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Dual Energy X-Ray Absorptiometry in Asthmatic Patients Treated By Inhaled Corticosteroid

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Abstract:
Background: *Inhaled corticosteroids have become the mainstay of maintenance treatment in asthma in adult. The systemic side effects of inhaled steroid are much less than systemic steroid needed for comparable asthma control. Long term use of systemic corticosteroid is known to cause osteoporosis.*
Aim of the study: *To assess the effect of inhaled corticosteroid on bone mineral density.*
Methodology: *This was a case- control study ducted during eight months period; 40 asthmatic patients, who visited specialized respiratory clinic, were encoded in this study. This patient s were diagnosed with pulmonary function test and reversibility test and treated with inhaled corticosteroid from 1-3 years. Data regarding the age, gender, Body mass index (BMI),and medicalhistory of chronic diseases, all were collected. Bone mineral density(BMD) of patients was assessed using dual energy X-ray absorptiometry (DXA) scan and Compared to the DXA scan of 40 control non asthmatic subject.*
Result: *Our result showed that Mean T score for asthmatic patients was(-1.4±1.01) and for controls was (0.5±0.2) it had had been significantly found that patients had lower T· score e than controls, P<0.05 and these patient with !longer duration (mean= 1.87) year were more likely to have osteopenia and orOsteoporosis than those with shorter duration (mean = 1.49) year, P=0.009.*
Patients who were using larger doses of treatment were more prone to develops
Osteopenia and osteoporosis
Conclusion: *Has shown that long-term useof inhaled corticosteroid at Moderate or high doses are associated with increased risk of osteopenia and osteoporosis.*
Keypoint: *(DXA) scan: DUAL ENERGY X-RAY ABSORPTIOMETRY, ICS: Inhaled corticosteroids.*
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I. Introduction

Asthma there is no universally agreed definition of asthma. Descriptions of condition focus on clinical, physiological and pathological characteristics stressing the central role of both chronic airway inflammation and increased airway hyper-responsiveness. Typical symptoms include wheeze, cough, chest tightness and dyspnea which are accompanied by the presence of airflow obstruction that is variable over short periods of time or reversible with treatment (1).

Osteoporotic features are a well –characterized consequence of the hypercortisolism associated with Cushing syndrome .however the therapeutics use of glucocorticoids is by far the most common form of glucocorticoid-induced osteoporosis. Glucocorticoids are used widely in the treatment of a variety of disorders, including chronic lung disorders, rheumatoid arthritis and other connective tissue diseases. Inflammatory bowel disease, and after transplantation.(2, 3, 5, 6, 7)

Dual –Energy X Ray Absorptiometry (DXA previously DEXA) it is mean of measuring bone mineral density (BMD) two X ray beams with different energy levels are aimed at the patient's bone when soft tissue absorption is subtracted out.(8,9)

The BMD it is a means of measuring bone mineral density (BMD), the BMD can be determined from the absorption of each beam by bone.(10).

DXA scans are used primarily to evaluate bone mineral density. And can also be used to measure total body composition and fat content with a high degree of accuracy (16)

Indication of uses women over the age of 65 should get a DXA scan. The date at which men should be tested is uncertainbut some sources recommend age 70.

Scoring severe osteoporosis (established) T-score less than -2.5. The WHO committee did not have enough data to create definitions for men or other ethnic groups.(17)

II. Patients And Methods

This was a case- control study, conducted during a period from 1st of August 2012 to 1st of April 2013.at specialized respiratory clinic, at Baghdad teaching hospital.

Patients (Cases):
A total of 40 asthmatic patients who were clients of Specialized respiratory clinic, were asked to participate in this study.

Diagnosis of Asthma:
In all patients asthma was diagnosed with PFT measuring FEV1 and VC and provided bases of reversibility test measuring forced expiratory maneuver after 15 minutes of inhalation of Beta 2 adrenoceptor agonist with increased FEV1 12%.

Controls: They were 40 non-asthmatic healthy subjects, all were health workers

Inclusion criteria:
Asthmatic patients who were treated with inhaled corticosteroid from 1-3 years.

