Original Article

Bone mineral density in asthmatic patients using low dose inhaled glucocorticosteroids

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Abstract. Inhaled glucocorticosteroids are clearly beneficial in subjects with moderate or severe asthma since they are well tolerated, reduce symptoms, and improve quality of life. Some studies suggest that inhaled glucocorticosteroids can adversely affect bone mineral density. The aim of this study is to determine the effects of inhaled glucocorticosteroid therapy on bone mineral density in female patients. Forty-five asthmatic female patients (36 premenopousal and 9 postmenopausal) and forty-six healthy control subjects were included in the study. Bone mineral density was measured from lumbar spine (L1-4) and femur (neck, trochanter, and Ward's triangle) by dual energy X-Ray absorptiometry. Age, occupation, menopause and smoking status, alcohol consumption, body mass index, previous fractures, family history of fractures, menstrual history, ooferectomy, number of pregnancies, the duration of lactation, physical activity and calcium intake were questioned according to the European Vertebral Osteoporosis Study Group (EVOS) form. Cumulative inhaled glucocorticosteroid dose was calculated. T score of femoral neck and T score and bone mineral density of Ward's triangle were significantly lower in asthmatic patients compared to control group but no statistically significant correlation was found between the disease duration, inhaled steroid treatment duration, cumulative inhaled dose and annual inhaled steroid dose and bone mineral density measurement. These results suggest that in asthmatic patients using low dose inhaled corticosteroids bone mineral density is lower than in healthy controls but it is still unclear if asthma by itself is a risk factor for osteoporosis.

Key words: Inhaled steroid, asthma, bone mineral density, osteoporosis

Introduction

Glucocorticoid treatment is effective in improving lung function, decreasing airway hyperresponsiveness, reducing symptoms, frequency and severity of exacerbations and improving quality of life in asthmatic patients. Inhaled glucocorticosteroids are the choice treatment for patients with persistent asthma at all levels of severity as these drugs can prevent severe acute exacerbations of asthma and can allow the decrease or withdrawal of oral glucocorticosteroids in these patients [1,2].

The safety profile of higher doses of inhaled glucocorticoids is clearly better than that of oral glucocorticoids [1]. Controlled clinical trials have shown that long–term treatment with high doses of inhaled glucocorticoids may be associated with systemic side effects, including skin thinning and easy bruising, adrenal suppression and decreased bone mineral density [1-4].

The aim of this study is to evaluate the effect of low dose inhaled glucocorticoids to bone mineral density in female asthmatic patients.

Methods

Patients who are followed regularly at the outpatient department of Respiratory Medicine, Dokuz Eylul University with mild or moderate asthma using inhaled glucocorticosteroids were invited to the study. Patients who accepted to participate complying with the inclusion criteria were included in the study. Inclusion criteria were: mild or moderate asthma and regular inhaled steroid treatment for at least the past six months. Exclusion criteria were: a course of oral or parenteral corticosteroids in the past six months or on more than two occasions ever, chronic obstructive pulmonary disease, treatment with any drugs affecting bone metabolism (except hormone replacement therapy), immobilisation over more than one month, any other systemic disease. A flow-volume spirometry was performed in the morning between 9^{00}-12^{00} am with Sensor Medics Vmax 22. Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, peak expiratory flow (PEF), $FEF_{\%25-75}$ (average flow rate between 25% of FVC and 75% of FVC) were measured. All tests were done according to the reference criteria of the American Thoracic Society. The severity of asthma was defined as mild persistent asthma, moderate asthma and severe asthma according to GINA guideline [1]. In mild asthma group patients with intermittent asthma were excluded; asthmatic patients with perennial symptoms and using regular inhaled steroids were included in the study. The duration of asthma, current drug treatment, compliance with treatment and all previous treatments with glucocorticosteroids were also questioned. The duration of use of each type of steroid inhaler and mean daily dose was determined from the paper records, and cumulative dose of inhaled glucocorticosteroids was expressed in milligrams by a respiratory medicine specialist. Age and menopause status matching healthy female controls were included in the study.

