STUDY OF BONE MINERAL DENSITY IN ASTHMATIC CHILDREN RECEIVING CORTICOSTEROIDS

By

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ABSTRACT

Background: *Inhaled corticosteroid (ICS) is the most effective controller therapy for children with persistent asthma. It significantly reduces hospital admission in asthma exacerbation and may be used alone for mild-to-moderate asthma exacerbation or in combination with systemic corticosteroids for moderate-to-severe asthma exacerbation. Decreased bone mineral density and growth suppression is one of the side effects of Corticosteroids use due to Blunting of pulsatile growth hormone release, down-regulation of growth hormone receptor expression, inhibition of insulinlike growth factor-1 bioactivity.*

Aim: *To measure the bone mineral density in asthmatic children receiving corticosteroid, to identify child at risk for diminished bone density before entering adulthood allowing for therapeutic interventions.*

Patients and Methods: *A cross sectional comparative study was performed on 90 asthmatic children aged between 5 and 12 years old, during the period from March 2020 up to March 2021. The patients were diagnosed as having a moderate persistent to severe asthma, as defined by the presence of daily symptoms, frequency of exacerbations and the use of inhaled bronchodilator according to GINA strategy. They were classified into three groups. Group I included 30 asthmatic patients with moderate or severe persistent asthma on inhaled corticosteroids. Group II included 30 asthmatic patients with moderate or severe persistent asthma on systemic corticosteroids. Group III was the control group and included 30 asthmatic patients not receiving corticosteroids. Total doses of inhaled corticosteroids (ICS) and oral corticosteroids (OCSs) were recorded, serum 25-hydroxyvitamin D3 levels were measured and dual-energy x-ray absorptiometry scan of the lumbar spine was performed.*

Results: *There was a significant difference in bone density between asthmatic children receiving steroids and control subjects. Reduction in bone mineral density was*

dependent on the duration of oral corticosteroid therapy. While inhaled steroid was associated with a minimal decrease in bone mineral density. Serum vitamin D was decreased in 83.3% of studied patients, regardless of the use of Corticosteroids or not. 16.7% of studied patients had normal serum vitamin D level.

Conclusion: *Oral and inhaled steroid therapy in children with moderate to severe asthma was associated with decrease in bone mineral density.*

Keywords: *Asthma, Bone mineral density, Corticosteroids, Vit D, DXA Scan.*

INTRODUCTION

Bronchial asthma is a chronic inflammatory disease of the airways characterized by bronchial hyperreactivity. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable degree of airway obstruction **(GINA, 2021)**.

Different studies in various nations have reported a 50% increase in the predominance of asthma over the course of last ten decade. Right now, it is assessed that asthma affects around 300 million people universally, and this number is expected to increase up to 400 million by 2025. Among youngsters and youths, bronchial asthma occurs with frequency of 5-10%. Asthma causes roughly 0.25 million deaths every year and forces a huge financial weight around the world **(Salama et al., 2010)**.

It is accepted that youth asthma is more predominant in modern capitals and populated nations. Then again, there is a lower probability of kids living in rural areas of developing nations to have asthma, and this difference correlated with environmental risk exposure and health care access **(Arram et al., 2012)**.

There are 8.9 million cracks overall each year due to osteoporosis; Osteoporosis is a predominant ongoing condition described by the debilitating and expanded porosity of bones, fundamentally raising the probability of breaks happening **(Johnell and Kanis, 2006)**.

The associated cracks are major causes of morbidity and significant medical service costs. Bone mineral mass assumes a critical part in deciding the fracture risk and while the advancement of bone mass starts during the fetal stages, the skeletal framework continues to develope and mature throughout childhood and adolescence. It is vital to take note that most of the skeletal mass is achieved before the end of the

second decade of life **(Kelly et al., 2008)**.

For the treatment of asthma in youngsters, inhaled corticosteroids (ICS) are viewed as the favored meds. They offer better administration, less side effects and a more elevated level of viability in preventing asthma exacerbations contrasted with cromones or leukotriene antagonists **(Castro-Rodriguez and Rodrigo, 2010)**.

The adverse consequence of corticosteroids on bone wellbeing is generally recognized. In grown-ups, the utilization of corticosteroids is connected to a decrease in bone mineral thickness. In any case, in kids, this circumstances and logical results relationship is more multifaceted and requires thought of extra factors like orientation, age, level, pubertal turn of events, and skeletal development. As per the drawn-out CAMP review, rehashed organization of oral corticosteroids uplifted the gamble of osteopenia, while high combined portions of breathed in corticosteroids prompted a decline in bone mineral density **(Kelly et al., 2008)**.

