The Effects of Inhaled Corticosteroids on Bone Mineral Density in Male Patients with Bronchial Asthma

Ali Al Ghuweri MD, Khaled Alkhawaldeh MD**, Abdullah Alzraiqat MD**, Ali Otom MD*, Ali Alrefai MD^, Abdelbaset Al-Rawashdeh MD**, Mohammad Al-Khazalegh MD*, Khaled Alnadi MD^^*

ABSTRACT

Objective: the aim of the study is to assess the effect of Inhaled steroids on bone density in male patients with bronchial asthma.

Methods: this retrospective analysis included 102 male patients with bronchial asthma, mean age 51 years (range; 22-80). All has been using inhaled beclomethasone dipropionate or budesonide with average dosage of 800 ug/day (600- 1200) at least for the last year. Patients then were subdivided into 3 groups according to duration of inhalational steroid use: group 1: < 5years (n= 17), group 2: 5-10 years (n= 57) and group 3: >10years (n= 28). Bone mineral density was measured from lumbar spine (L1-4) and non dominant proximal femur by dual energy X-Ray absorptiometry with a Hologic QDR-IO00 densitometer (Hololgic Inc., Waltham, Mass). ANOVA test was used in statistical analysis and $P<0.05$ was considered significant

Results: Over all frequency of osteoporosis and osteopenia within our study group were 48% and 43% respectively. In the left femur, those values were 58% and 8% respectively. Frequency of osteoporosis in lumbar vertebrae and left femur in the above 3 groups classified according to duration of inhalational steroid use were: group 1: 6% & 0%, Group 2: 42% & 9% and group 3: 71% &5% respectively. BMDs, T-scores and Z- scores were lower in group 2 and 3 compared to group 1($p<0.05$).

Conclusion: our study shows high frequency of osteoporosis among men treated with inhalational steroids. Therefore, screening strategy is recommended within 5 years after initiation of treatment.

Key words: Asthma, Bone mineral density, Inhaled steroid, Osteoporosis

JRMS June 2014; 21(2): 31-35 /DOI: 10.12816/0004539

Introduction

The potential of increasing osteoporosis with inhaled corticosteroid asthma therapy is a concern because of the availability of more potent inhaled corticosteroid agents and recommendations that inhaled corticosteroid therapy be initiated earlier in the course of asthma.[1]

Prolonged use of oral corticosteroids is a risk factor for osteoporosis. [2] However, the effect of inhaled corticosteroids (IC) on bone mineral density (BMD) of asthmatic patients remains

From the Departments of:
*Rehabilitation, The Royal Jordanian Rehabilitation Center, King Hussein Medical Center, (KHMC), Amman-Jordan
**Radiology, King Hussein Medical Center, (KHMC), Amman-Jordan
^Family Medicine, (KHMC)
^^ Internal Medicine, Chest Medicine Division, (KHMC)
Correspondence should be addressed to Dr. A. Ghuweri, (KHMC), E-mail: alighwiri1961@hotmail.com
Manuscript received June 16, 2013. Accepted November 28, 2013

controversial. Some studies concluded that BMD was significantly different in comparison with control subjects.[3-6] Studies have shown that osteoporosis and vertebral fractures are quite common in patients with advanced COPD and bronchial asthma using IC and have showed a significant relationship to the morbidity and mortality of these patients.[6]

Osteoporosis is rare among men compared to women, and this group of patients is not well screened for osteoporosis. Whether male patients with bronchial asthma and COPD who had been treated with IC have a high frequency of osteoporosis, and whether these patients require treatment and screening strategies to decrease osteoporotic fracture is not well established.

This retrospective study included group of male patients with Bronchial asthma with history of using inhaled steroids for the last several years. We included patients referred from out patient clinics, to assess bone density using dual energy x-ray Absorbtometry (DEXA scan). Our analysis included bone density in this group, to determine the frequency of osteopenia and osteoporosis, and whether preventive and screening strategies to decrease osteoporotic fractures should be added to the management of those patients.

Methods

After excluding 11 patients, this retrospective analysis included 102 men with bronchial asthma. There mean age was 51 years (range; 22-80).They were referred from out patient departments of Royal medical services hospitals to Nuclear Medicine department for Osteoporosis assessment. Patient's records for alcohol consumption, previous fractures, orchidectomy, thyroid function abnormalities, hormones and calcium intake were investigated, and consequently 11 patients were excluded.

