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Effects of alendronate combined with hormone replacement therapy on osteoporotic postmenopausal Chinese women

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Abstract

To evaluate the effect of alendronate combined with hormone replacement therapy (HRT) on postmenopausal osteoporotic Chinese women living in Taiwan, we treated 151 women (age range, 47-70 years; mean, 61 years) with conjugated equine estrogen (0.625 mg), medroxyprogesterone 5 mg, and elemental calcium 500 mg daily with either alendronate 10 mg (n = 79) or placebo (n = 72), and measured their bone mineral density (BMD) at the lumbar spine and hip every 6 months for 3 years. Urine *N*-telopeptide of type I collagen corrected by concentration of urine creatinine (NTx/Cr) and serum osteocalcin (OC) concentration was also measured at weeks 2, 4, and every 3 months from month 3 for 2 years. Significantly higher percentage increases in BMD at the lumbar spine ($P < .0001$, 2-way analysis of variance) throughout the 36-month treatment period were found in the alendronate plus HRT group than in the HRT-only group. However, there was no difference in BMD at the femoral neck and trochanter between these 2 groups. Treatment with alendronate plus HRT resulted in a 10.1% increase at the L-spine BMD and a 7.7% increase at the trochanter BMD at the end of the 3-year study period ($P < .01$, compared with baseline at both sites). A significant decline in urine NTx/Cr was observed at week 4 in the alendronate plus HRT group, whereas in the HRT-only group, a significant decline in urine NTx/Cr occurred at month 9. By the end of 24 months, urine NTx/Cr decreased by 49.7% in the alendronate plus HRT group ($P = .001$ compared with a 20.4% increase in the HRT group). A significant decline in serum OC level occurred at month 3 in the alendronate plus HRT group, whereas a similar decline was observed at month 6 in the HRT-only group. By the end of 24 months, serum OC decreased by 52.2% in the alendronate plus HRT group ($P < .001$ compared with a 1.5% increase in the HRT-only group). Subjects treated with alendronate plus HRT had a significantly greater percentage decrease in urine NTx/Cr ($P = .0001$) and serum OC ($P = .0007$) than subjects treated with HRT only throughout the 24-month treatment period by 2-way analysis of variance comparison. There was no difference in upper gastrointestinal or drug-related side effects between groups. In conclusion, our data suggest that the use of alendronate combined with HRT for 3 years was well tolerated and it significantly increased BMD at the L-spine and hip in postmenopausal Chinese women with osteoporosis. This regimen is safe and can be used in subjects who have no satisfactory response to a single agent or who have very low BMD with multiple risks. However, this study does not indicate whether HRT plus alendronate has any greater effect on BMD than alendronate alone.

1. Introduction

With increasing human life expectancy, up to 30% of postmenopausal women are now affected by osteoporosis, which has become a major public health problem in developed countries [1]. Up to 1% to 3% of cortical bone and 5% of trabecular bone is lost per year after menopause [2]. Vertebral fractures occur in 25% of postmenopausal

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women older than 70 years. The lifetime risk of hip fracture in women is 15%, which rises to 35% at the age of 90 years [2]. These fractures are associated with high rates (up to 20%) of morbidity and mortality [3,4].

The roles of hormone replacement therapy (HRT) and calcium supplement in the treatment of postmenopausal osteoporosis have been well established in the literature [5]. However, some women still lose bone despite HRT [6]. In recent years, various studies have revealed that bisphosphonates, a family of compounds with a long half-life and potent inhibitory effects on bone resorption, are effective in the treatment of postmenopausal osteoporosis [3,4,7]. Alendronate, a potent aminobisphosphonate, has been shown to be effective in increasing bone mineral density (BMD) after 3 to 5 years' use and can decrease fracture rates effectively [3,7-14]. At the time this study was begun, there were few studies on the effectiveness of alendronate combined with HRT and calcium in the treatment of postmenopausal osteoporosis [15]. However, some studies regarding the combination of alendronate and estrogen have been published in recent years, most of which showed favorable responses to both BMD and bone markers with these 2 agents combined [16-19].

