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Inhaled Corticosteroids Reduce Bone Mineral Density in Early Postmenopausal but Not Premenopausal Asthmatic Women

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ABSTRACT

Inhaled corticosteroids are widely used in the treatment of bronchial asthma, but it is still uncertain whether long-term use of the inhaled corticosteroids affects bone metabolism in asthmatic patients. In this study, we examined the effect of inhaled beclomethasone dipropionate (BDP) on bone mineral density (BMD) and biochemical markers of bone metabolism in pre- and early postmenopausal asthmatic women. Thirty-six (17 premenopausal and 19 early postmenopausal) asthmatic women and 45 healthy control (24 premenopausal and 21 early postmenopausal) women were investigated. All the asthmatic patients were treated with BDP (542 ± 298 μg/day; 100-1200 μg/day) without any systemic administration of corticosteroids for at least 1 year. In premenopausal women, BMD as well as the biochemical markers of bone metabolism did not differ between control subjects and BDP-treated asthmatic patients. By contrast, in early postmenopausal women, BMD was significantly lower in BDP-treated asthmatic patients than in control subjects. In these early postmenopausal women, serum intact osteocalcin concentration was lower in the BDP-treated asthmatic patients than in the control subjects whereas urinary free pyridinoline (F-PYD) and free deoxypyridinoline (F-DPD) concentrations did not differ between the groups. Thus, early postmenopausal, but not premenopausal, asthmatic patients who were treated with inhaled BDP had reduced BMD, which was associated with a decreased level of the bone formation marker. Ovarian hormones may be protective against the adverse effect of inhaled BDP on bone metabolism in the premenopausal patients. (J Bone Miner Res 2001;16:782–787)

Key words: inhaled corticosteroids, beclomethasone, bronchial asthma, postmenopausal women, osteocalcin

INTRODUCTION

INHALED CORTICOSTEROIDS have become the mainstay of long-term treatment of asthma.[1–3] Since guidelines for asthma treatment have been introduced, inhaled corticosteroids have been used widely in asthmatic patients. It is still uncertain whether long-term use of the inhaled corticosteroids has systemic effects on bone metabolism.[4,5] It has been reported that the inhaled corticosteroids affect growth in children.[6] However, previous studies have not drawn

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TABLE 1. CLINICAL CHARACTERISTICS OF PREMENOPAUSAL AND EARLY POSTMENOPAUSAL ASTHMATIC PATIENTS AND CONTROL SUBJECTS

	Premenopausal		*Postmenopausal*	
	Healthy subjects	*Asthmatic patients*	*Healthy subjects*	*Asthmatic patients*
n	24	17	21	19
Age (year)	46.6 ± 4.4	46.8 ± 4.4	52.4 ± 1.8	53.7 ± 4.6
Years after menopause (year)	—	—	3.3 ± 1.5	4.5 ± 2.3
Body mass index (kg/m^2)	22.3 ± 2.9	22.4 ± 2.4	23.2 ± 2.7	23.0 ± 2.5
Duration of asthma (year)	—	12.5 ± 8.5	—	14.0 ± 9.6
Dose of BDP at study (μg/day)	—	551 ± 275	—	534 ± 316
Cumulative dose of BDP for recent 2 years (mg)	—	345 ± 167	—	350 ± 152
FVC (% predicted)	—	87 ± 16	—	80 ± 16
FEV (% predicted)	—	68 ± 11	—	74 ± 11

Data are means ± SD.

consistent conclusions on the effects of inhaled corticosteroids on bone metabolism in adults.[5,7–13] One reason for this inconsistency is that the previous studies have been based on populations of asthmatic patients with different age, sex, and menstrual status. Another confusing factor is that some patients received oral corticosteroids in addition to inhaled corticosteroids in most studies.

In adult women, menstrual status affects bone mineral density (BMD). Postmenopausal bone loss has been assumed to progress rapidly during the first 5 years.[14–16] This raises the question whether early postmenopausal women may be more susceptible to any bone mineral loss caused by inhaled corticosteroids.

