Showa Univ J Med Sci **24**(4), 301～308, December 2012

**Original**

# Effects of 3 Years of Treatment with a Selective Estrogen Receptor Modulator for Postmenopausal Osteoporosis on Markers of Bone Turnover and Bone Mineral Density

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**Abstract**: Aim: The aim of the present study was to assess the changes in bone mineral density and bone turnover markers in long-term SERM. Methods: The study was performed on 25 female outpatients with primary osteoporosis treated at the Osteoporosis Department of Showa University School of Medicine. All patients had been on raloxifene (60 mg/day) for ≥ 3 years. The mean patient age was 67.1 years and the women were, on average, 18.4 years postmenopausal. Levels of bone turnover markers (urinary naltrexone [NTX] and bone-specific alkaline phosphatase [BAP]) and bone mineral density (BMD; front lumbar vertebrae, three proximal femur sites, and two distal radius sites) were determined before and then annually after starting raloxifene for a period of 3 years. Results: Over the 3-year treatment period, significant decreases were seen in both urinary NTX and BAP levels. Although BMD of the lumbar vertebrae and distal radius was increased over the 3 years after initiation of raloxifene treatment, the difference failed to reach statistical significance. The BMD of the femoral neck decreased, whereas that of the femoral trochanter and femoral intertrochanter area increased. Conclusions: The selective estrogen receptor modulator raloxifene is suitable for the treatment of osteoporosis in postmenopausal patients because it reduces bone turnover while maintaining adequate bone density.

**Key words**: raloxifene, SERM: selective estrogen receptor modulator, bone mineral density

## Introduction

In Japan, osteoporosis can be treated with bisphosphonates, selective estrogen receptor modulators (SERMs), parathyroid hormone (PTH), or calcitonin. Bisphosphonates improve bone mineral density (BMD) and inhibit bone resorption. However, there are some limitations associated with their use: patients have to take the drug soon after waking up, they must avoid lying down for at least 30 min, and they need to take the drug with approxi-

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mately 180 mL water. There are no such limitations imposed on the use of SERMs, making these drugs the preferred treatment option for osteoporosis. SERMs have been reported to increase the formation of collagen cross-links and to improve bone mineral properties[1,2]. However, only postmenopausal women can be administered SERMs, and physicians are required to select other drugs for the treatment of osteoporosis in men or premenopausal women. Compared with bisphosphonates, such as alendronate and risedronate, SERMs only slightly improve markers of bone turnover. In the present study, to evaluate the efficacy of SERM treatment, we investigated changes in multiple markers of bone turnover, as well as BMD at different sites, over a 3-year period in women who had been on the SERM raloxifene for at least 3 years beginning in 2007.

## Methods

*Subjects*

The subjects of the present study were 25 women who were attending the Osteoporosis Outpatient Unit of Showa University Hospital for the treatment of postmenopausal osteoporosis. All women had been on raloxifene (60.0 mg/day) for $>3$ years. The mean age of the women was 67.1 years (range 54–84 years), and they were, on average, 18.4 years postmenopausal (range 3–36 years).

*Methodology*

Markers of bone turnover (urinary cross-linked N-terminal telopeptides of type I collagen [NTX] and bone-specific alkaline phosphatase [BAP]) and BMD were determined in each patient before and then annually after starting raloxifene treatment. BMD was measured in the anteroposterior lumbar spine, the proximal femur (neck, intertrochanter, and trochanter), and the ultradistal radius (the ultradistal radius and distal one-third of the radius) by dual energy X-ray absorptiometry (Discovery A ; Hologic, Bedford, MA, USA).

*Statistical analysis*

Data are presented as the mean ± SD. Values obtained prior to initiating treatment were considered as reference (baseline) values. Differences were analyzed using Student's *t*-test, with $P < 0.05$ considered significant. All analyses were performed using Stat Mate III ver. 3.14 (ATMS, Tokyo, Japan).