According to Tsai and Tai [20], the adjusted prevalence rates of vertebral fractures among elderly men and women living in cities in Taiwan were 12% and 18%, respectively, which are similar to the rates reported in other countries. In Taiwan, only 13.5% of women with natural menopause receive HRT [21], a rate which is lower than that of the United States or Europe [21]. To our knowledge, there have been no large-scale studies investigating the effectiveness of alendronate combined with HRT on osteoporotic postmenopausal women in Asian countries. The purpose of this study was to investigate the effectiveness and tolerability of alendronate combined with HRT on osteoporotic postmenopausal Chinese women in Taiwan and to determine whether there was an additive effect when these 2 regimens were combined.

2. Materials and methods

2.1. Subjects

This study was a randomized, single-blind, and placebo-controlled study. Postmenopausal women (n = 151) aged 47 to 70 years (mean age, 61 years) were selected from outpatients of the Departments of Endocrinology/Metabolism, Gynecology, Orthopedics, and Family Medicine of Taichung Veterans General Hospital, Taichung City, Taiwan, from July 1998 to December 2000. Subjects with prevalent vertebral or nonvertebral fractures were excluded. Those with BMD below −2 SD of the young adult at either L-spine (L2-L4) or hip measured by dual-energy x-ray absorptiometry (DXA) were recruited. None had any history of fracture at any site in the past 10 years. Subjects with thyroid or parathyroid diseases, renal insufficiency (serum creatinine >2 mg/dL), cancer; those currently undergoing HRT, taking thyroid hormone or glucocorticoids, vitamin D supplements, or calcitonin; and those with recent peptic ulcer diseases or subjects with any other systemic illness or taking other medications that could affect bone mineral metabolism were excluded. Subjects who had previously undergone HRT, or taken vitamin D, calcitonin, or other bisphosphonates, were also excluded. The study protocol was approved by the ethics committee of the hospital, and informed consent was obtained from all the participants.

2.2. Treatments

All the recruited subjects received conjugated equine estrogen (Premarin, Wyeth-Ayerst [Asia], Taiwan) 0.625 mg, medroxyprogesterone (Provera, Wyeth-Ayerst [Asia]) 5 mg, and calcium carbonate providing elemental calcium of 500 mg/d. These subjects were randomized to take either alendronate 10 mg (Fosamax, purchased from MSD, Taipei, Taiwan) per day or placebo with a single-blind method. The whole treatment period was 3 years. Participants were instructed to take alendronate (or placebo) after overnight fasting and at least 30 minutes before any food or beverage intake in the morning. Compliance was measured by pill count and by questioning patients during monthly follow-up.

2.3. Bone mineral density

Bone mineral density of the lumbar spine (L2-L4), and left proximal femur, including femoral neck, trochanter, and Ward's triangle, was measured at baseline and every 6 months by DXA (DPX-L, Lunar System, WI) until the end of the study. Percentage changes from baseline BMD were calculated at 6, 12, 18, 24, 30, and 36 months after starting the treatment regimens.

2.4. Biochemical markers of bone metabolism

Urine and serum samples were obtained at baseline and weeks 2 and 4 followed by every 3 months from month 3 through month 36 after treatments for analysis of biochemical markers. Thus, early morning second void urine during fasting was collected for determination of *N*-telopeptide of type I collagen (NTx) by duplicate enzyme-linked immunosorbent assays with the Osteomark kit (Ostex International, Seattle, Wash) as a marker representing bone resorption and was expressed as a ratio over urine creatinine to avoid bias from hydration status. Serum osteocalcin (OC) was measured by duplicate radioimmunoassay method with the Oscatest kit (Henn, Berlin, Germany) as a marker representing bone formation. The intra-assay precision rates (coefficient of variation) were 8.6% and 2.6%, and the inter-assay precision rates (coefficient of variation) were 4% and 4%, respectively, for NTx and OC. However, there were few urine and serum samples remaining after month 24 (n = 40 in the alendronate-HRT group, n = 36 in the HRT group). Therefore, only data up to month 24 are presented.

