

**Assessment of the effect of long term in halation of corticosteroids(ICS)
for asthma control in children on fat distribution and bone density**

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Abstract

Background: Inhaled corticosteroid (ICS) are the most effective anti inflammatory medication for the treatment of persistent asthma).

Objective: To assess the effect of long term inhalation of corticosteroid (ICS) for asthma control in children on body fat distribution and bone density.

Patients: The study included 120 children aged (5- 10) years, they were classified into 3 groups. Group I, 40 moderately asthmatic children on low doses of (ICS). Group II, 40 severely asthmatic children on medium to high doses of (ISC). Group I and II comprised the patients group that were collected from allergy outpatient clinic of children hospital, Cairo university from the period between September 2016 and April 2017. Group III, 40 healthy control children of comparable age and sex

Methods: All children were subjected full history, clinical examination radiological studies, anthropometric measurements (weight, height mid upper arm, waist and hip circumference) as well as bone mineral density (BMD) assessed by The body mass index (BMI) was also calculated DEXA (Dual Energy X ray Absorptiometry) at lumbar spines L2- L4 levels.

Results: There is no significant difference in anthropometric measurements including body fat distribution as well as BMD in all studied groups, A positive correlation was found between BMD, duration of illness, dose of ICS, asthma symptoms and anthropometric measurements.

KeyWords: Asthmatic children- anthropometric measurement- bone mineral density.

تقييم تأثير العلاج بالكورتيزون المستنشق بالتحكم في حساسية الصدرية في الأطفال

على توزيع الدهون في الجسم وكثافة العظام

الهدف: الغرض من اجراء هذا البحث هو تقييم تأثير العلاج بالكورتيزون المستنشق لمدة طويلة للتحكم في حساسية الصدرية على توزيع الدهون في اجسام الأطفال وكثافة عظامهم.

المنهجية والعينة: قد أجرى البحث على ١٢٠ طفل تتراوح أعمارهم ٥ و ١٠ سنوات منقسمين الى ثلاث مجموعات المجموعة الأولى ٤٠ طفل مصابون بحساسية صدرية متوسطة يتم علاجهم بجرعات متوسطة من الكورتيزون المستنشق لا تقل عن ٣ سنوات، والمجموعة الثانية ٤٠ طفل مصابون بحساسية صدرية شديدة ويتناولون جرعات عالية من الكورتيزون المستنشق لمدة لا تقل عن ٣ سنوات، والمجموعة الثالثة ٤٠ طفل صحيح لا يعانون من أي أمراض مزمنة ويمثلون المجموعة الضابطة. وقد تم أخذ تاريخ مرضي مفصل من جميع المرضى والمجموعة الضابطة وكذلك فحص الكلينيكي دقيق وقياسات الطول والوزن ومحيط منتصف العضد وكذلك محيط الوسط والارداغ لتحديد أماكن تجمع الدهون. وقد تم أيضا قياس كثافة الكتلة العظمية باستخدام جهاز الدكسا وذلك للفقرات القطنية (٢-٤) كما تم حساب مؤشر كتلة الجسم BMI.

النتائج: أسفرت النتائج عن عدم وجود أي فروق ذو دلالة إحصائية في القياسات بما في ذلك توزيع الدهون في الجسم وكذلك كثافة الكتلة العظمية بين الثلاث مجموعات في حين كان هناك تأثير إيجابي بين كثافة الكتلة العظمية، جرعة الكورتيزون المستنشق، أعراض الحساسية والقياسات الانثروبولوجية بما في ذلك توزيع دهون الجسم.

Introduction:

Asthma is a worldwide problem with an estimated 300 million affected individuals. Nonetheless, based on the application of standardized methods to measure the prevalence of asthma and wheezing illness in children and adults, it appears that the global prevalence of asthma ranges from 1% to 18% of the population in different countries (GINA, 2008).

So, it is important to assess accurately the impact of such a wide spread illness and its treatment regarding efficacy and safety.

Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma. Studies demonstrated their efficacy in reducing asthma symptoms, improving quality of life, improving lung function, decreasing airway hyper-responsiveness, controlling airway inflammation, reducing frequency and severity of exacerbations and reducing asthma mortality. However, they do not cure asthma, and when they are discontinued deterioration of clinical control follows within weeks to months in proportion of patients (GINA, 2008).

Aim:

The aim of this research is to Assess the effect of long term use of ICS for asthma control on body fat distribution and bone density

Patients And Methods**Patients:**

The study is a case control study included 120 children of both sexes aged (5- 10) years.

patients were classified in 3 groups:

- ✦ Group I: 40 children with moderate asthma were using low doses of ICS for at least 3 years.
- ✦ Group II: 40 children with severe asthma on moderate to high doses of ICS for at least 3 years.
- ✦ Group (III): 40 healthy children not receiving any medications or complaining of any chronic illness.

The patient group (I), (II) were classified into moderate group (I) and severe group (II) according to GINA 2014 (step 2 and 3 are mild and step 4 and 5 severe).

They did not receive systemic corticosteroids and not suffering from other systemic chronic illness

Study Designs

After obtaining a verbal consent from caregivers all patients were subjected to: full history with special emphasis on, date of diagnosis, duration of illness, assessment of asthma severity using GINA 2014 classification of asthma severity, duration of treatment (not less than 3 years), dose and type of ICS and history of taking oral steroids (If date of last dose is less than 4 weeks the case is excluded)

Good clinical examination of chest and anthropometric measurements as follow: anthropometric measurements were taken in growth clinic of NRC.

The land marks and techniques used for measurements are those recommended by Cameron in 1978 as follows:

- ✦ Body weight, using seca delta scales, without coat, shoes (minimal clothes) and weight was recorded to the nearest 0.1 kgm
- ✦ Body height (in cm) was recorded and blotted on Egyptian body height percentile charts (Ghally et.al, 2002).
- ✦ Body mass index (BMI) was calculated according to the equation (BMI= weight in kg over height in cm² and blotted on Egyptian body mass index percentile charts (Ghally et.al 2002).
- ✦ The mid upper arm, waist and hip circumference were taken using a flexible non stretchable plastic tape and approximated to nearest 0.1 cm.
- ✦ Mid upper arm (in cm): Measured to the nearest 0.1 cm, using a plastic non stretchable tape, the child's arm hanged relaxed and the measurement was taken horizontally, midway between the inferior border of acromion and olecranon process.
- ✦ Waist circumference (in cm): With the child in the standing position at the level of the umbilicus at the end of a full expiration, contact with skin was continuous along the tape but the skin was not pressed inwards.
- ✦ Hip circumference (in cm): With the child in the standing position, at the level of the symphysis pubis.

Bone mineral density (BMD) were assessed by DEXA (Dual Energy X-ray Absorptiometry) at lumbar spines L2- L4 levels.

Statistical Analysis:

The graph displayed by the computer shows the following: the mean value expressed in gram/ Cm² and the Z-score compares one patients BMD (x) in standard deviations with the mean BMD for persons of the same age and gender (used for children). Z-score was used to differentiate normal and low BMD: Z-score > 1.0- low BMD, Z-score < -1.0- normal BMD.

Results:

Values of anthropometric measurements and fat distribution are shown in table (1) These values recorded no significant difference in all anthropometric values of patient's groups (I, II) and control group (III) NB: significant value is ≤ 0.05 .

Table (2) illustrated a comparison between Z-scores and BMD in lumbar vertebrae (L2- L4) among patients and controls.

The three studied groups did not show any statistically significant difference regarding both Z-scores and BMD.

A cut off value of -1 for BMD was taken and values below -1 were considered low BMD.

Table (3) shows that there was no statistically significant difference between the three studied groups regarding number of patients who had low BMD.

Correlation between BMD of lumbar vertebrae L2- L4 with duration of illness, dose of ICS, asthma symptoms and anthropometric measurements including body fat distribution are shown in table (4). A significant positive correlation was found between BMD of lumbar vertebrae, duration of illness and anthropometric measurements.

