

EFFECT OF MEDIUM AND HIGH DOSE INHALED BUDESONIDE ON BONE DENSITY IN ASTHMATIC PATIENTS

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ABSTRACT

Inhaled corticosteroids (ICS) are the most effective anti-inflammatory treatment for asthma and are currently accepted as the first-line therapy for persistent disease. The adverse effects of long-term or high-dose use of ICS on bone metabolism and associated risk of osteoporosis is controversial. The aim of this study is to assess the adverse effects of one-year medium and high-dose inhaled budesonide therapy on bone mineral density (BMD) in asthmatic patients.

39 asthmatic patients (29 female, 10 male) were admitted to the study. 25 patients with moderate-persistent asthma in group 1 were treated with medium-dose inhaled budesonide ($800 \mu\text{g}\cdot\text{day}^{-1}$); whereas 14 severe-persistent asthmatics in group 2 were treated with high-dose ($1600 \mu\text{g}\cdot\text{day}^{-1}$) inhaled budesonide therapy, in addition to inhaled beta-agonists.

BMD was measured at the beginning of the study, at 6th month, and at the end of first year by dual x-ray absorptiometry (Hologic QDR-4000, Bedford, MA, USA). Trabecular bone loss was assessed at the level of lumbar spine (LS) and femoral Ward's triangle (FW); cortical bone loss was assessed at the level of femoral neck (FN).

The mean age was 39 ± 9 in group 1 and 44 ± 10 in group 2. There were 9 patients (36%) with osteopenia and 3 (12%) with osteoporosis in group 1; whereas in group 2 there were 7 patients (50%) with osteopenia and 6 (42%) with osteoporosis at the beginning of the study. At the end of one-year study period, there was no significant change in BMD of asthmatic patients receiving medium or high-dose inhaled budesonide.

One-year treatment with medium or high-dose inhaled budesonide do not result in significant bone mass loss in moderate and severe persistent asthmatic patients.

Key words: Asthma, bone mineral density, corticosteroids, dual-energy x-ray absorptiometry

ÖZET

Astmatik Olgularda Orta ve Yüksek Doz İnhale Budesonid Tedavisinin Kemik Dansitesine Etkileri

İnhale kortikosteroidler (İK) astımda en etkili anti-inflamatuvar tedavidir ve halen persistan hastalığın tedavisinde ilk-seçenek ilaçlardır. Uzun süreli ya da yüksek doz İK tedavinin kemik metabolizmasına yan etkileri ve osteoporoz riskine etkisi tartışmalıdır. Bu çalışmanın amacı astmatik olgularda bir yıllık orta ve yüksek doz inhale budesonid tedavinin kemik mineral dansitesi (KMD) üzerine etkilerini araştırmaktır.

Çalışmaya 29'u kadın, 10'u erkek 39 astım olgusu alındı. Grup 1'i oluşturan orta-persistan astımlı 25 olgu inhale beta-agonistlerle birlikte orta doz inhale budesonid ($800 \mu\text{g}\cdot\text{gün}^{-1}$) alırken; grup 2'deki ağır persistan astımlı 14 olgu yüksek doz ($1600 \mu\text{g}\cdot\text{gün}^{-1}$) inhale budesonid ile tedavi edildi.

KMD çalışmanın başlangıcında, 6.ayda, ve ilk yılın sonunda dual x-ray absorptiometri (Hologic QDR-4000, Bedford, MA, ABD) ile ölçüldü. Trabeküler kemik kaybı lomber bölgede (LS) ve femoral Ward üçgeninde (FW); kortikal kemik kaybı ise femur boynu düzeyinde (FN) değerlendirildi.

Çalışmanın başlangıcında grup 1'de ortalama yaş 39 ± 9 ve grup 2'de 44 ± 10 idi. Grup 1'de 9 olguda (%36) osteopeni ve 3 olguda (%12) osteoporoz; grup 2'de 7 olguda (%50) osteopeni ve 6 olguda (%42) osteoporoz mevcuttu. Bir yıllık tedavi sonunda orta ve yüksek doz inhale budesonid alan astımlı olguların KMD'de belirgin değişiklik saptanmadı.

Sonuç olarak orta ve yüksek doz inhale budesonid, orta ve ağır persistan astımlı hastalarda belirgin kemik kütlesi kaybına yol açmamıştır.