2.5. Statistical analysis

The primary end point was the percentage change in BMD at the lumbar spine. The results of baseline

Table 1
Baseline characteristics of subjects in the 2 treatment groups (mean ± SEM)

	HRT + alendronate	HRT	*P*
Number	79	72	
Age (y)	61 ± 1	61 ± 1	.42
BMI (kg/m^2)	23.0 ± 0.3	23.8 ± 0.4	.07
Years since menopause (y)	14 ± 1	12. ± 1	.16
BMD, L2-L4 (g/cm^2)	0.85 ± 0.01	0.88 ± 0.01	.10
Femoral neck	0.67 ± 0.01	0.67 ± 0.01	.49
Trochanter	0.59 ± 0.01	0.60 ± 0.01	.22
NTx/Cr (nm/mmol · L)	25.81 ± 2.82	38.70 ± 7.80	.06
Osteocalcin (ng/mL)	15.41 ± 1.77	15.64 ± 1.35	.46

demographic characteristics and participant-related data in the combined alendronate-HRT and HRT-only groups are presented as mean ± SEM and were analyzed using a *t* test. The analyses of the changes in BMD and bone markers were conducted based on the intention-to-treat principle. For treatment effects, 2-way analyses of variance (ANOVA) were used to test for differences between both treatment groups. For time effects, 1-way ANOVA for repeated measurement was used to examine the changes within both treatment groups independently. Post hoc test was also performed for the comparisons of both treatment groups at each time point.

3. Results

3.1. Patient characteristics

From July 1, 1998, to December 31, 2001, a total of 1043 subjects were screened by DXA from outpatient clinics or via advertisement. Two hundred and eighty-five subjects (27.3%) fulfilled the criteria of osteoporosis. One hundred and thirty-four subjects were excluded either because they had various concomitant diseases or were taking medications that affect bone metabolism. A total of 151 postmenopausal women agreed to participate in this study. By randomization with the single-blind method, 79 subjects received a combination of HRT plus alendronate, and 72

