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Effects of alendronate on bone mineral density and bone metabolic markers in postmenopausal asthmatic women treated with inhaled corticosteroids

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Abstract

We have recently shown that long-term use of inhaled corticosteroids decreases bone mineral density (BMD) of the lumbar spine in postmenopausal asthmatic women. The present study aimed to evaluate the efficacy of alendronate in comparison with that of alfacalcidol (1-α-hydroxyvitamin D_3) for the treatment of BMD reduction in postmenopausal asthmatic patients who had inhaled corticosteroid therapy without regular use of systemic corticosteroids. Twenty-eight postmenopausal asthmatic patients with BMD T score of −1.0 or less were randomized to receive alendronate (5 mg/d) or alfacalcidol (1 μg/d). Bone mineral density was determined at baseline and 12 months after the treatment, and biochemical markers of bone metabolism were measured at baseline and after 6 and 12 months of treatment. The mean (±SD) BMD values at the lumbar spine, the total hip, and the Ward's triangle significantly increased by 4.9 ± 4.5% (P = .0005), 2.4 ± 2.2% (P = .0005), and 3.6 ± 5.2% (P = .02) at 12 months in the alendronate group, whereas the corresponding values did not significantly change in the alfacalcidol group. In the alendronate group, urinary *N*-telopeptide (NTx), serum osteocalcin, and serum alkaline phosphatase concentrations significantly decreased, and serum intact parathyroid (PTH) level significantly increased, from baseline at both 6 and 12 months. In the alfacalcidol group, urinary NTx showed modest but significant decrease, although the extent of the change was smaller than that in the alendronate group. We concluded that alendronate was effective to improve reduced BMD in postmenopausal asthmatic patients on inhaled corticosteroid therapy through the mechanism of inhibiting bone resorption.

1. Introduction

Inhaled corticosteroids are now widely used in the long-term management of bronchial asthma and chronic obstructive pulmonary diseases (COPDs) [1]. Although systemic use of corticosteroids is a well-known risk for osteoporosis, it remained unclear whether long-term use of inhaled corticosteroids can cause undesirable effects on bone metabolism [2,3]. Previous studies concerning the effects of inhaled corticosteroids on bone metabolism have drawn inconsistent results [4-10]. One reason for this inconsistency is that the previous studies have been based on study patients with differences as to sex, age, menstrual status, and coadministration of systemic corticosteroids. Therefore, we previously analyzed lumbar bone mineral density (BMD) and biochemical markers of bone metabolism in pre- and early postmenopausal asthmatic women treated with inhaled corticosteroids but with no systemic administration of corticosteroids for at least 1 year [11]. The results showed that lumbar BMD as well as the biochemical markers of bone metabolism did not differ between control premenopausal healthy subjects and inhaled corticosteroid–treated premenopausal patients, whereas the lumbar BMD and serum osteocalcin level were significantly lower in inhaled corticosteroid–treated postmenopausal patients than in control postmenopausal healthy subjects [11]. A recent quantitative systematic review [12] concluded that all

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considered inhaled corticosteroids appear to affect BMD and markers in patients with asthma and COPD or in healthy adults. In addition, it was recently reported that the risk of hip fracture was associated with exposure to inhaled corticosteroids [13]. Epidemiological studies indicate that recent common use of inhaled corticosteroids is associated with a decreased risk of death from asthma [14,15]. Thus, some therapeutic approaches for the reduced BMD would be necessary in inhaled corticosteroid–treated postmenopausal asthmatic women.

The aminobisphosphonate alendronate is a potent inhibitor of bone resorption mediated by osteoclasts both in vitro and in vivo [16,17]. Bisphosphonates have been shown to be effective in preventing bone loss and vertebral fracture not only in patients with postmenopausal osteoporosis [17-19] but also in those treated with systemic corticosteroids [20-23]. However, there is no therapeutic strategy for the prevention and intervention of bone loss in patients who use inhaled corticosteroids. In the present study, we aimed to evaluate the therapeutic benefit of alendronate, in comparison with that of alfacalcidol, for reduced bone mass in postmenopausal asthmatic patients receiving inhaled corticosteroids.