Exclusion Criteria:
- Patients who refused to participate.
- Patients who was on long term oral steroids.
- Patients with uncontrolled Asthma with frequent exacerbation (one in any week based on the GINA guideline)
- Those who were currently smoked and alcoholic.
- Patients who have another causes of osteoporosis like trauma, previous inflammatory arthritis, metabolic disorder (hemochromatosis), or endocrine disease (thyrotoxicosis and hypogonadism) and medications)

Methods:
Data were collected by taking full history from the patient and clinical examination. Data regarding the age, gender, and medical history of chronic diseases, all were collected. Body weight and height were checked for all patients and controls and their BMIs were calculated according to the standard equation:
BMI (kg\m2) = weight in kg \ height in squared meter.
BMD of the study subjects was assessed using dual energy X-ray absorptiometry (DXA) scan on lumber vertebrae.

T-score: The World Health Organization (WHO) operationally defines osteoporosis as a bone density that falls 2.5 standard deviations (SD) below the mean for young healthy adults of the same sex.
And categorized as follow: Normal:> -1, Osteopenia:-2.5< T-score < -1, OsteoporosisT- score < -2.5.

Statistical analysis:
Data management and statistical analysis were performed using SPSS (statistical package for social sciences) version 18, US.
مربعنص i .l(Data were entered and analyzed with appropriate statistical tests and procedures. Descriptive statistics 'were presented as mean: ±: standard deviationfor continuous variables and as frequencies (number) and proportions (%) for categorical variables. Cases and controls were groupedand compared according to the age, gender, BMI. Asthmatic patients were fatherly grouped according to the type of inhaled steroid (Buclomethasne, Budsonds, and Fluticasone) duration and dose of treatment. Student's T test was used to compare means and assess the significance of difference in between continuous variables. Chi square test was used to assess the significance- of association for categorical variables
Level of significance (P. value) was set at as ≤ 0.05 to be considered as significant difference or association. Finally, results were presented m tables and figures with an appropriate explanation about the finding.

III. Results

Atotalof80subjectswereenrolledinthiscases-controlstudy.40subjectswereasthmatic(cases)and40subjectswerenon-asthmatic(controls) Table1 shows the general characteristics of study groups, inasthmatic group there were 16 males (40%) and 24 females (60%) among controls 18 (45%) were males and 22 (55%) were females The mean age of the asthmaticgroup was 49.l±7.7yearsandthat of Controls was 46.6±8.4years.

The most prevalent age group inboth study group was (40-49).Itrepresented (4 2.5%) among cases and (52.5%) among controls. The mean BMI for asthmatic patients was 28.7 ± 6.5 Kg/m and for control was 26 .8±L4Kg/m obesity was presentin almost (61%) of asthmatic cases and (.39.1%) of the control. (48.5%) of cases were overweight while (51.5%) of controls. the remaining subject in both group were normal weight There was no significant differenceinage. Gender and BMI in between Asthmati candnon –asthmatic participants inall comparisonP>0.005

Table 1: general characteristics age, gender and BMI (mean comparison) and categories

Variable		Asthmatic (N=40)		Control (N=40)		Total		P
		N	%	N	%	N	%	
Gender	Male	16	40%	18	45%	34	42.5%	0.82
	Female	24	60%	22	55%	46	47.5%	
Age groups	< 40 years	8	20.0%	10	25.0%	18	22.5%	0.34
	40-49	17	42.5%	21	52.5%	38	47.5%	
	≥50	15	37.5%	9	22.5%	24	30.0%	
	Total	40	100%	40	100%	80	100%	
	Mean±SD	49.1 ± 7.7		46.6 ± 8.4		47.9 ± 10.1		0.22
BMI	Normal	10	41.7%	14	58.3%	24	100%	0.41
	Overweight	16	48.5%	17	51.5%	33	100%	
	Obese	14	60.9%	9	39.1%	23	100%	
	Mean±SD	28.7 ± 6.5		26.8 ± 5.3		27.8 ± 3.6		0.16

According to the T-score values, subjects were categorized either normal, or having osteopenia or osteoporosis. 18 (45%) of asthmatic patients and all the non-asthmatics (l00%) had normal T-score.
Osteopenia was present in 14 (35%) of asthmatic patients, and osteoporosis was present in 8 (20%) of them.
Mean T-score for asthmatic patients was (-l.4±1.01) and for controls was (0.5±0.2), All these findings were shown in table 2.
It had had been significantly found that patients had lower T-score than controls,, P<0.05 table 2.

