

# Long-Term Effect of Alendronate on Bone Mineral Density in Postmenopausal Type 2 Diabetes Mellitus

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## Abstract

The purpose of this study was to investigate the long-term effect of anti-resorptive agent, alendronate, on bone mineral density (BMD) in postmenopausal osteoporotic diabetic women. Twelve postmenopausal type 2 diabetic women (mean age;  $70.4 \pm 5.4$  yrs, duration of diabetes;  $13.1 \pm 3.9$  yrs) were administered alendronate sodium (5 mg/day) for 5 years. The radial BMD and urinary N-telopeptide cross-linked collagen type (NTx), one of biochemical markers, were measured every year. These parameters were compared with those in age-matched 12 control postmenopausal diabetic women not treated with alendronate. The radial BMD significantly ( $p < 0.05$ ) decreased by 5.30% at 2yr, 8.38% at 3yr, 9.71% at 4yr, and 11.12% at 5yr, in control subjects. While, radial BMD did not significantly change in diabetic women treated with alendronate. The decrease in radial BMD was significantly greater in control subjects than in subjects treated with alendronate at 3, 4, and 5year. Urinary NTx significantly decreased only in women with alendronate treatment. These data suggest that long-term administration of alendronate inhibits the decrease in BMD in postmenopausal type 2 diabetic women with low BMD.

**Keywords:** Alendronate; Bone mineral density; Type 2 diabetes mellitus; Urinary NTx

## Introduction

It has been reported that type 2 diabetes is a risk factor for hip, proximal humerus, and foot fractures among older women [1,2]. It is also demonstrated that postmenopausal women who have diabetes had a 1.40~1.70-fold higher risk of incident hip fracture than women without diabetes [3-5]. These studies suggest that fracture prevention efforts should be an important consideration in the treatment of diabetes in older women.

Several studies have indicated that the anti-resorptive agent alendronate, a potent aminobisphosphonate, has been shown to increase bone mineral density (BMD) at the hip and spine and decrease the incidence of osteoporotic fractures in older women [6-8]. In a previous study, we suggested that one year of alendronate treatment have a clinical significance in postmenopausal type 2 diabetic women with low BMD [9]. Similarly, Keegan et al. [10] reported that three years of alendronate treatment was associated with increased BMD at all studied, including 6.6% at the lumbar spine and 2.4% at the hip in older women with type 2 diabetes. While, Dagdelen et al. [11] reported that postmenopausal type 2 diabetes are resistant to long-term (4.8year) bisphosphonate treatment. The present study was examined to elucidate the long-term effect of alendronate on radial BMD, HbA1c, and changes in biochemical marker of resorption, urinary NTx, in postmenopausal women with type 2 diabetes.

## Materials and Methods

### Subjects

Twenty-four postmenopausal women who have type 2 diabetes mellitus (aged 59-80 year) were enrolled in the present study from April to September 2005. Inclusion criteria were 1) postmenopausal women of at least 10 year's duration of diabetes, 2) urinary N-telopeptide cross-linked collagen type (NTx) was more than 40 nmol bone collagen equivalents (BCE)/mmol creatinine(Cr), and 3) radial BMD was less than  $0.400 \text{ g/cm}^2$ . Potential subjects were excluded if they had a history of any illness affecting bone metabolism [e.g., renal failure, microalbuminuria ( $\geq 30 \text{ mg/g.cr}$ ), hepatic failure, active malignancy,

hyperthyroidism, hyperparathyroidism, or malabsorption], or had been treated for osteoporosis with hormone replacement therapy or calcitonin. Subjects treating with diuretics were also excluded. Their diabetic condition was stable and informed consent was obtained from the subjects. Thus, 12 subjects (mean age;  $70.4 \pm 5.4$  yrs, duration of diabetes;  $13.1 \pm 3.9$  yrs) were administered alendronate sodium (Banyu Pharma. Co., Osaka) per os in a dose of 5mg (once daily) or 35mg (once weekly), 30minutes before breakfast. Twelve subjects (mean age;  $70.1 \pm 6.4$  yrs, duration of diabetes;  $12.8 \pm 2.4$  yrs) refused to take medicine (alendronate) because of no clinical symptoms etc. They were served as a control. The therapeutic trial lasted 5 years. During the study, subjects continued their standard antidiabetic therapy, diet, oral hypoglycemic agents, or insulin. The dosage was appropriately changed to obtain better glycemic control in all the subject. The clinical characteristics of the subject are shown in Table 1.

