Ann Allergy Asthma Immunol xxx (2014) 1–6

Contents lists available at ScienceDirect

Are asthmatic patients prone to bone loss?

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ARTICLE INFO

Article history:
Received for publication October 18, 2013.
Received in revised form February 12, 2014.
Accepted for publication February 20, 2014.

ABSTRACT

Background: Recent studies suggest an association between allergic diseases, including asthma, and lower vitamin D level, a well-known risk factor of osteoporosis. However, it is not yet clearly known whether patients with asthma are prone to bone loss.

Objective: To evaluate whether the occurrence of airway hyperresponsiveness (AHR) or asthma is related to significant changes in bone mineral density (BMD).

Methods: We retrospectively enrolled 7,034 patients who had undergone a health checkup program, including BMD tests and methacholine bronchial challenge tests, at the Seoul National University Hospital, Healthcare System Gangnam Center, from November 1, 2004 to April 30, 2011. Asthma was ascertained by self-reported medical diagnosis by a physician. Patients with a history of systemic corticosteroid medication use were excluded from the study.

Results: Among a total of 7,034 patients, 216 (3.1%) had a positive AHR test result, and 217 (3.1%) had a history of asthma. Lumbar spine and femur BMD of patients with AHR were significantly lower than those without AHR (-0.53 ± 1.50 vs -0.03 ± 1.49, -0.47 ± 0.97 vs -0.22 ± 0.99, respectively; $P < .001$ for both). After being adjusted for age, sex, body mass index, smoking status, postmenopausal state, and previous history of hormone replacement therapy, the proportion of patients with osteopenia or osteoporosis was much higher in the AHR-positive group than in the AHR-negative group (odds ratio, 1.715; 95% confidence interval, 1.252-2.349) and in the ever-asthma group than in the never-asthma group (odds ratio, 1.526; 95% confidence interval, 1.120-2.079).

Conclusion: In the current study, AHR and asthma were related to clinically meaningful BMD decrease, although the causal relationship is unclear.

Introduction

Allergic diseases and osteoporosis are common in the general population worldwide. More than 20% of the general population has allergic diseases, including allergic rhinitis and asthma.[1] Prevalence of osteoporosis is as high as 13.1% for men and 24.3% for women in Korean adults aged 40 to 79 years.[2] Therefore, osteoporosis results in major personal and societal costs because of its high morbidity and mortality related to low-trauma fractures in elderly people.[3]

However, little attention has been paid to the association between allergic diseases and bone loss in the past. Most of the previous studies on bone mineral density (BMD) or osteoporosis in asthma were mainly focused on the adverse effects of prolonged corticosteroid treatment.[4] Systemic corticosteroid use, a known risk factor of osteoporosis, increases the risk of fractures in asthma patients in a dose- and duration-dependant manner.[4–6] Several studies have reported a dose-related association between use of an inhaled corticosteroid (ICS) and decline in BMD.[7,8] In recent decades, many studies have been performed on the association between allergic disease and vitamin D—an important factor in bone mineralization. The serum vitamin D levels of patients with asthma or airway hyperresponsiveness (AHR) are relatively lower compared with those of healthy controls, and lower levels of vitamin D were found to be related to increased asthma severity and more frequent exacerbations.[9,10]

Considering that life-long persistence of asthma developed in adulthood and the major role of vitamin D in bone mineralization, asthma morbidity itself can be a potential risk factor for bone loss. However, there are no definite data revealing the status of BMD in

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Jae-Woo Jung and Hye-Ryun Kang have contributed equally as first authors.
Disclosures: Authors have nothing to disclose.
Funding: This study was supported by grant HI10C2020 from the Korea Healthcare Technology R&D Project, Ministry for Health and Welfare, Republic of Korea.

1081-1206/14/$36.00 - see front matter
http://dx.doi.org/10.1016/j.anai.2014.02.013

patients with asthma. We performed a large-scale, cross-sectional study on patients who underwent an annual heath checkup and investigated the association between asthma or AHR and BMD.

Methods

Study Design

This was a cross-sectional study performed on patients older than 18 years who had undergone a health checkup program at the Seoul National University Hospital Healthcare System Gangnam Center from November 1, 2004 to April 30, 2011. Electronic medical records of the patients were reviewed. Among 7,078 patients who had undergone both BMD and methacholine bronchial provocation tests, 44 recipients with a history of systematic corticosteroid use were excluded, leaving a total 7,034 recipients for subsequent analysis. The BMD test was included in the routine basic health checkup program, and the methacholine bronchial provocation test was performed optionally in patients who had selected it. The methacholine bronchial provocation test and the BMD test were performed on the same day because all health checkup programs provided in our center are designed to be completed within a half day.

