

# Determinants of One-year Response of Lumbar Bone Mineral Density to Alendronate Treatment in Elderly Japanese Women with Osteoporosis

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The purpose of this study was to determine factors that could predict the one-year response of the lumbar bone mineral density (BMD) to alendronate treatment in elderly Japanese women with osteoporosis. Eighty-five postmenopausal women with osteoporosis, all of whom were between 55-88 years of age, were treated with alendronate (5 mg daily) for 12 months. Serum calcium, phosphorus, and alkaline phosphatase (ALP) and urinary NTX levels were measured at the baseline and 6 months, and lumbar (L1-L4) BMD was measured by dual energy X-ray absorptiometry at the baseline and 12 months. Multiple regression analysis was used to determine factors that were correlated with the percent change in lumbar BMD at 12 months. Lumbar BMD increased by 8.1 % at 12 months with a reduction in the urinary NTX level by 51.0 % at 6 months. Baseline lumbar BMD ( $R^2=0.226$ ,  $p<0.0001$ ) and percent changes in serum ALP and urinary NTX levels ( $R^2=0.044$ ,  $p<0.05$  and  $R^2=0.103$ ,  $p<0.001$ , respectively) had a negative correlation with the percent change in lumbar BMD at month 12, while the baseline number of prevalent vertebral fractures ( $R^2=0.163$ ,  $p<0.001$ ), serum ALP level, and urinary NTX level ( $R^2=0.074$ ,  $p<0.05$  and  $R^2=0.160$ ,  $p<0.001$ , respectively) had a positive correlation with it. However, baseline age, height, body weight, body mass index, years since menopause, serum calcium and phosphorus levels, and percent changes in serum calcium and phosphorus levels at 6 months did not have any significant correlation with the percent change in lumbar BMD at 12 months. These results suggest that lumbar BMD was more responsive to one-year of alendronate treatment in elderly osteoporotic Japanese women with lower lumbar BMD, more prevalent vertebral fractures, and higher bone turnover, who showed a greater decrease in

bone turnover at 6 months, regardless of age, years since menopause, and physique. Alendronate may be efficacious in elderly Japanese women with evident osteoporosis that is associated with high bone turnover, and the percent changes in serum ALP and urinary NTX levels at 6 months could predict the one-year response of lumbar BMD to alendronate treatment.

**Key Words:** Osteoporosis, alendronate, bone mineral density (BMD), cross-linked N-terminal telopeptides of type I collagen (NTX), alkaline phosphatase (ALP)

## INTRODUCTION

Osteoporosis most commonly affects postmenopausal women, placing them at significant risk for fracture - especially fractures of the vertebrae and the hip. Hormone replacement therapy is useful to prevent bone loss in early postmenopausal women, while bisphosphonates are useful to prevent osteoporotic fractures in elderly women. It has been established that the bisphosphonate, alendronate increases lumbar and femoral neck bone mineral density (BMD) and prevents vertebral and hip fractures in postmenopausal women with osteoporosis.<sup>1-3</sup> In particular, the efficacy of alendronate in preventing vertebral fractures was demonstrated in both women with existing vertebral fractures and women with low BMD but no vertebral fractures,<sup>1,2</sup> and furthermore, the reduction in the risk of morphometric vertebral fractures was consistent.

Recently, the measurement of bone markers has been developed. Bone resorption markers, such as

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urinary deoxypyridinoline and/or cross-linked telopeptides of type I collages, have been demonstrated to predict an increase in lumbar BMD in response to the treatment in early or late postmenopausal women with osteoporosis.<sup>4,8</sup> In particular, a highly significant correlation has been shown between the percent change in urinary cross-linked N-terminal telopeptides of type I collagen (NTX) level at 3 or 6 months and the percent change in lumbar BMD after 2 years of alendronate treatment in late postmenopausal osteoporotic women.<sup>7,8</sup> These reports suggest that when the stronger bone resorption is suppressed especially during the early period of osteoporosis in postmenopausal women, there is a greater increase in lumbar BMD. Thus, the usefulness of the measurement of bone markers has been confirmed. However, little attention has been paid to other factors that could possibly predict the response of lumbar BMD to alendronate treatment. The purpose of this study was to determine factors that could predict the one-year response of lumbar BMD to alendronate treatment in elderly Japanese women with osteoporosis.