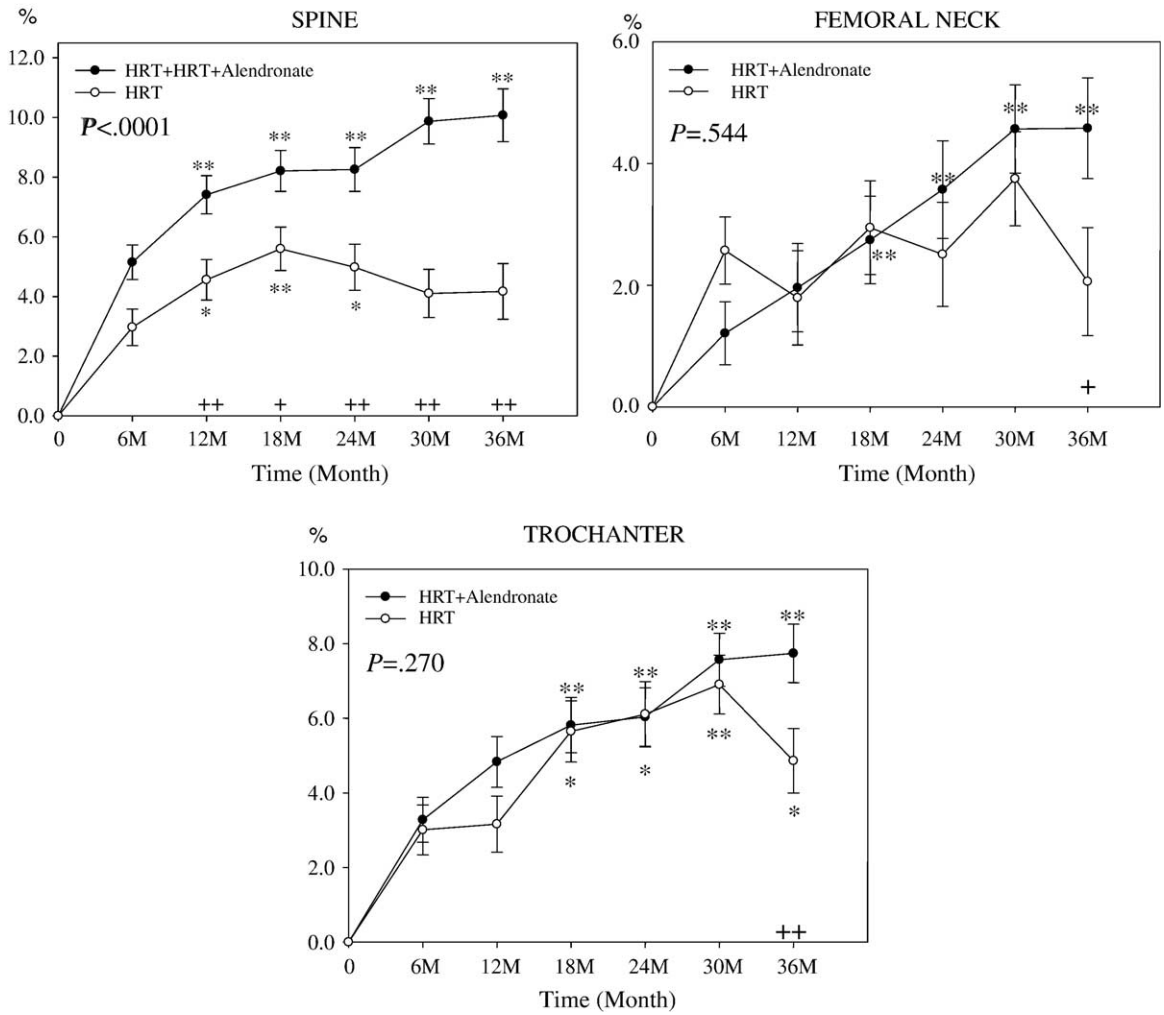

Fig. 1. Percentage changes in BMD at the sites measured. Filled circles, alendronate plus HRT group; open circles, HRT-only group. *$P < .05$ compared with baseline; **$P < .01$ compared with baseline, by 1-way ANOVA. *P* value indicates comparison of both groups by 3-way ANOVA. $^{+}P < .05$, the difference between both groups at each time point; $^{++}P < .01$, the difference between both groups at each time point by post hoc test.

subjects received HRT only. The baseline demographic characteristics of the 2 treatment groups are shown in Table 1. There were no differences in the mean age, body mass index (BMI), years since menopause, or BMD at all sites measured and levels of the 2 bone markers measured between the 2 treatment groups at baseline. One subject in the alendronate plus HRT group was terminated because of vertebral fracture. Twenty-nine subjects withdrew from the alendronate plus HRT group. Among them, 3 subjects had completed 2 years' treatment and 5 had completed 1 year's treatment. Twenty-eight subjects withdrew from the HRT group. Among them, 2 subjects had completed 2 years' treatment and 6 had completed 1 year's treatment.

3.2. Bone mineral density

Fig. 1 shows the time course of the percentage changes in BMD at the lumbar spine, femoral neck, and trochanter in the 2 treatment groups. The combination of alendronate with HRT significantly increased BMD in the L-spine (+10.1%, $P < .0001$), femoral neck (+4.6%, $P < .0001$), and trochanter (+7.7%, $P < .0001$) at the end of 36 months compared with baseline (1-way ANOVA). It is apparent that patients receiving alendronate plus HRT had significantly higher values of BMD at the lumbar spine ($P < .001$, 2-way ANOVA) throughout the whole treatment period than with patients in the HRT-only group, whereas the changes in BMD at the femoral neck and trochanter did not differ in either group throughout the whole treatment period. In the HRT group, significantly increased BMD (+4.9%, $P < .05$) was only found at the trochanter area at the end of 36 months. Significant differences in the percentage changes in BMD in both treatment groups were also detected from month 12 to month 36 at the L-spine and at month 36 at the femoral neck and trochanter as tested by post hoc test.