We investigated each patient's age, sex, smoking status, comorbidity (eg, hypertension, diabetes mellitus, asthma, and allergic rhinitis) diagnosed by a physician, body mass index (BMI), white blood cell counts, peripheral eosinophil counts, serum creatinine level, alanine transaminase level, alkaline phosphatase (ALP) level, serum total IgE level, pulmonary function, and presence of atopy. For women, information on menopause and history of hormone replacement therapy (HRT) was also recorded because of their potential to affect BMD. Atopy was defined as positivity to at least one common inhalant allergen in the skin prick test or the multiple allergen simultaneous test (MAST; Hitachi Chemical Diagnostics Inc, Mountain View, California). This study was approved by the institutional review board of Seoul National University Hospital, and informed consent was waived.

Methacholine Bronchial Challenge Test

Methacholine was inhaled as an aerosol using a nebulizer (DeVilbiss, Carlsbad, California) and Rosenthal-French dosimeter (Laboratory for Applied Immunology, Baltimore, Maryland) in 5 inspiratory capacity breaths.[11] The nebulizer used in the study delivered 9 μL of solution per 0.6-second actuation during inhalation. The methacholine concentrations used were 0.0625, 0.25, 1, 4, and 16 mg/mL. The test was stopped when the forced expiratory volume in 1 second (FEV_1) decreased 20% or more from the baseline. AHR was defined as the provocative concentration of methacholine that causes a 20% decrease in FEV_1 from the baseline (PC_{20}) being 16 mg/mL or lower.

BMD Evaluation

By using DEXA (LUNAR Prodigy; GE Medical, Chalfont St Giles, United Kingdom), we measured BMD of lumbar spines (L1-L4) and femur. On the basis of the lowest T scores, we classified the patients into 3 groups according to the criteria of the World Health Organization.[12] Normal BMD was defined as a T score of −1.0 SD or greater; osteopenia, between −1.0 and −2.5 SDs; and osteoporosis, −2.5 SDs or less.

Statistic Analysis

Analysis was performed with SPSS statistical software, version 17.0 (SPSS Inc, Chicago, Illinois). Both χ^2 and t tests were used for comparisons according to the presence of AHR or allergic disease. We performed linear regression tests and binary logistic regression tests to adjust for other factors that could affect BMD. A Pearson correlation analysis was used to confirm the association between AHR level and BMD. $P < .05$ was considered statistically significant.

Results

Patient Demographics

Among a total of 7,034 patients, 2,909 (41.4%) were male, and the mean (SD) age was 55.62 (10.78) years (Table 1). Hypertension, found in 27.4%, was the most common underlying disease, followed by diabetes, asthma, and allergic rhinitis. Skin tests or MASTs were performed in 73.4% of study patients (957 skin tests and 5,147 MASTs), and the atopy rate was 44.1%. In women, 65.6% were postmenopausal, and 15.4% had previous experience with HRT.

The mean (SD) FEV_1 predicted value of the study patients was 104.96% (14.51%), and the forced vital capacity (FVC) predicted value was 97.38% (12.12%). In the methacholine provocation test, 216 (3.1%) had positive AHR test results (Table 2). Among 217 patients with a history of physician-diagnosed asthma, 40 (18.4%) demonstrated AHR on testing. Of the 6,817 patients without a history of asthma, 176 (2.6%) had positive AHR test results.

Mean (SD) lumbar and femur BMD were −0.04 (1.49) and −0.23 (0.99), respectively. A total of 2,110 patients (30.0%) had osteopenia; 290 (4.1%) had osteoporosis.

Comparison of Clinical Characteristics According to AHR

When the patients were grouped according to AHR, the positive group was older and had a higher current smoking rate compared with the negative group ($P < .001$ for both; Table 2). Atopy rate was also higher in the AHR-positive group than in the AHR-negative group (56.4% vs 43.8%; $P = .007$). The mean (SD) FEV_1 predicted value (91.83% [13.37%] vs 105.38% [14.35%]; $P < .001$) and the mean (SD) FEV_1/FVC value (71.11% [7.79%] vs 79.49% [6.62%]; $P < .001$) were significantly lower in the AHR-positive group than in the AHR-negative group.