## MATERIALS AND METHODS

### Subjects

Eighty-five postmenopausal women with oste-

oporosis,<sup>9,10</sup> between 55-88 years of age, were recruited at our hospital from August to October, 2002. According to the Japanese criteria for osteoporosis in women, patients whose BMD was < 70% of the young adult mean (YAM) or 70-80% of the YAM with a history of osteoporotic fractures were diagnosed as having osteoporosis. All of them were treated with alendronate (5 mg daily) for 12 months. This dose has been recognized as effective for Japanese patients with osteoporosis.<sup>11,12</sup> None of the subjects suffered from any bone metabolic disease, and none had a history of hormone (estrogen) replacement therapy or had ever taken medication that affects bone metabolism prior to this study. All subjects were instructed to take 800 mg of calcium daily through food intake.

Pre- and post-treatment examinations included medical history, physical examination, radiographic examination of the thoracic and lumbar spine, lumbar BMD measurement, and blood and urine biochemical tests. The assessment of vertebral fractures on radiographs and lumbar BMD measurements were performed as described in the following sections. Serum calcium, phosphorus, and alkaline phosphatase (ALP) levels were measured using standard laboratory techniques. The urinary NTX level was measured by using the enzyme-linked immunosorbent assay. Table 1 illustrates the characteristics of the study subjects.

Informed consent was obtained from each

**Table 1.** Characteristics of Study Subjects

	Mean $\pm$ SD	Ranges
Age (years)	72.2 $\pm$ 7.8	55 - 88
Height (cm)	145 $\pm$ 7	125 - 164
Body weight (kg)	44.7 $\pm$ 8.3	25 - 62
Body mass index (kg/m <sup>2</sup> )	21.2 $\pm$ 3.3	13.7 - 28.3
Years since menopause	22.0 $\pm$ 6.6	7 - 37
Lumbar BMD (g/cm <sup>2</sup> )	0.574 $\pm$ 0.103	0.339 - 0.769
Percentage of the YAM	56.1 $\pm$ 10.1	33 - 75
Number of prevalent vertebral fractures per patient	3.0 $\pm$ 3.6	0 - 13
Serum calcium (mg/dl)	9.6 $\pm$ 0.5	8.9 - 10.9
Serum phosphorus (mg/dl)	3.3 $\pm$ 0.6	2.3 - 4.6
Serum ALP (IU/l)	223 $\pm$ 81	97 - 525
Urinary NTX (nmol BCE/mmol Cr)	71.4 $\pm$ 30.2	21.0 - 185.2

BMD, bone mineral density; YAM, young adult mean; ALP, alkaline phosphatase; NTX, cross-linked N-terminal telopeptides of type I collagen.

patient. Serum calcium, phosphorus, and ALP and urinary NTX levels were measured at 6 months, and at 12 months, the lumbar BMD was measured and radiographs of the thoracic and lumbar spine were assessed. The primary end point of this study was the correlation of the percent change in lumbar BMD at 12 months with factors that included baseline characteristics and changes in biochemical markers, such as serum calcium, phosphorus, and ALP and urinary NTX at 6 months. This study was carried out at Keiyu Orthopaedic Hospital, and the protocol was approved by the ethical committee of Keiyu Orthopaedic Hospital.

### Lumbar BMD measurement

BMD of the lumbar spine in the antero-posterior view was measured by dual energy X-ray absorptiometry (DXA) using a Hologic QDR 1500W instrument (Bedford, MA, USA). The coefficients of variation (CV,  $100 \times \text{standard deviation} / \text{mean}$ ) of 5 measurements each time with repositioning within 72 hours was less than 1.2% in 3 persons.

