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Effects of alendronate with or without hormone replacement therapy on bone mineral density in postmenopausal osteoporotic women

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Abstract

Introduction: Osteoporosis is an important problem in postmenopausal women. The use of best treatment is crucial to attaining appropriate therapeutic and prophylactic outcomes. Combination therapy versus single therapy may develop better results. This study was performed to determine the effects of alendronate alone versus plus hormone replacement therapy (HRT) on bone mineral density (BMD) in Iranian postmenopausal osteoporotic women.

Materials and Methods: In this randomized clinical trial 200 consecutive postmenopausal osteoporotic women since 2018 to 2020 were enrolled and randomly assigned to receive either alendronate 70 mg alone or plus HRT 0.625 mg CEE and 2.5 mg medroxyprogesterone acetate. The improvement in BMD, hot flash, vaginal dryness, dyspareunia, and mood disorders was assessed after 12 months and compared across the groups. SPSS software by Kolmogorov-Smirnov, Chi-Square, and Mann-Whitney-U tests.

Results: Complete improvement in BMD was seen in 20 and 47 percent in single and combination groups, respectively with statistically significant difference (P=0.001). According to results, the improvements in hot flashes (P=0.048), vaginal dryness (P=0.001), dyspareunia (P=0.002), and mood disorders (P=0.001) in women were better in combination group.

Conclusion: The addition of HRT to alendronate can increase the therapeutic effects on BMD and other symptoms in postmenopausal osteoporotic women and its use is recommended.

Keywords: Osteoporosis, Menopause, Prophylaxis

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Introduction

Postmenopausal age is an important period of life with initiation by vasomotor symptoms since five to ten years earlier (1). According to definition by world health organization (WHO) osteoporosis is bone mineral density (BMD) of 2.5 or more under youth mean measures and is common among postmenopausal women (1,2). Diagnosis and treatment of postmenopausal osteoporosis affect the fracture rate and quality of life (1). Eighty percent of osteoporotic women cases are primary without definite causes and result from postmenopausal ovarian failure and aging process (1). Screening and correct selection of high-risk patients is an important issue in patients with osteoporosis (2). Also, selection of the best treatment modality among bisphosphonates, parathyroid hormone, calcium, vitamin D, and hormone-replacement therapy (HRT) is another important problem (2). In cases with BMD over -1 no treatment is required. In cases with BMD between 1 and 2.5, treatment is required in cases with fractures. The women with BMD over 2.5 indicate treatment of osteoporosis (2). Since hip fracture is common among women, the use of prophylactic approaches by bisphosphonates and HRT is crucial (3). But some studies have recommended not using the HRT alone for this matter (4). If the goal is risk reduction of vertebral fracture each one of alendronate, risedronate, raloxifene, and parathyroid hormone is important and in cases, with non-vertebral fractures, the bisphosphonates are recommended (5). Longer use in earlier cases can help to further reduction of vertebral fractures (6). Also, bisphosphonates can decrease the stiffness and pain in the joints in postmenopausal women (6).

Combined treatments can increase BMD, bone strength, and bone formation (7). with various effects on different anatomical regions (8-16). HRT can maintain and increase BMD leading to a significant decrease in vertebral and non-vertebral fractures (15). Since bisphosphonates and HRT can affect the osteoclasts and osteoblasts, respectively (9,10). in cases without response to each one, combination therapy may be useful (11). HRT and alendronate combination is useful in Eastern Asian patients (12). But the effect in Middle-Eastern Asian cases is unclear. Regarding the increased rate of osteoporosis and further morbidity and mortality due to osteoporotic fractures in postmenopausal women in this study the comparative effects of alendronate alone or plus HRT on BMD in Iranian postmenopausal osteoporotic women were determined.