BMI, postmenopausal state, and history of HRT did not differ between the groups. Serum creatinine, calcium, and phosphorus

Table 1
Demographic characteristics of the study population

Characteristic	Finding (N = 7,034)
Male, No. (%)	2,909 (41.4)
Age, mean (SD), y	55.62 (10.78)
Body mass index, mean (SD)	23.94 (2.95)
Smoking status, non/ever/current, %	49.5/29.5/21.0
Postmenopausal state in females, No. (%)	1,907/2,909 (65.6)
Hormone replacement therapy in females, No. (%)	448/2,900 (15.4)
Hypertension, No. (%)	1,920 (27.4)
Allergic rhinitis, No. (%)	556 (10.6)
Diabetes mellitus, No. (%)	639 (9.1)
Bronchial asthma, No. (%)	217 (3.1)
Atopy, No. (%)	2,274/5,159 (44.1)
Airway hyperresponsiveness, No. (%)	216 (3.1)
Blood WBC counts, mean (SD), /μL	5,604.00 (1,597.23)
Blood eosinophil counts, mean (SD), /μL	156.51 (154.01)
Serum total IgE, mean (SD), U/mL	215.39 (652.06)
Alanine transaminase, mean (SD), IU/L	26.71 (20.74)
Creatinine, mean (SD), mg/dL	0.98 (0.22)
Alkaline phosphatase, mean (SD), IU/L	61.34 (19.21)
Calcium, mean (SD), mg/dL	9.24 (0.38)
Phosphorus, mean (SD), mg/dL	3.59 (0.56)
FEV_1, mean (SD), % predicted	104.96 (14.51)
FVC, mean (SD), % predicted	97.38 (12.12)
FEV_1/FVC, mean (SD), %	79.23 (6.81)
Bone mineral density	
Lumbar spine, mean (SD)	−0.04 (1.49)
Femur, mean (SD)	−0.23 (0.99)
Normal/osteopenia/osteoporosis, %	65.9/30.0/4.1

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; WBC, white blood cell.

Table 2
Comparison of clinical characteristics according to airway hyperresponsiveness

Characteristic	Airway hyperresponsiveness		*P* value
	Negative	Positive	
Patients, No. (%)	6,818 (96.9)	216 (3.1)	
Male, No. (%)	3,990 (58.5)	135 (62.5)	NS
Age, mean (SD), y	55.47 (10.76)	60.47 (10.56)	<.001
Body mass index, mean (SD)	23.93 (2.93)	24.22 (3.29)	NS
Smoking status, non/ever/current, %	49.9/29.5/20.5	35.6/29.4/35.1	<.001
Atopy, No. (%)	2,208/5,042 (43.8)	66/117 (56.4)	.007
Postmenopausal state in females, No. (%)	1,847/2,828 (65.3)	60/81 (74.1)	NS
Hormone replacement therapy in females, No. (%)	439/2,820 (15.6)	9/80 (11.3)	NS
Creatinine, mean (SD), mg/dL	0.98 (0.22)	0.99 ± 0.20	NS
Alkaline phosphatase, mean (SD), IU/L	61.15 (19.16)	67.07 (20.03)	<.001
Calcium, mean (SD), mg/dL	9.24 (0.38)	9.20 (0.37)	NS
Phosphorus, mean (SD), mg/dL	3.59 (0.55)	3.61 (0.74)	NS
FEV_1, mean (SD), % predicted	105.38 (14.35)	91.83 (13.37)	<.001
FVC, mean (SD), % predicted	97.51 (12.11)	93.18 (11.97)	<.001
FEV_1/FVC, mean (SD), %	79.49 (6.62)	71.11 (7.79)	<.001

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; NS, not significant.

levels also did not reveal any difference. The ALP level was significantly higher in the AHR-positive group than in the AHR-negative group (67.07 [20.03] IU/L vs 61.15 [19.16] IU/L; $P < .001$), although the values were within the reference ranges for both groups.

Comparison of BMD According to AHR

The lumbar spine BMD level was significantly lower in the AHR-positive group than in the AHR-negative group (−0.53 [1.50] vs −0.03 [1.49]; $P < .001$; Table 3). Femur BMD was also lower in the AHR-positive group compared with the AHR-negative group (−0.47 [0.97] vs −0.22 [0.99]; $P < .001$).

After exclusion of 217 patients who had ever been diagnosed as having asthma, the BMD of 6,817 patients according to the presence of AHR were compared. Similar to the results above, the BMD scores of both lumbar spine and femur were significantly lower in the AHR-positive group compared with the AHR-negative group (−0.39 [1.54] vs −0.02 [1.49], −0.45 [0.99] vs −0.22 [0.99]; $P = .002$ for both).