In this study, we have investigated the effects of inhaled beclomethasone dipropionate (BDP) on BMD and biochemical markers of bone metabolism in pre- and early postmenopausal asthmatic women. To assess the effects of inhaled BDP, we chose asthmatic patients who had not received any oral or parenteral administration of corticosteroids for at least 1 year before entry into this study.

MATERIALS AND METHODS

Subjects

Among 1451 (667 males and 784 females) outpatients who were diagnosed with bronchial asthma at the Miyatake Asthma Clinic by the American Thoracic Society criteria,[17] 274 women were aged 40–60 years. Among them, patients satisfying the following admission criteria were enrolled in this study. The admission criteria included no systemic corticosteroid administration for at least 1 year; never used estrogens, progestins, supplemental vitamin D, calcitonin, or bisphosphonates; no endocrine, metabolic, or renal disorders; and no lumbar spinal deformities. There were 36 patients who satisfied the admission criteria. The patients were fully ambulatory and their habitual physical activity was not disturbed. These patients were managed by inhaled BDP (542 ± 298 μg/day; 100-1200 μg/day) and disodium cromoglycate, β-stimulants, and/or theophylline. Clinical assessment and treatment of the 36 patients were managed by the same physician (A.M.) in the outpatient clinic every 2 weeks or 4 weeks for more than 2 years. All patients were shown how to inhale BDP using a metered-dose inhaler with a spacer (Volumatic; Glaxo SmithKline, Middlesex, UK, or Inspire-Ease; Schering-Plough, Kenilworth, NJ, USA). None of the patients were smokers.

Patients were divided into the following two groups according to their menstrual status as: a premenopausal group (n = 17) with regular menstrual cycles and a postmenopausal group (n = 19) with no menstrual bleeding for at least 1 year since their last period. Doses of BDP administered at the study as well as cumulative doses for the last 2 years were not different between the two groups (Table 1). Respiratory function estimated as forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were not different between the two groups (Table 1). Forty-five healthy women without hormone replacement therapy were recruited as control subjects. They also were divided into two groups: 24 premenopausal control subjects and 21 postmenopausal control subjects.

There were no differences in age, body height, body weight, and body mass index (BMI) between the premenopausal asthmatic patients and the premenopausal controls (Table 1). Age of menopause and duration after menopause as well as the previously mentioned parameters did not differ between the postmenopausal asthmatics and the postmenopausal controls (Table 1). The protocol in this study was approved by the regional ethical committee, and all the subjects gave their informed consent.

Measurement of BMD

BMD was measured at the lumbar spine (L2–L4) level by dual-energy X-ray absorptiometry (DXA) with a QDR-2000 densitometer (Hologic Inc., Waltham, MA, USA) by the same technician who did not have information about the clinical status of the patient. The Z scores were determined

by a comparison of the patient's measured BMD with age- and sex-matched reference values.

Biochemical markers of bone metabolism

We measured biochemical markers of bone metabolism in all the asthmatic patients and 18 healthy subjects. The 18 healthy subjects were selected randomly from 45 healthy women attending the study for BMD. Among them, 9 were premenopausal women and other 9 were postmenopausal women. The age (45.2 ± 4.2 years) and the BMI (21.3 ± 2.4 kg/m^2) of the 9 premenopausal healthy subjects were not significantly different from those of the 17 premenopausal asthmatic patients (Table 1; 46.8 ± 4.4 years and 22.4 ± 2.4 kg/m^2, respectively). The age (52.6 ± 1.4 years), the year after menopause (3.3 ± 1.2 years), and the BMI (23.3 ± 2.5 kg/m^2) of the 9 postmenopausal healthy subjects did not differ from those of the 19 postmenopausal asthmatic patients (Table 1; 53.7 ± 4.6 years, 4.5 ± 2.3 years, and 23.0 ± 2.5 kg/m^2, respectively). Serum intact osteocalcin concentration was determined by specific radioimmunoassay (RIA) kit (Yuka Medics, Ibaragi, Japan) as reported.[18] The intra- and interassay CV were 5.7% and 5.7%, respectively. Urinary free pyridinoline (F-PYD) and free deoxypyridinoline (F-DPD) concentrations were measured by high-performance liquid chromatography.[19] The intra- and interassay CV were 3.8% and 8.9%, respectively. Fasting blood and urine samples were collected from subjects between 9 a.m. and 11 a.m. on the same day when BMD was measured. Blood was centrifuged immediately, and serum and urine samples were stored at −70°C until assay.