3.3. Biochemical markers

Significant decreases in urine NTx/Cr (−68.8%) began at week 4 in the alendronate plus HRT group, whereas they occurred at month 9 in the HRT-only group. At the end of 24 months, urine NTx/Cr had decreased by 49.7% in the alendronate plus HRT group, whereas it had increased by 20.4% in the HRT-only group ($P = .001$, post hoc test). Patients who received treatment with alendronate plus HRT had significantly higher percentage decreases in urine NTx/Cr during the 24-month treatment period ($P = .0001$, 2-way ANOVA) (Fig. 2). A significantly decreased serum OC level (−40%) was detected starting at month 3 in the alendronate plus HRT group compared to that of the first 2 weeks from baseline. It occurred at month 6 in the HRT-only group. At the end of 24 months, it had decreased by 52.2% in the alendronate plus HRT group, whereas it had decreased by 1.5% in the HRT-only group ($P < .001$, post hoc test) (Fig. 2). Patients who received treatment with alendronate plus HRT had significantly higher percentage decreases in serum OC levels than those using HRT alone at the end of the 24-month treatment period ($P = .0007$, 2-way ANOVA) (Fig. 2).

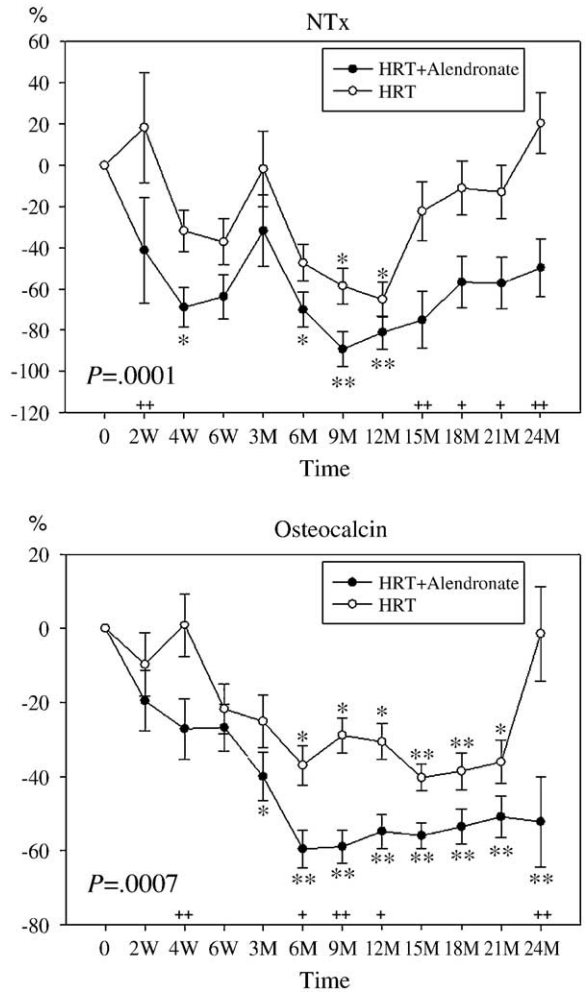

Fig. 2. Percentage changes in urine NTx/Cr and serum osteocalcin at each time point. Filled circles, alendronate plus HRT group; open circles, HRT-only group. *$P < .05$ compared with baseline; **$P < .01$ compared with baseline by 1-way ANOVA. P value indicates comparison between both treatment groups by 2-way ANOVA. $^{+}P < .05$, the difference between both groups at each time point; $^{++}P < .01$, the difference between both groups at each time point by post hoc test.