Anahtar kelimeler: Bronş astımı, kemik dansitesi, kortikosteroidler, dual x-ray absorptiometri

INTRODUCTION

Inhaled corticosteroids (ICS) are the most effective anti-inflammatory treatment for asthma and are currently accepted as the first-line therapy for persistent disease⁽¹⁾. Long-term use of ICS is usually required for control of asthma for the therapy is not curative. Furthermore, higher doses may be needed in severe persistent asthmatics⁽²⁾. Systemic corticosteroids are well-known to cause osteoporosis⁽³⁾. However, the adverse effects of long-term or high-dose use of ICS on bone metabolism and associated risk of osteoporosis is controversial. Some cross-sectional or short-term studies have indicated that ICS treatment may cause a reduction in bone formation^(4,5), while others have found normal or near-normal bone mineral density^(6,7,8). It was reported that chronically steroid-dependent asthmatics taking 800-2000 $\mu\text{g}\cdot\text{day}^{-1}$ ICS had minimal reduction in bone mass^(9,10); whereas bone mass did not change in patients taking 800 $\mu\text{g}\cdot\text{day}^{-1}$.¹¹

The aim of this study is to assess the adverse effects of one-year medium and high-dose inhaled budesonide therapy on bone mineral density (BMD; bone mineral content normalized for bone size) in asthmatic patients.

MATERIAL AND METHODS

Patients

39 asthmatic patients (29 female, 10 male), diagnosed and classified according to international guidelines⁽²⁾ were recruited from the outpatients clinic of Chest Diseases Department. The patients had been regularly followed for last two years and all had adequate medical records. Patients with any other respiratory disease than asthma; endocrine, metabolic, renal, hepatic, rheumatologic or bone disease, malabsorption,

alcoholism, immobilization or taking drugs related to bone metabolism such as hormone replacement therapy or systemic steroids were excluded from the study. No patient had history of vertebral or femoral fractures. Patients' characteristics, including smoking history and information on medication (type of drug and prescribed doses were obtained from patients and medical records), duration and number of short-courses (<15 days) of systemic corticosteroid treatment were recorded. All subjects were using short (salbutamol) or long-lasting beta-agonists (salmeterol) by inhalation on an as-needed or regular basis. 56% of patients had been using ICS regularly and 41% irregularly before the study period (for 6.17 ± 4.93 years). Duration of ICS therapy before study was similar in both groups (Table I). Twenty-five patients with moderate-persistent asthma in group 1 were treated with medium-dose ICS (800 $\mu\text{g}\cdot\text{day}^{-1}$ budesonide) in the form of dry powder inhaler; whereas 14 severe-persistent asthmatics in group 2 were treated with high-dose (1600 $\mu\text{g}\cdot\text{day}^{-1}$ budesonide) ICS therapy. The patients were monitored for correct inhalation and maintaining compliance every 2 months. Two patients in each group were given short-course (<15 days) systemic steroid for asthma attack during study period. A dietary evaluation was done for each subject and intake of proteins, phosphorus, calcium and vitamins were roughly recorded. A global evaluation of physical activity was done using a questionnaire to grade activity intensity as weak, moderate, intense. All patients were fully ambulatory and there was no difference in exercise level or nutritional parameters of two groups. Pulmonary function tests were performed according to recommendations of ATS, by spirometry (Minato AutoPal, Japan)⁽¹²⁾.

The study was approved by the Ethics Committee of our institution and all subjects gave written informed consent to participate.

Bone mineral density

Bone density was measured by dual-energy x-ray absorptiometry (Hologic QDR-4000, MA, USA) at the beginning of the study, at 6th month, and at 12th month. Local measurements on the lumbar spine (L2-L4) and the hip were performed for these are the sites of nontraumatic fractures due to osteoporosis. Trabecular bone loss was assessed at the level of lumbar spine (LS) and femoral Ward’s triangle (FW); cortical bone loss was assessed at the level of femoral neck (FN). The absolute value of BMD was expressed as gr.cm⁻². The standard deviation from the mean normal for young healthy people (subjects <35 years-old) was expressed as a T score. Osteopenia was defined as T score between 1- and -2.4; osteoporosis was T score -2.5 standard deviation according to the World Health Organization (WHO) criteria⁽¹³⁾. The scanner was calibrated daily using a phantom according to the recommendations of the manufacturer. The reproducibility of the densitometry was good, and the coefficient of variation was 0.5%.

Statistical analysis

The results are presented as mean ±SD. Differences between BMD values at the beginning and end of study period were analyzed with ‘two-tailed t- test for paired variables’. ‘t-test for independent samples’ was used to analyze the differences between the groups. A ‘P’ value of <0.05 was considered to be significant.

