Clinical significance of alendronate in postmenopausal type 2 diabetes mellitus

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SUMMARY
Objectives: To examine early changes in biochemical markers of bone turnover and bone mineral density (BMD) in a clinical trial of anti-resorptive agent alendronate versus alfacalcidol in postmenopausal women with type 2 diabetes mellitus.

Methods: 12 subjects (mean age; 73.1 ± 6.3 yrs, duration of diabetes; 13.2 ± 3.7 yrs) were administered alendronate sodium (5 mg/day) and 12 subjects (mean age; 70.7 ± 7.8 yrs, duration of diabetes; 12.8 ± 2.0 yrs) were administered alfacalcidol (0.5 μg/day) for 12 months. Urinary N-telopeptide cross-linked collagen type I (NTx), one of biochemical markers, and radial bone mineral density (BMD) were measured as a marker of bone turnover.

Results: After 12 months, urinary NTx did not change in women with alfacalcidol treatment, however urinary NTx significantly decreased after alendronate treatment. The BMD significantly decreased by 3.33% (p < 0.05) in women with alfacalcidol treatment, while the BMD did not decrease in women with alendronate treatment.

Conclusion: Alendronate that produces reduction in urinary NTx and inhibition of decrease in BMD may have a clinical significance to reduce the risk of bone fracture in postmenopausal type 2 diabetic women.

Key-words: Alendronate · Bone mineral density · Urinary NTx · Postmenopausal type 2 diabetes.

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RÉSUMÉ
Objectifs : Examiner les changements précoces dans les marqueurs biochimiques du turnover osseux et dans la densité minérale osseuse (DMO) au cours d’un essai clinique de l’agent anti-résorptif alendronate versus alfacalcidol chez des femmes postménopausiques présentant un diabète de type 2.

Méthodes : 12 sujets (âge moyen 73,1 ± 6,3 ans, durée du diabète 13,2 ± 3,7 ans) ont reçu de l’alendronate de sodium (5 mg/jour) et 12 sujets (âge 70,7 ± 7,8 ans, durée du diabète 12,8 ± 2,0 ans) ont reçu de l’alfacalcidol (0,5 μg/jour) pour 12 mois. Le N-telopeptide (NTx), un marqueur biochimique, et la densité minérale osseuse radiale ont été utilisés comme marqueurs du turnover osseux.

Résultats : Après 12 mois, le NTx urinaire n’était pas modifié chez les femmes sous alfacalcidol traitement, tandis que le NTx urinaire était significativement réduit chez les femmes sous alendronate. La DMO a diminué significativement de 3,33 % (p < 0,05) chez les femmes sous alfacalcidol, mais n’a pas diminué sous alendronate.

Conclusion : L’alendronate, permettant une réduction du NTx urinaire et s’opposant à la diminution de la DMO, peut avoir un intérêt clinique pour réduire le risque de fracture osseuse chez les femmes postménopausiques diabétiques de type 2.

Mots-clés : Alendronate · Densité minérale osseuse · NTx urinaire · Diabète de type 2 postménopausique.
Recent prospective studies reported that type 2 diabetes is a risk factor for hip, proximal humerus, and foot fractures among older women [1], and that postmenopausal women who have diabetes are at higher risk for hip fracture and women with type 2 diabetes had a 1.70-fold higher risk of incident hip fracture than women without diabetes [2]. These studies suggest that fracture prevention efforts should be a consideration in the treatment of diabetes.

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 [3-5]. To date, there is no available report regarding the effect of alendronate on bone turnover in postmenopausal type 2 diabetic women. The present study was examined to elucidate the early changes in biochemical marker of resorption, urinary NTx, and bone mineral density (BMD) in a clinical trial of alendronate versus alfacalcidol in postmenopausal women with type 2 diabetes mellitus.