Statistical analysis

Data are expressed as means ± SD. Comparison of the data between two groups was analyzed by unpaired *t*-test or Welch's *t*-test, as appropriate. Differences associated with $p < 0.05$ were considered statistically significant.

RESULTS

Studies in premenopausal subjects

BMD of the lumbar spine (L2–L4) in 17 premenopausal asthmatic patients was 1.014 ± 0.142 g/cm^2 (Z score, 0.28 ± 1.03), not significantly different from that in 24 premenopausal control subjects (1.053 ± 0.104 g/cm^2; Z score, 0.52 ± 0.80; Fig. 1A). Serum intact osteocalcin, urinary F-PYD, and F-DPD concentrations in the premenopausal asthmatics were not different from those in 9 of the premenopausal controls (Figs. 2A and 3A).

Studies in early postmenopausal subjects

BMD of the lumbar spine (L2–L4) in 19 early postmenopausal asthmatic patients was 0.889 ± 0.109 g/cm^2, which was significantly lower ($p < 0.001$) than BMD in 21 early postmenopausal control subjects (1.007 ± 0.099 g/cm^2; Fig. 1B). When BMD was expressed as a Z score, it was 0.06 ± 0.75 in the early postmenopausal asthmatics, which was significantly lower ($p < 0.02$) than the early postmenopausal controls (0.67 ± 0.70).

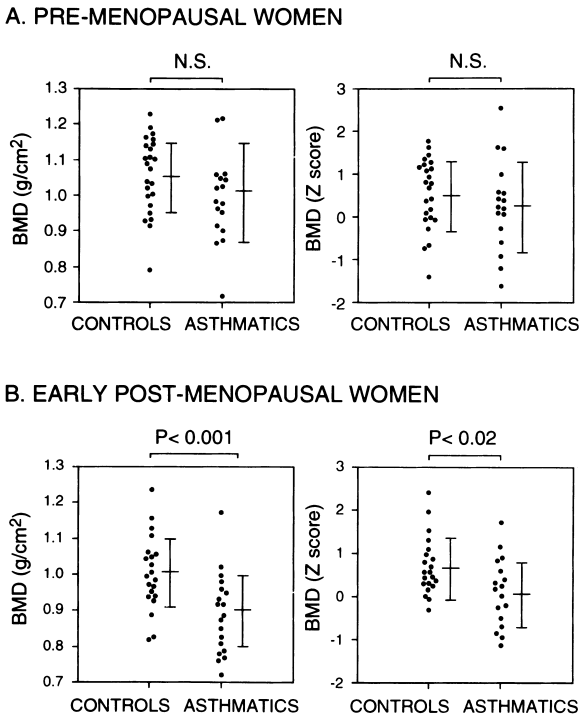

FIG. 1. Comparison of BMD of the lumbar spine (L2–L4) in inhaled BDP-treated asthmatic patients with that in control subjects. (A) BMD in premenopausal control subjects ($n = 24$) and that in premenopausal asthmatic patients ($n = 17$). (B) BMD in early postmenopausal control subjects ($n = 21$) and that in early postmenopausal asthmatic patients ($n = 19$). Means ± SD are shown to the right of each column of data points.