RESULTS

Characteristics of moderate-persistent (group 1) and severe-persistent (group 2) asthmatic patients were shown together with results of spirometric tests in Table I.

Table I: Demographic data and pulmonary function tests of asthmatic patients treated with medium-dose (group 1) and high-dose (group 2) inhaled budesonide

	Group 1	Group 2
Subjects n	25	14
Age yrs	39±9	44±10
Sex M/F	6/19	4/10
Pre/postmenapausal ratio	17/2	8/2
Inhaled steroid dosage µg.day ⁻¹	800	1600
Duration of steroid treatment yrs	5±5	7±4
FEV ₁ % pred	74±9	55±12
FEV ₁ /FVC %	72±5	59±10

Data are expressed as absolute value or mean ± SD. M: male; F: female; FEV1: forced expiratory volume in one second (%); FVC: forced vital capacity (%); %pred: percentage of predicted value

At the beginning of the study, there were 9 patients (36%) with osteopenia and 3 (12%) with osteoporosis in group 1; whereas in group 2 there were 7 patients (50%) with osteopenia and 6 (42%) with osteoporosis. Baseline BMD and T scores of two study groups were statistically different; BMD was lower in severe-persistent asthmatics (Table II).

Table II: Comparison of baseline bone mineral density and T scores of asthmatic patients treated with medium-dose (group 1) and high-dose (group 2) inhaled budesonide

	All patients	Group 1	Group 2	P value
LS BMD	0.92±0.15	0.97±0.12	0.83±0.17	0.006*
LS T score	-1.18±1.44	-0.71±1.18	-2.02±1.52	0.005*
FW BMD	0.61±0.17	0.67±0.14	0.49±0.15	0.001*
FW T score	-1.07±1.42	-0.52±1.21	-2.07±1.24	0.001*
FN BMD	0.88±0.14	0.92±0.13	0.81±0.12	0.018*
FN T score	-0.62±1.11	-0.30±1.07	-1.20±0.96	0.013*

*p<0.05 BMD: bone mineral density (gr.cm-2) LS: lumbar spine FW: femoral Ward’s triangle FN: femoral neck

Table III: Baseline, 6th and 12th month bone mineral density of asthmatic patients

	Baseline	6 th month	12 th month	P value*
LS BMD	0.92±0.15	0.92±0.15	0.94±0.14	0.103
FW BMD	0.61±0.17	0.61±0.17	0.62±0.16	0.134
FN BMD	0.88±0.14	0.88±0.13	0.88±0.13	0.840

*P value is obtained by comparison of baseline and 12th month BMD BMD: bone mineral density (gr.cm-2) LS: lumbar spine FW: femoral Ward’s triangle FN: femoral neck

There was no statistically significant difference in BMD of LS, FW and FN at the end of study period (Table III). When alterations in BMD of moderate-persistent and severe-persistent asthmatic patients using medium or high dose inhaled budesonide were considered, there was no significant change in BMD in both groups in one-year (Table IV).

DISCUSSION

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture risk by WHO, but only BMD can presently be objectively measured in clinical practice⁽¹³⁾. The WHO criteria for the diagnosis of osteopenia and osteoporosis are based on the patient’s comparison to peak adult bone mass and use standardized scores.

Table IV: Comparison of baseline and 12th month bone density of asthmatic patients treated with medium-dose (group 1) and high-dose (group 2) inhaled budesonide

	Baseline	Group 1 12 th month	P value	Baseline	Group 2 12 th month	P value
LS BMD	0.97±0.12	0.98±0.12	0.209	0.83±0.17	0.85±0.15	0.272
FW BMD	0.67±0.14	0.69±0.14	0.300	0.49±0.15	0.50±0.14	0.331
FN BMD	0.92±0.13	0.92±0.12	0.946	0.81±0.12	0.81±0.12	0.925

* P value is obtained by comparison of baseline and 12th month BMD. BMD: bone mineral density (gr.cm⁻²) LS: lumbar spine FW: femoral Ward's triangle FN: femoral neck

For chronic lung disease patients, osteoporosis is a serious health problem leading to pain, loss of independence and increased mortality⁽¹⁴⁾. Thoracic vertebral fractures further impair pulmonary function. It has been estimated that each vertebral compression fracture causes a 10% decrease in vital capacity in normal subjects⁽¹⁵⁾. To determine the criteria for obtaining bone densitometry, the risk factors of asthma patients for osteoporosis should be clarified. In the last decade, increasing doses of ICS have been used to treat asthma. However, both patients and physicians are concerned with potential effects of high doses on bone density. While there are considerable data on the effects of ICS on bone density, the data tend to be inconsistent as a result of differences in the methodology and design of the studies⁽¹⁶⁾. In some studies the assessment parameter has been biochemical markers of bone metabolism⁽⁴⁻⁸⁾, in others it has been bone densitometry or quantitative computed tomography^(9,10). The determinants of corticosteroid induced osteoporosis is not completely understood⁽¹⁷⁾. Individual or genetic susceptibility to bone loss and baseline bone density prior to steroid treatment may also influence bone density⁽¹⁶⁾.

