Effects of Fluticasone Propionate on Bone Mineral Density in Patients with Persistent Bronchial Asthma

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Abstract

Objective To evaluate osteoporosis in asthmatic patients.

Methods Bone mineral density (BMD) was measured using three different methods, namely computed X-ray densitometry (CXD), digital image processing (DIP), and dual energy X-ray absorptiometry (DXA). The BMD data were standardized using the sex- and age-matched mean value of BMD.

Patients One hundred and twenty-eight patients with persistent asthma.

Results The standardized BMD expressed as Z-score in asthmatic patients was significantly lower than the norm (Z-score -0.48 ± 1.17 , mean $\pm$ SD). In patients who had been continuously treated with oral corticosteroids (OCS), the standardized BMD was significantly lower than that in patients treated without OCS. In addition, the standardized BMD in patients 60 years and over (Z-score -0.71 ± 1.10 , mean $\pm$ SD, $n=58$) had decreased to a greater extent than the decrease seen in patients under 60 years (Z-score -0.30 ± 1.21 , $n=70$). Moreover, BMD in these older patients decreased after a 6-month treatment protocol involving the use of an inhaled corticosteroid, fluticasone propionate (FP). During the 6 months, the treatment did not affect BMD in patients who were receiving FP for the first time. Although the BMD did not decrease in patients treated with FP without OCS, the BMD in patients treated with both FP and OCS decreased during the 6 months.

Conclusion These results indicate that the continuous administration of OCS in patients with severe persistent asthma, particularly in older patients, may affect BMD in the short term even at a low OCS dose.

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Key words: osteoporosis, corticosteroids, older patients

Introduction

Inhaled corticosteroids (ICS) are currently the first-line treatment for bronchial asthma. The systemic effects of ICS, such as suppression of the hypothalamic-pituitary-adrenal axis, are generally less than the effects of oral corticosteroids (OCS) (1, 2). An evidence-based approach to the analysis of systemic activity and the safety of ICS is essential to allow appropriate risk-benefit decisions to be made for individual patients with bronchial asthma. OCS are well known to have adverse effects on bone mineral density (BMD), and to accelerate bone loss and hence double the risk of fracture in patients taking more than 7.5 mg of prednisolone daily (3). Osteoporosis is a fracture syndrome that results from low BMD. BMD is a major determinant of the fracture risk in patients with corticosteroid (CS)-induced osteoporosis, as the fracture risk increases progressively when the BMD falls below a specific fracture threshold (4).

Several studies have examined the effects of ICS on BMD in asthmatic patients, with conflicting results (5, 6). Fluticasone propionate (FP, 500 μ g/day) has been shown not to cause any adverse effects on BMD in mild and moderate adult asthmatics after a one-year treatment period (5). In contrast, there is some concern that prolonged treatment with high doses of ICS reduces bone mass in prepubertal asthmatic children (6). It appears that high doses (more than 400 μ g/day in children and more than 800 μ g/day in adults) of beclomethasone dipropionate (BDP) may affect bone metabolism and BMD (7).

Several techniques are available for measuring BMD. Among these, dual energy X-ray absorptiometry (DXA) is the most reliable, and usually the lumbar spine is the target (8). However, this method requires a special device and evaluation at the lumbar spine is time consuming. We measured BMD in adult asthmatic patients using three different methods, namely DXA, computed X-ray densitometry (CXD), and digital image processing (DIP). BMD was measured at the distal edge of the radius in DXA, as this was more convenient than the lumbar spine and not influenced by lumbar spinal deformities. The

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second metacarpal bone was also utilized to measure BMD by CXD or DIP. These methods are convenient for hospital outpatient departments.

Two kinds of ICS, BDP and FP, have been used in Japan. The systemic effects of FP, such as growth and bone turnover, appear to be smaller than those of BDP (9–11). Here, we investigated whether BMD in adult patients with persistent bronchial asthma is lower than the norm. We also examined the change in BMD in patients receiving FP or FP plus OCS.

Materials and Methods

Subjects

One hundred and twenty-eight patients (20 to 87 years old, mean $\pm$ SD 55.1 $\pm$ 16.2 years, 56 males, 72 females) with persistent bronchial asthma underwent BMD evaluation. Male patients consisted of 17 patients under 40 years, 18 patients 40 years and over and under 60, and 21 patients 60 years and over. Female patients consisted of 8 patients under 40 years, 27 patients 40 years and over and under 60, and 37 patients 60 years and over. Only 8 patients (8 females) had previously received alfacalcidol (0.5–1 μ g/day). The other 120 patients had not been treated with either bisphosphonates, or calciotropic hormones. Thirty-six patients (19 males and 17 females) had received OCS continuously. Three patients (2 males and 1 female) out of 36 had not used ICS. The other 33 patients had used ICS, FP (400–800 μ g/day) or BDP (800–1,600 μ g/day), together with OCS. Thirty-four patients out of 36 had received prednisolone (2.5–15 mg/day) and the rest had received betamethasone (0.25–0.5 mg/day). Ninety-two patients (37 males and 55 females) had not received any continuous systemic administration of CS. Sixty patients (21 males and 39 females) of these 92 had already received ICS, FP (100–800 μ g/day) or BDP (200–1,600 μ g/day), without OCS.