### Biochemical markers

Following an overnight fast, we obtained a second-void 2-h urine collection. All samples were frozen at  $-20^\circ\text{C}$ . Urinary N-telopeptide cross-linked collagen type I [NTx, nmol bone collagen equivalents(BCE)/mmol creatinine(Cr)] was measured with an enzyme-linked immunosorbent assay [12]. Urinary NTx was measured at baseline and every year.

### Bone mineral density

Bone mineral density (BMD,  $\text{g/cm}^2$ ) of radius (ultradistal) were

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Received September 14, 2011; Accepted October 10, 2011; Published November 20, 2011

Citation: Ikeda T, Iwata K (2011) Long-Term Effect of Alendronate on Bone Mineral Density in Postmenopausal Type 2 Diabetes Mellitus. J Diabetes Metab S1:002. doi:10.4172/2155-6156.S1-002

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	Alendronate (n=12)	Control (n=12)
Age (yr)	70.4±5.4	70.1±6.4
BMI (kg/m <sup>2</sup> )	23.8±4.2	24.1±3.5
Treatment of diabetes		
Diet	1	1
OHA	5	6
Insulin	6	5
HbA1c (%)	7.6±1.4	7.3±1.5
Duration	13.1±3.9	12.8±2.4
Urinary NTx (nmol BCE/mmol Cr)	68.7±12.5	60.3±13.2
BMD (g/cm <sup>2</sup> )	0.296±0.066	0.318±0.041

OHA: oral hypoglycemic agent, BMD: bone mineral density

Table 1: Characteristics of the subject.

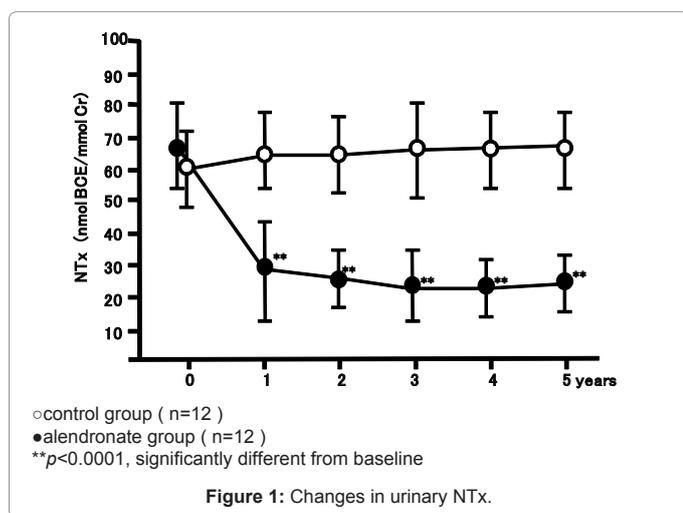


Figure 1: Changes in urinary NTx.

