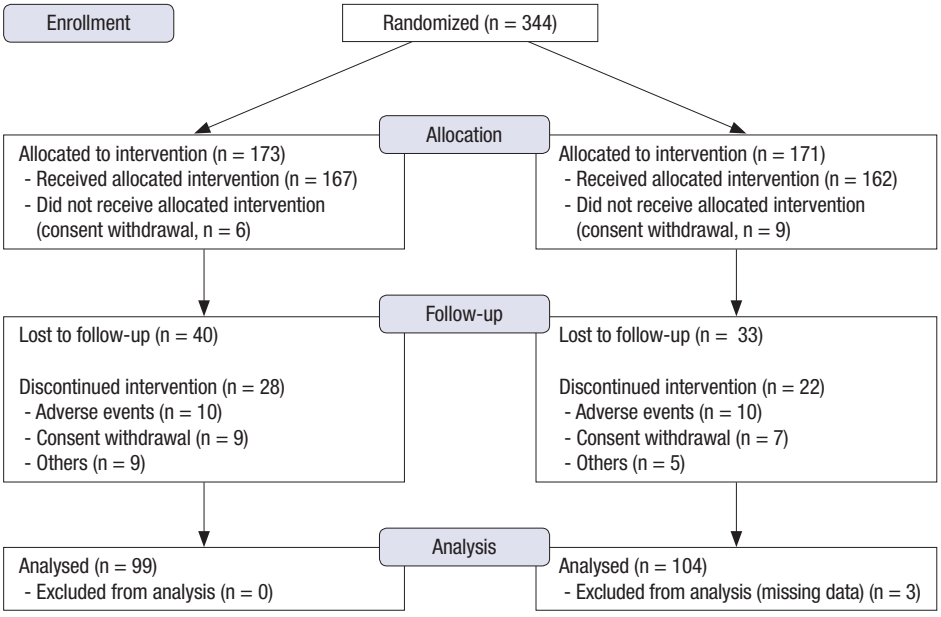

Fig. 1. Flow diagram of the study.

Table 1. Baseline characteristics of participants

Characteristics	Complete (n = 203)			Drop-out (n = 142)		
	HT alone (n = 99)	HT + ALEN (n = 104)	*P*	HT alone (n = 74)	HT + ALEN (n = 68)	*P*
Age, yr	58.8 ± 5.9	59.4 ± 6.4	0.502	58.7 ± 7.2	60.5 ± 6.1	0.256
Age at menarche, yr	16.5 ± 2.0	16.8 ± 2.0	0.565	16.7 ± 1.5	16.4 ± 1.6	0.459
Age at menopause, yr	49.2 ± 4.3	48.6 ± 4.8	0.346	49.8 ± 3.9	49.0 ± 6.0	0.376
Years since menopause, yr	9.3 ± 6.7	10.4 ± 6.9	0.270	8.8 ± 7.9	11.5 ± 9.0	0.199
Parity, No.	3.2 ± 1.6	3.2 ± 1.4	0.941	3.3 ± 1.3	3.4 ± 1.3	0.688
BMI, kg/m^2	23.8 ± 2.9	23.2 ± 3.1	0.235	23.7 ± 3.2	24.8 ± 2.6	0.156
Type of menopause			0.330			0.588
Surgical	15 (15.2)	11 (10.6)		11 (14.9)	8 (11.8)	
Natural	84 (84.8)	93 (89.4)		63 (85.1)	60 (88.2)	
History of HT			0.402			0.964
Never	80 (80.8)	79 (76.0)		59 (79.7)	54 (79.4)	
Ever	19 (19.2)	25 (24.0)		15 (20.3)	14 (20.6)	
BMD, g/cm^2						
Lumbar spine 2–4	0.790 ± 0.085	0.776 ± 0.095	0.284	0.783 ± 0.136	0.792 ± 0.110	0.671
Total hip	0.755 ± 0.109	0.728 ± 0.131	0.127	0.734 ± 0.137	0.745 ± 0.106	0.702
T-score of BMD						
Lumbar spine 2–4	–2.6 ± 0.7	–2.7 ± 0.8	0.367	–2.7 ± 1.1	–2.7 ± 1.0	0.825
Total hip	–1.4 ± 0.7	–1.6 ± 0.8	0.089	–1.4 ± 1.0	–1.5 ± 0.8	0.651
Bone turnover marker						
OC, ng/mL	17.1 ± 12.1	15.2 ± 10.4	0.251	14.2 ± 10.6	15.0 ± 9.2	0.659
DPD, nM/mMCr	7.9 ± 3.2	7.9 ± 3.3	0.998	8.7 ± 5.7	8.4 ± 4.3	0.723

Data are presented as mean ± SD or number of participants (%).
HT = hormone therapy, ALEN = alendronate, BMI = body mass index, BMD = bone mineral density, DPD = deoxypyridinoline, OC = osteocalcin, SD = standard deviations.

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ference in the mean change in BMD at the lumbar spine (6.9% vs. 7.9%) and the total hip (3.7% vs. 3.8%) (Fig. 2). Age, baseline BMD, years since menopause, and history of HT did not affect the change in BMD after adjusting for variables, regardless of whether the women received ALEN (data not shown).