### Assessment of vertebral fractures

Radiographs of the thoracic and lumbar spine were obtained in order to find evidence of vertebral fractures. A vertebral fracture was defined according to the vertebral height obtained from lateral X-ray films based on the Japanese criteria.<sup>9,10</sup> The vertebral height was measured at the anterior (A), central (C), and posterior (P) parts of the vertebral body, and the presence of a vertebral fracture was confirmed when (1) a more than a 20% reduction of vertebral height (A, C, and P), compared with the neighboring vertebrae, was observed; (2) C/A or C/P was less than 0.8; or (3) A/P was less than 0.75. An assessment of vertebral fractures was performed for the T4-L4 spine.

### Statistical analysis

Data are expressed as the mean  $\pm$  standard deviation (SD). The significance of longitudinal changes in lumbar BMD and urinary NTX and serum calcium, phosphorus, and ALP levels were

determined by one-way ANOVA with repeated measurements. The correlation between percent change in lumbar BMD and various factors was examined through multiple regression analysis. Furthermore, the correlation between percent change in lumbar BMD and serum ALP and urinary NTX levels was examined through single regression analysis. All statistical analyses were performed using the Stat View-J5.0 program on a Macintosh computer. A significance level of  $p < 0.05$  was used for all comparisons.

## RESULTS

### Changes in lumbar BMD, and serum calcium, phosphorus, and ALP and urinary NTX levels

Table 2 shows the longitudinal changes in lumbar BMD, and serum calcium, phosphorus, and ALP and urinary NTX levels. The mean percent change in lumbar BMD was + 8.1% at 12 months compared with the baseline, and this change was significant ( $p < 0.0001$ , one-way ANOVA with repeated measurements). The mean change in serum ALP and urinary NTX levels at 6 months was - 8.9% and - 51.0%, respectively, and these changes were significant (both  $p < 0.0001$ , one-way ANOVA with repeated measurements). However, serum calcium and phosphorus levels did not significantly change.

### Correlation between percent changes in lumbar BMD and various factors

Table 3 shows the correlation between the percent changes in lumbar BMD at 12 months and a variety of factors. The multiple regression analysis illustrated that the baseline lumbar BMD ( $R^2 = 0.226$ ,  $p < 0.0001$ ) and percent changes in serum ALP and urinary NTX levels ( $R^2 = 0.044$ ,  $p < 0.05$  and  $R^2 = 0.103$ ,  $p < 0.001$ , respectively) had a negative correlation with the percent change in lumbar BMD at 12 months, while the baseline number of prevalent vertebral fractures ( $R^2 = 0.163$ ,  $p < 0.001$ ) and serum ALP and urinary NTX levels ( $R^2 = 0.074$ ,  $p < 0.05$  and  $R^2 = 0.160$ ,  $p < 0.001$ , respectively) had a positive correlation with it. However, baseline age, height, body weight, body mass

**Table 2.** Changes in Lumbar BMD and Biochemical Markers

	Baseline	6 months	12 months	<i>p</i> value One-way ANOVA
Lumbar BMD (g/cm <sup>2</sup> )	0.574 ± 0.103		0.615 ± 0.097	<0.0001
(% change from baseline)			(+8.1 ± 10.4)	
Serum calcium (mg/dl)	9.6 ± 0.5	9.5 ± 0.6		N S
(% change from baseline)		(-0.6 ± 6.7)		
Serum phosphorus (mg/dl)	3.3 ± 0.6	3.4 ± 0.5		N S
(% change from baseline)		(+5.2 ± 18.9)		
Serum ALP (IU/l)	223 ± 81	195 ± 59		<0.0001
(% change from baseline)		(-8.9 ± 19.0)		
Urinary NTX (nmol BCE/mmol Cr)	71.4 ± 30.2	32.3 ± 13.4		<0.0001
(% change from baseline)		(-51.0 ± 19.6)		

Data are expressed as mean ± SD. One-way analysis of variance (ANOVA) with repeated measurements was used to determine significance of longitudinal change in parameters. BMD, bone mineral density; ALP, alkaline phosphatase; NTX, cross-linked N-terminal telopeptides of type I collagen.