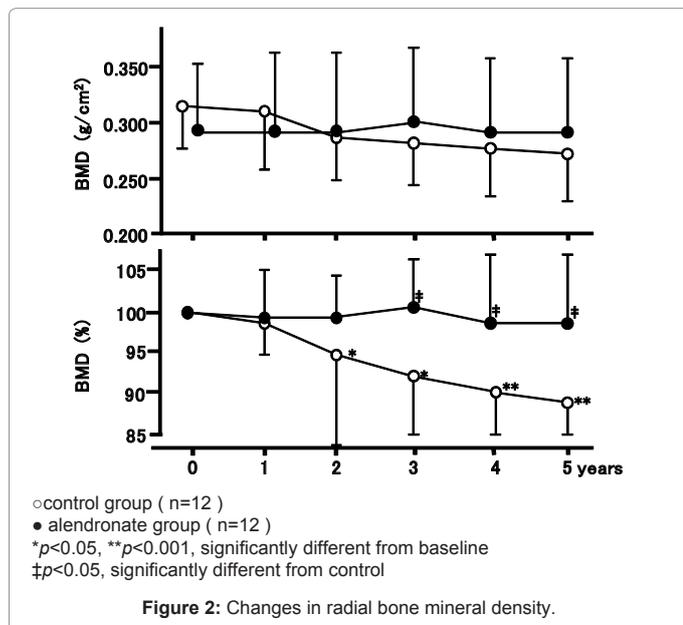


Figure 2: Changes in radial bone mineral density.

measured by dual-energy X-ray absorptiometry at baseline and every year.

### Statistical analysis

The data were expressed as the means ± SD. Statistical difference

between groups was determined by ANOVA and two-tailed Student's paired *t*-test. Wilcoxon test were used to evaluate the intra-subject variability of the NTx and radial BMD. Correlation was tested using Pearson's method. A *p* value <0.05 was considered statistically significant.

## Results

### Characteristics of the subject

Characteristics of the subject were shown in (Table 1). The age, BMI, duration of diabetes, mode of therapy, HbA1c level, urinary NTx, and radial BMD were not significantly different between two groups. Alendronate were well tolerated in all subjects. Abnormal laboratory findings of renal or hepatic function did not occur by alendronate administration.

### Glycemic control

The basal HbA1c value was 7.6 ± 1.4% and 7.3 ± 1.5% in alendronate and control group. HbA1c level fell progressively from baseline to 7.3 ± 1.4% and to 7.0 ± 1.2% in two groups after 5 years, respectively. There were no significant differences (*p*<0.60) between two groups.

### Changes in urinary NTx

As shown in (Figure 1), baseline levels of urinary NTx were 68.7 ± 12.5 nmol BCE/mmol Cr and 60.3 ± 13.2 nmol BCE/mmol Cr in subjects treated with alendronate and controls, respectively. There were no significant differences between two groups. After 1 year, urinary NTx was significantly (*p*<0.0001) decreased to the level of 31.3 ± 12.6 nmol BCE/mmol Cr in subjects treated with alendronate, and these values were maintained for 5 years. In control subjects, urinary NTx did not significantly (*p*<0.2) change from 60.3 ± 13.2 nmol BCE/mmol Cr to 67.4 ± 12.8 nmol BCE/mmol Cr for 5 years.

### Changes in radial BMD

As shown in (Figure 2), baseline levels of radial BMD were 0.296 ± 0.066 g/cm<sup>2</sup> and 0.318 ± 0.041 g/cm<sup>2</sup> in subjects treated with alendronate and controls, respectively. There were no significant differences between two groups. After 5 years, the radial BMD was 0.294 ± 0.058 g/cm<sup>2</sup> and 0.279 ± 0.044 g/cm<sup>2</sup> in subjects treated with alendronate and controls, respectively. The mean percent change in radial BMD fell gradually and significantly (*p*<0.05) from baseline to the level of 88.88 ± 5.90 % at 5 year in control subjects. While, the mean percent change in radial BMD at 5 year slightly, but not significantly, decreased to the level of 99.30 ± 8.36 % in subjects treated with alendronate. The percent decrease in radial BMD was significantly greater in control subjects compared to subjects treated with alendronate at 3, 4, and 5 year.

### Correlation between decrease in urinary NTx and change in radial BMD

There was no significant correlation between the decrease in urinary NTx and change in radial BMD (*r*=0.098, *p*=0.762).