Aim of the Study

The aim of this study is to measure the bone mineral density in asthmatic children receiving corticosteroid, to identify child at high risk for diminished bone density before entering adulthood and early interventions.

Sample size was calculated according to the following formula:

$n = (Z\alpha/2+Z\beta)2 *2*\sigma2 / d2$ (Daniel, 1999)

The value $Z\alpha/2$ represents the critical point on the Normal distribution at $\alpha/2$, such as 1.96 for a 95% confidence level, where α is 0.05. Similarly, $Z\beta$ signifies the critical point at β, which is 0.2 for an 80% power, with a critical value of 0.84. σ^2 is the standard deviation of bone mineral density, estimated at 0.18 g/cm² for normal females based on a previous study **Luengo et al. (1997)**, and is the expected difference in bone mineral density between control and asthmatic patients under corticosteroid treatment, set at 0.09 g/cm².

To determine the required sample size, we use the formula:

$$n = ((Z\alpha/2 + Z\beta)^2 * 2 * (\sigma^2)) / (d)^2$$

Plugging in the values:

$$n = ((1.96 + 0.84)^2 * 2 * (0.18)^2) / (0.09)^2 = 30$$

Therefore, we need to enroll a minimum of 30 children in each group for this study.

Ethical Consideration:

1. Approval by the ethical committee of AL- Azhr Faculty of Medicine was obtained before the study.
2. An informed written consent was taken from all parents before study
3. The steps of the study, the aim and the potential benefits all were discussed with the parents.
4. All the data of the patients and the results are confidential.
5. No conflict of interest regarding the study or the publication.
6. The patient has the right to withdraw from the study any time.
7. No funds regarding the study or publication.

Inclusion Criteria:

1. Children with physician diagnosed asthma.
2. Children aged between 5 and 12.
3. Corticosteroid therapy in group Ia and Ib.
4. Children had asthma symptoms in the last 12 months.

Exclusion Criteria:

1. History of any chronic diseases other than asthma, especially autoimmune disorders.
2. Family history of metabolic bone disease.
3. Use of medications in addition to those prescribed for asthma.

Study procedures:

This is a cross sectional comparative study that was carried out on 90 asthmatic children aged between 5 and 12 years selected from those attending the outpatient clinic of Al- Zahraa Hospital, Al-Azhar University, during the period from March 2020 up to March 2021.

The patients were diagnosed as having a moderate persistent to severe asthma, as defined by the presence of daily symptoms, frequency of exacerbations and the use of inhaled bronchodilator according to GINA 2022 strategy. Children included in the study were divided into the following three groups:

Group I: included 30 asthmatic patients with moderate or severe persistent asthma on inhaled corticosteroids (200 mcg twice daily).

Group II: included 30 asthmatic patients with moderate or severe persistent asthma on systemic

corticosteroids (1-2 mg/kg) daily for 10 days.

Group III: control group and included 30 asthmatic patients not receiving corticosteroids.

The study involved keeping track of the amounts of inhaled corticosteroids (ICS) and oral corticosteroids (OCSs) administered, measuring serum 25-hydroxyvitamin D3 levels, and conducting dual-energy x-ray absorptiometry scans of the lumbar spine.

All studied cases will be subjected for the following:

1. **Detailed history taking with special emphasis on:** age and sex, symptoms, recurrence of symptoms, hastening as well as exasperating elements, Effect of asthma on everyday action, history of intensifications, history of other atopic sickness, family ancestry and information on steroid use as respect the course, measurements and span of organization.
2. **Complete Clinical examination including:**

A. General examination:

Anthropometric measurements

Vital signs

B. Systemic examination including:

Chest Ex for signs of RD, air entry and adventitious sounds.

Heart examination.

Abdominal examination.

Laboratory assessment including:

1. S.Ca, S.Ph using Cornley AFT-C Electrolyte Analyzer.
2. S.A.Ph by spectrophotometer 5010 for chemical investigation.
3. S.vit D (stat fax for ELIZA test).

Radiological study:

DXA Scan: participants will undergo a Serial dual-energy x-ray absorptiometry (DXA) scans of the lumbar spine for bone mineral density (BMD), DXAs should not be performed unless the child can be safely positioned without sedation and Total body bone mineral density (g/cm2) and z-scores will be obtained for each participant.