Height and weight of patients were measured and body mass index was calculated.

All patients have been treated by IC for more than one year ranging from 1 to 20 years with doses ranging from 600 to 2000ug/day.

Patients were subdivided into 3 groups according to duration of inhalation steroid use into: group 1: < 5years (n= 17), group 2: 5-10 years (n= 57) and group 3: >10years (n= 28).

Bone mineral density from lumbar spine (L1–L4) in the posteroanterior projection and femoral neck (left side), was measured with dual-energy x-ray absorptiometry (QDR 1000; Hologic).

The results were reported as absolute densities (in grams per square centimeter) and as T scores and Z scores. T score refers to the number of standard deviations by which the observed bone density (in grams per square centimeter) deviates above or below the predicted normal bone density for young adults, while Z score express the number of standard deviations deviates above or below the predicted bone density for that age group. Osteopenia (low bone mass) was defined as T-score ranging between 1 and -2.5, while osteoporosis was defined as T-score < -2.5. Semiquantitative elaboration of all T and Z scores were in comparison with preset ethnic group normal values, and not in comparison with Jordanian population data. ANOVA test has been used in statistical analysis and $P<0.05$ was considered significant.

Results

First group of patients (Group 1): BMD values for Lumbar spine (L1-L4) were ranging from1.0884 to 0.4296 with a mean value of 0.776 g/cm2. T scores for lumbar spine were ranging from (1.2) to (-4.2) with a mean value of (-1.36). Z- Scores for lumbar spine were ranging from (1.1) to (-1.7) with a mean value of (-0.95). Second group of patients (Group 2): BMD values for Lumbar spine (L1-L4) were ranging from 0.942to0.3442 with a mean value of 0.686 g/cm2. T scores for lumbar spine were ranging from (0) to (-4.9) with a mean value of (-2.1). Z- Scores for lumbar spine were ranging from (0) to (-3.8) with a mean value of (-1.7) Third group of patients (Group 3): BMD values for Lumbar spine (L1-L4) were ranging from 1.0762 to 0.393with a mean value of 0.625 g/cm2. T-scores for lumbar spine were ranging from (1.1) to (-4.5) with a mean value of (-2.6). Z-scores for lumbar spine were ranging from (0.4) to (-3.5) with a mean value of (-2.25). BMD values, T-scores and Z-scores were significantly lower in group 2 and 3 compared to group 1($p<0.05$).

T-scores for left femur in group 1 were ranging from 2.2 to -2.5 with a mean value of -1.1, and in group 2 were ranging from 2.9 to -3.4 with a mean value of -0.68, while in group 3 were ranging from 1 to -2.7 with a mean value of -1.

Table I: Patient's characteristics and DEXA scan results in the 3 groups of patients divided according to duration of IC use:

	Group 1 (n=17)	Group 2 (n=57)	Group 3 (n=28)	Significance
Age	31-76(48)	22-75 (39)	30-78(52)	NS
BMI	18-34 (25)	14-36 (24)	19-34 (24)	NS
Duration of IC use in (years)	1-4 (2.8)	5-10 (5.7)	10-20 (13.5)	S *P=0.00(F=104) #P=0.00 (F=70.6)
Daily Dose of IC (L1-L4)	800-2000(850)	700-2000(800)	600-2000(820)	NS
BMD(gm/cm2) mean (L1-L4)	1.0884-0.4296 0.776	0.942-0.3442 (0.686)*	1.0762- 0.393 (0.625)#	S *P=0.01(F=6.8) #P=0.003 (F=9.9)
T-score (Mean) (L1-L4)	(1.2)- (-4.2) (-1.36)	(0)- (-4.9) (-2.1)*	(1.1)-(-4.5) (-2.6)#	S *P=0.001 (F=11.4) #P=0.003(F=9.9)
Z-score (mean)	(1.1)- (-1.7) (-0.95)	(0)- (-3.8) (-1.7)*	(0.4)-(-3.5) (-2.25)#	S *P=0.017 (F=6.1) #P=0.004 (F=9)
(Left femur) T-score	(2.2)- (-2.5) (-1.1)	(2.9)- (-3.4) (-0.68)	(1)-(-2.7) (-1)	NS

Significance between groups 1 and 2(*) and groups 1 and 3(#) derived from ANOVA test.