*Ethical considerations*

This study was approved by the Ethics Committee of Showa University School of Medicine (Approval No. 1169). All patients provided written informed consent prior to participating in the study.

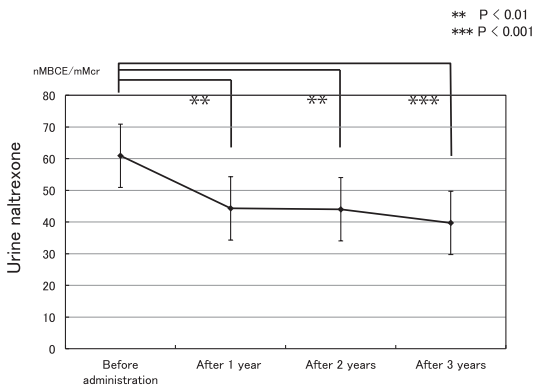


Fig. 1. Urinary levels of type I collagen cross-linked N-telopeptides (NTX) before and after 1, 2, and 3 years of treatment with raloxifene (60.0 mg/day). There was a significant decrease in NTX levels after 1 year, and although there was a tendency for levels to decrease in subsequent years, values were maintained at around 40 bone collagen equivalents (BCE)/mmol creatinine (Cr).
Data are the mean ± SD., $^{**}P < 0.01$, $^{***}P < 0.001$ compared with baseline (before treatment) values.

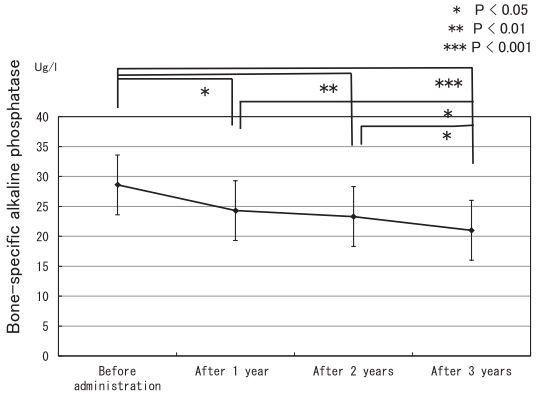


Fig. 2. Changes in bone-specific alkaline phosphatase (BAP) before and after 1, 2, and 3 years of treatment with raloxifene (60.0 mg/day). Significant decreases (20-25 μg/L) were observed beginning 1 year after the initiation of therapy.
Data are the mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with baseline (before treatment) values.

## Results

*Markers of bone turnover*

Prior to starting raloxifene treatment, mean urinary NTX levels in the 25 women were 61.9 ± 32.6 nmol bone collagen equivalents (BCE)/mmol creatinine (Cr). After 1, 2, and 3 years treatment, urinary NTX levels were 44.3 ± 27.4, 41.7 ± 26.9, and 38.5 ± 17.5 nmol BCE/mmol Cr, respectively ($P < 0.01$, $P < 0.01$, and $P < 0.001$ compared with baseline, respectively). As indicated in Fig. 1, urinary NTX levels decreased significantly from 1 year after initiation of raloxifene treatment.

Prior to raloxifene treatment, baseline BAP levels were 29.0 ± 15.0 μg/L. After 1, 2, and 3 years of treatment, BAP levels had decreased to 24.3 ± 11.3, 23.4 ± 10.3, and 20.8 ± 11.1 μg/L, respectively ($P < 0.05$, $P < 0.01$, and $P < 0.001$ compared with baseline, respectively). As for urinary NTX levels, BAP levels started to decrease significantly from 1 year after the start of raloxifene treatment (Fig. 2).

*Bone mineral density* (Table 1)

There were no significant changes in the BMD of L2-L4 over the 3-year treatment period (Fig. 3a). Most importantly, none of the patients experienced any new compression fractures over this time.