The proportion of participants with no BMD increase was similar in both groups, regardless of site (Table 2). When BMD response was stratified on baseline age or T-score using a cutoff of 60 or –2.5, respectively, the mean BMD change and the proportion of subjects with a reduction in BMD did not differ between the 2 groups at all sites tested (data not shown).

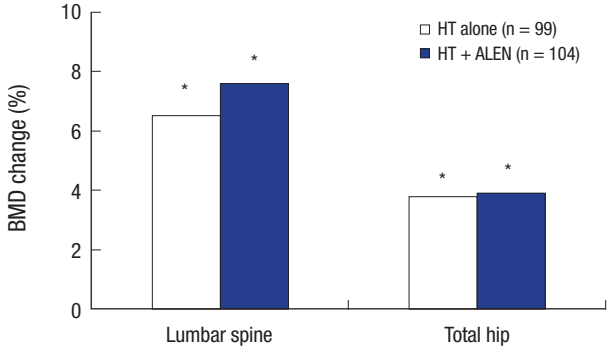


Fig. 2. Mean percent changes in BMD. Differences between the 2 groups were not significant.
BMD = bone mineral density, HT = hormone therapy, ALEN = alendronate.
*$P < 0.05$ vs. baseline.

Table 2. Proportion of participants with no BMD increase in the 2 treatment groups

Sites	HT alone (n = 99)	HT + ALEN (n = 104)
Lumbar spine	12 (12.1)	11 (10.6)
Total hip	17 (17.2)	22 (21.1)
Either	27 (27.3)	29 (27.9)

Data are presented as number of participants (%); There was no statistical difference between groups.
BMD = bone mineral density, HT = hormone therapy, ALEN = alendronate.

Changes in biochemical markers of bone turnover

The baseline levels of markers of bone turnover were comparable between the 2 groups (Table 1). Fig. 3 presents mean values of serum OC and urinary DPD at each time point. Levels of bone formation and resorption markers decreased significantly compared with the baseline values with both treatments. The pattern of change over time was similar between the 2 treatments for both markers, but the combination therapy suppressed serum OC and urinary DPD to a significantly greater extent than HT alone at each time point. When bone turnover markers were stratified again on baseline age or T-score using the same cutoffs as described above, women aged ≥ 60 years or those with T-score > –2.5 showed similar suppression of serum OC and urinary DPD after treatment in both groups (data not shown).

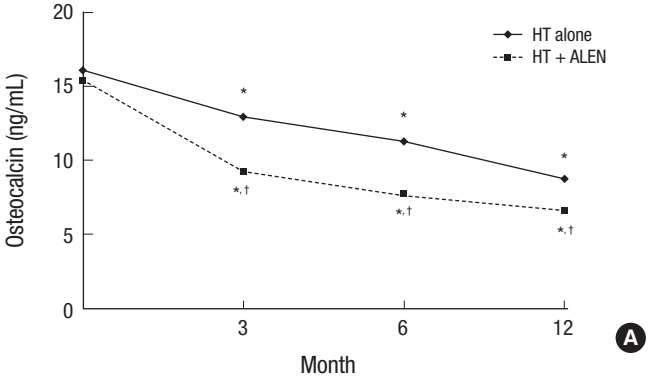
Adverse effects

Table 3 presents adverse effects in study participants according to the treatment regimen. The total number of subjects who experienced any adverse effects and the distribution of adverse

Table 3. Adverse effects of treatment on participants

Adverse effects	HT alone (n = 99)	HT + ALEN (n = 104)
Participants with any adverse effects	30 (30.3)	36 (34.6)
Problems experienced (multiple choices)		
Mastalgia	11 (12.2)	13 (12.5)
Vaginal spotting/bleeding	10 (11.1)	8 (7.7)
GI trouble	5 (5.5)	11 (10.6)
Musculoskeletal pain	3 (3.3)	3 (2.9)
Fracture	0 (0.0)	2 (1.9)
Others	20 (20.2)	25 (24.0)

Data are presented as number of participants (%); There was no statistical difference between groups.
HT = hormone therapy, ALEN = alendronate, GI = gastrointestinal.



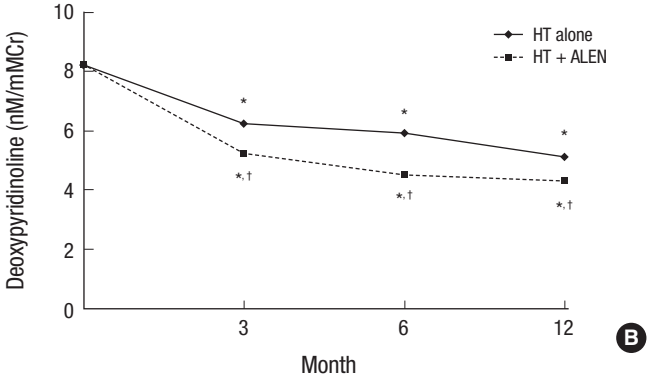


Fig. 3. Mean changes in biochemical markers of bone turnover. (**A**) OC, (**B**) DPD. Combination therapy suppressed serum levels of osteocalcin and urinary DPD by a significantly greater extent than HT alone at each time point.
OC = osteocalcin, DPD = deoxypyridinoline, HT = hormone therapy, ALEN = alendronate.
*$P < 0.05$ vs. baseline; †$P < 0.05$ vs. HT alone.

effects in both groups were similar.

