Bone mineral density in asthmatic patients on inhaled corticosteroids in a developing country

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Abstract:

INTRODUCTION: Prolonged use of oral corticosteroids is a risk factor for osteoporosis. However, the effect of inhaled corticosteroids (ICS) on bone mineral density (BMD) of asthmatic patients remains controversial.

OBJECTIVES: We aimed to determine the prevalence of osteopenia and osteoporosis in our patients with asthma receiving ICSs for more than one year compared with patients who did not have asthma and to determine the risk factors for osteopenia and osteoporosis among the asthmatic patients.

METHODS: This was a cross-sectional study conducted from August 2007 to July 2009. Asthmatic patients aged 18 years and older who had been on ICS for at least one year and a control group of subjects not on ICS were included. BMD was measured using DEXA (dual energy X-ray absorptiometry) scan. The WHO classification of T-scores for osteopenia and osteoporosis were used.

RESULTS: A total of 143 subjects were recruited (69 asthmatics and 74 control subjects). T-scores of the spine, femur, and hip of the asthmatics *vs* the control subjects were mean, -0.72 *vs* -0.57 (P=0.98); median, -0.60 *vs* -0.80 (P=0.474); and mean, 0.19 *vs* 0.06 (P=0.275); respectively. T-scores of the spine, femur, and hip showed significant negative correlation with age and significant positive correlation with body mass index (BMI).

CONCLUSION: The risk factors for osteoporosis and osteopenia among asthmatic patients were older age and lower BMI, but not the cumulative dose of ICS. Asthmatic patients on ICS have no added risk of osteoporosis or osteopenia as compared with non-asthmatic subjects.

Key words:

Asthma, asthma, bone mineral density, inhaled corticosteroids

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The prevalence of asthma in Malaysia is 4.1% among adults, as reported in the Second National Health and Morbidity Survey conducted by the Ministry of Health of Malaysia.[1] According to this report, 19.4% of adult asthmatics were on inhaled corticosteroids (ICS). ICSs are the recommended therapy for chronic persistent asthma in both the Malaysian[2] and international guidelines.[3] However, there is no recommendation on whether asthmatic patients should be screened or treated for osteoporosis. The use of oral glucocorticoid equivalent of >5 mg prednisolone daily for >3 months is a strong risk factor for reduced bone mineral density (BMD).[4,5] On the other hand, evidence for the effects of ICS on BMD has been conflicting.

Several short-term prospective studies of less than two years have suggested that ICS reduce bone formation as demonstrated by lowered osteocalcin level,[6,7] but not all have concluded that BMD was significantly different compared with control subjects.[6-10] As a matter of fact, one study actually showed that larger cumulative ICS doses were associated with higher BMDs and a reduction in the number of patients at risk

of fracture.[11] A large proportion of the patients with moderate to severe asthma treated in our hospital are on long-term moderate-to-high doses of ICS and they usually require rescue courses of oral corticosteroids during exacerbations. We aimed to determine the prevalence of osteopenia and osteoporosis in our patients with asthma receiving ICS for more than one year compared with subjects who did not have asthma and to determine the risk factors for osteopenia and osteoporosis among our asthmatic patients.

Methods

This study was conducted in Hospital Tengku Ampuan Afzan in Kuantan, Malaysia. The hospital is an 800-bed tertiary referral center for medical and surgical disciplines. The emergency department of the hospital provides acute asthmatic care to patients and the specialist respiratory clinic sees 40 asthmatic patients per month. The standard course of oral prednisolone given for acute exacerbations is 30 mg daily for five days.

This is a cross-sectional study conducted over the

period of August 2007 to July 2009. Consecutive adult asthmatic patients aged 18 years or older who attended the asthma clinic of our hospital and who had been on ICS continuously for at least the past one year were included after obtaining written informed consent. They were compared with a control group of adults who were not on ICS, recruited from non-respiratory medical outpatient clinics. Control subjects also fulfilled all inclusion and exclusion criteria but they were not receiving ICS. Patients who had known factors affecting BMD which included calcium supplement consumption and hormone replacement therapy were excluded from the study. Also excluded were current smokers and ex-smokers who smoked more than 100 cigarettes in the past, i.e., ever smokers who smoked less than 100 cigarettes in their lifetime are allowed to participate in the study. Regarding alcohol consumption, male subjects who consumed >21 units/week and female subjects >14 units/week were classified as "significant alcohol consumption." The asthmatic patients were interviewed regarding the severity of the disease and details of treatment based on historical recall which included the dose and the type of ICS and average number of rescue courses of oral corticosteroids per year.