Statistical analysis: information gathered were explored, coded and measurable examination of gathered information was finished by utilizing SPSS program (factual bundle of sociology; IBM SPSS Measurements for Windows, Variant 21.0. Armonk, NY: IBM Corp. Interpretation of likelihood values was as per the following: $P<0.05$ is a huge.

RESULTS

Our results will be demonstrated in the following tables:

Table (1): Demographic Data and anthropometric measurements of the studied groups

Patient ch.ch	Group I (ICS)	Group II (OCS)	Group III (No Steroid)	P value
Age/years	8.13±2.22	8.93±2.04	8.40±2.35	0.367
Sex:				
Male **Female**	18(60%) 12(40%)	16(53.3%) 14(46.7%)	20(66.7%) 10(33.3%)	0.574
Weight (Kg)	22.88±6.77	26.70±7.75	23.66±7.55	0.112
Height(cm)	122.63±13.06	128.60±13.28	122.33±12.70	0.116
BMI (kg/m2)	15.05±2.49	15.86±2.82	15.62±3.29	0.539

This table showed that there was no statistically significant difference between studied groups regarding demographic and anthropometric measurements.

Table (2): Clinical data among the studied groups

	Group I (ICS)	Group II (OCS)	Group III (No Steroid)	P value
History of another atopic disease:				
Yes	18(60%)	15(50.0%)	15(50.0%)	
No	12(40%)	15(50.0%)	15(50.0%)	0.699
Family history of atopic disease:				
Yes	17(56.7%)	11(36.7%)	14(46.7%)	
No	13(43.3%)	19(63.3%)	16(53.3%)	0.300
Exacerbation over past 12 months: **Mean ±SD** **Median** **Min-max**	 7.20 1.39 7.00 4-9	 6.06 1.46 6.0 4-9	 7.5 1.13 7.0 5-9	 0.003*
Frequency of symptoms per week: Mean ±SD **Median** **Min-max**	2.73 1.14 3.0 1-4	2.26 1.01 2.0 1-4	3.1 1.28 3.0 1-6	 0.035
Waking up at night: **Yes** **No**	 15(50.0%) 15(50.0%)	 15(50.0%) 15(50.0%)	 12(40%) 18(60%)	 1.00
Activity limitation: **Yes** **No**	 15(50.0%) 15(50.0%)	 21(70.0%) 9(30.0%)	 14(46.7%) 16(53.3%)	 0.114

significance test (p value<0.05)

This table shows statistically significant difference regarding

exacerbation frequency while insignificant regarding other clinical data.

Table (3): Chest and cardiac examination among the studied groups

Chest and cardiac exam.	Group I (ICS)	Group II (OCS)	Group III (No Steroid)	P value
Chest examination				
Normal	21(70.0%)	20(66.6%)	21(70.0%)	
Decrease air entry	1(3.3%)	0(0.0%)	0(0.0%)	
Prolonged expiration	1(3.3%)	2(6.7%)	0(0.0%)	0.722
Wheezy chest	6(20.1%)	8(26.7%)	9(30.0%)	
Medium sized crepitation	1(3.3%)	2(6.7%)	0(0.0%)	
Signs of respiratory distress(RD)				
No RD	20(66.6%)	19(63.3%)	21(70%)	
Tachypnea (RD I**)**	8(26.7%)	9(30.0%)	7(23.3%)	1.000
Sub Costal Retraction (RD II**)**	2(6.7%)	2(6.7%)	2(6.7%)-	

significance test (p value<0.05)

This table show that there was no significant difference between studied groups regarding chest and cardiac examination.

Table (4): Laboratory findings among the studied groups

Lab. findings	Group I (ICS)	Group II (OCS)	Group III (No Steroid)	P value
Serum Ca++ (mg/dl)	7.26±1.47[a]	7.38±1.49[a]	9.49±2.03[b]	0.000*
Serum ph (mg/dl)	3.86±1.02[a]	3.95±0.87[a]	5.90±0.99[b]	0.000*
Alkaline phosphatase (iu/L)	456.97±120.82[a]	466.07±141.91[a]	88.60±22.52[b]	0.000*
Vit D level (mean± SD) (Nmol/L)	32.23±7.69[a]	34.80±6.29[a]	42.00±7.15[b]	
Sufficient ≥ 30ng/ml	0(0.0%)	0(0.0%)	5(16.7%)	0.000*
Insufficient 19-29 ng/ml	16(53.3%)	23(76.7%)	25(83.3%)	
Deficient < 20 ng/ml	14(46.7%)	7(23.3%)	0(0.0%)	

*significance test (p value<0.05)

There was highly statistically significant decrease in serum Ca++ and serum ph in group I and II, and increase Alkaline phosphatase in group II. There was a highly significant decrease in Vitamin D level in group I and group II in comparison with group III.