We performed linear regression analysis of BMD with the factors known to affect it. After linear regression of lumbar spine BMD with age, sex, BMI, smoking, postmenopausal state, HRT, and AHR, statistical significance was sustained in AHR ($P = .001$). To exclude the possibility of asthma medications affecting BMD, adjusted multiple regression analysis was also performed in a subgroup of patients without a history of asthma, showing the same significant difference in BMD according to AHR ($P = .03$). This difference was not found in the case of femur BMD.

We compared the proportion of patients with osteopenia and osteoporosis by the presence of AHR (Fig 1). Osteopenia and osteoporosis were found in 44.6% and 6.1% in the AHR-positive group, whereas only 29.5% and 4.1% were in the AHR-negative group ($P < .001$). The odds ratio (OR) of osteopenia or osteoporosis in patients with AHR was 2.052 compared with patients without AHR (95% confidence interval [CI], 1.564-2.692; $P < .001$). After adjusting for confounding factors, the statistical significance was maintained (OR, 1.715; 95% CI, 1.252-2.349; $P = .001$).

The study patients were classified into 3 groups according to PC_{20} of the methacholine provocation test and correlated with BMD (Fig 2). There were 6,671 patients whose PC_{20} were higher than 25 mg/mL, 147 with PC_{20} values between 16 and 25 mg/mL, 216 with PC_{20} values of less than 16 mg/mL. Mean (SD) BMD scores of the lumbar spine were relatively lower in groups with severe AHR (−0.02 [1.48], −0.23 [1.68], −0.53 [1.50]; $r = 0.06$; $P < .001$). This correlation was also observed in femur BMD with a correlation coefficient of 0.041 ($r = 0.41$; $P = .001$).

Comparison of BMD According to History of Asthma Diagnosis

We compared BMD according to the history of asthma (Fig 3A). Mean (SD) lumbar spine BMD of the ever-asthma group was −0.45 (1.55), being significantly lower than that of the never-asthma

Table 3
Comparison of mean (SD) bone mineral density by airway hyperresponsiveness and sex

Bone mineral density	Airway hyperresponsiveness		*P* value	Adjusted *P* value[a]
	Negative	Positive		
Total				
Lumbar spine	−0.03 (1.49)	−0.53 (1.50)	<.001	.001
Femur	−0.22 (0.99)	−0.46 (0.97)	<.001	NS
Male				
Lumbar spine	0.12 (1.47)	−0.47 (1.58)	<.001	.001
Femur	−0.04 (0.94)	−0.34 (0.97)	<.001	NS
Female				
Lumbar spine	−0.24 (1.49)	−0.64 (1.37)	.03	NS
Femur	−0.47 (1.01)	−0.67 (0.94)	NS	NS

Abbreviation: NS, not significant.
[a]Adjusted by age, sex, body mass index, smoking, postmenopausal state, and hormone replacement therapy.

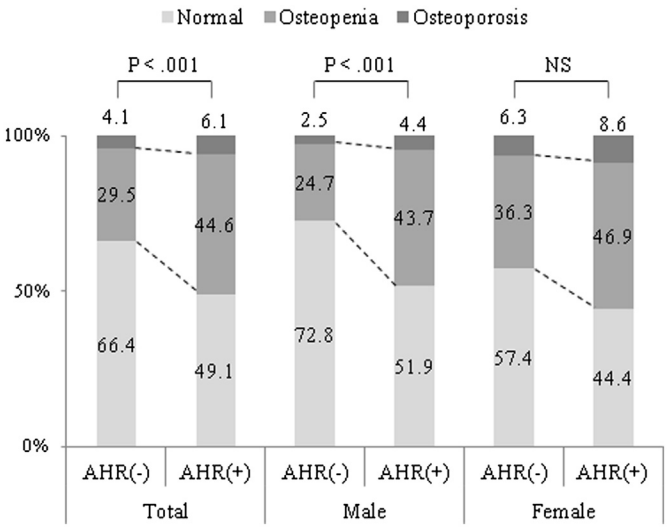

Figure 1. Proportion of patients with normal bone density, osteopenia, and osteoporosis according to airway hyperresponsiveness (AHR). *P* values calculated with the χ^2 test. NS indicates not significant.