BMD of each subject was assessed using dual energy X-ray absorptiometry (DEXA) which was performed by the radiographer using a whole-body bone densitometer (Hologic Discovery W, Bedford, USA). T-score was used to define osteopenia ($-2.5 <$T-score< -1.0) and osteoporosis (T-score< -2.5) based on the WHO classification. Control of asthma was assessed according to the GINA guidelines[3] which classified the patients' asthma as controlled, partly controlled, or uncontrolled.

Statistical analysis

All ICS received by patients were converted into budesonide equipotent doses for data analysis. Physical activity was measured using the *physical activity index*[12] (PAI). PAI is the sum of the number of hours spent for each activity on an average day multiplied by the activity's weight factor, which is determined by the intensity level of the activity.

Results are expressed as mean±SD or median (interquartile range [IQR]). The data were analyzed using Statistical Package for the Social Sciences (SPSS) version 12.0 (Chicago, USA). Statistical significance was taken at $P<0.05$. Categorical variables and parametric and non-parametric continuous variables were analyzed using Chi-square, Student *t*-test, and Mann-Whitney statistical tests depending on their normality. Tests for correlation between T-scores and age, body mass index (BMI), and PAI were also performed. Factors affecting BMD among asthmatics which were found to be significant on univariate analysis were then subjected to multivariate analysis using binary logistic regression.

Results

A total of 143 subjects were recruited. Sixty-nine patients were asthmatics and were on ICSs for the past one year and the rest were control subjects. The ICSs used comprised of budesonide, fluticasone, and beclomethasone. The mean daily budesonide equipotent dose was 673±206 µg/day (range, 200 to 1 200 µg/day). The majority of the patients and control subjects were females and the characteristics of both groups are shown

in Table 1. There were no statistical significant differences between the two groups, except that the control subjects had more physical activity compared with the asthmatics.

From the DEXA scan results, there were no differences in the T-scores of the hip, femur, and spine between the asthmatics and the control group [Table 2]. More control subjects than asthmatic patients had osteopenia or osteoporosis [Figure 1], although this difference was not statistically significant (51.4% vs 43.4%, P=0.592).

Overall, 10 (7.0%) asthmatic patients had osteoporosis, 58 (40.6%) patients had osteopenia, and the remaining had normal BMD. There were no significant difference in terms of gender, smoking status, alcohol consumption, and family history of osteoporosis/osteopenia between patients with osteoporosis/osteopenia and those with normal BMD [Table 3]. Among the asthmatic patients, there was significant negative correlation and significant positive correlation between age and BMI, respectively, and the T-scores of the spine, hip, and femur [Table 4]. Among female asthmatic patients, osteoporosis and osteopenia were present in 11.7% and 48.3%

Table 1: Characteristics of asthmatic patients and control patients

Characteristic	Asthmatic patients (*n*=69) No. (%)	Control patients (*n*=74) No. (%)	P value
Male: Female	12:57	8:66	0.257
Age (year)	52 IQR: 15	52 IQR:10	0.187
Body mass index (BMI) (kg/m²)	27.5±5.4	25.0±5.1	0.331
PAI	27.7 IQR: 3.2	28.9 IQR: 1.9	0.028
No. of ever-smokers	4 (5.8)	1 (1.4)	0.162
No. of subjects with "significant alcohol consumption"	2 (2.9)	4 (5.4)	0.455
No. of postmenopausal women	24 (41)	36 (54)	0.228
No. with family history of osteoporosis	2 (2.9)	6 (8.1)	0.176

IQR = Interquartile range

Table 2: Mean or median T-score among asthmatic patients and control subjects

Site	Asthmatic patients (*n*=69)	Control subjects (*n*=74)	P value
Spine	−0.72 ± 1.30	−0.57 ± 1.29	0.980
Femur	−0.60 IQR: 1.7	−0.80 IQR: 1.1	0.474
Hip	0.19 ± 1.14	0.06 ± 0.99	0.275