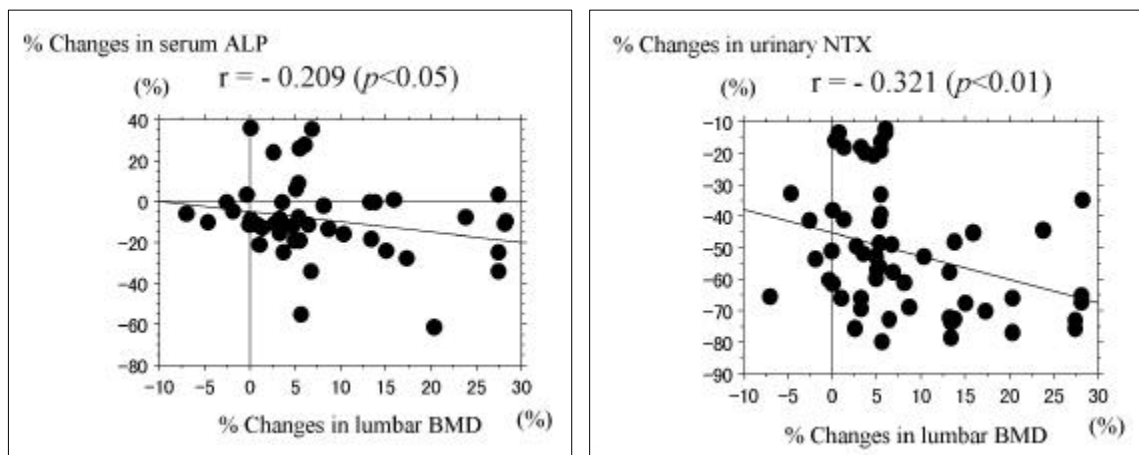
**Table 3.** Correlation of Percent Change in Lumbar BMD and Factors

Dependent variable	Independent variable	Regression coefficient	R <sup>2</sup>	<i>p</i> value
Age (years)	% Change in lumbar BMD (%)	0.048	0.004	N S
Height (cm)	% Change in lumbar BMD (%)	-0.108	0.026	N S
Body weight (kg)	% Change in lumbar BMD (%)	-0.046	0.003	N S
Body mass index (kg/m <sup>2</sup> )	% Change in lumbar BMD (%)	0.008	0.001	N S
Years since menopause	% Change in lumbar BMD (%)	0.026	0.002	N S
Lumbar BMD (g/cm <sup>2</sup> )	% Change in lumbar BMD (%)	-0.005	0.226	<0.0001
Number of prevalent vertebral fractures per patient	% Change in lumbar BMD (%)	0.138	0.163	<0.001
Serum calcium (mg/dl)	% Change in lumbar BMD (%)	-0.001	0.001	N S
Serum phosphorus (mg/dl)	% Change in lumbar BMD (%)	0.007	0.017	N S
Serum ALP (IU/l)	% Change in lumbar BMD (%)	2.108	0.074	<0.05
Urinary NTX (nmol BCE/mmol Cr)	% Change in lumbar BMD (%)	1.161	0.160	<0.001
% Change at 6 months				
Serum calcium (%)	% Change in lumbar BMD (%)	-0.017	0.001	N S
Serum phosphorus (%)	% Change in lumbar BMD (%)	-0.018	9.334 e <sup>-5</sup>	N S
Serum ALP (%)	% Change in lumbar BMD (%)	-0.383	0.044	<0.05
Urinary NTX (%)	% Change in lumbar BMD (%)	-0.605	0.103	<0.01

Multiple regression analysis was used to examine the correlation of the percent change in lumbar BMD at 12 months with various factors. SE, standard error; BMD, bone mineral density; ALP, alkaline phosphatase; NTX, cross-linked N-terminal telopeptides of type I collagen.

index, years since menopause, serum calcium and phosphorus levels, and percent changes in serum calcium and phosphorus levels at 6 months did not have a significant correlation with the percent change in lumbar BMD at 12 months. The single

regression analysis showed a negative correlation between the percent changes in lumbar BMD at 12 months and serum ALP and urinary NTX levels at 6 months ( $r=-0.209$ ,  $p<0.05$  and  $r=-0.321$ ,  $p<0.001$ , respectively) (Fig. 1).



