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ORIGINAL ARTICLE

Effectiveness of raloxifene on bone mineral density and serum lipid levels in post-menopausal women with low BMD after discontinuation of hormone replacement therapy

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SUMMARY

Objective: **To evaluate the effect of raloxifene on bone mineral density (BMD) and serum lipid levels in post-menopausal women who had discontinued hormone replacement therapy (HRT).**

Methods: **Thirty-four post-menopausal women with low BMD who had taken 60 mg of raloxifene daily for 12 months after discontinuing HRT were evaluated retrospectively. Information about their demographics, fracture history, BMD, lipid profiles and adverse events were collected from medical records and intranet database. The outcome measures were changes in the spine (L2–L4) and femur BMD, serum lipid concentrations, fracture rate and tolerability.**

Results: **The post-menopausal women had a significant increase in their spine (L2–L4) and femur BMD from their baseline BMD [spine, 2·9 ± 4·6% ($P < 0·001$); femur, 3·0 ± 6·6% ($P = 0·01$)]. Serum low-density lipoprotein (LDL) cholesterol was significantly reduced by 22·6% below baseline after 12 months ($P = 0·007$). No fractures were observed during therapy. Raloxifene was well tolerated. The most common adverse event was hot flash, which was generally mild.**

Conclusions: **Raloxifene increases BMD at important skeletal sites, and lowers LDL cholesterol with tolerable adverse events.**

***Keywords*: bone mineral density, fracture, lipid, raloxifene**

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INTRODUCTION

Decreased levels of oestrogen in post-menopausal women lead to accelerated loss of bone mineral density (BMD) (1). This decrease in BMD leads to increased susceptibility to fractures, which results in substantial morbidity and mortality (1–3). Fifty per cent of women over the age of 50 years will experience an osteoporosis-related fracture sometime during their lifetime (3). Hormone replacement therapy (HRT) has been shown to be effective in reducing post-menopausal bone loss (4–7). However, the use of HRT with unopposed oestrogen is associated with increased risk of endometrial carcinoma and breast cancer (8–10). The FDA recently required that the 'Indications' labels on HRT products be changed from treatment and preventative therapy to only preventative therapy (6). More importantly, in May 2002, the investigators of the Women's Health Initiative (WHI) study stopped its study 3 years earlier and recommended that HRT not be prescribed for long-term use (10). Although the study demonstrated a one-third reduction in the rates of hip and vertebral fracture with HRT, the WHI authors recommended the use of alternative agents for the prevention and treatment of osteoporosis to avoid increased risk of

breast cancer (10). This news has led to the reconsideration of HRT's long-term use and, in many patients, its discontinuation. However, when HRT is discontinued, a period of rapid bone loss ensues, similar to that seen immediately after menopause (11–13). Thus, a therapy that could prevent post-menopausal bone loss without stimulating reproductive tissues would be desirable.

Raloxifene, a selective oestrogen receptor modulator (SERM), affects bone and lipid metabolism in a manner similar to that of oestrogen, while simultaneously antagonizing the effect of oestrogen in the uterus and breast (14–16). Delmas *et al.* found that raloxifene increased BMD by 2·4% without stimulating the proliferation of the endometrium (16). Results from the Multiple Outcomes of Raloxifene Evaluation (MORE) study also indicated that raloxifene treatment reduces the incidence of new vertebral fractures (17). However, the efficacy of raloxifene in decreasing bone loss that occurs after HRT withdrawal is unknown. This retrospective study was performed to evaluate the effects of raloxifene on BMD and serum lipid levels in post-menopausal women who had discontinued HRT.