Table (5): DXA findings among the studied groups

DXA Findings	Group I (ICS)	Group II (OCS)	Group III (No Steroid)	P value
Bone mineral density (Z-Score)	-7.78±0.97[ab]	-8.2467±0.90[b]	-7.59±1.00[a]	0.003*
Bone Mineral Density Interpretation:				
NORMAL	21(70%)	20(66.6%)	27(90.0%)	
LOW	9(30.0%)	10(33.4%)	3(10.0%)	

*significance test (p value<0.05)

There was a significant decrease in bone mineral density (BMD) among group I and II in comparison with group III.

BMD was more decreased in group II (OCS) than group I and III.

Table (6): Correlation between Bone mineral density and oral steroid duration among group II

	Bone mineral density	
	r	**P value**
Duration of OCS therapy in days / year	-0.432	0.017
(Last dose /day) (mg/day)	-0.278	0.137

This table shows a negative correlation between bone mineral density and duration of oral Corticosteroids among patients in group II.

DISCUSSION

Asthma is the most widely recognized constant provocative illness in the pediatric population. The constant irritation is characterized by limitation of broad and differed reversible airflow, which cause different symptoms like repetitive wheezes, chest tightness, dyspnea, and cough **(Sims et al., 2020)**.

Inhaled corticosteroid (ICS) is the best regulator treatment for youngsters with persistant asthma with numerous mechanisms of action: Anti-inflammatory, decrease of airway responsiveness, inversion of β2 receptor downregulation, and preventing airway remodeling. Benefits are seen within 2-3 weeks of beginning treatment **(Papi et al., 2020)**.

Despite the fact that ICS use in kids is significant and successful, there are non- continuous, however possibly serious, unfavorable impacts related with their utilization. These include height deficits, increased vulnerability to infection, and hypothalamic-pituitary- adrenal (HPA) axis suppression, possibly resulting in adrenal crises or growth retardation in kids **(Hossny et al., 2016)**.

Oral corticosteroid (OCS) is a powerful treatment for intense asthma, and assumes a significant part in the longterm management of serious asthma. It is especially significant if: Starting therapy with SABA (short-acting beta-2 agonist) fails to accomplish improvement, exacerbations while on OCS or Past history of exacerbation requiring OCS **(Fuhlbrigge and Kelly, 2014**; **Heffler et al., 2018)**.

Using systemic corticosteroids frequently, particularly at higher doses, has been linked to various negative effects in children with exacerbations, such as stunted growth, decreased bone density, and behavioral changes **(Ramsahai and Wark, 2018)**.

Regarding the characteristics of the studied cases, our results indicated no significant differences between the studied groups regarding the demographic values (P value>0.05). Such findings were in agreement with **Ozkaya et al. (2012)** that indicated no statistically significant difference between pediatric asthmatic patients administered Fluticasone and the healthy control group regarding each of age, gender, weight, height and BMI.

Regarding the clinical data among the studied groups, the current study results demonstrated a significant increase in the history of exacerbation over past 12 months among group III (No Steroid) and group I(ICS) in comparison with group II (OCS) (P value=0.003). This finding was in agreement with **Alangari (2014)** who indicated that short bursts of OCS treatment are effective in reducing the severity and duration of an asthma exacerbation in children.

Kearns et al. (2020) conducted a study and found moderate evidence indicating that combining high doses of inhaled corticosteroids (ICS) with systemic corticosteroids can lower the likelihood of hospitalization when treating moderate-to- severe asthma exacerbations in emergency departments.

Regarding the laboratory findings among the studied cases,

our results indicated a significant decrease in serum calcium and phosphorus among group I (ICS) and group II (OCS) in comparison with group III (No Steroid) (P value<0.001). These findings were in agreement with **Loba-Jakubowska et al. (2003)** who indicates that about 50% of asthmatic children had calcium-phosphate metabolism disorders and decrease of bone mineralization was observed in 40% of patients.