**Fig. 1.** Correlation between Percent Changes in Lumbar BMD and Serum ALP and Urinary NTX Levels. Single regression analysis was used to examine the correlation between the percent change in lumbar BMD at 12 months and serum ALP and urinary NTX levels at 6 months. A significant correlation was found between the percent change in lumbar BMD at 12 months and serum ALP and urinary NTX levels at 6 months ( $r = -0.209$ ,  $p < 0.05$  and  $r = -0.301$ ,  $p < 0.01$ , respectively).

### Incidence of vertebral fractures

At the end of 12 months of treatment, plain X-ray examination of the thoracic and lumbar spine revealed no evidence of new thoracic or lumbar vertebral fractures in any of the patients. During the 12 months of treatment, nonvertebral osteoporotic fractures also did not occur in the hip, wrist, or shoulder in any of the patients.

### DISCUSSION

This study confirmed that a one-year treatment with alendronate increased the lumbar BMD by 8.1% in elderly women with osteoporosis. A double-blinded and well-controlled study demonstrated that one-year treatment with alendronate increased the lumbar BMD by 6.2% in Japanese postmenopausal women (mean age, 63 years) with osteoporosis.<sup>11</sup> Our results on lumbar BMD in Japanese elderly women (mean age, 72 years) with osteoporosis were slightly better than those of the previous well-controlled study. The factors that could predict the one-year response of the lumbar BMD to alendronate treatment were considered to be baseline lumbar BMD, number of prevalent vertebral fractures, serum ALP and urinary NTX levels, and percent changes in serum ALP and urinary NTX levels at 6 months. One of the

reasons for this slightly greater response of lumbar BMD to alendronate treatment may be that our subject had a more evident case of osteoporosis than those of the previous study.<sup>11</sup>

The normal range of the urinary NTX level in Japanese women (30-44 years of age) has been reported to be 9.3-54.3 nmol BCE/mmol creatinine.<sup>13</sup> Therefore, the elderly women in this study appeared to illustrate high bone turnover osteoporosis. In this population, anti-resorptive agents such as bisphosphonates were considered to be efficacious, and urinary NTX level was reduced by 51.0% at 6 months, which was greater than the minimum significant change (24.7%) in Japanese postmenopausal women.<sup>14</sup> The one-year outcome of alendronate treatment was thought to be satisfactory because the increase in the lumbar BMD was slightly greater than that in the previous study<sup>11</sup> and new vertebral or nonvertebral osteoporotic fractures were prevented.

On the other hand, the normal range of the serum ALP level in Japanese people is 100-340 IU/l. Therefore, unlike bone resorption markers, such as urinary NTX, the increase in serum ALP levels could not be detected at the baseline. The measurement of bone-specific ALP or osteocalcin levels might be necessary to determine the status of bone formation in elderly Japanese women with osteoporosis. However, in response to the alendronate treatment, even the serum total ALP

levels were observed to decrease by 8.9%, which is less responsive to the treatment than urinary NTX.

Consistent efficacy of alendronate in preventing vertebral fractures was demonstrated in postmenopausal osteoporotic women with or without existing vertebral fractures.<sup>1,2</sup> Conversely, it has not yet been established as to which patients are more responsive to alendronate treatment among postmenopausal women with osteoporosis. In the FIT study reported by Black et al.,<sup>1</sup> the alendronate treatment reduced the risk of one or more new morphometric vertebral fractures by 47% in postmenopausal osteoporotic women with existing vertebral fractures, while the risk of two or more fractures was reduced by 90%. Using these results, it was speculated that the alendronate treatment may be more efficacious in patients with more evident osteoporosis. In this study, regardless of age, years since menopause, and physique, a lower lumbar BMD, greater number of prevalent vertebral fractures, and higher levels of serum ALP and urinary NTX were significant factors that could result in a greater response of the lumbar BMD to alendronate treatment. This suggests that alendronate may be efficacious in elderly Japanese women with evident osteoporosis that is associated with high bone turnover.