3.4. Compliance and tolerability

Compliance was checked by pill count at every visit. The amount of pills consumed was more than 85% for every subject included. In this study, the combined alendronate-HRT regimen was generally well tolerated. Twenty-nine subjects withdrew from the combined alendronate-HRT group for the following reasons (from patients' complaints): personal reasons (23), epigastralgia (1), esophageal irritation (2), intolerance to HRT (2), and back pain (1). One subject was terminated because of vertebral fracture resulting from a fall during an earthquake. Twenty-nine subjects withdrew from the HRT-only group for the following reasons (from patients' complaints): personal reasons (22), epigastric discomfort (2), intolerance to HRT (1), general discomfort (1), back pain (1), hemoptysis (1), and an episode of a light stroke (1). Except for one vertebral fracture mentioned above, which occurred in the alendronate-HRT group, no

other vertebral or nonvertebral fractures occurred in either group during the treatment period. There were no significant differences in the incidences of upper gastrointestinal or other clinically adverse events and in the incidences of vertebral or nonvertebral fractures in the 2 treatment groups compared by Fisher exact test.

4. Discussion

Since the early 1970s, numerous studies have proved that HRT reduces bone loss. Tsai et al [22] found that conjugated equine estrogen plus medroxyprogesterone increased BMD in spinal and hip sites by 6% and 4.6% to 7.9%, respectively, after 12 months' treatment in postmenopausal Taiwanese women. In our study, BMD increased 4.2%, 4.6%, and 4.9% at the L-spine, femoral neck, and trochanter, respectively, in the HRT-only group at the end of the 36-month treatment period (compared with baseline BMD, a significant increase in BMD was only found at the trochanter area, $P < .05$). However, some studies showed that for long-term preservation of BMD, women should take estrogen for at least 7 years after menopause and even this duration of therapy may have little residual effect on BMD among women 75 years of age and older [5].

Bisphosphonates have been demonstrated to inhibit osteoclast-mediated bone resorption both in vitro and in vivo in animals and humans [4,23]. Alendronate sodium, a potent aminobisphosphonate, has been shown to exert a positive effect on bone mass and bone strength in postmenopausal women [5,13,14]. The findings of the Alendronate Phase III Osteoporosis Treatment Study Group [13] indicated that the increases in lumbar spine BMD in the alendronate-treated group were most rapid during the first 6 months of treatment, with continued increases during the second and third years. In the Fracture Intervention Trial [10], alendronate decreased the risk of vertebral, hip, and wrist fractures by about 50% and decreased all clinical fractures by 28% among women with vertebral fractures. It was found that 4 years of alendronate treatment also decreased the risk of all clinical fractures in women with low hip BMD [10]. Thus, the National Osteoporosis Foundation (Washington, DC) recommended that estrogen or alendronate should be offered to postmenopausal women with either vertebral fractures or osteoporosis confirmed by bone densitometry [10].

There were no large-scale, worldwide studies on the effect of alendronate combined with estrogen in the treatment of osteoporotic postmenopausal women when this study was begun. Tiras et al [2] found that 10 mg alendronate combined with HRT produced significantly higher percentage increases in BMD at the L-spine than using HRT alone (8.4% vs 2.6%, respectively) after 12 months' treatment. A 2-year study indicated that the use of 10 mg alendronate daily plus estrogen produced greater increases (8.3%) in BMD at the lumber spine than using either agent alone [24]. In our study, we found significantly higher percentage increases in BMD at the L-spine in subjects who received alendronate plus HRT than in subjects who received HRT alone. These increments occurred during the first 6 months and continued to rise throughout the 3-year treatment period. The magnitude of increment in BMD at the L-spine in the alendronate plus HRT group (10.1%) was consistent with that reported by Yen et al [25], who found that alendronate therapy for 12 months increased BMD by 6% to 11% in osteopenic postmenopausal Chinese women in Taiwan. Our study showed a greater increase in BMD at the L-spine than that found by Lau et al [26], who reported a 5.5% increase in BMD in osteoporotic postmenopausal Hong Kong Chinese women after treatment with alendronate 10 mg for 12 months. The response to alendronate differs at various sites, but seems greater at the L-spine based on many previous studies as well as on our study. It is still not known if this relates to the lower turnover rate observed in cortical bone such as the hip. To our knowledge, there are no large-scale studies in regard to ethnic differences in the responses to alendronate treatment. A few studies have indicated that there does not seem to be any difference in the response to alendronate among African Americans and whites or Chinese and whites [27,28]. Nonetheless, the amplitude of treatment responses of Chinese women in our study is similar to or even greater than that reported in other series. This reflects the heterogeneity in the factors affecting the BMD and the responses to treatment.