Materials and methods

Subjects

Twenty-four postmenopausal women who have type 2 diabetes mellitus (aged 60-81 year) were enrolled in the present study. Inclusion criteria were 1) postmenopausal women of at least 10 year’s duration of diabetes, 2) urinary N-telopeptide cross-linked collagen type I (NTx) was more than 40 nmol bone collagen equivalents(BCE)/mmol creatinine(Cr), and 3) radial bone mineral density (BMD) was more than 0.400 g/cm². Potential subjects were excluded if they had a history of any illness affecting bone metabolism [e.g., renal failure, microalbuminuria (< 30mg/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, at randomly 12 subjects were administered alendronate sodium (Banyu Pharma. Co., Osaka) per os in a dose of 5 mg, once daily, 30 minutes before breakfast, and 12 subjects were administered alfacalcidol (Teijin Co., Tokyo) per os in a dose of 0.5 μg, once daily before breakfast. The therapeutic trial lasted 12 months. During the study, subjects continued their standard antidiabetic therapy, diet, oral hypoglycemic agents, or insulin. Change of dosage was in principle avoided during the study. The clinical characteristics of subjects are shown in Table I.

Biochemical markers

Following an overnight fast, we obtained a second-void 2-h urine collection. All samples were frozen at -20°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 [6]. Urinary NTx was measured at baseline and every 6 months.

Bone mineral density

Bone mineral density (BMD, g/cm²) of radius (ultradistal) were measured by dual-energy X-ray absorptiometry at baseline and 12 months.

Statistical analysis

The data were expressed as the means ± SD. A repeated measures analysis of variance and two-tailed Student’s paired t-test was used for statistical evaluation. Non-parametric analysis (Wilcoxon test) was used to evaluate changes in NTx and BMD. A p value < 0.05 was considered statistically significant.

Results

Characteristics of the subject

Characteristics of the subject were shown in Table I. The age, the BMI, the duration of diabetes, the mode of therapy, the HbA1c level, the urinary NTx, and the BMD were not significantly different between two groups.

Alendronate and alfacalcidol were well tolerated in all subjects. Abnormal laboratory findings of renal or hepatic function did not occur by alendronate or alfacalcidol administration.

Glycemic control

The basal HbA1c value was 8.0 ± 1.8% and 8.1 ± 1.5% in alendronate and alfacalcidol group, respectively. Glycemic control remained stable during the study period, and the

Table I

<table>
<thead>
<tr>
<th>Characteristics of subjects.</th>
<th>alendronate (n = 12)</th>
<th>control (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>73.1 ± 6.3 (60-81)</td>
<td>70.7 ± 7.8 (59-80)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5 ± 4.5</td>
<td>24.1 ± 2.9</td>
</tr>
<tr>
<td>Treatment of diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>OHA</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Insulin</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.0 ± 1.8</td>
<td>8.1 ± 1.5</td>
</tr>
<tr>
<td>Duration (y r)</td>
<td>13.2 ± 3.7</td>
<td>12.8 ± 2.0</td>
</tr>
<tr>
<td>Urinary NTx (nmol BCE/mm mol Cr)</td>
<td>69.5 ± 12.9</td>
<td>59.8 ± 13.2</td>
</tr>
<tr>
<td>BMD (g/cm²)</td>
<td>0.297 ± 0.052</td>
<td>0.300 ± 0.048</td>
</tr>
</tbody>
</table>

HbA1c level was not significantly changed 12 months after treatment with alendronate or alfacalcidol (8.0 ± 1.5% or 7.9 ± 1.6%), respectively.

**Change in urinary NTx**

As shown in Figure 1, baseline levels of urinary NTx were 69.5 ± 12.9 nmol BCE/mmol Cr and 59.8 ± 13.2 nmol BCE/mmol Cr in subjects treated with alendronate and in subjects treated with alfacalcidol, respectively. There were no significant differences between two groups. After 6 and 12 months, urinary NTx was significantly (p < 0.0001) decreased to the level of 33.9 ± 23.1 and 28.1 ± 13.6 nmol BCE/mmol Cr in subjects treated with alendronate. However, urinary NTx did not change in subjects treated with alfacalcidol at 6 and 12 months (61.6 ± 11.7 and 58.6 ± 12.2 nmol BCE/mmol Cr).