In the proximal femur, there were significant decreases in the BMD of the femoral neck

Table 1 Bone mineral density at various sites before (baseline) and after 1, 2, and 3 years of treatment with raloxifene.

| | Bone mineral density ($mg/cm^2$) | *P*-value* |
|---|---|---|
| Anteroposterior lumbar spine (L2–L4) | | |
| Baseline | 0.730 ± 0.141 | |
| 1 year | 0.730 ± 0.155 | 0.97 |
| 2 years | 0.728 ± 0.154 | 0.78 |
| 3 years | 0.738 ± 0.164 | 0.46 |
| Proximal femur | | |
| Femoral neck | | |
| Baseline | 0.549 ± 0.070 | |
| 1 year | 0.538 ± 0.082 | 0.89 |
| 2 years | 0.528 ± 0.097 | $P < 0.05$ |
| 3 years | 0.521 ± 0.093 | $P < 0.05$ |
| Femoral trochanter | | |
| Baseline | 0.453 ± 0.072 | |
| 1 year | 0.476 ± 0.091 | $P < 0.05$ |
| 2 years | 0.504 ± 0.071 | $P < 0.01$ |
| 3 years | 0.499 ± 0.077 | $P < 0.001$ |
| Intertrochanter | | |
| Baseline | 0.717 ± 0.108 | |
| 1 year | 0.727 ± 0.128 | 0.34 |
| 2 years | 0.746 ± 0.125 | $P < 0.05$ |
| 3 years | 0.754 ± 0.132 | $P < 0.01$ |
| Ultradistal radius | | |
| Baseline | 0.306 ± 0.076 | |
| 1 year | 0.304 ± 0.076 | 0.87 |
| 2 years | 0.301 ± 0.065 | 0.68 |
| 3 years | 0.294 ± 0.062 | 0.17 |
| Distal one-third of the radius | | |
| Baseline | 0.462 ± 0.083 | |
| 1 year | 0.460 ± 0.079 | 0.89 |
| 2 years | 0.459 ± 0.079 | 0.80 |
| 3 years | 0.467 ± 0.068 | 0.51 |

Data show the mean ± SD.
*P-values are for comparisons with baseline values.

after 2 and 3 years of treatment with raloxifene, but not after 1 year (Fig. 3b). In contrast, the BMD of the femoral trochanter and intertrochanter increased significantly over the treatment period (Fig. 3c, d).

Finally, raloxifene treatment had no significant effect on the BMD of the ultradistal radius or the distal one-third of the radius (Fig. 3e, f).

## Discussion

Raloxifene, a SERM, is a member of the benzothiophene family that does not have a steroidal backbone. It inhibits bone resorption without affecting the endometrium and