Measuring BMD

The BMD of 32 patients was measured at the distal edge of the radius by DXA using a QDR-4500SL densitometer (Hologic Inc., Waltham, MA, USA). The BMD of 96 patients was measured at the second metacarpal bone by CXD (66 patients) or DIP (30 patients). The measuring value of BMD was standardized and expressed as Z-score. Z-score was calculated by the following formula. Z-score = (P-MAM)/SDAM, P: measuring value in the patient. MAM: the mean value of the same sex and the same aged people measured by the same method, SDAM: the standard deviation (SD) of the mean value of the same sex and the same aged people measured by the same method.

Statistics

For continuous variables, differences between groups were compared using analysis of variance (ANOVA) and post hoc multiple comparisons were performed using Tukey-Kramer's method. Two independent groups were compared using Wilcoxon signed-rank test or the paired t-test.

Results

BMD in patients with persistent bronchial asthma

All data were standardized using the sex- and age-matched mean value and SD of BMD as mentioned above. We used the standardized BMD (Z-score) to analyze data, because raw data of BMD vary with sex and age, and because we used three different methods to measure BMD. The standardized BMD (Z-score) of patients with persistent bronchial asthma was significantly smaller than that of normal subjects (-0.48 ± 1.17 , mean $\pm$ SD, $n=128$) (Fig. 1A). We analyzed BMD in men and women separately. The standardized BMD in 56 men as well as 72 women was significantly decreased. There was no significant difference in the standardized BMD between men and women (Fig. 1B). Next, the patients were divided into the following three groups according to systemic administration of CS. The first group (group I) consisted of patients who had received neither ICS nor systemic CS, and planned to start ICS therapy. The second group (group II) consisted of patients who had received ICS therapy, but had not been administered any CS continuously or systemically for the past 2 years. The third group (group III) consisted of patients who had received OCS continuously. Most patients in group III received ICS therapy in addition to OCS therapy. The standardized BMD (Z-score) of group III was significantly smaller than that of the other two groups (group I, 0.00 ± 1.19 , mean $\pm$ SD, $n=32$; group II, -0.30 ± 1.01 , $n=60$; group III, -1.22 ± 1.09 , $n=36$) (Fig. 1C). We analyzed the body weight of patients in every group because body weight may affect BMD. Body weight of patients was not significantly different among these three groups. Furthermore, the standardized BMD of men was not significantly different from that of women in every group (Fig. 1D).

Effects of ICS on BMD in patients with persistent bronchial asthma

In order to investigate the effects of FP on BMD, we compared the BMD between patients who had not been treated by ICS and those receiving FP for the first time. The FP dose was 296 ± 101 μ g daily (mean $\pm$ SD, $n=14$). For all FP patients, no CS other than FP was administered. The BMD in these patients did not change significantly in the 6 months after they started receiving FP (Fig. 2A). As shown in Fig. 1C, the BMD in the patients using ICS but not any systemic CS had not decreased significantly compared to BMD of patients who had received neither ICS nor systemic CS. We then examined the effects of FP on BMD in all patients using FP. We divided the patients using FP but not OCS into three groups according to the daily dose of FP (less than 200 μ g, $n=7$; 200 μ g to 400 μ g, $n=30$; or 400 μ g and over, $n=22$). Furthermore, we investigated the effect of FP plus OCS on BMD, as the BMD in patients who had received continuous OCS therapy was significantly smaller than that of the other patient groups. FP did not affect BMD in patients using FP but not OCS during the 6 months regardless of the daily FP dosage (Fig. 2B). FP alone did not affect the BMD in 44 patients monitored over 6 months as well