Table (1) Values of anthropometric measurements of patients group (I), (II) and control group (III)

Measure	Range	Mean+ S.D
Height (Cm)	group I (n= 40)	109.00- 165.00 138.52+17.41
	group II (n= 40)	105.00- 167.00 131.45+17.24
	group III (n= 40)	105.00- 154.00 127.25+16.19
Weight (Kg)	group I (n= 40)	17.00- 51.00 32.06+12.43
	group II (n= 40)	17.00- 66.00 31.53+12.05
	group III (n= 40)	15.40- 48.00 27.68+10.02
BMI (kg/ cm ²)	group I (n= 40)	8.43- 23.63 16.28+3.86
	group II (n= 40)	14.60- 26.10 17.66+3.05
	group III (n= 40)	11.40- 21.10 16.26+2.89
Mid upper arm circumference (cm)	group I (n= 40)	15.00- 25.80 19.46+3.25
	group II (n= 40)	16.00- 29.00 19.55+3.18
	group III (n= 40)	15.00- 25.00 18.83+2.87
Waist Circumference (Cm)	group I (n= 40)	54.00- 72.50 61.66+6.01
	group II (n= 40)	53.00- 73.00 62.00+5.69
	group III (n= 40)	48.80- 76.00 60.23+8.10
Hip Circumference (Cm)	group I (n= 40)	53.00- 90.00 70.70+9.12
	group II (n= 40)	60.00- 90.00 72.29+10.54
	group III (n= 40)	54.20- 90.00 68.38+10.47

Table (4) Correlations between BMD (gm/ cm²) of lumbar vertebrae with duration of illness, dose of ICS, asthma symptoms and anthropometric measurements

	Duration Of Illness	Nocturnal Symptom	Daytime Symptom	Dose Of Ics	Height	Weight	BMI	Mid Upper Arm C	Waist C	Hip C	
BMD (gm/ cm ²) of lumbar vertebrae	R	0.526	-0.128	-0.064	0.104	0.643	0.784	0.618	0.711	0.636	0.778
	P	0.000	0.430	0.695	0.661	0.000	0.000	0.000	0.000	0.000	0.000
	Sig.	HS	NS	NS	NS	HS	HS	HS	HS	HS	HS

Discussion:

Asthma is a worldwide problem with an estimated 300 million affected individuals. Nonetheless, based on the application of standardized methods to measure the prevalence of asthma and wheezing illness in children and adults, it appears that the global prevalence of asthma ranges from 1% to 18% of the population in different countries (GINA, 2008).

In Egypt, the prevalence of asthma among school children aged (5- 15) years was found to be 8.2% (Abu Gahel et.al., 2008) while, (El- Shafy et.al., 2006) found that the prevalence of childhood asthma in Cairo metropolitan was 16.8%.

Inhaled corticosteroids have been used for the treatment of asthma in children for more than 20 yr. During this time, a substantial number of studies have been performed evaluating the safety and efficacy of this therapy. Generally, the results have been reassuring. Inhaled corticosteroids have a marked effect on both the immediate and the long-term aims of asthma therapy (Pederson, 2001). However concern about the potential for systemic adverse events, including linear growth and suppression of adrenal glands, has resulted in reluctance of many physicians and parents to use ICS (Altintas et.al., 2005).

There are a few clinical trials assessing the effect of ICS on bone density and risk of fractures in children (Markku Etul 2010).

In the current case control study we assessed the effect of long term inhalation of corticosteroids (ICS) for asthma control in children on body fat distribution and bone mineral density (BMD).

The research study included anthropometric measurements and bone density for group (I) (40 children, (5- 10) years old with moderate asthma receiving low doses of ICS), group (II), (40 children (5- 10) years old with

Table (2) Comparison between Z-scores and BMD of lumbar vertebrae (L2- L4) among the patients and control group.