Corticosteroids have complex direct and indirect effects on skeletal tissue. The major indirect effect is inhibition of calcium absorption in intestine which may lead to secondary hyperparathyroidism⁽¹⁸⁾. The major direct effect on bone is a dose-related decrease in formation, probably mediated by a decrease in the replication and differentiation of osteoblast precursors. Corticosteroids can have both stimulatory and inhibitory effects on bone resorption⁽¹⁸⁾. Whatever the mechanisms, decreased bone mass is an important adverse effect of corticosteroid excess.

Bone mass provides the best prediction of fracture risk⁽¹⁹⁾. Although several techniques are available to measure bone mass, dual energy x-ray absorptiometry

is the most widely accepted⁽⁶⁾. It can be used for serial monitoring of BMD as well as response of bone to pharmacologic interventions.

The reports on the adverse effects of long-term or high dose use of ICS on bone metabolism and associated risk of osteoporosis is controversial. Reduction in bone density in patients with asthma treated with high doses of ICS for at least 6 months has been seen in a few retrospective studies in adults^(10,21), but not in others in either adults^(7,11,22), or children^(23,24).

Toogood et al⁽²⁵⁾ investigated bone density of lumbar spine in adult asthmatics. Their study showed that the daily dose, but not the cumulative lifetime dose of ICS therapy, might adversely affect bone density. Bone density was also lower in association with the duration of past oral corticosteroid therapy.

Egan et al⁽¹⁰⁾ compared the effects of fluticasone propionate 1000 µg.day⁻¹ with beclomethasone dipropionate 2000 µg.day⁻¹ in patients with moderate to severe asthma on bone density over 2 years. Spinal vertebral bone density was normal at baseline and remained unaltered following 2 years of treatment with fluticasone propionate, but fell by 3.3% in absolute terms following treatment with beclomethasone dipropionate (though remaining within the normal range) by quantitative CT, but remained unchanged by dual-energy x-ray absorptiometry. There was no change at any other limb or in any biochemical markers of bone metabolism. This study suggests that high doses of long-term ICS may minimally decrease bone density, although there may be a differential effect between different corticosteroids.

Medici et al⁽²⁶⁾ compared the effects of fluticasone propionate 400 µg.day⁻¹ with beclomethasone dipropionate 800 µg.day⁻¹ and fluticasone propionate 750 µg.day⁻¹ with beclomethasone dipropionate 1500 µg.day⁻¹ in 69 asthmatics over one-year. Little or no evidence of any important differences between

these doses were seen on bone density or bone metabolism.

Luengo et al⁽¹¹⁾ measured BMD by dual energy x-ray absorptiometry in asthmatic patients treated with 300-1000 µg.day⁻¹ inhaled beclomethasone or budesonide and compared with BMD of age-matched healthy subjects at 2 years. There were no significant difference in BMD loss between patients and healthy controls. They found no correlation either between inhaled steroid doses or duration of treatment and BMD values. There was not significant change in BMD of asthmatic patients receiving medium or high dose ICS at the end of one-year therapy in our study. Asthma was well-controlled in both treatment groups, with a low rate of asthma exacerbations and systemic corticosteroid use. The findings of our study largely concur with the recent studies some of which were mentioned above. Baseline BMD and T scores of two study groups were statistically different in our study; BMD was lower in severe-persistent asthmatics. This difference may be explained by the possible effect of more frequent systemic corticosteroid therapy on bone mass in this group of patients, but we do not have adequate information on past courses of systemic corticosteroids in our study population. Also, limitation of physical activity in severe disease, and alterations in nutrition may be contributing factors.

The results of this study suggest that one-year treatment with medium or high-dose inhaled budesonide do not result in significant bone mass loss in moderate and severe persistent asthmatic patients. Longer follow-up studies on the adverse effects of ICS in asthmatic patients are suggested.