Age, occupation, menopause and smoking status, alcohol consumption, previous fractures, family history of fractures, menstrual history, ooferectomy, number of pregnancies, the duration of lactation, physical activity and calcium intake were questioned according to the European Vertebral Osteoporosis Study Group (EVOS) form [5, 6]. Height and weigth of patients were measured and body mass index was calculated. Bone mineral density was measured from lumbar spine (L1-4) and femur (neck, trochanter and Ward's triangle) by dual energy X-Ray absorptiometry. The results were reported as absolute densities (in grams per square centimetre) and as T scores. The latter express the number of standard deviations by which the observed bone density (in grams per square centimetre) deviates above or below the predicted normal bone density for young adults. Osteopenia is defined as a bone mineral density between 1 and 2.5 standard deviations below the young adults (T score), while osteoporosis is defined as a bone mineral density of > 2.5 standard deviations below the mean for young adults. All patients were investigated for secondary osteoporosis with laboratory tests. Serum samples analysed for calcium, phosphorus, alkaline phosphates and parathormone and urine samples were analysed for calcium, creatinine. The total score for physical activity (maximum 19) was calculated as the sum of outdoor walking time score and exercise score according to EVOS form [5,6]. Total calcium intake and calcium score was also calculated according to the EVOS scoring system.

The statistical analysis was done by using SPSS 11.0. Mean values and standard deviations were calculated and compared using t-test statistics. Fisher exact test was used for the categorical variables. Pearson correlation test was conducted to assess the relationship between bone mineral density measurements and continuous variables such as duration of menopause, illness and inhaled steroid use. All cases were grouped according to parameters below and logistic regression analysis was made; age (below and above 45 years), menopause status (premenopausal and postmenopausal), parity (births above and below 2), lactation (lactation time above and below 12 months), total activity score (above and below 8), Ca score (above and below 4). Finally logistic regression analysis was undertaken to explore the effects of steroid use on bone mass. Dependent variable was bone mass categorized as low and normal as explained above. Independent variables included in the logistic regression model were age, menopause status, lactation, total activity score and calcium score.

Results

Forty-five asthmatic patients and forty-six healthy control subjects were included in the study. The subjects' characteristics are shown in Table 1.

No statistically significant difference was found for age, menopausal status, the duration of menopause between two groups. In the patient group three subjects were considered underweight, thirteen cases normal weight, twenty overweight and nine cases obese. In the control group five cases were found underweight, twenty

Table 1. Subject's characteristics.

	Asthma group (n = 45)	Control group (n = 46)
Age (year)	44.04 ± 8.67	44.43 ± 8.68
BMI (kg/m2)	27.62 ± 5.39	25.05 ± 3.62
Menopausal status		
Premenopusal	36	33
Postmenopousal	9	13
Duration of menopause (year)	2.31 ± 5.76	1.75 ± 3.60
Cigarette smoking (Yes/No)	9/36	13/33
Parity	2.33 ± 1.06	1.69 ± 1.07
Lactation time (mount)	24.85 ± 19.22	15.68 ± 13.38
Number of fractures in patients	7/38	5/41
Number of fractures in family	6/39	8/37
Total activity score	9.77 ± 3.84	9.52 ± 3.53
Calcium score	3.49 ± 1.07	3.38 ± 1.11

BMI: Body mass index.

Table 2. Clinical finding of asthmatic patients.

	Mean ± SD	(Min-Max)
Duration of asthma (years)	7.95 ± 8.70	1 - 37
Inhaled steroid treatment duration (year)	2.79 ± 1.77	1 - 7
Annual inhaled steroid dose (mg)	120.06 ± 53.73	18.60 - 242.00
Cumulative inhaled steroid dose (mg)	345.68 ± 289.20	30.00 - 1140.00
Disease severity (% FEV 1)	89.71 ± 17.13	49 - 130
Daily inhaled steroid dose (μgr)	326.43 ± 145.24	52 - 674

normal weight, eighteen overweight and three obese. No statistically significant difference was found for body mass index distribution and also for smoking, alcohol consumption, physical activity score, calcium intake fracture history between two groups ($p>0.05$). When the number of pregnancies and the duration of lactation were compared between the two groups, both were found to be significantly higher in the control group. The clinical findings of asthmatic patients were given in Table 2. Systemic corticosteroid treatment history was found only in nine patients of 45. Fourteen patients were using nasal steroids.