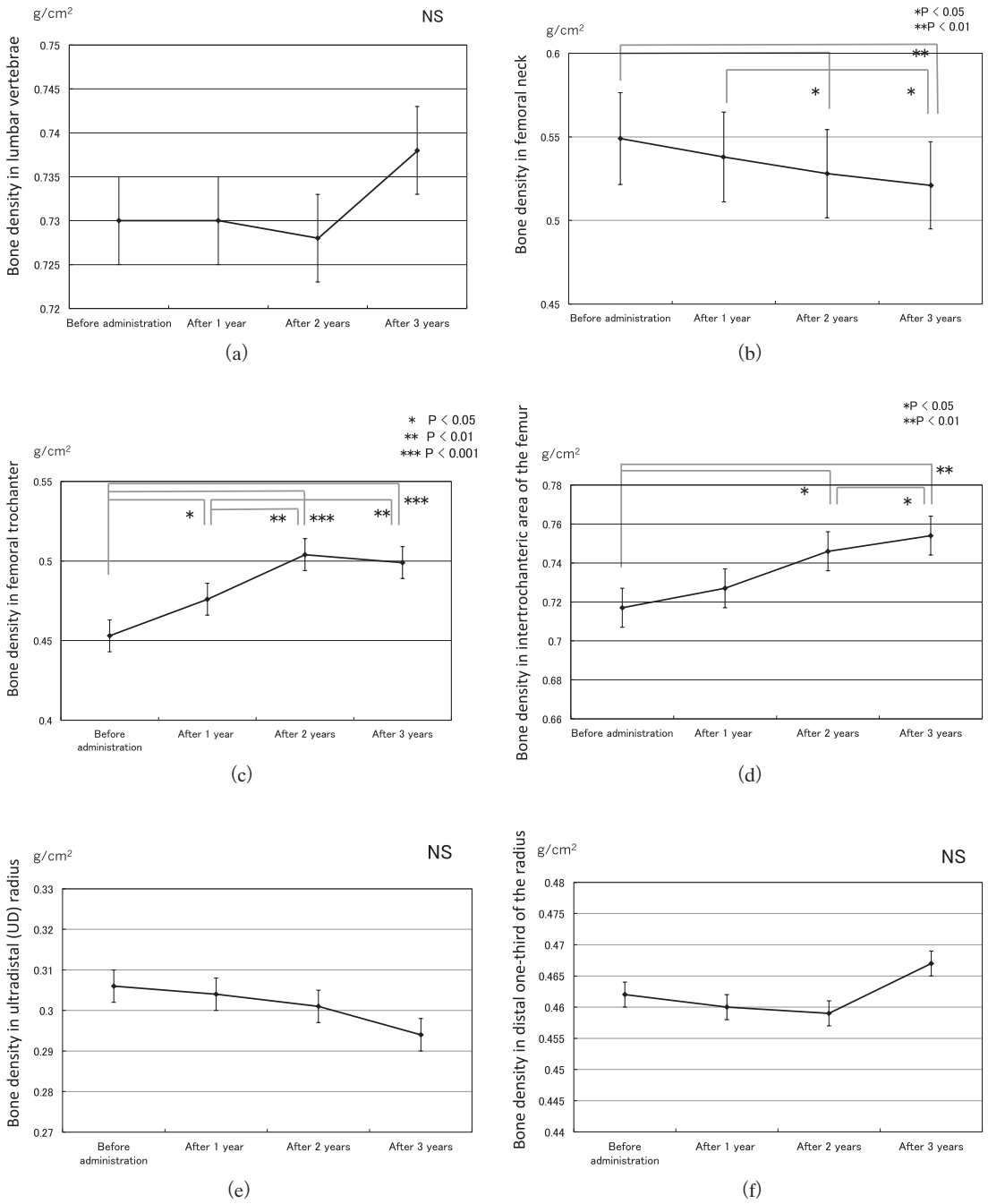


Fig. 3. Changes in the bone mineral density (BMD of (a) the second to fourth lumbar vertebrae (L2–L4), (b) femoral neck, (c) femoral trochanter (troch), (d) intertrochanteric area, (e) ultradistal radius, and (f) distal one-third of the radius before and after 1, 2, and 3 years of treatment with raloxifene (60 mg/day). Significant increases were seen in the BMD of the femoral trochanter and intertrochanteric area, whereas the BMD of the femoral neck decreased significantly after 2 and 3 years of treatment.
Data are the mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with baseline (before treatment) values.

increases bone mass[3]. The side effects of raloxifene include hot flashes, sweating, dizziness, gastrointestinal disorders, and edema or convulsions of the lower limbs[4,5]. In Showa University Hospital, we have also observed mild symptoms, such as breast enlargement; however, no serious side effects, such as deep vein thrombosis, have been encountered.

There are several options for the treatment of osteoporosis, including active vitamin $D_3$, vitamin $K_2$, and calcium, as well as bisphosphonates, SERMs, and PTH. Treatment for osteoporosis needs to be tailored to meet individual patient requirements. For example, bisphosphonates, SERMs, and calcitonin inhibit bone resorption, whereas PTH promotes bone formation. To determine the best treatment regimen for our patients, we perform simple X-ray examinations of the thoracic and lumbar vertebrae; biochemical tests of the blood and urine; measure BMD of the lumbar vertebrae, femur, and radius; and determine levels of bone turnover markers and PTH. These examinations provide information regarding the presence or absence of vertebral fractures, as well as the number of fractures if present; the young/adult ratio of BMD; whether bone turnover is high or low; whether serum calcium, phosphorus, and magnesium levels are in the normal range; and the presence or absence of parathyroid dysfunction. Using this information, we develop therapeutic strategies for individual patients and determine the need for further referral to a physician or obstetrician.