	Mean+ S. D	P. Value
Z-Score Of Lumbar Vertebrae	group I (n= 40)	-0.16+0.54 0.990
	group II (n= 40)	-0.14+0.54 P>0.05
	group III (n= 40)	-0.17+0.42 NS
BMD (gm/ cm ²) of Lumbar vertebrae	group I (n= 40)	0.56+0.12 0.227
	group II (n= 40)	0.55+0.11 P>0.05
	group III (n= 40)	0.51+0.06 NS

Ns: Non Significant

Table (3) Pattern of BMD in patients and control group

	Normal	Low BMD	P- Value
Cases of group I (n= 40)	34 (85%)	6 (15%)	0.072
Cases of group II (n= 40)	34 (85%)	6 (15%)	NS
Cases of group III (n= 40)	40 (100%)	0 (0%)	

Ns: Non Significant

severe asthma receiving moderate to high doses of ICS as well as 40 healthy children with comparable age and sex).

Patients classification follow that of GINA guidelines 2014 that classified features suggesting asthma in children ≥ 5 years into 5 steps according to clinical features before treatment as well as by daily medication regimen and response to treatment. Mild asthma is that controlled with step 1 or 2 (as needed SABA or low dose ICS). Moderate asthma is that controlled with step 3 (low dose ICS/ LABA) and severe asthma, step 4, 5, controlled with moderate to high dose ICS/ LABA± add on therapy or remain uncontrolled despite this treatment.

In our study It was found that there is no significant difference in anthropometric measurements (height, weight, BMI (kg/ cm²), Mid upper arm (cm), waist and hip circumference) with the three studied groups.

These results come in accordance with Monterio- Antonyo et.al (2002) who stated that the children and adolescents suffering from asthma could grow normally and attain their full genetic potential growth by treating the disease correctly.

On the contrary Agertoft and Bederosis in 2000, reported that growth rates were significantly reduced during the first years of budesonide treatment, these changes in growth rate were not significantly associated with adult height. Anthroopoulos et.al. (2007) stated that asthmatic children who received long term ICS attain normal adult height.

Two studies done by Kelly (2012) and Loke (2015) to evaluate long term outcomes of inhaled corticosteroids on growth showed a difference of only 0.7% in adult height.

In our study it was also found that neither bronchial asthma nor ICS had an adverse effect on BDM studied by DEXA scan, as there was no

statistically significant difference between the three studied groups regarding these parameters. this may reflect the safety of ICS on bone mineralization.

Our study was in agreement with the cross sectional and prospective longitudinal studies on children with asthma done by Griffiths et.al 2004 and Roux et.al in 2003. They stated that no negative effect of ICS on BMD was recorded.

It was found in our work that there is no significant difference in anthropometric measurements, BMD and Z-score in lumber spine L2- L4 in the three studied groups These come in accordance with Allen 2006, who concluded that avoidance of inhaled corticosteroid therapy has been observed to lead to poorer asthma control, poorer growth as result of poorer asthma control, increased morbidity and hospitalizations, and more frequent need for courses of treatment with systemic corticosteroids. This finding supports the recent studies in which impaired growth was not noticed in asthmatic children receiving ICS in doses that have been considered safe.

Results the present study also showed a positive correlation between BMD (gm/cm^3) of lumber vertebrae L2- L4, duration of treatment, dose of ICS and anthropometric measurement including body fat distribution (waist, hip and mid arm circumference). This indicate the tendency of central obesity among these patients with long term treatment specially high doses of ICS.

These results were in agreement with those obtained by Yoon and co-workers in 2016 who stated that long term use of ICS may be associated with adverse effects such as cataract, osteoporosis, fractures, reduction in growth velocity in children as well as body fat distribution.

Conclusion:

Long term use of ICS in conventional doses did not have any important side effects on bone mineral density and fat distribution and we strongly encourage its use in conventional doses as a safe and effective treatment of bronchial asthma in Egyptian asthmatic children also children treated with inhaled corticosteroid for a long time should be followed closely (every three months') for any side effects and stepping down of treatment if patients were well controlled to avoid adverse side effects that may occur with higher doses of ICS for long periods.

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