Changes in bone markers are known to occur early in the treatment course [19]. In our study, a significant decrease (−68.8%) in urine Ntx/Cr from baseline was observed at week 4 in the alendronate plus HRT group, whereas it occurred at month 9 in the HRT-only group. A significant decrease (−40%) in serum OC level from baseline occurred at month 3 in the alendronate plus HRT group, whereas it was observed at month 6 in the HRT-only group. Our findings suggest that the use of alendronate combined with HRT is effective in slowing the rate of bone turnover, and in our study its effect occurred early and persisted throughout the treatment period. Although HRT also slowed the bone turnover rate, this occurred later with lesser magnitude in our study.

In most recent studies, the combination of alendronate and estrogen had an additional benefit on BMD compared to estrogen alone [2,16-19,24]. On the other hand, some studies showed that the combination of these 2 agents did not produce any extra gain in bone mass when compared with either treatment alone [29]. However, a similar favorable effect on the BMD and biochemical markers was also observed with the combination of raloxifene and alendronate [30]. Although there was a beneficial effect on BMD, more large-scale studies are needed to determine whether a combination of 2 antiresorptive agents can effectively reduce the risk of fractures. A meta-analysis showed that a 1% improvement in spine BMD was associated with a 3% decrease (95% confidence interval

0.02-0.05) in the relative risk of vertebral fracture [31]. But the reductions in risk observed were greater than predicted from improvement in BMD [31]. Thus, it is largely agreed that although increased BMD does not fully equate with fracture reduction, increases in BMD may contribute to a reduction in the risk of fracture.

There were some limitations of this study. Because the apparent equality of the treatment regimens in a single-blind, randomized, placebo-controlled study and the effects of alendronate on BMD and bone markers have been well documented, we did not design a treatment group with alendronate alone. Instead, our aim was to observe the effects of combining alendronate with HRT on Chinese postmenopausal women, and the effects in the combination group were apparent under comparisons with 2-way ANOVA and post hoc test. However, this does not indicate whether HRT plus alendronate has a greater effect on BMD than alendronate alone. Evio et al [29] found that alendronate plus HRT for 2 years increased BMD by 11.2% at the L-spine and 2.7% at the femoral neck, whereas alendronate alone for 2 years increased L-spine BMD by 9% and increased femoral neck BMD by less than 2%, and there was no statistical difference between the 2 treatment regimens. Greenspan et al [18] found that alendronate plus HRT for 3 years increased L-spine BMD by 10.4% and total hip BMD by 5.9%; whereas alendronate alone for 3 years increased L-spine BMD by 7.7% and total hip BMD by 4.2%, with significantly greater gain in BMD in the combination group in both sites (all $P < .01$). In our study, alendronate plus HRT increased L-spine and femoral neck BMD by 8.3% and 3.6% at 24 months and by 10.1% and 4.6% at 36 months, respectively. Another limitation of this study was that the results of bone markers in the HRT group were not as significant as expected. Urine bone markers are usually less stable than serum bone markers and have some within-person variability [32]. Because of the long treatment period of this study, fewer cases were retained after month 24, and even some smaller changes in markers may have had a significant influence on the final results. Although compliance was confirmed by pill count at every visit, nonresponse to HRT and the true compliance of non-responding patients were taken into consideration [32]. There were also some strengths of this study. It was conducted in a single center, using a single bone densitometer. It is the first 3-year, placebo-controlled study that observed the effects of combining alendronate with HRT on Chinese postmenopausal women.

Alendronate is by far the most potent agent in the treatment of osteoporosis. However, data regarding the efficacy and safety of therapy combining bisphosphonate and HRT are limited. Our findings demonstrated that the use of alendronate combined with HRT for 3 years in postmenopausal women resulted in significantly greater increases in BMD at the lumbar spine than using HRT alone. In addition, this regimen is safe and well tolerated. It can be used in subjects who have no satisfactory response to a single agent or who have very low BMD with multiple risks.

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