2. Patients and methods

2.1. Study patients

Among 727 Japanese postmenopausal women who were diagnosed with bronchial asthma by the American Thoracic Society criteria [24] at the Miyatake Asthma Clinic, 409 had measurement for their BMD by dual-energy x-ray absorptiometry. Among these 409 patients, 36 satisfied the following admission criteria: no regular use of systemic corticosteroids for at least 1 year; no history of treatment with any estrogens, progestins, bisphosphonates, calcitonin, menatetrenone, or ipriflavone; no use of supplemental vitamin D within the previous 3 months; no endocrine, metabolic, or renal disorders; no lumbar spinal deformities; no bone fracture; and with BMD of the lumbar spine (L2-L4) T score −1.0 or less. There was no patient with serum calcium concentration below reference ranges. Among them, 28 patients who gave their informed consent were enrolled in this study. None of them were smokers. These patients were fully ambulatory and their habitual physical activity was not disturbed. They were treated with inhaled fluticasone propionate (GlaxoSmithKline, Tokyo, Japan), inhaled beclomethasone dipropionate (Schering-Plough, Osaka, Japan), or inhaled budesonide (AstraZeneka, Osaka, Japan), and some of them were coadministered with disodium cromoglycate (Fujisawa, Osaka, Japan), inhaled β-stimulants, and/or theophylline. The patients properly used a metered-dose inhaler with a spacer (Volumatic, GlaxoSmithKline, or Inspire-Ease, Schering-Plough). All the patients were managed by the same physician (AM) in the outpatient clinic every 2 or 4 weeks.

2.2. Study design

The study was performed on 28 postmenopausal asthmatic women. The study patients were divided into 2 treatment groups: oral alendronate sodium hydrate (Banyu Pharmaceutical, Tokyo, Japan) 5 mg/d in the early morning after an overnight fast or alfacalcidol (1-α-hydroxyvitamin D_3; Teijin Pharma, Osaka, Japan) 1 μg/d after the morning meal. Assignments to the alendronate or alfacalcidol group were randomly performed. All patients were given supplemental calcium as 1.0 g of calcium lactate (133 mg of elemental calcium) twice daily after the morning and evening meals. For the main objective, to analyze the effect of alendronate, we set to double the patient number of the alendronate group. During the study period, all patients continued to use inhaled corticosteroids with changes of their doses when necessary. Some patients were allowed to receive for a short time oral or parenteral corticosteroids to treat exacerbation of asthma symptoms. All patients were prohibited from taking any other drugs affecting bone metabolism than the test drug during the study period.

Bone mineral density was measured at baseline and at 12 months after the treatment. Biochemical markers of bone metabolism were determined at baseline and at 6 and 12 months. The protocol in this study was approved by the regional ethical committee, and written informed consent was obtained from all the patients after they had been provided with sufficient information about this study.

2.3. Laboratory studies

Bone mineral density was measured at the lumbar spine (L2-L4) and the hip (total hip and Ward's triangle) by dual-energy x-ray absorptiometry (Hologic QDR-2000, Waltham, Mass). The measurement was performed by the same technician who was not informed about the clinical status of the patient.

Serum and urinary samples were obtained at baseline and after 6 and 12 months of treatment. Blood and second morning void urine samples were collected from patients after an overnight fast. Serum calcium, phosphorus, creatinine, albumin, total alkaline phosphatase, intact parathyroid hormone (PTH) (1-84) and 1,25-$(OH)_2D_3$, and urinary calcium and creatinine levels were measured by standard laboratory methods (Falco Biosystems, Kyoto, Japan). Serum osteocalcin was measured by immunoradiometric assay (Mitsubishi Chemical, Tokyo, Japan) (control range, 2.5-13.0 ng/mL). Urinary *N*-telopeptide (NTx) were measured by enzyme-linked immunosorbent assay (Osteomark, Mochida Pharmaceutical, Tokyo, Japan) and adjusted by urinary creatinine (control range, 14.3-89.0 nmol of bone collagen equivalents per millimole of creatinine for postmenopausal subjects).

Respiratory function was estimated as forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) by spirometry (Autospiro AS-600, Minato Medical Science, Osaka, Japan).