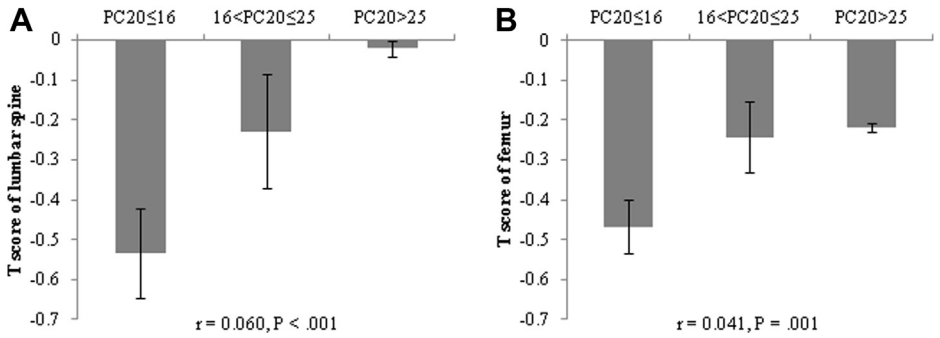

Figure 2. Correlation between bone density and severity of airway hyperresponsiveness. A, T score of lumbar spine; B, T score of femur. PC_{20} indicates the provocative concentration of methacholine that decreased forced expiratory volume in 1 second forced expiratory volume in 1 second by 20% from the baseline value. *P* values were calculated with correlation analysis.

group (−0.03 [1.50]; $P < .001$). However, such differences were not found in femur BMD. We compared the proportion of patients with osteopenia and osteoporosis by the presence of allergic diseases (Fig 3B). Osteopenia and osteoporosis were found in 39.2% and 7.4% in the ever-asthma group, whereas only 29.7% and 4% were in the never-asthma group, respectively ($P < .001$). The proportion of patients with osteopenia or osteoporosis was much higher in the ever-asthma group than in the never-asthma group (OR, 1.709; 95% CI, 1.303–2.243; $P < .001$), and the statistical significance was maintained even after correction of the abovementioned factors (OR, 1.526; 95% CI, 1.120–2.079; $P = .007$). When comparing BMD according to the presence of allergic rhinitis or atopy, no significant differences were found ($P > .05$).

Subgroup Analysis According to Sex

In males, the BMD levels of the lumbar spine and femur were significantly lower in the AHR-positive group compared with the AHR-negative group (−0.47 [1.58] vs 0.12 [1.47], −0.34 [0.97] vs −0.04 [0.94], respectively; $P < .001$ for both; Table 3). After adjusting already mentioned confounding factors, statistical significance was sustained only in lumbar spine BMD ($P = .001$).

In females, only the lumbar spine BMD level was lower in the AHR-positive group compared with the AHR-negative group (−0.64 [1.37] vs −0.24 [1.49]; $P = .03$). However, this difference did not persist after linear regression.

Discussion

Our study demonstrated a significant reduction of BMD in patients who had positive AHR test results but never had a history of systematic corticosteroid. The proportion of patients with osteopenia or osteoporosis was much higher in the patients with AHR or a history of asthma compared with those without AHR or a history of asthma. These findings suggest that the BMD and AHR or asthma are closely related, although the exact causal relationship cannot be explained. Other than AHR or asthma, not all allergic conditions were associated with BMD because this association was not observed in patients with allergic rhinitis or atopic sensitization in our study.

Currently, there are limited data on the bone density in asthmatic patients, and most previous studies were mainly focused on bone loss according to steroid treatment. Glucocorticoid is a well-known risk factor of secondary osteoporosis[13] and can affect bone metabolism by directly inhibiting vitamin D–dependent calcium absorption when maintained systemically. Systemic corticosteroids in asthma patients are known to induce osteoporosis and increase the risk for fractures. One long-term, prospective study demonstrated that repeated oral corticosteroid use for a period of years can produce a dosage-dependent reduction in BMD.[5] Ruegsegger et al[6] suggested that bone may also be lost on alternative day therapy with oral corticosteroid in asthmatic patients, especially in trabecular bone. However, systemic use of steroids has rapidly decreased after the introduction of ICSs in recent decades.

Several studies have reported that use of ICSs was also associated with a dose-related decline in BMD.[7,8] Wong et al[7] reported an inverse relation between cumulative ICS dose and BMD at the lumbar spine and proximal femur. Another study reported an association between the decline in BMD and the number of puffs per year of use in premenopausal women.[8] On the other hand, the effects of ICSs on BMD are not reported to be significant in several