IQR = Interquartile range

Table 3: Characteristics of asthmatic patients with normal and abnormal BMD

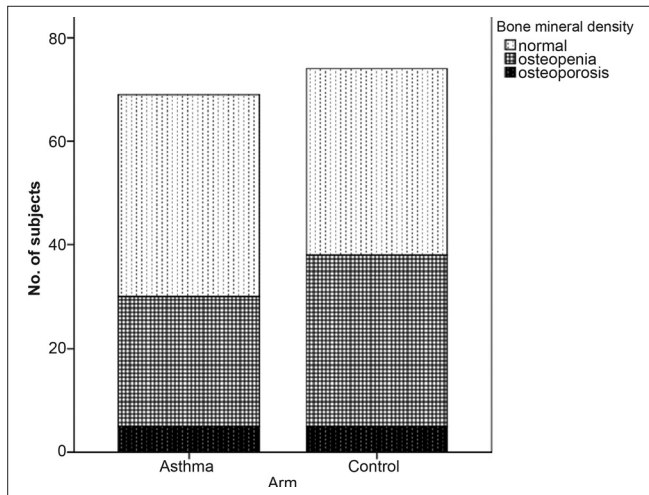|	Normal	Osteopenia/ Osteoporosis	P value
Male: Female	10:65	10:58	0.813
Ever smoker: Never smoker	2:73	3:65	0.57
Alcoholic: Non-alcoholic	3:72	3:65	0.902
Family history of osteoporosis			
Yes: No	2:73	6:62	0.110

BMD = Bone mineral density

Figure 1: Proportion of osteopenia and osteoporosis among asthmatic patients and controls

of post-menopausal women, respectively, compared with only 1.6% and 33.3% of pre-menopausal women, respectively (P=0.006).

We subjected the age and BMI of the study patients to binary logistic regression (the outcome being either normal BMD or osteoporosis/osteopenia) and found that older patients were more likely to have osteoporosis/osteopenia of the spine (odds ratio [OR]=1.04, confidence interval [CI] 1.01=1.08), femur (OR=1.05, CI=1.01-1.09), and hip (OR=1.06, CI=1.01-1.12) and patients with higher BMIs were less likely to have osteoporosis/osteopenia of the spine (OR=0.94, CI=0.88-1.01), femur (OR=0.88, CI=0.82-0.96), and hip (OR=0.77, CI=0.66-0.89).

Among asthmatic patients, duration of asthma, asthma control, cumulative budesonide-years, and rescue oral prednisolone did not affect risks of osteopenia and osteoporosis [Table 5].

Discussion

Decreased BMD appeared to be largely under detected, even among our control subjects. A high percentage of control subjects were found to have osteopenia/osteoporosis, which would have otherwise gone undetected if not for their participation in this study. Similarly, it was through the National Osteoporosis Risk Assessment in the US that of 200,160 postmenopausal women (which included 1912 Asians), 39.6% were found to have osteopenia and 7% with osteoporosis.[13] A study conducted in Malaysia reported a prevalence of osteoporosis of 24.1% in 514 disease-free, uterus-intact non-hormone replacement therapy-using women.[13]

For any meaningful analysis of the effects of ICS on BMD, a detailed evaluation of the baseline characteristics of the asthmatic group and the control group was essential to reduce bias during analysis. Although the number of female patients in our control group was higher than in the asthmatic group [Table 1], the difference in male to female ratio was not statistically significant between the two groups. All other characteristics were also matched between the two groups except for PAI, which was higher in the control group. One would expect a higher BMD

Table 4: Correlation of T score of spine, femur and hip with age, BMI, and PAI

	T-score spine		T-score femur		T-score hip	
	R	P value	R	P value	r	P value
Age	−0.230	0.006	−0.287	0.001	−0.328	<0.001
BMI	0.194	0.02	0.383	<0.001	0.536	<0.001
PAI	−0.039	0.646	0.043	0.613	0.026	0.757

BMI = Body mass index; PAI = Physical activity index

Table 5: Asthma control, cumulative budesonide-years, rescue oral prednisolone, and duration of asthma in patients with normal BMD and patients with osteopenia/osteoporosis

	Bone mineral density		P value
	Normal N=39 (%)	Osteopenia/ osteoporosis N=30 (%)	
Asthma control			
Controlled	16 (41.0)	14 (46.7)	0.896
Partly controlled	10 (25.6)	7 (23.3)	
Uncontrolled	13 (33.4)	9 (30.0)	
Cumulative budesonide-years (μg -year)			
Less than 5 000	25 (64.1)	22 (73.3)	0.715
5 000 to less than 10 000	9 (23.1)	5 (16.7)	
10 000 or more	5 (12.8)	3 (10.0)	
Rescue oral steroid for past one year			
None	30 (76.9)	20 (66.7)	0.344
One or more	9 (23.1)	10 (33.3)	
Duration of asthma			
10 years or Less	12 (30.8)	10 (33.3)	0.651
10-20 years	13 (33.3)	7 (23.3)	
More than 20 years	14 (36.9)	13 (43.4)	

(BMD) Bone mineral density

among subjects who are more physically active, but this increase in the level of activity did not result in a significant difference in the T-scores of the control subjects compared with the asthmatic patients. The PAI value depended largely on the accuracy of the patient's historical recall of physical activities conducted in an "average day." Furthermore, the larger PAI IQR in the asthmatic patients suggests that the values obtained skewed toward the extremes. Although gender, genetic background (i.e., family history), cigarette smoking, alcohol consumption, and menopausal status are believed to be among the important factors influencing BMD,[14] our results suggested that these factors did not significantly affect the BMD of our study subjects. However, the number of patients recruited into our study who actually had a history of ever-smoking, alcohol consumption, or a family history of osteoporosis was small.