2.4. Statistical analysis

All results are shown as means ± SD. Comparison between 2 groups was investigated using unpaired Student *t* test or paired *t* test. The comparison of asthma status and inhaled corticosteroid used was performed with χ^2 test and by paired *t* test. Differences associated with $P < .05$ were considered statistically significant.

3. Results

3.1. Patients and study course

Clinical characteristics of the 28 postmenopausal asthmatic women enrolled in this study, categorized to the treatment group, are shown in Table 1. Eighteen patients were allocated to the alendronate group, while 10 patients were allocated to the alfacalcidol group. For the whole group, mean age was 62.6 ± 5.7 years. There were no statistically significant differences of baseline clinical characteristics including age, postmenopausal duration, body mass index, asthma status defined by World Health Organization classification [25], inhaled corticosteroids used, and their doses between groups. Respiratory function estimated as FVC and FEV_1 were also not different.

Table 1
Baseline clinical characteristics of study patients

	Alendronate (n = 18)	Alfacalcidol (n = 10)	*P*
Age (y)	61.8 ± 5.8	64.2 ± 5.3	.290
Duration after menopause (y)	11.0 ± 6.4	13.6 ± 6.8	.323
Body mass index (kg/m^2)	22.9 ± 3.1	25.1 ± 3.5	.097
Asthma status (step 2/3/4)[a]	14/2/2	5/4/1	.198
Inhaled corticosteroids			
Fluticasone propionate	16	6	
Beclomethasone dipropionate	1	1	
Budesonide	1	3	.170
Dose of inhaled corticosteroids at study ($\mu g/d$)[b]	428 ± 199	570 ± 313	
FVC (% predicted)	86.9 ± 14.8	84.9 ± 15.3	.738
FEV_1 (% predicted)	71.5 ± 8.1	66.1 ± 10.2	.135
BMD (g/cm^2)			
Lumbar spine	0.773 ± 0.075	0.771 ± 0.074	.946
Total hip	0.665 ± 0.075	0.683 ± 0.074	.546
Ward's triangle	0.370 ± 0.054	0.394 ± 0.066	.307
BMD (T score)			
Lumbar spine	−2.15 ± 0.67	−2.17 ± 0.071	.942
Total hip	−2.56 ± 0.81	−2.36 ± 0.80	.535
Ward's triangle	−2.83 ± 0.42	−2.65 ± 0.51	.323
Calcium (mg/dL)	9.5 ± 0.4	9.3 ± 0.2	.153
Phosphorus (mg/dL)	3.7 ± 0.4	3.5 ± 0.4	.216
Alkaline phosphatase (U/L)	279 ± 46	245 ± 53	.087
$1,25\text{-}(OH)_2D_3$	53.9 ± 12.9	59.2 ± 12.5	.302
Intact PTH (pg/mL)	40.1 ± 9.1	50.5 ± 13.0	.020
Osteocalcin (ng/mL)	7.6 ± 2.4	7.4 ± 2.1	.827
Urinary NTx/Cr (nmol BCE/mmol)	77.7 ± 28.3	76.8 ± 25.6	.827
Urinary calcium/creatinine	0.15 ± 0.07	0.18 ± 0.11	.453

Data are presented as mean ± SD or n. Dose of beclomethasone is divided by 2 for the conversion and that of budesonide is set as the same dose of fluticasone. BCE indicates bone collagen equivalent.

[a] Asthma status is according to WHO classification.

[b] Dose of inhaled corticosteroids is expressed as that of fluticasone.

Among the study patients enrolled, 3 patients were excluded in the efficacy analysis because of the following reasons. Of 18 patients in the alendronate group, 1 patient dropped out of the study because of nausea and 1 because of appetite loss. Of 10 patients in the alfacalcidol group, 1 patient withdrew for personal reasons. During the course of this study, fracture was not observed in any of the patients. No serious change in the laboratory data was observed. According to the investigator (AM), no other event attributed to the study drugs occurred. Thus, 16 patients in the alendronate group and 9 in the alfacalcidol group were examined for the efficacy analysis.