Serum intact osteocalcin concentration was higher in early postmenopausal control subjects than that in premenopausal controls (12.1 ± 4.1 ng/ml vs. 5.2 ± 1.6 ng/ml; $p < 0.001$). Urinary F-PYD and F-DPD concentrations were also higher in the early postmenopausal controls than those in premenopausal controls (F-PYD, 12.4 ± 2.8 μmol/mol creatinine vs. 9.1 ± 2.1 μmol/mol creatinine, $p < 0.02$; F-DPD, 3.9 ± 0.9 μmol/mol creatinine vs. 2.8 ± 0.6 μmol/mol creatinine, $p < 0.01$). These biochemical markers were also higher in early postmenopausal asthmatic patients than those in premenopausal asthmatic patients (osteocalcin, 8.2 ± 3.1 ng/ml vs. 5.5 ± 2.2 ng/ml, $p < 0.005$; F-PYD, 12.7 ± 3.6 μmol/mol creatinine vs. 9.9 ± 3.0 μmol/mol creatinine, $p < 0.02$; F-DPD, 4.2 ± 1.3 μmol/mol creatinine vs. 2.8 ± 0.8 μmol/mol creatinine, $p < 0.001$).

In the early postmenopausal asthmatics, serum intact osteocalcin concentration was 8.2 ± 3.1 ng/ml, significantly ($p < 0.01$) lower than that in 9 of the early postmenopausal controls (12.1 ± 4.1 ng/ml; Fig. 2B). By contrast, urinary concentrations of F-PYD and F-DPD in the early postmenopausal asthmatics were not different from those in the early postmenopausal controls (Fig. 3B).

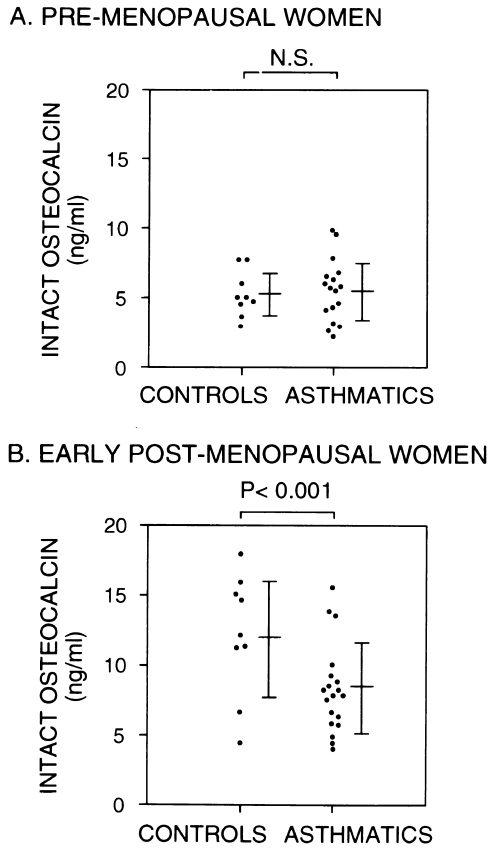

FIG. 2. Comparison of serum intact osteocalcin concentration in inhaled BDP-treated asthmatic patients with that in control subjects. (A) Serum intact osteocalcin concentration in premenopausal control subjects ($n = 9$) and that in premenopausal asthmatic patients ($n = 17$). (B) Serum intact osteocalcin concentration in early postmenopausal control subjects ($n = 9$) and that in early postmenopausal asthmatic patients ($n = 19$). Means ± SD are shown to the right column of data points.