## Discussion

Several investigators have reported higher bone mass in type 2 diabetic patients [13,14]. While, other investigators have reported that individuals with type 2 diabetes had lower bone density relative to nondiabetic control subjects [15-17]. Thus contradictory results were obtained in the bone density in type 2 diabetes. In recent prospective studies, type 2 diabetes is a risk factor for bone fractures in older women, and that postmenopausal diabetic women had a 1.40~1.70-fold

higher risk of incident hip fracture than women without diabetes [1,3-5]. These suggest that fracture prevention efforts should be necessary in the treatment of diabetic women, especially in postmenopausal women.

Radial BMD gradually and significantly decreased in control subjects at 2, 3, 4 and 5 year in the present study. This result agreed with the report of Keegan et al that BMD decreased in diabetic women treated with placebo for 3 years [10]. Dagdelen et al. [11] have indicated that postmenopausal type 2 diabetes are resistant to long-term bisphosphonate treatment. Keegan et al. [10], however, reported that three years of alendronate treatment was associated with increased BMD (6.6% at the lumbar spine and 2.4% at the hip) in women with type 2 diabetes. In the present study, alendronate treatment significantly decreased urinary NTx, one of biochemical markers of bone resorption, and inhibited the decrease in radial BMD for 5 years. The present result confirmed that alendronate is available for improving bone turnover in postmenopausal women with type 2 diabetes. The differences of these results may be due to the difference of species and/or experimental methods. Although Schwartz et al. [18] have reported that long-term use of thiazolidinediones caused reduction of whole body bone mineral density in older type 2 diabetic women, there were no subjects treated with thiazolidinediones in the present study.

Several studies have reported that urinary NTx is a more specific marker of bone resorption in patients treated with bisphosphonates compared with other markers [19,20]. There have been a report that changes in urinary NTx following therapy were predictive of improvements of bone mineral density in elderly women, and that the percent decrease in urinary NTx had the greatest association with long-term increases in BMD [21]. Garnero and colleagues found an association between changes in biochemical markers at 6 month and increased spinal BMD after 2 years in postmenopausal women treated with bisphosphonates [22]. It has been reported that subjects with the greatest drop in urinary cross-linked collagen (65% or more) demonstrated the greatest gains in radial bone density [21]. In the present study, significant correlation was not observed between the decrease in urinary NTx and change in radial BMD. This difference may be due to the small number of our present study.

In the present study, alendronate treatment significantly decreased urinary NTx by 60% in postmenopausal diabetic women, and inhibited the decrease in mean radial BMD for 5 years, although the mean radial BMD progressively and significantly decreased by 11% in control subjects. It has been reported that a 70% reduction in resorption biochemical markers of bone turnover would reduce fracture risk by 40% [23], and that in a meta-analysis of placebo-controlled trials, 1% increase in spine BMD at 1 year was association with an 8% reduction in nonvertebral fracture risk in postmenopausal women [8]. These and the present results suggest that alendronate administration would be expected at least to inhibit the decrease in BMD and to reduce the risk of bone fracture in postmenopausal osteoporotic type 2 diabetic women. The present study was not large enough to examine fracture outcomes. Viegas et al. [24] have reported that the prevalence of vertebral fractures has higher in postmenopausal type 2 diabetic women with lower bone mineral density. However, Yamaguchi et al. [25] have suggested that type 2 diabetes patients have an increased risk of vertebral fractures independent of bone mineral density. Further studies should be necessary to know if this result is associated with improvement of BMD in other bone sites and is able to reduce fractures.

Finally, the subjects had stable glycosylated hemoglobin levels throughout the study, although the diabetic treatment was appropriately changed. These suggest that alendronate treatment did modify neither the modalities of the anti-diabetic treatment nor the glycemic pattern.

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This article was originally published in a special issue, [Diabetic Osteoporosis](#) handled by Editor(s). Dr. Laura McCabe, Michigan State University, USA