Original Article

The Efficacy of Selective Estrogen Receptor Modulators Monotherapies in Postmenopausal Women with Osteopenia

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Background: The impact of osteopenia as a risk factor for fractures is underrecognized. Moreover, the efficacy of selective estrogen receptor modulators (SERMs) in postmenopausal women with osteopenia is limited. This study aimed to evaluate the efficacy of SERMs in postmenopausal women with osteopenia. **Methods:** Thirty-two postmenopausal women with osteopenia were treated with 3 types of SERMs medication: raloxifene (group I, N=15), bazedoxifene (group II, N=8), and raloxifene with cholecalciferol (group III, N=9). Bone mineral density (BMD) was measured using dual energy X-ray absorptiometry scans before treatment to after 3 years of treatment once a year. **Results:** Patients in group I showed significant increases in hip BMD, -1.93 to -1.73 and spine BMD, -1.85 to -1.67. In addition, patients in groups II and III showed significant increases in hip BMD, -1.93 to -1.69 and -2.22 to -1.86, respectively and spine BMD, -2.1 to -1.3 and -2.22 to -1.37, respectively. The BMD increased in the hip and spine by 9.7% and 10.3%, respectively in group I, 38.0% and 12.4%, respectively in group II, and 38.2% and 16.2%, respectively in group III. **Conclusions:** In this study, we found that SERMs could improve spine and hip BMD. In conclusion, preemptive treatment using SERMs is necessary for postmenopausal women with osteopenia. None of the patients experienced fractures during the follow-up period.

Key Words: Postmenopause · Raloxifene hydrochloride · Selective estrogen receptor modulators · Vitamin D

INTRODUCTION

Osteoporosis is a systemic and progressive skeletal disease characterized by reduced bone density, with a consequent increase in bone fragility and long-term fracture risk.[1] Due to the increase in mortality rate after osteoporotic fractures, those are emerging as a socioeconomic problem.[2] Osteopenia is a precursor of osteoporosis and is defined as a bone mineral density (BMD) between 1.0 and 2.5 standard deviations below the mean of peak bone mass in healthy, young normal people (T-score between -1.0 and -2.5).[3] The prevalence of osteopenia ranges from 27.1% to 51.6%, with a reportedly high prevalence among postmenopausal women in Asian countries, where the population is aging rapidly.[4-6] Compared with osteoporosis, the impact of osteopenia as a risk factor for fractures is underrecognized. A recent study suggests that osteopenia is also a significant risk factor

for fragility fractures in older women.[7] Moreover, a large community-based study in the U.S. reported that about half of all fragility fractures occur in women who were diagnosed osteopenia.[8,9] For osteoporosis patients, selective estrogen receptor modulators (SERMs) are widely used and their efficacy has been proven.[10-12] However, medication efficacy of SERMs for postmenopausal women with osteopenia is limited. The purpose of this study is to evaluate the efficacy of SERMs in postmenopausal women with osteopenia.

METHODS

This retrospective study was approved by the Institutional Review Board (IRB) at our hospital (IRB no. 2022-07-003). From January 2012 to May 2019, 97 postmenopausal osteopenia women patients were enrolled. Women with BMD between 1.0 and 2.5 standard deviations below peak bone mass for healthy premenopausal women were included, regardless of the presence of prevalent vertebral fractures. Among them with following conditions were excluded, (1) current bone disorders other than postmenopausal osteoporosis; (2) history of endometrial hyperplasia or gynecological diseases that could be adversely affected by SERMs; (3) history of cancer in the last 5 years; (4) active venous thromboembolic disease, and endocrine disorders requiring pharmacologic therapy, except type II diabetes.

Thirty-two postmenopausal women, who were diagnosed with osteopenia, were allocated to one of 3 treatment groups and monitored for 3 years. All patients were treated by SERMs and 3 types of medication were used: raloxifene (60 mg/day; group I, N=15), bazedoxifene (20 mg/day; group II, N=8) and raloxifene (60 mg/day) with cholecalciferol (8 mg/day; group III, N=9). BMD was measured by dual energy X-ray absorptiometry (DXA) scan (Horizon DXA system; Hologic Inc., Marlborough, MA, USA), from before treatment to after 3 years of treatment once a year.

Table 1. Demographic data for participants

	Group I (N=15)	Group II (N=8)	Group III (N=9)	P-value
Age (yr)	60.8±5.4	52.2±4.3	67±6.2	0.611
BMI (kg/m²)	19.9±1.1	19.8±1.3	19.4±0.9	0.642
Drug adherence rate (%)	87.3±11.0	88.7±5.7	85.3±7.4	0.211

BMI, body mass index.

The Kolmogorov-Smirnov test was used for the determination of data normality. Comparisons of variables between time points within each group were performed using a Wilcoxon signed rank test according to the number of comparisons. All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA), and statistical significance was set at P value less than 0.05.

RESULTS

The average follow-up duration was 40.1 months (range, 36-78). The mean age of the patients was 60.3 years (range, 48-72) with a mean body mass index of 23.1 ± 4.1 kg/m². The time from menopause was a mean of 7.3 years (range, 3.3-11.3). The mean period of treatment was 3.7 years (range, 3-5). The drug adherence rate for group I was 87.3% (standard deviation [SD], 11.0) the rate for group II was 88.7% (SD, 5.7) and the rate for group III was 85.3% (SD, 7.4). There was no significant difference between the 3 groups (Table 1).