Materials and Methods

In this randomized clinical trial, Iranian postmenopausal osteoporotic women since 2018 to 2020 were enrolled. Postmenopausal status was established if they had amenorrhea length of minimally 12 months or serum FSH level over 40 IU/L. Among them, 200 consecutive cases with BMD more than 2 standard deviations under hip/lumbar spinal vertebra versus young females by DXA method were enrolled. The cases with background disease or positive drug history (including HRT/alendronate) in the last year that could affect bone metabolism were excluded. Cases with contraindication for alendronate/HRT were excluded. The contraindications for alendronate were drug/ingredient hypersensitivity, hypocalcemia, active gastrointestinal disorders including dysphagia, esophageal symptomatic diseases, gastritis, duodenitis, peptic ulcer, and creatinine clearance between 35 and 60 ml/min. contraindications for HRT were suspected breast cancer, history of endometrial adenocarcinoma, idiopathic vaginal bleeding, active hepatic disease, acute thrombotic/thromboembolic disease, chronic hepatic disease, estrogen-dependent thrombotic/thromboembolic events, active/previous endometriosis, leiomyoma, uncontrolled hypertension, active gallbladder disease, estrogen-dependent migraine headache, hyperlipidemia, and acute intermittent porphyria.

Helsinki Declaration was respected across the study. The informed consent form was signed by all participating patients. The study was approved by local ethical committee with code IR.GUMS.REC.1396.459. Women were randomly assigned to receive either alendronate 70 mg alone or plus HRT 0.625 mg conjugated equine estrogen (CEE) and 2.5 mg medroxyprogesterone acetate. Cases were learned to use alendronate with high-volume water and non-lying-down position for minimally 30 minutes. Also, calcium bicarbonate 500 mg/day and regular exercise were recommended. In the 2nd to 4th lumbar spine and hip,

the BMD was measured by the DXA method in a single hospital by a unique operator and device initially and after 12 months of treatment. The improvement of fewer than 15%, 15%-25%, and over 25% was considered negative, partial, and complete, respectively. Also, the improvement in hot flashes (subjective), vaginal dryness (subjective), dyspareunia (subjective), and mood disorders (Beck scale) were compared after 12 months across the groups. The therapeutic adverse effects were determined in groups.

Data analysis was performed by statistical package for social sciences (SPSS) software version 24.0 to compare the groups for background and outcome variables. The utilized tests were Kolmogorov-Smirnov, Chi-Square, and Mann-Whitney-U. The P values under 0.05 were considered statistically significant.

Results

The mean age, menarche age, and menopausal age were the same across the groups (Table 1). Obese cases were present in 11.0% and 7.0% in single and combination cases without significant difference (P > 0.05). Also, according to Table 2 body mass index of two groups did not have any significant difference.

Table 1. Background variables across the groups.

Variable	Group	Mean ± Standard Deviation	P-Value
Age	Single	58.2 ± 5.1	0.317
	Combination	57.5 ± 5.3	
Menarche age	Single	11.8 ± 0.7	0.914
	Combination	11.8 ± 0.7	
Menopause age	Single	50.3 ± 1.6	0.877
	Combination	50.3 ± 1.6	

Table 2. Body mass index across the groups.

Group	Underweight	Normal	Overweight	Obese	P-Value
Single	2.0%	59.0%	28.0%	11.0%	0.714
Combination	1.0%	62.0%	30.0%	7.0%	

According to Table 3, the BMD complete improvement was seen in 20 and 47 percent in single and combination groups, respectively with statistically significant difference (P=0.001). According to Table 4, the improvements in hot flashes (P=0.048), vaginal dryness (P=0.001), dyspareunia (P=0.002), and mood disorders (P=0.001) in women were better in combination group.

Table 3. Bone mineral density improvement across the groups.