Table 2: T score mean +categories (normal, osteopenia, osteoporosis)

T-score	Asthmatic		Control		Total		P
	N	%	N	%	N	%	
Normal	18	45%	40	100%	58	72.5%	0.001
Osteopnia	14	35%	0	0%	14	17.5%	
Osteoporosis	8	20%	0	0%	8	10%	
Mean± SD	-1.4 ± 1.01		0.54 ± 0.2		-0.4±1.2		<0.001

Thefrequencydistributionofthethreetypesofmedications,revealedthat 22 (55%)patients were using Beclomethasone, 10 (25%)used Fluticasoneand8(20 0%)wereusingBudsonide.

The mean dose of Beclomethas oneinhaled was 673 Mg, mean dose of Fluticasoneinhaled was320 Mgandmeandose of Budsonideinhaled was500Mg. شکلحرThe mean treatment duration for Beclome tha sone, Fluticasone and Budsonide were (1.9,1.4and1.6) years, respectively, table3.

Table3: Distributionoftypeanddoseofmedicationusedamong asthmaticpatients(N-40)

Medication type	Frequency (n (%)	Mean dose Mg	Mean duration (year)
Beclomethasone	22 (55.0)	673	1.9
Fluticason	10(25.0)	320	1.4
Budsonide	8 (20.0)	500	1.6

Association between Treatment and T score.

The distribution of T-score categories by the types of treatment, no significant association between the type of treatment and the T-score, P>0.05, Table 4. On the other hand it had been significantly found that incidence of adverse effect of treatment was directly associated with the duration of treatment, those patients with longer duration (mean 1.87) year were more likely to have osteopenia and or osteoporosis than those with shorter duration (mean = L49) year,, P=0.009,, Table 5 and Figure 1. The dose of treatment also showed a significant direct association with

The score categories. Patients who were using larger doses of treatment were more prone to develop osteopenia and osteoporosis, the association was significant with all medication used, but the highly significant association was with Beclomethasone and Budsonide (P<0.001) and least significant with Fluticason than other two medications (P=0.012}. Table 6.

Table 4: Distribution of T-scores according to the type of treatment.

Type of medication	Normal T-score	Abnormal T-score			Total	P
		Osteopnia	Osteoporosis	Both		
Beclomethasone	8 (36.4%)	8 (36.4%)	6 (27.3%)	14 (63.6%)	22 (100%)	0.13
Fluticasone	4 (40%)	6 (60%)	0 (0%)	6 (60%)	10 (100%)	
Budsonide	6 (75%)	0 (0%)	2 (25%)	2 (25%)	8 (100%)	

Table 5. Comparison of mean duration of treatment in betweenpatients with normal and abnormal T-score among asthmatic

T-score categories	Mean duration of treatment(years)	P
Normal	1.49 ± 0.36	0.009
Osteopnia and Osteoporosis	1.87 ± 0.32	

Figure 1. Box plot of mean Duration of treatment of asthmatic patients according to the T-score categories.(N=40).