DISCUSSION

This study demonstrated that concomitant treatment with HT and ALEN for 1 year did not provide a significant extra benefit in BMD over HT alone in postmenopausal Korean women with low BMD. However, the levels of bone turnover markers were reduced to a significantly greater extent in the combination therapy compared to HT alone.

Our finding is consistent with previous negative studies reporting a comparable BMD response with 1-year combination therapy and hormonal therapy alone (16-19). However, other studies demonstrated a positive effect of combined therapy on BMD (22-24). Since the HT regimen (CEE + MPA) used in the current study was similar to those used in the previous studies (17,23), the BMD response to HT is one possible explanation for differences across the studies. In the present study, the increase in BMD after HT alone for 1 year at the lumbar spine (7%) or hip (3.8%) was greater than that in the positive studies (2.5%–4% at the lumbar spine and 2%–3% at the hip) (22-24), but similar to that of negative studies (16-19). Interestingly, BMD changes at 1 year of combination therapy in this study are similar to those achieved in the positive studies described above. When the BMD increase induced by HT alone is high, further BMD gain by the addition of ALEN to HT might be expected to be minimal.

The reason for different responses to HT, even among Asian women, is not clear and further studies are warranted. In fact, the magnitude of BMD increase by HT alone in the present study was comparable to that in previous reports in osteoporotic (26) and healthy (27) postmenopausal Korean women.

In addition, progestogen could have favorable independent effects on bone metabolism (3,28,29). The addition of MPA to CEE significantly increases spine BMD compared to CEE alone (3). In the present study, MPA was given continuously with CEE, contributing to the better BMD response to HT.

Age, initial BMD, and previous hormone use are significant variables affecting BMD response to HT (2). These variables, however, had no influence in our study. This might be explained in part by the inclusion of study subjects with low BMD. The proportion of participants with no BMD increase in HT group in this study was within the range previously reported (15), and the proportions were not different between the 2 groups. Although a suboptimal response might be a possible indication of combination therapy, our results suggest that improvement of an inadequate response to HT by 1-year addition of ALEN should not be expected.

As BMD continues to increase at least for several years with either estrogen or bisphosphonate therapies, the study duration of the current study might be too short. Although the duration of 1 year might be useful for evaluating rapid responses to osteoporosis treatment, it might take longer to get final responses. Indeed, positive responses were observed only after 2 to 3 years of ALEN in combination with HT (16,17,30). Of note, the type of bisphosphonate may also be an important factor; for example, the increase in BMD at the femoral neck was reported to be greater with 1-year combination therapy using risedronate than with HT only (18).

Bone turnover markers are associated with changes in bone mass and fracture risk in postmenopausal women with osteoporosis (31-33). In the current study, HT reduced levels of both DPD and OC by as early as 3 months in women with low BMD, which confirms previous reports (17,26). In addition, the combination therapy suppressed the bone turnover markers to a greater degree than HT alone from 3 months of treatment onward, in agreement with most previous studies (17,24).

There is a growing concern over adverse events such as osteonecrosis of jaw or atypical subtrochanteric fracture due to oversuppression of bone turnover with combination therapy. However, previous studies showed that bone markers remained within the normal premenopausal range with combination therapy (34) and the addition of HT to etidronate prevented the bone mineralization defects associated with etidronate (35). Moreover, no impairment of bone quality by combining bisphosphonates with HT was found from bone morphometry data (34). Importantly, improvements in the hip structure analysis indices were significantly greater with combination therapy than with either HT or ALEN monotherapy (36), which suggests a mechanism for potential fracture reduction. From these aspects, long-term data including fracture risk and adverse events are necessary to define the exact role of combination therapy.

This study has several limitations. First, our study was not designed to evaluate fracture risk and bone quality. Although combination therapy is expected to provide an additional fracture reduction from a logistic model (37), to date no study on combination therapy has been powered to detect a reduction in the risk of fracture. Second, the dropout rate in the present study was relatively high. Third, an ALEN-only arm was not included in the study, so it is not possible to separate the effect of combined therapy from that of ALEN alone. In addition, we did not measure and control for serum vitamin D levels.

In conclusion, 1-year combination therapy of ALEN and HT did not increase bone mass over HT alone in postmenopausal Korean women with low BMD. Further studies are needed to evaluate long-term changes in BMD and fracture risks when bisphosphonate is added to HT.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

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AUTHOR CONTRIBUTION

Conceptualization: Yoon BK, Choi YM. Data curation: Yoon BK, Lee DY. Formal analysis: Lee DY. Funding acquisition: Yoon BK, Choi YM. Investigation: Yoon BK, Lee DY, Park MC, Cho SH, Park HM, Choi YM. Writing - original draft: Yoon BK, Lee DY. Writing - review & editing: Yoon BK, Lee DY, Choi YM.

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