Figure 1. (A) BMD in 128 patients with persistent asthma was measured at metacarpal bones by the CXD or DIP methods, or at the radius by the DXA method. The value of BMD was standardized using the sex- and age-matched mean value and SD of BMD. Standardized BMD was expressed as Z-score. The standardized BMD in asthmatic patients decreased significantly (**, $p < 0.01$). (B) Standardized BMD in both male (56) and female (72) patients was decreased significantly. The standardized BMD in women was not different from that in men (**, $p < 0.01$; NS: not significant). (C) Patients with persistent bronchial asthma were divided into the following groups according to their experience of continuous administration of systemic CS for the past 2 years. The first group (group I, $n=32$) consisted of patients who had received neither ICS nor OCS, and planned to start receiving FP. The second group (group II, $n=60$) consisted of patients who had received ICS, but not been administered any systemic CS continuously for the past 2 years. The third group (group III, $n=36$) consisted of patients who had received systemic OCS continuously. Most patients in group III had received ICS therapy in addition to OCS. The standardized BMD of group III was significantly smaller than that of the other two groups (**, $p < 0.01$; NS: not significant). (D) Group I consisted of 16 male and 16 female patients, Group II consisted of 21 male and 39 female patients, and Group III consisted of 19 male and 17 female patients. The standardized BMD of women in each group was not significantly different from that of men in the same group (NS: not significant).

as 12 months (Fig. 2C). Forty-four patients consisted of 17 males and 27 females. The standardized BMD in men as well as women did not change significantly during the 12 months (Fig. 2D). However, the BMD in patients using both FP and OCS significantly decreased during the 6 months. The daily dose of FP in these patients was $590 \pm 200 \mu\text{g}$ (mean $\pm$ SD, $n=20$) (Fig. 2E). Twenty patients using both FP and OCS consisted of

9 males and 11 females. Standardized BMD of men was not different from that of women (Fig. 2F). The daily dose of OCS in these patients was $5.9 \pm 3.4 \text{ mg}$ (mean $\pm$ SD) as prednisolone.

BMD in older patients with persistent bronchial asthma

We divided all patients into two groups according to age. The standardized BMD expressed as Z-score was significantly

Figure 2. (A) The standardized BMD in patients who had not been previously treated with ICS, and who received FP the first time in this treatment regime, did not change significantly in the 6 months after they started receiving FP. The FP dose was 296 ± 101 µg (mean $\pm$ SD, $n=14$) daily. (B) The patients receiving FP but not OCS were divided into three groups according to the daily dose of FP. FP did not affect the standardized BMD in patients receiving FP but not OCS during the 6 months regardless of the daily FP dose (less than 200 µg, $n=7$; 200 µg to 400 µg, $n=30$; 400 µg and over, $n=22$; NS: not significant). (C) The standardized BMD did not change significantly in 44 patients who had been treated with FP without OCS after 12 months of treatment (NS: not significant). (D) Forty-four patients who had been treated with FP without OCS consisted of 17 male patients and 27 female patients. The standardized BMD in women as well as men did not change significantly after 12 months of treatment (NS: not significant). (E) The standardized BMD in patients using both FP and OCS decreased significantly during the 6 months ($n=20$, *, $p<0.05$). (F) Twenty patients using both FP and OCS consisted of 9 males and 11 females. The standardized BMD in women was not significantly different from that in men (NS: not significant).

Figure 3. (A) The standardized BMD was significantly lower in patients 60 years and over than in patients under 60 (*, $p < 0.05$). (B) The standardized BMD in 37 female patients 60 years and over was not significantly different from that in 21 male patients 60 years and over. The standardized BMD in 35 female patients under 60 years was not significantly different from that in 35 male patients under 60, either (NS: not significant). (C) We measured BMD twice at intervals of 6 months in 45 patients 60 years and over and 41 patients under 60 years. The standardized BMD in patients 60 years and over significantly decreased after the 6-month treatment, although the standardized BMD in patients under 60 did not decrease after the treatment (*, $p < 0.05$; NS: not significant). (D) Forty-five patients 60 years and over, whose BMD was measured twice, consisted of 16 males and 29 females. The standardized BMD in women was not significantly different from that in men (NS: not significant). (E) The standardized BMD in 26 patients 60 years and over treated with FP without OCS did not decrease significantly after the 6-month treatment (NS: not significant).

lower in patients 60 years and over (-0.71 ± 1.10 , mean $\pm$ SD, $n = 58$) than patients under 60 (-0.30 ± 1.21 , $n = 70$) (Fig. 3A). Body weight of the patients was not significantly different between these two groups, and there was no significant difference of the standardized BMD between men and women (Fig. 3B). Furthermore, we investigated the effect of CS therapy on BMD in these older patients, by measuring BMD twice at intervals of 6 months ($n = 45$, 16 males and 29 females). Fourteen patients of 45 used both ICS and OCS. The remaining 31 patients used only ICS. The BMD in the patients 60 years and over was significantly lower after the 6-month treatment (Fig. 3C). There was no significant difference of the standardized BMD between men and women in these older patients (Fig. 3D). However, the BMD in 26 patients treated with FP but not OCS did not decrease significantly (Fig. 3E), suggesting that the decrease in BMD in these older patients is due to OCS. In contrast, the BMD in the patients under 60 years did not de-

crease after treatment (Fig. 3C).