In 2000, the US National Institutes of Health defined bone strength as 70% BMD and 30% ossein[6]. Bone turnover, microstructure, microfracture, and calcification are the factors contributing to ossein. Of these, bone turnover is the most easily measured in clinical practice using markers of bone turnover[7,8], such as NTX levels in the blood and urine, BAP, tartrate-resistant acid phosphatase-5b, and N-propeptide of type I procollagen. Undercarboxylated osteocalcin (ucOC) is another marker of bone turnover that can be used as an index of sufficient vitamin K levels in the blood. If blood ucOC levels are high, vitamin $K_2$ may be administered. Furthermore, levels of pentosidine or homocysteine can be used as predictors of vertebral fractures[9]. Although these measures provide clinically important information, they are currently not covered by osteoporosis insurance in Japan, which is an issue that needs to be resolved.

In the present study, raloxifene decreased NTX by 28% over the course of 1 year. In another study, we found that alendronate decreased NTX by 66% over the course of 1 year[10]. In the present study, raloxifene significantly decreased both urinary NTX (a marker of bone resorption) and BAP (a marker of bone formation), and inhibited bone turnover. We did not observe atypical femur fractures[11,12] or jaw osteonecrosis[13], which have been reported previously as complications associated with the use of bisphosphonates, and this may be due to the lower potency of raloxifene. If significant inhibition of bone resorption markers is necessary, then bisphosphonates are the better choice; however, in patients undergoing dental treatment, those exhibiting only slightly enhanced levels of bone resorption markers, or in those who are recovering from fractures (i.e. those in whom bone turnover should not be excessively inhibited), it is preferable to use SERMs.

There were no significant decreases in the BMD of the lumbar vertebrae or radius. However, there was a decrease in the BMD of the femoral neck and an increase in the BMD of the femoral trochanter. The femoral trochanter has more spongy bone than the femoral neck[14], which may explain the increase in BMD in the trochanter over the course of drug treatment. According to a bridging study of raloxifene conducted in Japan[4], the BMD of the lumbar vertebrae in the raloxifene-treated group was significantly higher than that of the placebo-treated group after 24 weeks, with the former group also exhibiting a significantly higher mean increase in BMD after 1 year of treatment (3.5%). In the multiple outcomes of raloxifene evaluation (MORE) trial, the BMD of the lumbar vertebrae and femoral neck increased by 2.6% and 1.3%, respectively, significantly higher than that in the placebo-treated group[15]. No significant differences of the BMD of the lumbar vertebrae were observed between before administration and after 3 years in the present study, although there was a tendency for the BMD of the lumbar vertebrae to increase with treatment. The radius is not a weight-bearing bone and is not easily affected by mechanical stress. Wiping the floor with hands is a good exercise for the radius; however, modern lifestyles offer few opportunities to perform such tasks. We recommend that people perform intentional weight-bearing exercises for the radius (e.g. wall-pushing exercise) and femoral neck (e.g. standing on one leg with the eyes open)[16], both of which contain cortical bone.

In conclusion, in the present study we examined the effects of raloxifene, a SERM, on BMD and markers of bone turnover over a 3-year period. During this time, there was a significant decrease in markers of bone turnover. Although there was a tendency for increased BMD of the lumbar vertebrae over the same period, the differences failed to reach statistical significance. Thus, raloxifene appears to be suitable for use in postmenopausal women in whom bone turnover needs to be decreased gradually while BMD is maintained.

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[Received September 25, 2012 : Accepted November 10, 2012]