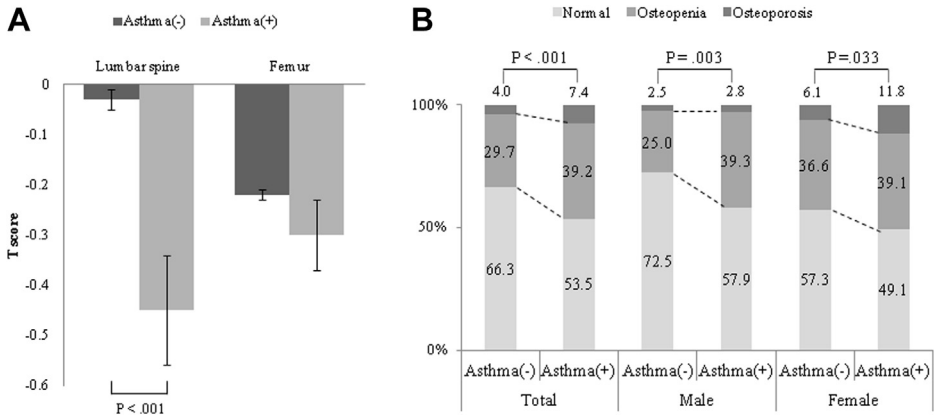

Figure 3. Comparison of bone mineral density according to presence and absence of diagnosed asthma. A, T score of lumbar spine and femur; B, proportion of osteopenia or osteoporosis. *P* values were calculated with the *t* test (A) and χ^2 test (B).

studies.[4,14,15] Kinberg et al[15] reported that asthmatic children receiving corticosteroid treatment did not appear to have adversely affected bone mass according to use of ICSs, oral corticosteroids, or a combination of these. In meta-analyses, long-term use of ICSs in patients was not related to significant change in bone density.[16,17]

Until now, no study has evaluated the relation between allergic disease itself and bone density. By excluding patients with a history of systemic steroid use, the effect of glucocorticoids on BMD was minimized and the difference in BMD according to AHR itself could be evaluated in this study. Although we had no information about ICS use in patients diagnosed as having asthma, the difference of BMD according to the presence of AHR was observed even after excluding patients diagnosed as having asthma. This finding implies that the correlation between AHR and BMD is not a secondary finding of ICS treatment in asthma.

Given that steroid effect was minimized in our study, what made this difference in BMD in patients with AHR or asthma? We speculate that vitamin D can be one of the factors that affects BMD in these patients. The effect of vitamin D on the bone density has been established through extensive research. The cross-sectional study by the US National Health and Nutrition Examination Survey III group reported that serum 25-hydroxyvitamin D levels correlate with pelvis BMD in adult women.[18] Vitamin D deficiency causes secondary hyperparathyroidism, and parathyroid hormone stimulates the transformation of preosteoclasts into mature osteoclasts, which cause osteopenia and osteoporosis and increase the risk of fracture.[19] Moreover, meta-analyses on 12 random clinical studies revealed that vitamin D intake of more than 400 IU/d reduces the risk of nonvertebral fractures.[20] In addition to its role in bone mineralization, vitamin D has various essential roles in the immune system, such as activation and proliferation of lymphocytes, differentiation of T_H lymphocytes, homing of tissue-specific lymphocytes, production of antibody isotypes, and immune regulation.[21] Several epidemiologic studies have reported that vitamin D is associated with asthma. In asthma patients, vitamin D insufficiency was more frequently found than in the healthy population[10] and related to increased AHR, higher eosinophil counts, and higher IgE levels in children.[22] In addition, vitamin D is known to be related to poor asthma control, resulting in more frequent hospitalizations and emergency department visits.[22,23] In some genetic studies, polymorphisms on the vitamin D receptor gene have shown relationships with asthma and atopy.[24,25] For the correlation between BMD and AHR or asthma observed in our study, we cautiously speculate that long-term vitamin D deficiency in patients with AHR and asthma may contribute to their vulnerability to osteopenia and osteoporosis.

Along with BMD, ALP is a marker of bone turnover and bone remodeling. Because ALP increases in osteoporosis and active bone formation, it is used as an indirect marker that indicates a decrease in vitamin D.[26,27] Although ALP levels were within the reference range in both groups of our study, a slight increase of ALP and a reduced BMD score were observed in the AHR-positive group but not in the AHR-negative group. This finding also supports potential differences between the 2 groups in terms of vitamin D status.

In our study, the difference of BMD according to AHR in the logistic regression analysis was maintained only for lumbar spine but not for femur. Moreover, femur BMD was not different according to the presence of asthma history. The discrepancies relate mainly to different patterns of bone loss at the various sites. Current osteoporosis guidelines propose that the lumbar spine BMD may be a useful measure of bone loss because the spinal bone tends to be lost faster than the femur.[28] The North American Menopause Society recommends that the spine BMD may be a useful indicator of bone loss, particularly in early postmenopausal women, and the International Society for Clinical Densitometry also proposes the spine as the preferred site, with the total hip as an alternative.[28] Therefore, it is not surprising that the difference of BMD in the logistic regression analysis was maintained only for lumbar spine but not for femur in our study.