Serum, urine and bone mineral density parameters of both groups were shown in Table 3.

T score of femoral neck and T score and bone mineral density of Ward's triangle were significantly lower in asthmatic patients compared to control group. No statistically significance was observed for serum calcium, phosphorus, alkaline phosphatase, PTH and urinary calcium excretion between both groups. In Pearson' correlation analysis significant negative correlations were found between the duration of menopause and bone mineral density measurements of lumbar spine, femoral neck, trochanter and Ward's triangle (r=-0.489, r= -0.346,

Table 3. Serum, urine and bone mineral density parameters in both groups.

	Asthma group (n:45)	Control group (n:46)	P
Lomber BMD	0.925 ± 0. 211	0.927 ± 0.229	n.s.
T lomber	- 1.26 ± 1.31	- 0.80 ± 1.28	n.s.
Femoral neck BMD	0.746 ± 0.127	0.792 ± 0.097	n.s.
T femoral neck	- 1.47 ± 1.27	- 1.00 ± 0.99	< 0.05
Ward's triangle BMD	0.612 ± 0.151	0.697 ± 0.142	< 0.05
T Ward's triangle	- 1.66 ± 1.38	- 0.90 ± 1.28	< 0.05
Trochanter BMD	0.637 ± 0.120	0.651 ± 0.103	n.s.
T trochanter	- 0.98 ± 1.33	- 0.66 ± 1.09	n.s.
Serum Ca	9.40 ± 0.54	9.50 ± 0.55	n.s.
Serum Phosphors	3.53 ± 0.57	3.76 ± 0.95	n.s.
ALP	115.97 ± 77.51	145.41 ± 65.03	n.s.
Urine Ca (mg/day)	156.23 ± 95.90	194.64 ± 107.04	n.s.
PTH	50.04 ± 22.59	45.71 ± 18.00	n.s.

BMD: bone mineral density.
n.s.: not significant.

r= -0.459, r= -0.477) in asthmatic patients. And also significant negative correlations were found between the duration of menopause and bone mineral density of lumbar spine and Ward's triangle (r = - 0.325, r = - 0.353) in the control group. No statistically significant correlation was found between the disease duration, inhaled steroid treatment duration, cumulative inhaled dose and annual inhaled steroid dose and bone mineral density measurement. Lumbar and proximal femoral bone mineral density scores are grouped as osteopenia and osteoporosis according to T scores in both asthmatic and control group. The cases having osteopenia or osteoporosis at least in two regions according to T scores are accepted as having low bone mass and the others as normal. When the effect of age was adjusted, inhaled corticosteroid treatment was found to increase the risk of low bone mass 2.8 times (% 95 Confident Interval: 1.11-7.30)

Discussion

This study showed that bone mineral density in asthmatic patients on inhaled glucocorticosteroid therapy was lower than healthy controls in all regions. But statistically significant difference was found only in femoral neck T score and in Ward's triangle bone mineral density and T scores. The clinical indications for inhaled corticosteroid therapy of asthma have widened considerably over the past 20 years, and advent of more potent drugs, more concentrated formulations and more efficient delivery systems has greatly expanded its therapeutic potential [7]. The effects of inhaled corticosteroid therapy on bone metabolism are not certain but are a concern with increasing use of moderate and high doses for longer periods of time. The potential of increasing osteoporosis with inhaled corticosteroid asthma therapy is a concern because of the avaibility of more potent inhaled corticosteroid agents and recommendations that inhaled corticosteroid therapy be initiated earlier in the course of asthma [8-10]. However there are no data to suggest that long term treatment with inhaled corticosteroids is associated with an increased risk of fractures. In the literature there are many cross-sectional and prospective studies that showed the negative effects of inhaled corticosteroids on bone metabolism and bone mineral density [11-16] whereas many others did not find any significant change [17-24].