METHODS

Study subjects

This study included post-menopausal women with low BMD who had taken 60 mg of raloxifene daily in a university-affiliated hospital in Seoul, Korea, from January 2003 to April 2004. The study included only those women who had the baseline BMD measurements right before the start of raloxifene therapy. Women were eligible for evaluation if they had the mean spine and femur BMD that were 1·5 SD below peak bone mass, were less than 80 years of age, had been post-menopausal for at least 2 years, had used HRT for at least 1 year and discontinued HRT within a month preceding their raloxifene therapy. Women who had undergone hysterectomy were eligible if they were aged 45–80 years. Women had to receive a 500 mg calcium supplement daily. Those who had a history of other metabolic bone diseases, any cancer within the previous 5 years, thromboembolic or endocrine disorders, disease states requiring glucocorticoid therapy (asthma, chronic obstructive pulmonary disease (COPD), lupus, etc.) and abnormal renal (Scr > 2·0 mg/dL) or hepatic functions were excluded. Those who had recently received bisphosphonate or other treatments including steroids known to affect the bone and lipid metabolism were also excluded.

Treatment protocol and follow-up

Post-menopausal women who had started taking 60 mg of raloxifene with 500 mg calcium supplement daily within a month of HRT discontinuation were observed for 12 months. These patients were followed every 2 months in an outpatient clinic. Data from the medical records and intranet database of the patients taking raloxifene were collected retrospectively for 12 months. Information regarding their demographics [age, BMI, years since menopause (YSM), and previous history of hysterectomy] and fracture history were obtained. BMD and lipid profiles were evaluated at the baseline (a month before) and a year after raloxifene therapy. In addition, any adverse events that were possibly related to the use of raloxifene were collected by reviewing their medical charts.

Assessment of outcomes

The BMD of the spine and femur were measured within a month before and a year after the raloxifene 60 mg daily therapy using dual-energy X-ray absorptiometry (DEXA) with Lunar (Lunar PDX-L, Madison, WI, USA). Total-, low-density lipoprotein- (LDL), high-density lipoprotein-(HDL) cholesterol and triglycerides (TG) were also measured within a month before and a year after the raloxifene therapy. Vertebral fractures at the baseline and during the 12-month period were confirmed through a review of spine radiographs by a radiologist using published criteria (18). The outcomes were the percentage change of BMD in the spine (L2–L4) and femur, and percentage change in the lipid levels during the 12-month treatment period.

In addition, sub-analysis was performed to determine if the differences in the YSM could account for the differences in BMD. Subjects were grouped into those whose YSM were ≤10 years and those whose YSM were >10 years. A correlation

analysis was performed to evaluate bone response to raloxifene according to the baseline BMD.

Statistical analysis

Treatment differences were assessed using an analysis of variance on percentage changes from the baseline. Paired *t*-tests were used to determine whether or not the percentage change in outcomes was significantly different. Simple regression analysis was used to evaluate the bone response to raloxifene according to the baseline BMD. All treatment comparisons were two-sided, and statistical significance was defined as $P \leq 0{\cdot}05$. Statistical analyses were conducted using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline characteristics

A total of 34 post-menopausal women with low BMD were found to be eligible for evaluation. The mean age was 59·26 ± 7·61 years and had a mean BMI of 22·53 ± 2·17 kg/m^2. The mean T-scores of spine and femur were 2·08 ± 0·69 and 1·71 ± 0·50 below peak bone mass respectively. Four of the 34 women had at least one vertebral fracture (11·8%). None of these women had asthma, COPD or endocrine disorders requiring glucocorticoid therapy. The baseline characteristics of the women are summarized in Table 1.