Not surprisingly, the older asthmatic patients in this study had lower BMD compared with younger patients, while patients with higher BMI had higher BMD compared to patients with lower BMI. This observation has also been reported by other studies such as the one conducted by Burger *et al.*[15] who reported that the BMD yearly rate of change increased and decreased with advancing age and BMI, respectively.

The results of our study suggest that the duration of asthma,

asthma control, cumulative budesonide dose-years, and rescue oral prednisolone did not significantly affect the risk of osteopenia and osteoporosis among patients with bronchial asthma. The cumulative budesonide-years used in our study is the product of the mean daily equipotent dose of inhaled budesonide and the number of years on ICS; representative of the cumulative dose of ICS described in other studies, such as the one conducted by Toogood *et al*.[11]

Although several studies have shown that ICS either decrease or did not significantly affect BMD,[9,10,16-18] the study of 69 patients reported by Toogood *et al*.[11] showed a higher lumbar BMD Z-score in patients with a greater cumulative lifetime exposure to ICS (median >3 g) and a reduction in the number of patients at risk of fracture. We also found that the majority of our asthmatic patients (62.5%) who had higher cumulative ICS dose (more than 10 000 µg-years of cumulative budesonide-years) have normal BMD, although this was not statistically significant. We postulate that a higher dose of ICS given to asthmatic patients could have resulted in better asthma control which will then lead to an increase in physical activities and improved BMD.

In a large retrospective cohort study which included more than 100 000 patients in each arm, van Staa *et al*.[19] analyzed fracture risk among ICS users, inhaled bronchodilator users, and control subjects. The relative rates of non-vertebral, hip, and femur fractures among ICS users were higher than the control group, but not significantly different compared with the bronchodilator group. The authors concluded that ICS users had a higher risk of fracture, but this increased risk may be related to the underlying respiratory illness. They also found that the rate of fracture declined when treatment with ICS was discontinued.

Boulet *et al*.[6] studied 37 asthmatic subjects who had been using 800 µg/day or greater of beclomethasone or budesonide for more than 18 months, matched to a control group and found no significant difference in BMD between the two groups. In a separate study,[9] 374 patients with mild asthma were randomized to receive inhaled budesonide, inhaled beclomethasone dipropionate, or non-corticosteroid treatment for two years, and the authors reported that there was no difference in the change of BMD between the three groups. It is worthwhile to note that the median daily doses of inhaled budesonide and beclomethasone were 389 µg and 499 µg, respectively, which one can argue were in the lower range of ICS dosages used to treat bronchial asthma and are unlikely to have any significant effect on BMD. To study the effect of high-dose ICS on BMD, Hughes *et al*.[10] recruited 59 patients with moderate-to-severe asthma and randomized them to receive inhaled fluticasone propionate 500 µg twice daily and inhaled budesonide 800 µg twice daily for one year. They, too, concluded that treatment with high doses of either inhaled fluticasone propionate or budesonide during the one year of treatment did not demonstrate any significant difference in BMD. The short one-year duration of study may not be sufficient to observe any effect that ICS may have on BMD.

Prolonged use of oral steroids leads to BMD deterioration and ultimately an increased risk of fracture,[20] a fact not many clinicians will dispute. We attempted to include the usage of oral steroids as rescue therapy in our study to evaluate the effect of oral steroids on BMD in our study population. As expected, more patients who received one or more courses of rescue oral steroids in the preceding year had osteopenia or osteoporosis compared with those who did not, but the difference was not statistically significant. The small number of subjects in this sub-group analysis probably explained the lack of statistical significance. Furthermore, the one-year duration may be too short to demonstrate any effect of intermittent courses of oral steroids on BMD.

In conclusion, asthmatic patients on ICS had no added risk of osteoporosis or osteopenia. Risk factors for osteoporosis and osteopenia among asthmatic patients are older age and lower BMI but not the cumulative dose of ICS.

The major limitation of our study was the dependence on historical recall in the process of data gathering.

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