Table II: Frequency of osteopenia and osteoporosis in Lumbar spine (L1-L4), according to DEXA scan T- scores and WHO criteria.

Duration	**Normal**	**Osteopenia (Low bone mass)**	**Osteoporosis**	**Total**
< 5 years	(2 out of 17) 12%	(14 out of 17) 82%	(1 out of 17) 6%	17
(5-10) years	(5 out of 57) 9%	(28 out of 57) 49%	(24 out of 57) 42%	57
(10-20) years	(2 out of 28) 7%	(6 out of 28) 21%	(20 out of 28) 71%	28
Total	9 %	47%	44%	102

Table III: Frequency of osteopenia and osteoporosis in left proximal femur (NOF), according to DEXA T- scores and WHO criteria

Duration	**Normal**	**Osteopenia (Low bone mass)**	**Osteoporosis**	**Total**
< 5 years	(13 out of 17) 76%	(4 out of 17) 24%	(0 out of 17)	17
(5-10) years	(18 out of 57) 32%	(34 out of 57) 60%	(5 out of 57) 9%	57
(10-20) years	(10 out of 28) 36%	(14 out of 28) 50%	(4 out of 28) 14%	28
Total	40%	51%	9%	102

There was no significant difference in T-scores between the 3 groups (p> 0.05).

Table I shows patients characteristics and DEXA scan results in the 3 groups of patients divided according to duration of IC use.

Over all frequency of osteoporosis and osteopenia within our study group were 48% and 43 % respectively. In the left femur those values were 58% and 8 % respectively. Frequency of osteoporosis in lumbar vertebrae and left femur in the above 3 groups classified according to duration of inhalational steroid use were: group 1: 6% and 0%, Group 2: 42% and 9% and group 3: 71% and 5% respectively. Table II shows frequency of osteopenia and osteoporosis in L1-L4 in the 3 groups according to duration of IC use. Table III shows frequency of osteopenia and osteoporosis in left proximal femur within the 3 groups.

Discussion

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. [7-12]

El *et al* [4] reported lower bone density in asthmatic patients using low dose inhaled corticosteroids compared to healthy controls but it is still unclear if asthma by itself is a risk factor for osteoporosis. Packe and Hanania found that bone mineral density was reduced in asthmatic patients using high dose inhaled corticosteroids.[5,8] Study by 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.[11]

Some authors reported minimal or no significant change in bone density in patients with BA during the first few years after IC use.[12-15] Kuan *et al* correlated the change in those patients to aging and low BMI.[12] Even in our study the frequency of osteoporosis during first 5 years of IC use was relatively low (6 %). We believe that this period is not enough to induce significant effect and cause osteoporosis, and the only one case of osteoporosis and cases of ostepenia in first group can be due to aging process rather than IC effect. On the other hand; our study shows significant difference in BMDs, T-scores and even Z-scores in the other 2 groups. Also, the marked increase in frequency rate by more than 4 folds in the group of patients that has been using IC for more than 5 years can support the IC effect. This difference can't be explained by aging and secondary cause due to IC effect is more convencing.

Osteoporosis affects 40% of white women older than 45 years of age and 15% of white men older than 50 years of age in United States.[16] In our group study IC had tremendous effect on bone density and frequency of osteopenia and osteoporosis. Over all frequency of osteopenia and osteoporosis in our study group were 47% and 44% respectively.

Most our study group (83%) has been using IC for more than 5 years which can explain the high frequency of osteopenia and osteoporosis in our study group. Such finding can recommend the need for DEXA scan screening for all patients before 5 years after initiation of IC therapy.

In many studies oral corticosteroid treatment is a confounding factor and some of them were criticized because the possible effect of oral corticosteroid that these patients had taken was not fully taken into account.[8,9,17] So we excluded the patients if there was a course of oral or parenteral corticosteroids over the last six months. Still; no one can tell if this period is enough, and if persistent effect of previous systemic Cortisone administrations is present. Also; these results can show the importance of a future prospective study of asthmatic men before or just started on inhaled steroids, with follow-up over two or three years, if not more.

Corticosteroids have been thought to predominantly affect trabecular bone,[1] although some studies suggest that cortical bone may be affected to a similar extent.[11,18] Our results show the predominant effect on trabecualr bone compared to cortical bone. Frequency of osteoporosis and osteopenia in trabecular bone were 44 % and 47%respectively vs. 8% and 51% in cortical bone.