Table 1. Baseline characteristics of women with low BMD

	N = 34
Age (mean ± SD) (years)	59·26 ± 7·61
BMI (mean ± SD) (kg/m^2)	22·53 ± 2·17
Years since menopause (mean ± SD)	10·35 ± 7·81
HRT use (mean ± SD) (years)	(3·2) 5·7 ± 3·2
Women with previous hysterectomy, *n* (%)	14 (58·8)
Concomitant illness, *n* (%)	
Hypertension	9 (26·5)
Diabetes mellitus	2 (5·9)
Dyslipidemia	4 (11·8)
Osteoarthritis	2 (5·9)
Women with fracture history, *n* (%)	
Vertebral	4 (11·8)
Non-vertebral	0
BMD (mean ± SD)	
Spine (g/cm^2)	0·870 ± 0·086
Femur (g/cm^2)	0·694 ± 0·059
DEXA scan findings	
Spine, T-score	− 2·08 ± 0·69
Femur, T-score	−1·71 ± 0·50
Cholesterol (mean ± SD) (mg/dL)	
Total	201·08 ± 33·26
LDL-C	122·58 ± 34·80
HDL-C	56·07 ± 18·17
Triglycerides (mean ± SD) (mg/dL)	113·37 ± 71·74

BMI, body mass index; HRT, hormone replacement therapy; BMD, bone mineral density; DEXA, dual-energy X-ray absorptiometry; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

The effect of raloxifene on BMD and lipid profile

There were significant increases in the BMD of the spine and femur after 12 months of treatment with raloxifene. There was a mean spine BMD increase of 2·9 ± 4·6% at 12 months ($P < 0{\cdot}0001$). Among these patients, 58·8% had a spine BMD increase of 2% or greater. Significant BMD increases were also noted in the femur (3·0 ± 6·6%, $P = 0{\cdot}01$) (Table 2). The response to raloxifene at the femur and spine was similar. No fractures were observed in these 34 post-menopausal women during 1 year of raloxifene therapy.

The serum concentrations of total and LDL-C decreased significantly after 12 months of raloxifene therapy. Total-C was lowered by 10·2% ($P = 0{\cdot}02$) and LDL-C by 22·6% ($P = 0{\cdot}007$) compared with the baseline. Although there was an observed increase in HDL-C and a decline in TG, the findings were not statistically significant (Table 3).

Effects of YSM on the outcome of raloxifene

The baseline characteristics of the group whose YSM ≤ 10 years were significantly different from those of the group whose YSM > 10 years in terms of age ($P < 0{\cdot}0001$) and BMI ($P = 0{\cdot}049$). The group whose YSM ≤ 10 years was younger and had a smaller BMI than the group whose YSM > 10 - years. There was no significant difference between the group whose YSM ≤ 10 years and the group whose YSM > 10 years with respect to the increase in their BMD in the spine ($P = 0{\cdot}79$). Mean

Table 2. Change in DEXA findings in women with low BMD

	Baseline (mean ± SD)	1 year (mean ± SD)	% change (mean ± SD)	*P*-value
Spine (g/cm^2)	0·871 ± 0·086	0·896 ± 0·081	2·9 ± 4·6	<0·0001
Spine, T-score	−2·08 ± 0·69	−1·85 ± 0·67	0·23 ± 0·31	<0·0001
Femur (g/cm^2)	0·694 ± 0·059	0·715 ± 0·070	3·0 ± 6·6	0·01
Femur, T-score	−1·72 ± 0·50	−1·54 ± 0·59	0·18 ± 0·38	0·012

Table 3. Change of serum lipid levels in women with low BMD

	Baseline (mean ± SD)	1 year (mean ± SD)	% change (mean ± SD)	*P*-value
Total Cholesterol (mg/dL)	203·02 ± 33·26	182·13 ± 28·62	−10·2 ± 16·2	0·02
LDL-C (mg/dL)	124·52 ± 36·35	96·29 ± 24·75	−22·6 ± 22·9	0·007
HDL-C (mg/dL)	57·62 ± 16·63	62·65 ± 11·99	8·90 ± 28·1	0·067
Triglycerides (mg/dL)	110·72 ± 69·09	102·75 ± 54·03	−7·4 ± 51·8	0·513

percentage changes of the BMD in the spine of groups whose YSM ≤ 10 years and YSM > 10 years were 3·2 ± 4·9% and 2·7 ± 4·2% respectively. However, there was a difference between the two groups with respect to the increase in their BMD in the femur (P = 0·05). The BMD of the femur in the