Over 12 months, cumulative dose of inhaled corticosteroids (expressed as that of fluticasone propionate) was 162 ± 79 mg in the alendronate group, which was not significantly different from that in the alfacalcidol group (237 ± 107 mg; $P = .057$). During the study period, some patients (5 of 16 in the alendronate group and 4 of 9 in the alfacalcidol group) were given oral corticosteroids for the treatment of asthma attack: 12 months' cumulative dose of oral corticosteroids (expressed as that of prednisolone) was 35.5 ± 84.5 and 48.6 ± 67.7 mg in the alendronate group and in the alfacalcidol group, respectively. There was no significant difference between groups ($P = .643$).

3.2. BMD measurements

Baseline BMD measured at the lumbar spine (L2-L4), the total hip, and the Ward's triangle was not different between patients in the alendronate group and those in the alfacalcidol group (Table 1). Mean percent changes in BMD from baseline to 12 months after treatment are demonstrated in Fig. 1. BMD at the lumbar spine (L2-L4) significantly increased by 4.9 ± 4.5% ($P = .0005$) in the alendronate group, whereas that did not significantly change in the alfacalcidol group (+1.7 ± 4.0%; $P = .255$). BMD at the total hip and the Ward's triangle also significantly increased in the alendronate group by 2.4 ± 2.2% ($P = .0005$) and 3.6 ± 5.2% ($P = .02$), respectively. There was no significant change in BMD at the 2 determinants in the alfacalcidol group (+0.1 ± 3.0% [$P = .949$] at the total hip and +2.0 ± 6.6% [$P = .484$] at the Ward's triangle).

3.3. Biochemical markers of bone metabolism

At baseline, biochemical markers of bone metabolism of serum calcium, phosphorus, alkaline phosphatase, $1,25\text{-}(OH)_2D_3$, and osteocalcin, and urinary NTx and calcium/creatinine did not differ between the 2 groups, although serum intact PTH level was significantly lower in the alendronate group than in the alfacalcidol group (Table 1). Table 2 shows the mean percent changes in the biochemical markers at 6 and 12 months. There was a statistically significant decrease in serum alkaline phosphatase, serum osteocalcin, and urinary NTx at both 6 and 12 months after alendronate treatment. Serum intact PTH significantly

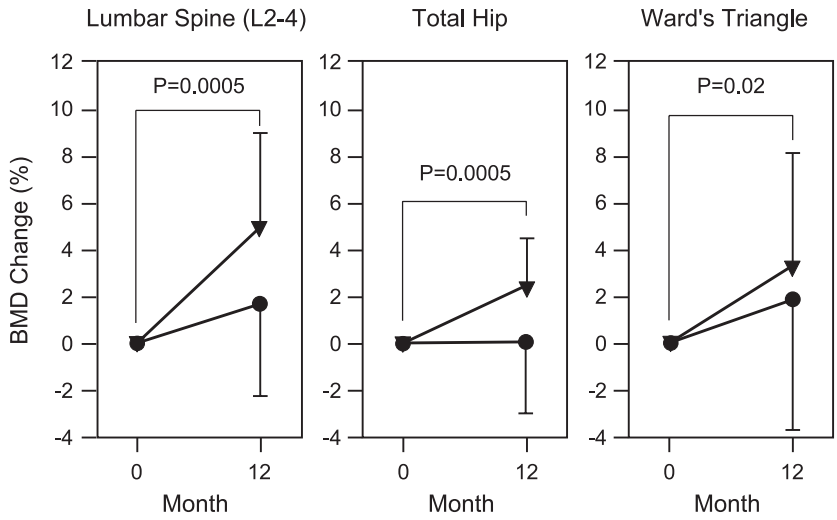

Fig. 1. Percent changes from baseline in BMD at the lumbar spine (L2-L4), the total hip, and the Ward's triangle after treatment with alendronate or alfacalcidol. Data show mean ± SD. Filled circles and filled triangles represent the alfacalcidol and alendronate groups, respectively. *P* values are shown when there is statistical difference from baseline.

increased at 6 and 12 months in the alendronate group. In the alfacalcidol group, there was a significant decrease in serum alkaline phosphatase and 1,25-$(OH)_2D_3$ at 6 months, a significant decrease in urinary NTx at both 6 and 12 months, and a significant increase in serum calcium at 12 months. The extent of the changes in serum alkaline phosphatase, serum osteocalcin, urinary NTx, and serum intact PTH in the alendronate group was significantly more than that in the alfacalcidol group. Serum phosphorus and urinary calcium/creatinine levels were not altered in the both groups (Table 2).