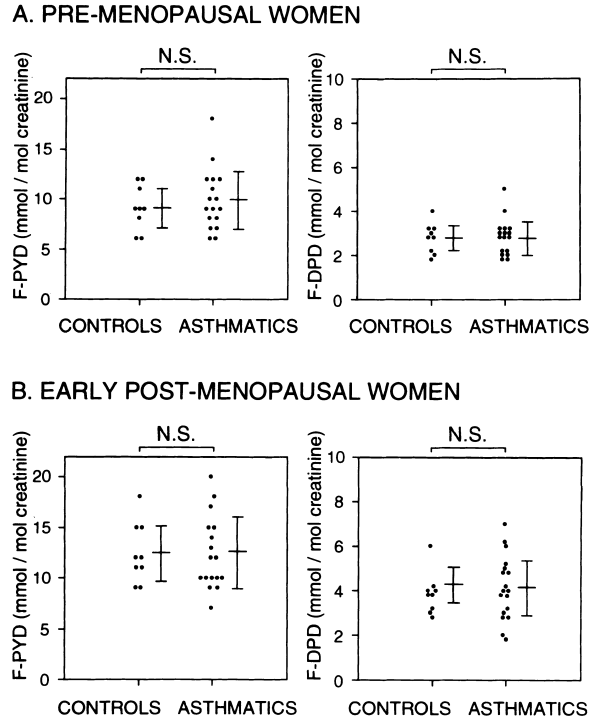

FIG. 3. Comparison of urinary F-PYD and F-DPD concentrations in inhaled BDP-treated asthmatic patients with those in control subjects. (A) Urinary F-PYD and F-DPD concentrations in premenopausal control subjects ($n = 9$) and those in premenopausal asthmatic patients ($n = 17$). (B) Urinary F-PYD and F-DPD concentrations in early postmenopausal control subjects ($n = 9$) and those in early postmenopausal asthmatic patients ($n = 19$). Means ± SD are shown to the right column of data points.

DISCUSSION

There have been several reports concerning the effects of inhaled corticosteroids on bone metabolism in asthmatic patients. Pack et al.[20] showed that asthmatic patients receiving high-dose (1000–2000 μg/day) inhaled BDP as well as intermittent systemic corticosteroids had reduced BMD. Their study included both men and women and did not specify whether the female patients were in premenopausal state or in postmenopausal state. Ip et al.[8] showed in their study on male and premenopausal female asthmatic patients that a decrease of BMD was observed only in female patients. Boulet et al.[21] showed no significant change of BMD as well as bone metabolism markers in asthmatic patients treated with inhaled corticosteroids, although their study did not distinguish sex and menstrual states of the patients. Hanania et al.[11] showed that long-term use of inhaled corticosteroids was accompanied by a reduction of BMD, which was not observed in patients receiving bronchodilators alone. Toogood et al.[12] showed that a daily dose, but not duration, of inhaled corticosteroid therapy may adversely affect BMD, and that estrogen therapy in postmenopausal women may offset this bone-depleting effect in postmenopausal women. A recent study proved a negative relation between total cumulative dose of inhaled corticosteroids and BMD in asthmatic patients aged 20–40 years.[22] Thus, such conflicting results on the effects of inhaled corticosteroids on BMD appear to be caused by the difference and variation in study patients with age, sex, menstrual status, and coadministration of systemic corticosteroids.

In this study we reported analysis under more carefully defined conditions. We studied asthmatic women of aged 40–60 years who had received long-term treatment of inhaled corticosteroids. Patients older than 60 years of age were excluded from this study, because osteophytes and spinal deformities frequently observed in these patients may bias the measurement of BMD at lumbar spine. Any subjects who had ever had any sex hormone replacement therapy or had any rescue or systemic administrations of corticosteroids within 1 year before entry into the study also were excluded. In addition, none of the study subjects had received supplemental vitamin D, calcitonin, or bisphosphonates. The data on 36 patients corresponding to such criteria, out of 1451 outpatients, were analyzed. The results

clearly showed that BMD was lower in early postmenopausal asthmatic patients treated with inhaled BDP than that in early postmenopausal control subjects. However, BMD in premenopausal asthmatics was not different from that in premenopausal controls. These observations were consistent when we analyzed both measures (absolute value and Z score) of BMD. Thus, it is unlikely that the present results are deduced from lack of statistical power given the small number of patients studied. Doses of BDP at the study as well as cumulative doses of BDP for the last 2 years were not significantly different between premenopausal asthmatics and early postmenopausal asthmatics (Table 1). Therefore, the inhaled corticosteroids were found to have an adverse effect on BMD only in early postmenopausal asthmatic women, not in premenopausal asthmatic women.