Table 4. Change in DEXA findings according to years since menopause (YSM)

	YSM ≤ 10 year (mean ± SD)	*P*-value*	YSM > 10 year (mean ± SD)	*P*-value*	*P*-value**
No.	21		13		
Age (years)	55·10 ± 5·73		66·00 ± 5·00		<0·0001
BMI (kg/m^2)	21·87 ± 1·48		23·60 ± 2·71		0·049
Women with previous hysterectomy, *n* (%)	6 (30)		8 (62)		0·058
DEXA findings					
Spine (g/cm^2)					
Baseline	0·873 ± 0·082	0·006	0·866 ± 0·094	0·040	0·828
1 year	0·901 ± 0·078		0·889 ± 0·087		0·682
% change	3·2 ± 4·9		2·7 ± 4·2		0·790
Spine T-score					
Baseline	−2·05 ± 0·68	0·006	−2·13 ± 0·73	0·017	0·757
1 year	−1·81 ± 0·65		−1·92 ± 0·72		0·675
Change	0·24 ± 0·34		0·21 ± 0·27		0·844
Femur (g/cm^2)					
Baseline	0·697 ± 0·064	0·003	0·689 ± 0·052	0·816	0·712
1 year	0·731 ± 0·065		0·692 ± 0·072		0·115
% change	4·5 ± 6·6		1·4 ± 5·7		0·05
Femur T-score					
Baseline	−1·70 ± 0·54	0·003	−1·75 ± 0·44	0·872	0·747
1 year	−1·40 ± 0·55		−1·74 ± 0·61		0·118
Change	0·30 ± 0·35		0·01 ± 0·35		0·079

*P-value from baseline; **P-value between groups.

group whose YSM > 10 years increased at a much lesser rate than that of the group whose YSM ≤ 10 years (Table 4). The regression lines in the BMD of the spine and the femur were not statistically significant.

Adverse events

The most common adverse event noted was the hot flash, which was observed in two women. These hot flashes were generally mild and did not require discontinuation of treatment. Symptoms that usually accompany hot flashes, like insomnia and sweating, were not observed. Other minor adverse events observed were nausea ($n = 1$), peripheral oedema ($n = 1$) and leg cramps ($n = 1$). For women who had undergone breast examination and mammography, no abnormal mammogram or breast sonogram results were found for 1 year. No evidence of increased risk of endometrial hyperplasia was found among those who had undergone transvaginal ultrasonography. In addition, vaginal bleeding or breast tenderness was not observed.

DISCUSSION

A substantial decrease in bone density of the lumbar spine has been shown in post-menopausal women who had recently discontinued HRT (11–13). Results of the study show that treatment with raloxifene not only helps prevent this loss, but is also associated with a gain of over 2% in the mean BMD of the spine and femur at 1 year. This change in the BMD was within the ranges reported in a previous raloxifene study (16). Delmas *et al.* found that the mean difference in the change in the BMD between the raloxifene group and the placebo group was 2·4 ± 0·4% for the lumbar spine, the total hip and the total body (16). The similarity of the BMD responses to raloxifene in different body regions that contain trabecular or the cortical bone suggests that the effect of raloxifene on these two bone types is similar. This is in contrast with other anti-resorptive agents like bisphosphonates, which preferentially increase BMD in the spine (19). One hypothesis accounting for the differential effect of bisphosphonates was based on the increase in the amount of mineral per volumetric unit of bone (20). Such an effect is more likely to be observed in sites rich in cancellous bone, such as the lumbar spine, characterized by higher turnover rates than the cortical bone (21). Thus, the relatively large increase in BMD, observed with anti-resorptive agents that markedly reduce bone turnover (below the normal pre-menopausal range) could be initially because of filling of the remodelling space (greatest in cancellous bone) and later to an increase in bone mineral per unit volume of bone (also greatest in cancellous bone).