4. Discussion

The present study was aimed to clarify the efficacy of alendronate as well as that of alfacalcidol for the treatment of reduced BMD in postmenopausal asthmatic patients treated with inhaled corticosteroids without regular use of systemic corticosteroids. The results clearly showed that daily treatment with 5 mg oral alendronate for 12 months was effective in increasing BMD at the lumbar spine, the total hip, and the Ward's triangle in the postmenopausal asthmatic women. Analysis of bone metabolism markers showed that alendronate markedly depressed the bone resorption marker urinary NTx (around −60%) at 6 and 12 months. It also decreased the bone formation markers serum alkaline phosphatase and serum osteocalcin (around −30%). In addition, alendronate was found to increase serum intact PTH concentrations (around +45%). These results are similar to the previous reports on the effects of this bisphosphonate on the bone metabolism markers in

Table 2
Changes in biochemical markers of bone metabolism in study patients receiving over 12 months inhaled corticosteroids and alendronate or alfacalcidol

	Treatment	6 mo		12 mo	
		% Changes	P^a	% Changes	P^a
Calcium	Alendronate	−0.9 ± 5.6	.488	−1.3 ± 3.7[b]	.169
	Alfacalcidol	+1.3 ± 2.9	.234	+3.3 ± 3.2	.015
Phosphorus	Alendronate	−2.0 ± 12.2	.388	−0.3 ± 11.1	.815
	Alfacalcidol	+2.5 ± 9.2	.565	+6.5 ± 12.6	.177
Alkaline phosphatase	Alendronate	−29.3 ± 7.8[b]	<.0001	−30.5 ± 12.8[b]	<.0001
	Alfacalcidol	−10.2 ± 6.8	.011	−5.3 ± 12.2	.157
1,25-$(OH)_2D_3$	Alendronate	−0.3 ± 21.9	.934	+0.8 ± 34.5	.704
	Alfacalcidol	−16.2 ± 22.1	.046	−4.8 ± 27.8	.432
Intact PTH	Alendronate	+48.5 ± 47.6[b]	.002	+44.7 ± 58.8[b]	.015
	Alfacalcidol	−9.2 ± 23.1	.143	−10.2 ± 37.5	.228
Osteocalcin	Alendronate	−35.6 ± 36.4[b]	.0013	−36.9 ± 47.1[b]	.0003
	Alfacalcidol	+5.0 ± 22.9	.844	−2.5 ± 20.0	.532
Urinary NTx/Cr	Alendronate	−62.2 ± 18.8[b]	<.0001	−64.0 ± 21.3[b]	<.0001
	Alfacalcidol	−28.1 ± 18.1	.0033	−23.4 ± 23.7	.013
Urinary calcium/creatinine	Alendronate	+119.4 ± 365.3	.311	+13.9 ± 70.6	.783
	Alfacalcidol	+252.7 ± 671.5	.289	+323.1 ± 850.6	.275

Data are mean (±SD) percent changes from baseline.
[a] Statistical value of differences from baseline.
[b] Statistically significant difference from alfacalcidol treatment ($P < .05$).

patients with postmenopausal osteoporosis [26,27] and in those receiving oral corticosteroids [28].

Lau et al [29] have recently shown that treatment with 10 mg/d of alendronate for 1 year significantly increased BMD in female patients with asthma or COPD. In their investigation, about half of the study patients were premenopausal women and some patients had continuous treatment with oral corticosteroids. Only 18% of the patients had lumbar spine BMD T score less than −2.0 in that study. In our study, by contrast, we focused on postmenopausal asthmatic patients without regular use of oral corticosteroids in whom lumbar spine BMD T score is −1.0 or less. The averaged lumbar BMD T score was less than −2.0 in our study patients. Although direct comparison is not possible, the percent increases in the lumbar spine, the total hip, and the Ward's triangle at 12 months of alendronate treatment in our study patients appear to be more than those in the study patients of Lau et al [29]. This may be because of the difference in baseline characteristics of the study patients: more patients with less BMD and no patient with regular use of systemic corticosteroids in our study. Furthermore, in the present study, we determined biochemical markers of bone metabolism. Thus, this is the first demonstration to examine the effects of the bisphosphonate on BMD as well as bone metabolism markers in postmenopausal asthmatic patients treated with inhaled corticosteroids but without continuous use of systemic corticosteroids.