Many diverse factors are involved in the development of osteoporosis. Other than vitamin D deficiency, the known risk factors for osteoporosis are as follows: old age, postmenopausal status, use of oral corticosteroid for longer than 3 months, estrogen deficiency at an early age, low body weight, excess alcohol use, tobacco smoking, low physical activity, history of fracture as an adult, and family history of osteoporosis.[13] After adjustment for BMD-affecting factors verifiable in our study participants, regression analysis revealed that the AHR-positive group had an increased risk of lower BMD scores than the AHR-negative group. Among various factors that affect BMD, the most important factor is aging and menopause.[12] To correct the effect of estrogen on BMD, we performed subgroup analysis according to sex. As a result, the difference of BMD according to AHR was sustained only in males, but there was no statistically significant difference in females. The effect of estrogen and progesterone on asthma is well known. Although asthma exacerbation and hospitalization increased during premenstrual and menstrual phase, HRT and oral contraceptive therapy were associated with a decrease in asthma exacerbation and improved lung function in asthmatic patients.[29] BMI is another factor known to affect both AHR and osteoporosis, but in a contrasting manner: high BMI is associated with AHR, whereas low BMI is associated with increased risk of osteoporosis.[13,30] Considering this, we adjusted for BMI in our analysis of AHR and BMD, and their significant association remained after adjustment. Tobacco smoking is an important factor affecting both AHR and osteoporosis. To adjust for confounding by smoking, we performed linear regression and binary logistic regression tests; BMD levels of the lumbar spine and femur were rather higher in the current smoker group compared with the nonsmoker group (data not shown). Therefore, we could conclude that the association between AHR and osteoporosis was not determined by smoking.

Although we have adjusted for many factors that affect BMD, this study has a limitation in that some variables were investigated through a questionnaire-based survey. Furthermore, many factors that can affect vitamin D levels, such as level of physical activity, duration of outdoor sun exposure, and intake of vitamin supplements, were not included because they were difficult to quantify. The health checkup program of the study participants was designed for healthy adults free of active underlying disease. Therefore, it is unlikely that the study result is merely due to low levels of outdoor activity. Another important limitation of our study was that it was cross-sectional. Thus, we could not determine the causality between AHR and decreased BMD. In our study, the positive rate of methacholine challenge was only 18.4% among the patients with a history of asthma. This relatively low positive rate may be attributed to loose inclusion criteria for asthma. In fact, there was no limit for years after diagnosis of asthma in the questionnaire used in the study. Therefore, asthma diagnosis based on symptom only, transient wheezing in infancy, childhood asthma during the preschool period, and eosinophilic bronchitis without AHR could be counted as asthma. In a longitudinal study, more than half of children and adolescents with asthma were in symptomatic remission during a mean follow-up of 30 years.[31] In adults with asthma, reported prevalence of remission ranges from 5% to 40%.[32]

Despite numerous research on the clinical effects of vitamin D, objective data on vitamin D and allergic disease are still insufficient to draw a clear conclusion. In our study, there were no measurements of vitamin D, so we could not determine whether there was a causal relationship between vitamin D deficiency and AHR. However, our study demonstrated the significant negative correlation between AHR or asthma and decreased BMD in Korean adults and also found that osteopenia and osteoporosis were more frequent in

patients with AHR or asthma. Considering the results of our study, we suggest physicians pay additional attention to bone loss when providing care to patients with asthma.

References

[1] Galassi C, De Sario M, Biggeri A, et al. Changes in prevalence of asthma and allergies among children and adolescents in Italy: 1994-2002. *Pediatrics*. 2006;117:34–42.

[2] Shin CS, Choi HJ, Kim MJ, et al. Prevalence and risk factors of osteoporosis in Korea: a community-based cohort study with lumbar spine and hip bone mineral density. *Bone*. 2010;47:378–387.

[3] Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet*. 1999;353:878–882.

[4] Gatti D, Senna G, Viapiana O, Rossini M, Passalacqua G, Adami S. Allergy and the bone: unexpected relationships. *Ann Allergy Asthma Immunol*. 2011;107:202–206.

[5] Kelly HW, Van Natta ML, Covar RA, Tonascia J, Green RP, Strunk RC. Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the childhood Asthma Management Program (CAMP) study. *Pediatrics*. 2008;122:e53–e61.