The multiple regression analysis showed that the percent changes in serum ALP and urinary NTX levels at 6 months had a negative correlation with the percent change in the lumbar BMD at 12 months ( $R^2=0.044$  and  $R^2=0.103$ , respectively), which suggests that the reduction in bone turnover at 6 months could predict the one-year response of lumbar BMD to alendronate treatment. The single regression analysis showed a negative correlation between the percent changes in the lumbar BMD at 12 months and serum ALP and urinary NTX levels at 6 months ( $r=-0.209$  and  $r=-0.321$ , respectively). Greenspan et al.<sup>9</sup> illustrated a correlation between percent changes in the urinary NTX level at 6 months and the lumbar BMD at 2 years ( $r=-0.41$ ). Thus, our results on percent changes in urinary NTX and lumbar BMD may be almost consistent with a previous report.<sup>9</sup> Urinary NTX may be 2.34-fold more sensitive compared with serum ALP according to the  $R^2$  values. That is, urinary NTX may be more useful

in predicting the one-year response of lumbar BMD to alendronate treatment than serum total ALP. It may possibly be hard to use serum total ALP as an excellent predicting marker for evaluating the response of lumbar BMD to alendronate treatment. Our results suggest that as the bone turnover is suppressed in a stronger manner, especially at 6 months in postmenopausal women with osteoporosis, the greater the increase in lumbar BMD at 12 months.

It is well known that secondary elevation of serum parathyroid hormone (PTH) levels is observed frequently after the treatment of alendronate (10 mg daily) in Caucasians.<sup>15</sup> Because subjects in this study did not take any vitamin D supplementation, it will be interesting to examine the changes in serum PTH levels after alendronate treatment (5 mg daily). Although serum PTH levels were not measured, apparent hypocalcemia was not observed 6 months after the alendronate treatment in our subjects who were instructed to take 800 mg of calcium daily through food intake. However, the alteration of serum calcium and PTH levels after the alendronate treatment (5 mg daily) in Japanese patients with osteoporosis were clearly shown<sup>11</sup>; alendronate decreased serum calcium levels and increased serum PTH levels. Thus, vitamin D supplementation should have been considered in our subjects.

Of this study, there are several limitations to note. First, there was no placebo control group. Therefore, it was difficult to compare the true positive effects of the alendronate treatment with that of the placebo. Although the results on lumbar BMD were satisfactory, further studies are needed to confirm the true effects of alendronate treatment. Second, because side effects were not assessed adequately, the tolerability against the alendronate treatment in our subjects remains uncertain. However, it can be said that the compliance of this study was 85% because 85 of 100 patients recruited at the beginning of the trial was able to complete the trial. Although the tolerability against the alendronate treatment (5 mg daily) has already been shown in Japanese patients with osteoporosis,<sup>11</sup> further studies are needed to clarify the tolerability against the alendronate treatment in our subjects (elderly Japanese elderly women with osteoporosis).

In conclusion, the results of this study suggest that lumbar BMD was more responsive to one-year of alendronate treatment in elderly osteoporotic Japanese women with lower lumbar BMD, more prevalent vertebral fractures, and higher bone turnover, who showed a greater decrease in bone turnover at 6 months, regardless of age, years since menopause, and physique. Alendronate may be efficacious in elderly Japanese women with evident osteoporosis that is associated with high bone turnover. Also, the percent changes in serum ALP and urinary NTX levels at 6 months can predict the one-year response of the lumbar BMD to the alendronate treatment.

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