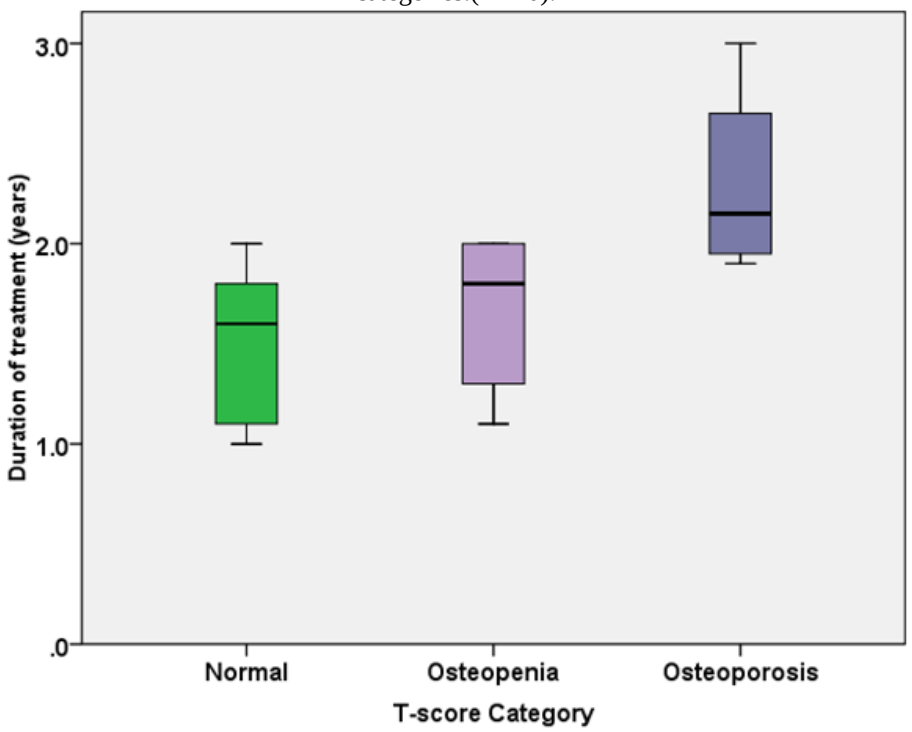

Table 6. Comparison of mean dose in different types of medications by T-score categories of asthmatic group

Type		N	Mean	Std. Deviation	Range	P
Beclomethason	Normal	8	250	92.6	200 - 400	<0.001
	Osteopenia	8	475	349.5	200 - 1000	
	Osteoporosis	6	1500	0	-	
	Total	22	672.73	567.5	200- 1500	
Fluticason	Normal	4	175.00	86.6	100 - 250	0.012
	Osteopenia	6	416.67	129.1	250-500	
	Total	10	320.00	165.3	100-500	
Budsonide	Normal	6	333.33	103.3	200-400	<0.001
	Osteoporosis	2	1000	0	-	
	Total	8	500.00	320.7	200-1000	

IV. Discussion

There was no significant difference in age, gender and BMl in between asthmatic and non-asthmaticsubject in general characteristic. According to the T-score values in this study subjects (asthmatic and control) were categorized either normal or having osteopenia or osteoporosis, it had been significantly found that asthmatic patients had lower T score than control. In comparsion with other study. Reid et al. (18) andPacke et aL(19) describereduction in bone mass in patients receivinginhaled steroids. Hanamaet al (19) they found a significantlylower osteocalcin level with a reduction in bone density measurements in the group taking inhaled corticosteroids than in the group that had taken only bronchodilators.WhileWolfeet et al (19) were unable to confirm any significant reduction in bone loss in a small group of asthmatic patients followed for 36-62 months. Tshizuka et al. (20) found that in 128 patients that inhaled steroids did not produce bone loss measured by DXA. When administered alone.

The distribution of the three types of medications in our study.Revealed that beclomethazone.fluticasone and budsunide. Thereis no significant association between type of treatment and T-score. This may attributed to small size sample of asthmatic patients which agreed with Boulet et al (21) studied of 37 asthmatic patients who had using 800 µg\ day or greater of

beclornethasone 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 374 patients with mild asthma were randomized to receive inhaled budesonide. inhaled beclomethasonedipropionate, 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.

In our study, it had been significantly found that incidence of adverse effect of treatment was directly associated with duration of treatment.

Those patients with longer duration (mean -1.87) year were more likely to have osteopenia and or osteoporosis than those with shorter duration (mean – 1.49) year P =0.009 Packe and Coworker (22) also found a reduction in bone density with high dose of ICS for period of 3 years.

Hughs et al (22)recruited59 patients with moderate to severe asthma and randomized them to receive inhaled fluticasone propionate 500µg twice daily and inhaled budesonide800 µg twice daily for one year .

They too concluded that treatment with high dose of either inhealed fluticasone propionate or inhaled budesonide during one year treatment did not demonstrate the significant difference in BMD. The short one year duration of study may be not sufficient to observe any effect that ICS may have on BMD.