[6] Ruegsegger P, Medici TC, Anliker M. Corticosteroid-induced bone loss. A longitudinal study of alternate day therapy in patients with bronchial asthma using quantitative computed tomography. *Eur J Clin Pharmacol*. 1983;25:615–620.

[7] Wong CA, Walsh LJ, Smith CJ, et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet*. 2000;355:1399–1403.

[8] Israel E, Banerjee TR, Fitzmaurice GM, Kotlov TV, LaHive K, LeBoff MS. Effects of inhaled glucocorticoids on bone density in premenopausal women. *N Engl J Med*. 2001;345:941–947.

[9] Chinellato I, Piazza M, Sandri M, Peroni D, Piacentini G, Boner AL. Vitamin D serum levels and markers of asthma control in Italian children. *J Pediatr*. 2011;158:437–441.

[10] Freishtat RJ, Iqbal SF, Pillai DK, et al. High prevalence of vitamin D deficiency among inner-city African American youth with asthma in Washington, DC. *J Pediatr*. 2010;156:948–952.

[11] Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999: this official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med*. 2000;161:309–329.

[12] Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of a WHO Study Group. *World Health Organ Tech Rep Ser*. 1994;843:1–129.

[13] Boling EP. Secondary osteoporosis: underlying disease and the risk for glucocorticoid-induced osteoporosis. *Clin Ther*. 2004;26:1–14.

[14] Etminan M, Sadatsafavi M, Ganjizadeh Zavareh S, Takkouche B, FitzGerald JM. Inhaled corticosteroids and the risk of fractures in older adults: a systematic review and meta-analysis. *Drug Saf*. 2008;31:409–414.

[15] Kinberg KA, Hopp RJ, Biven RE, Gallagher JC. Bone mineral density in normal and asthmatic children. *J Allergy Clin Immunol*. 1994;94:490–497.

[16] Sharma PK, Malhotra S, Pandhi P, Kumar N. Effect of inhaled steroids on bone mineral density: a meta-analysis. *J Clin Pharmacol*. 2003;43:193–197.

[17] Halpern MT, Schmier JK, Van Kerkhove MD, Watkins M, Kalberg CJ. Impact of long-term inhaled corticosteroid therapy on bone mineral density: results of a meta-analysis. *Ann Allergy Asthma Immunol*. 2004;92:201–207.

[18] Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B, et al. Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U.S. adults. *J Bone Miner Res*. 2009;24:935–942.

[19] Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266–281.

[20] Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2009;169:551–561.

[21] Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol*. 2008;8:685–698.

[22] Brehm JM, Celedon JC, Soto-Quiros ME, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med*. 2009;179:765–771.

[23] Brehm JM, Schuemann B, Fuhlbrigge AL, et al. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. *J Allergy Clin Immunol*. 2010;126:52–58.

[24] Poon AH, Laprise C, Lemire M, et al. Association of vitamin D receptor genetic variants with susceptibility to asthma and atopy. *Am J Respir Crit Care Med*. 2004;170:967–973.

[25] Raby BA, Lazarus R, Silverman EK, et al. Association of vitamin D receptor gene polymorphisms with childhood and adult asthma. *Am J Respir Crit Care Med*. 2004;170:1057–1065.

[26] Hulth AG, Nilsson BE, Westlin NE, Wiklund PE. Alkaline phosphatase in women with osteoporosis. *Acta Med Scand*. 1979;206:201–203.

[27] Villareal DT, Civitelli R, Chines A, Avioli LV. Subclinical vitamin D deficiency in postmenopausal women with low vertebral bone mass. *J Clin Endocrinol Metab*. 1991;72:628–634.

[28] Bonnick SL, Shulman L. Monitoring osteoporosis therapy: bone mineral density, bone turnover markers, or both? *Am J Med*. 2006;119:S25–S31.

[29] Haggerty CL, Ness RB, Kelsey S, Waterer GW. The impact of estrogen and progesterone on asthma. *Ann Allergy Asthma Immunol*. 2003;90:284–291.

[30] Shore SA. Obesity and asthma: implications for treatment. *Curr Opin Pulm Med*. 2007;13:56–62.

[31] Vonk JM, Postma DS, Boezen HM, et al. Childhood factors associated with asthma remission after 30 year follow up. *Thorax*. 2004;59:925–929.

[32] Upham JW, James AL. Remission of asthma: the next therapeutic frontier? *Pharmacol Ther*. 2011;130:38–45.