The outcomes of our study demonstrated a noteworthy rise in alkaline phosphatase levels in group I (ICS) and group II (OCS) when compared to group III (No Steroid) (P value<0.001). These findings align with a previous study conducted by **Anuradha et al. (2019)**, who reported median alkaline phosphatase values of 225 U/L for the ICS group and 198.5 U/L for the control group. The disparity between the two groups was statistically significant.

Our results indicated a significant decrease in vitamin D level among group I (ICS) and group II (OCS) in comparison with group III (No Steroid) (P value<0.001). Vitamin D levels were significantly insufficient among group I (ICS) and significantly deficient among group II (OCS) in comparison with group III (P value<0.001). This coincides with **Searing et al. (2010)** who indicated that corticosteroid use is associated with lower vitamin D serum levels in asthmatic children.

Huang et al. (2019) revealed that a low serum 25-hydroxyvitamin D level is related with serious asthma intensifications, lower lung capability, and diminished reaction to corticosteroids. Asthmatic kids have a more serious risk of lack of vitamin D because of changing way of life like decreased outside life, working inside, utilization of sunscreen, diminished daylight exposure, and dietary changes, and asthma-control in those youngsters has been noted to be poor.

Our results indicated a significant decrease in bone mineral density (BMD) among group I (ICS) and II (OCS) in comparison with group III (P value<0.001). These results were in agreement with **Chalitsios et al. (2021)** who suggested that exposure to OCS or ICS is independent risk factors for bone health in patients with asthma and steroid administration at the lowest possible level to maintain asthma control is recommended. A previous study by **Sidoroff et al. (2015)** indicated that ICS use

during childhood may be related to a decrease in BMD at late school age.

Kelly et al. (2008) discovered that administering multiple bursts of oral corticosteroids over several years can lead to a dose-dependent decrease in bone mineral density and an increased likelihood of osteopenia in children with asthma. Additionally, the use of inhaled corticosteroids (ICS) has the potential to hinder bone mineral accumulation in boys going through puberty.

Zazzali et al. (2015) and **Sullivan et al. (2017)**, in these studies found that the assessment of adverse events related to oral corticosteroid (OCS) usage in patients with asthma revealed higher risk estimates of bone-related complications in connection with the use of OCS. **Thanuja and Savitha (2020)** demonstrated that prolonged usage of high doses of budesonide exceeding 800 μg/day can result in a decrease in bone mineral density (BMD).

Our results indicated the presence of negative correlation between bone mineral density and the duration of oral corticosteroid use among patients in group II (OCS) (P value<0.05). **Price et al. (2020)** found that there was increased fracture risks with chronic OCS and that the predominant effect of OCS on BMD occurs within 6 months of treatment. Additionally, **Chalitsios et al. (2021)** suggested that there was a connection between the use of (OCS) and the development of osteoporosis. Furthermore, individuals who undergo six or more OCS treatments annually are at a higher risk of experiencing fragility fractures.

CONCLUSION

- There was statistically significance difference in bone mineral density demonstrated between asthmatic children receiving corticosteroids and control subjects.
- The administration of oral corticosteroid bursts resulted in a decrease in bone mineral density that was dependent on the duration.
- Inhaled corticosteroid was associated with a smaller decrease in bone mineral density. Decreased serum vitamin D was noted in all studied subjects regardless of the use or the route of corticosteroid therapy (83.3% of studied patients had decreased serum vitamin D).

RECOMMENDATION

- Awareness of the potentially harmful effects of SCS, regardless of the dose, duration or frequency of administration, needs to be raised further among healthcare professionals.
- We must educate the parents and caregivers about the potential benefits of carefully observing the corticosteroids duration and dosage as this is essential both for follow-up treatment and to prevent complications.
- Advice appropriate non-pharmacological methods to improve bone health such as exercise, calcium and protein rich diet.
- Starting Vitamin-D and calcium supplementation for all asthmatic children predicted to need chronic therapy, Treating Vitamin-D insufficiency and deficiency and continue monitoring Vitamin-D status.
- We recommend monitoring of all children and adolescents receiving glucocorticoids for duration of 3 months or longer.
- Development of new therapies to better control the disease and avoid asthma symptoms/exacerbations that will require SCS.

LIMITATIONS

- Relatively small sample size.
- Cases were taken from single hospital.
- Collected data about corticosteroid therapy was based on the parents recall of the dose and duration of treatment.

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