Boulet et al (23) found the correlation between daily ICS dose and bone loss over time in high dose group ,these changes were minimal over period of 3 years and YehChunnkuan et al (24) suggested that the duration of asthma, asthma control ,cumulative budesonide dose-year, and rescue oral prednisolone (systemic steroid) did not significantly affect the risk of osteopenia and osteoporosis among patients with bronchial asthma.

The cumulative budesonide year used in their 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 studied such the one conducted by Toogood et al (25)Wolfeet et al (19) were unable to confirm any significant reduction in bone in small group of asthmatic patients followed for 36-62 months. In our study the dose of treatment also show the significant direct association with the T –score categories.

Patients who were using larger doses of treatment were more prone to develop osteopenia and osteoporosis, the association with all medication used but the highly significant association was with baclomethson (475-1500 µg) budesonide(1000 µG) P <0.001 and least significant with fluticasone (417µg) than other two medication P=0.0012.

Egan et al. (25) also have reported a difference in spine BMD in a group of moderate to severe asthmatic patients taking either fluticasone propionate (FP) I000 µg/day or beclomethasonedipropionate (BDP) 2000 µg/day. BMD was measured by quantitative computed tomography (QCT) in a two year prospective randomized study, In study by Packeet al .(26) reported reduced vertebral bone density in asthmatic patients receiving 1000-2000 µg BDP for one year. While the same researchers then assessed inhaled budesonide (BUD) (mean daily dose 800 µg) over one year with 13 of the 20 patients having been given systemic steroids previously. This group was compared with 20 patients on high dose BOP (mean daily dose 1000 µg.) and no difference in mean BMD was seen between the two groups.

While Bouletet al .(21)compared the effects of inhaled BDP in doses of at least 800 µg a day over an 18 month period in37 asthmatic subjects and in a control group who had taken few or no inhaled corticosteroids (<500 µg\day). They failed to show a significant difference in bone density although there was a significantly lower level ofosteocalcin in the group taking higher doses of inhaled corticosteroids.

Herralaet al. (27) studied the effects of l000 µg inhaled BDP in Asthmatic women and failed to show, any significant change in BMD after one year.

Marystoneet al. (28) did show a slight reduction in BMD in women using inhaled corticosteroids compared with a group who had never used them. There was no significant difference however in men.

While Egan et al (25) have reported a difference in spine BMD in group of moderate to severe asthma taking either 1000 µg /day or BDP 2000 µg/day BMD was measured by quantitative computed tomograph y (QCT) in a two year prospective randomized study. The BMD of vertebral trabecular bone: decreased significantly with BDP but not with FP which showed a slight rise at two years comparedbaseline ,no changes were seen in mean level of markers of bone formation / resorpation.

Pauwels et al (29, 30)in double blind multicenter cross over study of one year duration compared bone markers and BMD in 167patients taking FP with l73 on BOP. FP treatment resulted in

Significantly higher osteocalcin levels ($p<0.001$) and higher BMD in the spine ($p = 0.05$), femoral neck {$p<0.01$}, and Ward's triangle ($p = 0.01$) compared With BDP.

V. Conclusion

- It has shown that long-term use of inhaled corticosteroid at moderate or high doses is associated with increased risk of osteopenia and osteoporosis.
- Risk factors for osteoporosis and osteopenia among asthmatic patients are the dose of ICS and duration of treatment t
- those patients with longer duration (mean= l.87) year were more likely to have osteopenia and or osteoporosis than those with shorter duration (mean = 1.49) year

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Patients who were using larger doses of treatment were more prone to developosteopenia and osteoporosis. The highly significant association with Beclomethasone and Budsonide and least significant with Fluticasone.

VI. Recommendation

If high doses of inhaled corticosteroids are used a screening bone DXA scan may be indicated.
To minimize the riskofadverseeffects, werecommendthefollowing:

- StepdowntreatmenttothelowestpossibledoseofICSthat maintains symptoms control.
- Increasethemedicationfrequencywhiledecreasingthedaily dose.
- Optimizecompliance.
- Optimizedelivery(usespacerinadults,spacerandfacemask in children.
- Evaluateandtreat thesideeffect ofICS.

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