This study had some limitations that probably affected our results; first one is the absence of real control group due to the retrospective nature of this study and lack of routine screening for healthy men or asthmatic patients with out IC use. In our study design we compared 3 groups which were different in duration of IC use, and first group (<5 years IC use) was considered a control group during our analysis. The second limitation was the relatively low number of patients. Also; the absence of serial measurement to monitor the rate of bone loss in our study group can be considered a limitation in this study. To our knowledge, this study was the first one that investigated the effect of IC on bone density exclusively in men.

Conclusion

Osteoporosis is frequently encountered among men patients with BA using Inhaled corticosteroids. This effect appears to depend on duration of use and consequently on cumulative dose. This effect can be expected within 5 years of IC use, and such patients may require treatment and screening strategies to decrease the risk of osteoporotic fracture.

References

1. **Van Staa TP, Leufkens HG, Cooper C.** The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int* 2002 Oct; 13(10):777-787.
2. **Manolagas SC.** Steroids and osteoporosis: the quest for mechanisms. *J Clin Invest* 2013 May 1; 123(5):1919-21.
3. **Israel E, Banerjee TR, Fitzmaurice GM, *et al.*** Effects of inhaled glucocorticoids on bone density in premenopausal women. *N Engl J Med* 2001; 345: 941-947.
4. **El O, Gulbahar S, Ceylan E, Ergor G, *et al.*** Bone mineral density in asthmatic patients using low dose inhaled glucocorticosteroids. *J Investig Allergol Clin Immunol* 2005; 15(1): 57-62.
5. **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.
6. **van Staa TP, Leufkens HGM, Cooper C.** Use of inhaled corticosteroids and risk of fractures. *J Bone Miner Res* 2001; 3:581–588.
7. **Ip M, Lam K, Yam L, *et al.*** Decreased bone mineral density in premenaupousal asthma patients receiving long-term inhaled steroids. *Chest* 1994; 105: 1722-1727.
8. **Packe GE, Douglas JG, McDonald AF, *et al.*** Bone density in asthmatic patients taking high dose inhaled beclamethasone dipropionate and intermittent systemic cotcisteroids. *Thorax* 1992; 47:415-417.
9. **Toogood JH, Baskerville JC, Markov AE, *et al.*** Bone mineral density and the risk of fracture in patients receiving longterm inhaled steroid therapy for asthma. *J Allergy Clin Immunol* 1995; 96:157-166.
10. **Bonala SB, Reddy BM, Silverman BA, *et al.*** Bone mineral density in women with asthma on long-term inhaled corticosteroid therapy. *Ann Allergy Asthma Immunol* 2000; 85:495-500.
11. **Wong CA, Walsh LJ, Smith CJP, *et al.*** Inhaled corticosteroid use and bone mineral density in patients with asthma. *Lancet* 2000; 355:1399-1403.
12. **Kuan YC, How SH, Azian AA, *et al.*** Bone mineral density in asthmatic patients on inhaled corticosteroids in a developing country. *Ann Thorac Med* 2012 Apr;7(2):69-73.
13. **Tattersfield AE, Town GI, Johnell O, *et al.*** Bone mineral density in subjects with mild asthma randomised to treatment with inhaled corticosteroids or non-corticosteroid treatment two years. *Thorax* 2001; 56: 272-278.
14. **Medici TC, Grebski E, Hacki M, *et al.*** Effect of one year treatment with inhaled fluticasone proprionate or beclamethasone dipropionate on bone density and bone metabolism: a randomised parallel group study in adult asthmatic subjects. *Thorax* 2000; 55: 375-382.
15. **Wheelock C, Glass J, St Anna L.** Clinical Inquiry. Do inhaled steroids reduce bone mineral density and increase fracture risk? *J Fam Pract* 2012 Aug; 61(8):493-508.
16. **Ledford D, Apter A, Brenner AM, *et al.*** Osteoporosis in the corticosteroid treated patient with asthma. *J Allergy Clin Immunol* 1998; 102: 353-
17. **Agertoft L, Pedersen S.** Bone mineral density in children with long-term treatment with inhaled budesonide. *Am J Respir Crit Care Med* 1998; 157: 178-183.
18. **Conti A, Sartorio A, Ferrero S, *et al.*** Modifications of biochemical markers of bone and collagen turnover during corticosteroid therapy. *J Endocrinol Invest* 1996;19:127-130