**Change in BMD**

As shown in Figure 2 baseline levels of BMD were 0.297 ± 0.052 g/cm² and 0.300 ± 0.048 g/cm² in subjects treated with alendronate and in subjects treated with alfacalcidol, respectively. There were no significant differences between two groups. After 12 months, the BMD was 0.301 ± 0.054 g/cm² and 0.290 ± 0.045 g/cm² in subjects treated with alendronate and alfacalcidol, respectively. In percentile change, the BMD significantly (p < 0.05) decreased to the level of 96.67 ± 2.85% in subjects treated with alfacalcidol at 12 months. However, BMD at 12 months slightly increased to the level of 101.35 ± 4.48% in subjects treated with alendronate.

**Correlation between decrease in urinary NTx and increase in BMD**

There was no significant correlation between the decrease in urinary NTx and increase in BMD (not shown in Figure).

**Discussion**

Several investigators have reported higher bone mass in type 2 diabetic patients [7, 8], and other investigators have reported that individuals with type 2 diabetes had lower bone density relative to nondiabetic control subjects [9, 10]. Thus the results examined on the bone density in type 2 diabetes are conflicting. However, recent prospective studies reporting that type 2 diabetes is a risk factor for bone fractures in older women, and that postmenopausal diabetic women had a 1.70-fold higher risk of incident hip fracture than women without diabetes [1, 2] suggest that fracture prevention efforts should be necessary in the treatment of diabetic women, especially in postmenopausal women.

In the present study, alendronate treatment significantly decreased urinary NTx, one of biochemical markers of bone resorption, and inhibited the decrease in radial BMD after 12 months in postmenopausal women with type 2 diabetes mellitus, although urinary NTx did not change and radial BMD significantly decreased in subjects with alfacalcidol treatment. These results suggest that alendronate, rather than alfacalcidol, is more available for improving bone turnover in diabetic women. Although the anti-resorptive agent alendronate, a potent aminobisphospho-
nate, has been shown to increase BMD at the hip and spine and decrease the incidence of osteoporotic fractures in older women [3-5], this is the first report indicating that the anti-resorptive agent alendronate decreases urinary NTx and inhibits the reduction of BMD in postmenopausal type 2 diabetic women.

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 percentage decrease in urinary NTx had the greatest association with long-term increases in BMD [11]. Garnero and colleagues found an association between changes in biochemical markers at 6 months and increased spinal BMD after 2 years in postmenopausal women treated with bisphosphonates [12]. In spite of the 12 month study duration, compared to baseline values, the alendronate treated group did not show a statistically significant change in BMD. These indicate that 12 months may not have been long enough to observe a change in this variable.

This study has several limitations. Other biochemical markers for evaluating bone turnover were not included in this study. However, several studies have reported that urinary NTx is a more specific marker of bone resorption in patients treated with bisphosphonates compared with other markers [13, 14]. Although 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 [11], in the present study there was no significant correlation between the decrease in urinary NTx and increase in radial BMD. Furthermore, there were no significant correlations between the change in urinary NTx or radial BMD and age, body mass index, basal HbA1c level, plasma lipid levels (LDL-cholesterol, HDL-cholesterol, and triglyceride), and mode of diabetic therapy (diet, oral hypoglycemic agents, and insulin), respectively.

Alendronate treatment significantly decreased urinary NTx by 50% in diabetic women. It has been reported that a 70% reduction in resorption biochemical markers of bone turnover would reduce fracture risk by 40% [15], and that a 30% decrease in urinary cross-linked collagen at 6 months predicted a bone density increase of 2.8-4.1% for the radius regions after 2.5 year time point [11]. In this study, alendronate treatment increased mean BMD by 1.35% after 12 months, although alfacalcidol treatment reduced mean BMD by 3.33%. This change in BMD seems to be very small. However, it has been reported in a meta-analysis of placebo-controlled trials of antiresorptive agents conducted in postmenopausal women that each 1% increase in spine BMD at 1 yr was association with an 8% reduction in non-vertebral fracture risk [15]. These suggest that alendronate administration would be expected to increase BMD and to reduce the risk of bone fracture in postmenopausal type 2 diabetic women. The present study was not large enough and not long enough to examine fracture outcomes. Further studies should be needed.

In conclusion, antiresorptive agent alendronate that produce both reductions in urinary NTx and inhibitions of reduction in BMD have a clinical significance in the treatment of postmenopausal type 2 diabetic women.

References