Packe and Hanania found that bone mineral density was reduced in asthmatic patients using high dose inhaled corticosteroids [12, 13]. And in another study Wong et al found an inverse relationship between cumulative inhaled corticosteroid dose and bone mineral density in a large cross-sectional study both before and after adjustment for age and sex. In their study the median duration of treatment was 6 years and the median cumulative dose was 876 mg and most of the patients

were premenopausal [16]. In our study we showed that low doses of inhaled steroid treatment can also cause osteopenia in asthmatic patients. Although the cumulative inhaled steroid dose was lower and the duration of treatment was shorter it is interesting that even with such low cumulative doses we found a significant decrease of bone mineral density. This also may explain why we found no correlation between bone mineral density and the duration of treatment and cumulative inhaled steroid dose.

In many studies oral corticosteroid treatment is a confounding factor and some of them were critised because the possible effect of oral corticosteroid that these patients had taken was not fully taken into account [13, 14, 24, 25]. So we excluded the patients if there was a course of oral or parenteral corticosteroids over the past six months or on more than two occasions ever. In our study only 9 of forty-five patients had a history of systemic steroid treatment in the past.

It is unclear whether asthma by itself is a risk factor for osteoporosis. Creating a control group of asthmatic patients not on inhaled corticosteroid treatment was impossible for our patient population so we included a healthy control group. But this present study tried to control the effect of physical activity on bone mineral density. In each group the physical activity score was the same and none of patients had exercise-induced asthma. Also immobilization was questioned and none of our cases had an immobilization period for any reason. Bone mineral density is affected by many other factors including menopause, cigarette smoking, hormone replacement therapy, body mass index, dietary calcium intake, lactation and parity [26]. There was no significant difference regarding cigarette smoking, dietary calcium intake, hormone replacement therapy and body mass index between two groups. There was only one patient using hormone replacement therapy in each group. Menopause is considered to be one of the most potent risk factors of osteoporosis. We tried to eliminate the effect of menopause by forming a menopause status matching control group. And in our study most of the patients (80%) were premenopausal. Corticosteroids have been thought to predominantly affect trabecular bone [27], although some studies suggest that cortical bone may be affected to a similar extent [16, 28]. Our results support an effect on cortical bone in addition to trabecular bone, as we found a decrease in bone mineral density both at the femoral neck (predominantly cortical bone) and Ward's triangle (predominantly trabecular bone). Although when logistic regression analysis was performed lactation time and parity were not found to be risk factors, as a limiting factor of our study the lactation time and parity was higher in our asthmatic group.

When the effect of age was adjusted in the logistic regression analysis, the risk for low bone mass was 2.8 times higher in asthmatic patients as compared to control group. When compared to control group low bone mass is found to be significantly higher in patients who have low body mass index. Body mass index is known as one of the determinant factors of bone mineral density. Our finding suggests that BMI, already known as a determinant factor on bone density, gains more importance in asthmatic patients. The study by Ip et al supports our results. In their study gender, high dose inhaled corticosteroid treatment and low BMI were considered risk factors for osteoporosis [11].

Inhaled glucocorticosteroids are at present the most effective control medications in asthma. But only regular treatment can cause effective symptom control. Therapy should be maintened to decrease airway hyperresponsiveness, reduce exacerbations and improve quality of life. But after asthma control is achieved, drug dose can be decreased. It seems sensible to use the minimum necessary dose to control the disease and prevent possible adverse effects on bone metabolism. Current evidence suggests that in adults systemic effects of inhaled glucocorticosteroids are not a problem at doses of 500 μg or less beclamethasone dipropionate or equivalent daily, but some patients may be sensitive to systemic effects at lower doses. As we found bone mineral density with low dose inhaled corticosteroid treatment, patients with other risk factors should be evaluated carefully for osteoporosis.

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