Patients in the MORE study experienced a significant reduction in their risk of vertebral fracture at 3 years of raloxifene therapy (17). Thus, although their BMD response to raloxifene in their spines was substantially less than that observed for bisphosphonates, the reduction in their risk of vertebral fracture appeared to be similar (19). Approximately two-thirds of vertebral fractures do not produce clinical symptoms and remain unreported (21, 22). Therefore, the reduction in new clinical vertebral fractures may underestimate the actual 1-year efficacy of raloxifene for vertebral fractures.

This study demonstrated that the effects of raloxifene are consistent regardless of the women's YSM. Because of these similar increases in the BMD regardless of the duration of the menopause associated with raloxifene use, it would be expected that a population with more severe osteoporosis or with prior fractures would exhibit similar results.

Cardiovascular disease is a major health problem and is the leading cause of death among post-menopausal women (23). The decrease in LDL-C with raloxifene use as seen in this study may be expected to reduce the risk of coronary artery disease based on current epidemiological data illustrating reduced risk with declining LDL. An epidemiological study has found that the levels of LDL-C are related to the risk of coronary disease among both men and women (24). One such trial of a lipid-lowering agent found that 30% reduction in LDL-C levels is associated with 46% reduction in cardiovascular events (24). This suggests that the 22·6% reduction in LDL-C levels observed in this study, if sustained overtime, may lower the incidence of heart disease by as much as 35%. However, the reduction in LDL-C levels in this study was larger than that in previous studies (16, 25). Changes in LDL-C are because of various factors other than raloxifene, including diets, exercise and medications. Further research is therefore neces-

sary to elucidate the effectiveness of raloxifene in reducing LDL-C in post-menopausal women. The reduction in LDL–C without any change in the HDL-C or TG concentrations is consistent with previous results (16, 25). The Heart and Estrogen/progestin Replacement Study (HERS), which enrolled women with established coronary disease, found no benefit from HRT compared with a placebo for non-fatal myocardial infraction or death from coronary heart disease (26).

For women who had undergone breast examination and mammography, no abnormal mammogram or breast sonogram results were found for 1 year. No evidence of increased risk of endometrial hyperplasia was found among women who had undergone transvaginal ultrasonography. Previous findings of hot flashes and leg cramps with raloxifene therapy were also noted in this study; however, none of the women discontinued the treatment because of these symptoms. Most importantly, raloxifene did not cause vaginal bleeding or breast tenderness, which often limits the use of oestrogen therapy. Thus, it appears that long-term compliance could be greatly beneficial with raloxifene treatment. In addition, raloxifene can be administered without progestins. Other options for the maintenance of BMD after HRT discontinuation include a bisphosphonate such as alendronate (27). However, alendronate is known to cause upper gastrointestinal tract events (28).

The limitations of this study were that there was no placebo group and was evaluated retrospectively. In addition, because bone turnover marker tests were not performed, it was not possible to analyse the effect of raloxifene on bone metabolism. Another limitation of this study was that the patients had only moderately low BMDs and few incidences of prior osteoporotic fractures at the baseline. Although increases in BMD in patients treated with raloxifene were associated with reduced risk of fracture, this study was not comprehensive enough to determine such reducing effect. Also, because the duration of this study was limited to 12 months, the effects of HRT discontinuation and the addition of raloxifene over a longer period cannot be ascertained. Therefore, a randomized controlled trial for a longer period of time is necessary to be certain with the effect of raloxifene over a year.

The results demonstrated that a 1-year treatment of raloxifene increases BMD and lowers total and LDL-C serum concentrations in post-menopausal women with low BMD. This suggests that raloxifene may be useful in the prevention and treatment of osteoporosis and cardiovascular disease in post-menopausal women. The use of raloxifene can be considered whenever HRT is discontinued in post-menopausal women with risk factors for osteoporosis.

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