We previously demonstrated that serum intact osteocalcin concentration was depressed in postmenopausal asthmatic patients receiving inhaled corticosteroids, compared with postmenopausal control subjects. By contrast, urinary pyridinoline and deoxypyridinoline concentrations did not differ between the postmenopausal asthmatic patients and the postmenopausal control subjects [11]. It indicated that inhaled corticosteroids cause reduced bone formation rather than increased bone resorption. Therefore, approaches to increase bone formation would be ideally desirable for the treatment of bone loss in inhaled corticosteroid–treated postmenopausal asthmatic patients. The main mechanisms of action of alendronate are interference with osteoclast function and, thus, inhibition of bone resorption [16,17]. In fact, the present data on the bone metabolism markers revealed that alendronate inhibited bone resorption but did not stimulate bone formation. Bisphosphonates are known to be effective in preventing bone loss in patients with systemic corticosteroid therapy with decreased bone formation [20-23,28]. The sum of these observations suggests that the inhibitory effects of alendronate on bone resorption in the postmenopausal state may surpass the inhibition of bone formation by inhaled corticosteroids.

In contrast to alendronate, no significant change in BMD at any of the studied sites was observed by treatment with alfacalcidol for 12 months. We, however, found that alfacalcidol could significantly decrease urinary NTx (around 30%) at 6 and 12 months of the treatment, although the extent of the change was significantly smaller than that by alendronate. In addition, there was a significant decrease in serum alkaline phosphatase at 6 months of the alfacalcidol treatment. It has been previously shown that alfacalcidol elicited a slight but significant increase in lumbar BMD and a significant decrease in urinary pyridinoline and deoxypyridinoline concentrations in early postmenopausal women [30]. These results indicate that alfacalcidol has potential to increase bone mass by reducing bone resorption in early postmenopausal women. Our results also suggest that alfacalcidol also can reduce bone resorption in postmenopausal asthmatic patients treated with inhaled corticosteroids, although it did not lead to a significant increase of bone mass after 12 months. The mechanisms for reducing bone resorption by alfacalcidol are not well known. 1,25-$(OH)_2D_3$ has been shown to stimulate in vitro bone resorption [31]. In our study, alfacalcidol treatment failed to increase serum 1,25-$(OH)_2D_3$ concentration, consistent with the previous report [32]. Thus, direct effects of the converted 1,25-$(OH)_2D_3$ on bone resorption are unlikely to operate in vivo. Alfacalcidol treatment resulted in a tendency for serum calcium to increase, whereas alendronate elicited a tendency for serum calcium to decrease. Serum intact PTH tended to decrease by the alfacalcidol treatment; in contrast, it significantly increased by the alendronate treatment. Thus, the effects of the two drugs on serum calcium and intact PTH appeared completely different. The results are similar to the previous reports on postmenopausal women [26,27,30,33]. Increased calcium uptake by alfacalcidol might lead to decrease in serum PTH level, while the antiresorptive effect of alendronate may presumably result in a tendency for serum calcium to decline, thereby stimulating PTH secretion.

Much evidence has been accumulated showing that use of inhaled corticosteroids leads to bone loss, which should be prevented or treated [11-13,34]. In postmenopausal asthmatic patients who use inhaled corticosteroids, decreased bone formation in addition to increased bone resorption are involved in the pathogenesis of the bone loss. In the present study, we demonstrated the effectiveness of alendronate for improving reduced BMD in postmenopausal asthmatic patients receiving inhaled corticosteroids, mainly through the mechanism of reducing bone resorption. Alfacalcidol also elicited its effect to reduce bone resorption, but it failed to bring about increase in bone mass at 12 months of the treatment. Therefore, the bisphosphonate alendronate rather than alfacalcidol is desirable for the intervention of reduced bone mass in postmenopausal asthmatic patients treated with inhaled corticosteroids.

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