Group	Negative	Partial	Complete	P-Value
Single	12.0%	68.0%	20.0%	0.001
Combined	4.0%	49.0%	47.0%	

Table 4. Improvements in various measures across the groups**.**

Group	Ne Hot flash	Dyspareunia	Vaginal dryness	Mood disorders
Single	42.0%	38.0%	50.0%	48.0%
Combined	56.0%	61.0%	71.0%	71.0%
P-Value	0.048	0.001	0.002	0.001

There were therapeutic adverse effects in 7.0% and 10.0% of patients in single and combined groups, respectively without significant difference (P=0.447). The side effects were headache (1 case), gastrointestinal (2 cases), and skeletal (4 subjects) in single group, and gastrointestinal (4 cases), skeletal (3 subjects), and hypersensitivity (3 cases) in combination group (P=0.220).

Discussion

Osteoporosis is an important problem in postmenopausal women and appropriate therapy is essential in these patients. In this study, it was shown that the addition of HRT to alendronate resulted in better improvement in bone mineral density as same as a hot flash, vaginal dryness, dyspareunia, and mood disorders in postmenopausal women. Dasilva LLibre et al (16) reported that combination therapy versus alendronate alone significantly reduced improvement time. Also, the therapeutic costs and fracture risk are reduced significantly was decreased that resulted in a higher quality of life. We could not assess the costs and

fracture risk but in our study, the combination therapy had significantly better outcomes.

Tiras et al (17) reported that alendronate was significantly more effective than HRT and the combination of them has also more effects. Alendronate is an appropriate therapeutic option for patients with contraindication or who refuse HRT therapy. In our study alendronate had good efficacy, especially with HRT addition. Cortet et al (18) reported that both etidronate and alendronate significantly increased BMD but the efficacy of alendronate was higher. Conversely, therapeutic adverse effects and discontinuations for side effects are higher in the alendronate group. In our study also gastrointestinal adverse effects were more common but there was no discontinuation case.

Greenspan et al (9) declaimed that alendronate 10 mg daily was superior to HRT but combination of them was superior to each one alone as same as our study. Pines and colleagues (19) reported that three and six-month intervals of measurement of BMD was predictive of outcomes in alendronate users. In our study 12-month follow-up was useful and showed a significant difference between combination and single therapy. Eivo et al (20) converse to our study reported that in elderly postmenopausal women with osteoporosis there was no difference between HRT plus alendronate therapy versus each one alone.

Tseng and colleagues (21) reported that alendronate plus HRT for three years was good-tolerated and had a significant effect on BMD in the spinal vertebra that was in line with our study. Mobley et al (22) reported good efficacy for alendronate alone but the efficacy was higher for combination therapy of alendronate and HRT. Tuppurainen et al (23) found that HRT combined with clodronate led to no BMD increase versus HRT alone. Comparison with clodronate alone was possible to show similar results with our study.

The study by Gambacciani et al (15) demonstrated that addition of HRT to alendronate can be more useful to prevent osteoporosis as shown in our study. Yoon and colleagues (16) conversely demonstrated that combination of alendronate and HRT had no efficacy in Korean postmenopausal women with low BMD. But there was good efficacy in our population. Rossouw et al (24) compared two groups of 8000 postmenopausal women including HRT and placebo cases and reported no difference between groups for cardiovascular effects but also led adverse effects. But in our study addition of HRT led to better prevention of osteoporosis without an increase in adverse effects.

There were some limitations in our study; firstly, it was not programmed for evaluation of fracture risk and bone quality. However, combination therapy leads to a further reduction in fractures versus a logistic model, there are few studies about the reduction of fracture risk by combination therapy. Secondly, the serum level of vitamin D was not measured across the study. Thirdly it was limited to women that tolerated HRT in a therapeutic phase that was programmed to reduce lost cases after randomization.

Conclusions

Totally, according to the obtained results in this study, it may be concluded that addition of HRT to alendronate can increase the therapeutic effects on BMD and other symptoms in postmenopausal osteoporotic women and its use is recommended. However further studies with an enrollment of another study group as HRT alone can be effective for better interpretation of efficacy and safety of HRT and alendronate combination.

Author contributions

FA and **MAM** done this research and write manuscript, **AM**, **FA** and **MAM** Guidance and assistance in data collection and analysis of the results.

Conflict of interest

All authors declare that they have no conflict of interest.

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