Wong et al.[22] recently showed that total cumulative dose of inhaled corticosteroids is negatively associated with BMD in 196 asthmatic patients (119 women) aged 20–40 years. Because we could not determine the exact duration of use of steroid inhaler and mean daily dose, total cumulative dose of inhaled corticosteroids could not be calculated in the study patients. However, duration and severity (expected from dose of BDP) of asthma were not significantly different between the premenopausal asthmatic patients and the early postmenopausal asthmatic patients (Table 1). It suggests no difference of total cumulative dose of inhaled corticosteroids between the both groups. Thus, it seems unlikely that the decreased BMD in the early postmenopausal patients is caused by higher total cumulative dose of inhaled corticosteroids, although this possibility cannot be excluded completely.

In the present investigation, serum intact osteocalcin as well as urinary F-PYD and F-DPD concentrations were higher in early postmenopausal control subjects than in premenopausal control subjects. These results indicate that increased bone turnover occurred in early postmenopausal women compared with premenopausal women, which is consistent with the previous reports.[23,24] Among the premenopausal women, the biochemical markers of bone metabolism did not differ between BDP-treated asthmatic patients and control subjects (Fig. 2A). In contrast, serum intact osteocalcin concentration was significantly depressed in early postmenopausal asthmatics receiving inhaled BDP compared with early postmenopausal control subjects (Fig. 2B). Urinary F-PYD and F-DPD concentrations did not differ between the early postmenopausal asthmatic patients and the early postmenopausal control subjects (Fig. 3B). Because intact osteocalcin is a marker of bone formation,[25] reduced bone formation is likely to be a cause for decreased BMD in early postmenopausal asthmatics treated with inhaled BDP. Generally, it is accepted that systemic administration of corticosteroids depresses bone formation.[26,27] In this regard, inhaled corticosteroids also have the inhibitory effect on bone formation in early postmenopausal asthmatic patients.

It is well known that bone formation as well as bone resorption increase in early postmenopausal women.[28] Thus, one of the main mechanisms by which ovarian hormones protect bone loss is the inhibition of bone resorption rather than the stimulation of bone formation.[29] These observations do not appear to be consistent with our results that premenopausal asthmatic women did not suffer from inhaled BDP-induced reduction of bone formation. Hall et al.[30] showed that hormone replacement therapy is effective in preserving BMD in rheumatoid arthritis patients treated with corticosteroids. In their study, patients taking estrogen alone lost significantly more bone than did the other patients taking estrogen and progestins. Based on these results, they suggest that progestins may be the more important component in hormone replacement therapy when it is used to treat patients taking corticosteroids.[30] In this regard, progestins have been shown to compete with corticosteroids for glucocorticoid receptors in osteoblasts.[31] There is also increasing evidence that estrogen, at higher doses, stimulates osteoblast function.[32] Together, it is suggested that ovarian hormones are effective on inhaled BDP-induced bone loss probably via maintaining or stimulating osteoblast function.

In conclusion, we showed that early postmenopausal asthmatic patients treated with inhaled BDP without any systemic corticosteroids had reduced BMD. The bone loss in these patients may be caused by decreased osteoblast function. In contrast, inhaled BDP had no adverse effect on premenopausal asthmatic patients. Thus, we assume that endogenous ovarian hormones are protective against the adverse effect of inhaled BDP on bone metabolism in the premenopausal patients. Physicians should be aware of potential bone loss in early postmenopausal asthmatic patients taking inhaled corticosteroids, even when the patients are not given systemic corticosteroids. The effectiveness of hormone replacement therapy on the bone loss needs to be determined.

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