Comparison of the three methods used to measure BMD

As we measured BMD using three different methods, we investigated the effects of FP on BMD in each group (CXD, DIP, DXA). We measured BMD twice at intervals of 6 months in 30 patients using FP without OCS by CXD, 10 patients by DIP, and 19 patients by DXA. The FP dose was $305 \pm 157 \mu\text{g}$ (mean $\pm$ SD) in the CXD group, $260 \pm 97 \mu\text{g}$ in the DIP group, and $266 \pm 123 \mu\text{g}$ in the DXA group. BMD in the CXD group changed from $2.27 \pm 0.45 \text{ mmAl}$ to $2.24 \pm 0.46 \text{ mmAl}$ (mean $\pm$ SD), the DIP group from $2.48 \pm 0.51 \text{ mmAl}$ to $2.43 \pm 0.51 \text{ mmAl}$ (mean $\pm$ SD), and the DXA group from $0.424 \pm 0.098 \text{ g/cm}^2$ to $0.425 \pm 0.068 \text{ g/cm}^2$ (mean $\pm$ SD) during the 6 months. FP did not affect BMD significantly during the 6 months in any group.

Discussion

Osteoporosis is a serious health problem associated with pain, loss of independence, and increased mortality. Each vertebral compression fracture has been estimated to cause a 10% decrement in FVC in normal subjects (12). Therefore, the effect of osteoporosis on pulmonary function in bronchial asthma is likely substantial. Patients with persistent bronchial asthma usually receive chronic treatment with ICS, while some patients require OCS with ICS.

We evaluated BMD in 128 patients with persistent bronchial asthma. The sex- and age-adjusted BMD (Z-score) in these patients was significantly lower than the norm. When we divided these patients into two groups according to continuous use of OCS in the past 2 years, the BMD of patients treated with OCS was significantly lower than that of patients treated without OCS. These results suggest that decreased BMD in asthmatic patients is primarily due to the use of OCS. However, we cannot eliminate the possibility that the severity of the asthma itself may cause a decrease in BMD.

CS are the most effective anti-inflammatory medications currently available for the treatment of asthma, although the mechanisms by which these drugs act to relieve asthma symptoms are not completely understood. ICS are the preferred route of administration for long-term maintenance therapy, as they produce a significantly lower incidence of adverse reactions than OCS (13). The local adverse effects of ICS include oropharyngeal candidiasis, hoarseness, and cough due to irritation of the upper airways (14). Although patients requiring high doses of ICS for asthma control may be at long-term risk of bone loss, the loss is likely to be to a much smaller extent than with maintenance OCS therapy (13). Furthermore, many studies support the safety of ICS on BMD in asthmatic patients (15, 16). However, because most studies have excluded a priori individuals older than 50 or postmenopausal women to avoid the confounding influences of age and menopausal status on bone loss, the relative safety of ICS therapy in these susceptible populations remains unknown. In our investigation, BMD standardized by the sex- and age-matched mean value of BMD (Z-score) in older patients was significantly lower than the standardized BMD in patients under 60 years old. Moreover, BMD in these older patients decreased significantly after the 6-month treatment. The BMD in humans decreases with increasing age, with decrease being particularly marked in postmenopausal women. A recent study has demonstrated that ICS treatments decrease the BMD in postmenopausal women (17). Thus, BMD in older asthmatics, especially women, should be measured regularly and osteoporosis in these patients needs to be treated adequately.

In our investigation, BMD did not change in patients treated with FP alone over 6 or 12 months. Surprisingly, the BMD in patients treated with both FP and OCS significantly decreased during the 6-month treatment. The BMD in older patients also decreased, presumably due to OCS therapy. In the patients with severe persistent bronchial asthma, continuous administration of OCS is sometimes required together with a high dose of

ICS to control their symptoms. We should be very careful with the decrease of BMD in these patients even at a low OCS dose. We used three different methods to investigate BMD in this study for hospital reasons. We think it is better to use the same method and utilize cancellous bone in order to analyze the effect of CS on BMD more accurately.

In summary, the standard FP dose (200–400 µg/day) does not affect the BMD in patients with mild or moderate persistent asthma. However, combination therapy of FP (400–800 µg/day) and OCS in patients with severe persistent asthma may affect the BMD in the short term. Therefore, patients with severe persistent asthma receiving both ICS and OCS should be considered for bone densitometry screening. In future studies, it will be important to investigate whether OCS, such as a low dose of prednisolone, may affect the BMD in patients with severe persistent asthma in the short term or not.

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