Patients in group I showed significant increases in hip BMD, -1.93 to -1.73 and spine BMD, -1.85 to -1.67. Also, patients in group II and group III showed significant increases in hip BMD, -1.93 to -1.69, -2.22 to -1.86 and spine BMD, -2.1 to -1.3, -2.22 to -1.37 (Table 2). In group I, BMD increased in the hip and spine by 9.7% (P=0.035) and 10.3%

Table 2. Changes in BMD during treatment

	Baseline	3 years after	P-value
Hip BMD			
Group I	-1.93±0.25	-1.73±0.33	0.018
Group II	-1.93±0.32	-1.69±0.20	0.034
Group III	-2.22±0.19	-1.86±0.17	0.042
Spine BMD			
Group I	-1.85±0.31	-1.67±0.22	<0.001
Group II	-2.10±0.22	-1.30±0.27	0.023
Group III	-2.22±0.20	-1.37±0.24	0.031

BMD, bone mineral density.

Table 3. Percentage changes in BMD from baseline at 3 years

Characteristics	Group I	Group II	Group III
Hip BMD	9.7±1.0	38.0±4.2	38.2±4.5
P-value	0.035	0.046	0.048
Spine BMD	10.3±1.1	12.4±1.2	16.2±1.3
P-value	0.021	0.032	0.002

BMD, bone mineral density.

(*P*=0.021). In group II, were increased 38.0% (*P*=0.046) and 12.4% (*P*=0.032), in group III, were increased 38.2% (*P*=0.048) and 16.2% (*P*=0.002) in hip and spine, respectively. In group III, BMD was increased the larger than other groups (Table 3). All patients did not have any fractures during the follow-up period.

DISCUSSION

Fractures are a major complication of osteopenia and osteoporosis. The 10-year cumulative incidence of fragility fractures was 44.3% in women with osteoporosis.[7] Moreover, according to the 2020 report of the Korean Society for Bone and Mineral Research, osteoporotic fractures are associated with functional limitation and excess mortality of 17%.[13] Osteopenia can progress to osteoporosis if left untreated. Baek et al. [7] reported that the 10-year cumulative incidence of fragility fractures was 37.5% in women with osteopenia. And more, they emphasized the risk of fracture in osteopenia as well as osteoporosis and the need for its treatment.

Estrogen deficiency can accelerate the loss of bone mass and cause deterioration of bone quality.[14] Hence, proper treatment is needed for postmenopausal women, who are more likely to develop osteopenia or osteoporosis.[14] SERMs provide the beneficial effects of estrogen on skeletal tissue without negative effects on other organs.[15] In an in vitro study, raloxifene, the SERMs used in treating osteoporosis, decreased the rate of bone remodeling and attenuated osteoclast activity but maintained osteoblast activity.[16] Moreover, some studies revealed that raloxifene was proven effective in reducing vertebral fractures in postmenopausal women with osteoporosis.[17,18]

In this study, we could find that the SERMs can significantly improve the BMD in postmenopausal women with osteopenia. Hence, we assumed that SERMs treatment is decreased the risk of fractures in patients with osteopenia. However, in Korea, access to pharmaceutical intervention to prevent osteoporosis in patients with T-score in the osteopenic range is limited because the National Health Insurance (NHI) does not provide coverage for these patients. Postmenopausal women with osteopenia, had a 1.31-fold increased risk of overall fracture compared with women with normal BMD.[7] In a recent study, it was projected that if the NHI expanded its coverage to include drug ther-

apy for osteopenic patients at high risk of fractures, the cumulative number of fractures that would have been prevented between 2011 and 2015 would have increased 2.3 times.[19] Moreover, in a societal perspective, the estimated incremental cost-effectiveness ratios for the base cases that had T-scores between -2.0 and -2.4 and began drug therapy at the age of 55, 60, or 65 years were $16,472, $6,741, and -$13,982 per quality-adjusted life year gained, respectively.[20] Hence, the prescription of SERMs in osteopenia patients through the expansion of Korean National Health Insurance coverage would help reduce the prevalence of fractures and save socioeconomic costs.

This study has several limitations. First, this study had a small sample size, and the study results need to be generalized with caution. Second, this study did not check bone turnover markers. Bjarnason et al. [11] reported that changes in bone turnover were related to fracture risk during 3 years of raloxifene therapy. Although bone quantity, as measured by DXA, is an important factor contributing to bone strength, bone quality is another component that is potentially important for bone strength and fracture risk. If bone turnover markers had been included in this study, efficacy of SERMs could have been more accurately assessed. Third, we may have selection bias. The baseline BMD of group III was relatively lower than other groups. It can be assumed that patients with relatively lower BMD were prescribed additional vitamin D based on the examiner's preference. Fourth, low adherence to drugs are not only limited to SERMs therapy but it is also observed in other osteoporotic medications.[21-24] Ringe et al. [25] reported the rate of patients' compliance with raloxifene as 80%. Similarly, we found that of medication was 87%. Kripalani et al. [26] suggested behavioral or informative interventions which were aimed to increase the adherence to drugs. In that study, Interventions could increase adherence. However, it did not change significantly the related clinical outcomes. If compliance can be increased through effective strategies, the effect of medication can be further maximized. Fifth, studies are conflicting regarding effect of vitamin D on BMD. Reid et al. [27] insisted that the benefit of using vitamin D to improve BMD is questionable. However, Liu et al. [28] suggested that the SERMs with vitamin D may have some additive effect on improving BMD. However, there are a few reports that assess the effect of SERMs with vitamin D. In this study, SERMs with vitamin D tended to have

a larger increase of BMD than SERMs monotherapies. Hence, additional studies need to assess the effect of SERMs with vitamin D on BMD.

CONCLUSION

Osteopenia can progress to osteoporosis if left untreated. Moreover, osteopenia itself may increase the risk of overall fractures. In thais study, we could find that the SERMs improved spine and hip BMD. In conclusion, preemptive treatment using SERMs in postmenopausal women with osteopenia could be necessary.

DECLARATIONS

Ethics approval and consent to participate

The retrospective study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board (IRB no. 2022-07-003).

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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