REFERENCES

1. National Heart, Lung and Blood Institute. International consensus report on the diagnosis and management of asthma. *Clin Exp Allergy* 1992;22 (suppl):28-37.
2. Global Initiative for Asthma. Global strategy for asthma management and prevention: NHLBI/WHO workshop report. Bethesda MD: National Institutes of Health, publication No: 95-3659,1995.
3. Luckert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 1990;112: 352-364.
4. Meeran K, Hattersley A, Burrin J, et al. Oral and inhaled corticosteroids reduce bone formation as shown by plasma osteocalcin levels. *Am J Respir Crit Care Med* 1995;151:333-336.
5. Leech JA, Hodder RV, Ooi DS, Gay J. Effects of short-term inhaled budesonide beclomethasone dipropionate on serum osteocalcin in premenopausal women. *Am Rev Respir Dis* 1993;148:113-115.
6. Hughes JA, Conry BG, Male SM, Eastell R. One-year prospective open study of the effect of high dose inhaled steroids, fluticasone propionate, and budesonide on bone markers and bone mineral density. *Thorax* 1999;54:223-229.
7. Boulet LP, Milot J, Gagnon L, et al. Long-term influence of inhaled corticosteroids on bone metabolism and density. *Am J Respir Crit Care Med* 1999;159:838-844.
8. Herrala J, Puolijoki H, Impivaara O, et al. Bone mineral density in asthmatic women on high dose inhaled beclomethasone dipropionate. *Bone* 1994;15:621-623.
9. Packe GE, Douglas JG, McDonald AF, et al. Bone density in asthmatic patients taking high-dose inhaled beclomethasone dipropionate and intermittent systemic corticosteroids. *Thorax* 1992;47:414-417.
10. Egan JJ, Maden C, Kalra S, et al. A randomized, double-blind study comparing the effects of beclomethasone and fluticasone on bone density over two years. *Eur Respir J* 1999;13:1267-1275.
11. Luengo M, del Rio L, Pons F, Picado C. Bone mineral density in asthmatic patients treated with inhaled corticosteroids: a case-control study. *Eur Respir J* 1997;10:2110-2113.
12. American Thoracic Society. Standardization of spirometry. *Am J Respir Crit Care Med* 1995;152:1107-1136.
13. Consensus development conference: diagnosis, prophylaxis and treatment of osteoporosis. *Am J Med* 1993;94:646-650.
14. Orwoll ES, Klein RF. Osteoporosis in men. *Endocrin Rev* 1995;16:87-116.
15. Leech JA, Dulberg C, Kellie S, et al. Relationship of lung function to severity of osteoporosis in women. *Am Rev Respir Dis* 1990;141:68-71.
16. Efthimiou J, Barnes PJ. Effect of inhaled corticosteroids on bones and growth. *Eur Respir J* 1998;11:1167-1177.
17. Baylink DJ. Glucocorticoid-induced osteoporosis. *N Engl J Med* 1983;309:306-308.
18. Hosking DJ. Effect of corticosteroids on bone turnover. *Respir Med* 1993;87 (suppl):15-21.
19. Compston JE, Cooper C, Kanis JA. Bone densitometry in clinical practice. *BMJ* 1995;310:1507-1510.
20. Stead RJ, Horsman A, Cooke NJ, Belchetz P. Bone mineral density in women taking inhaled corticosteroids. *Thorax* 1990; 45:792-797.
21. Hanania NA, Chapman KR, Sturtridge WC, et al. Dose related

- decrease in bone density among asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol* 1995; 96:571-579.
22. Wolff A, Adelsberg B, Aloia J, Zitt M. Effect of inhaled corticosteroid on bone density in asthmatic patients: a pilot study. *Ann Allergy* 1991;67:117-121.
23. Baraldi E, Bollini MC, De Marchi A, Zacchello F. Effect of beclomethasone dipropionate on bone mineral content assessed by x-ray densitometry in asthmatic children: a longitudinal evaluation. *Eur Respir J* 1994;7:710-714.
24. Martinati LC, Bertoldo F, Gasperi E, et al. Effect on cortical and trabecular bone mass on different anti-inflammatory treatments in preadolescent children with chronic asthma. *Am J Respir Crit Care Med* 1996;153:232-236.
25. Toogood JH, Baskerville JC, Markov AE, et al. Bone mineral density and the risk of fracture in patients receiving long-term inhaled steroid therapy for asthma. *J Allergy Clin Immunol* 1995;96:157-166.
26. Medici TC, Grebski E, Hacki M, et al. Effect of one year treatment with inhaled fluticasone propionate or beclomethasone dipropionate on bone density and bone metabolism: a randomized parallel group study in adult asthmatic subjects. *Thorax* 2000;55:375-382.