

Original article

Assessment of bone age and growth parameters of Egyptian children with bronchial asthma

Background: Asthma is the most common chronic respiratory condition of childhood worldwide and good asthma care extends beyond providing medications to improve outcome. Nevertheless, the goal of different therapeutic approaches is not only to treat the disease, but to improve patients' quality of life and prevent the long-term consequences of childhood asthma.

Objectives: to assess the bone age and growth parameters in asthmatic children and to investigate the impact of asthma severity, control and asthma treatment on the childhood growth parameters.

Methods: This cross-sectional controlled study included 40 asthmatic children recruited from Pediatric Allergy, Immunology and Rheumatology Clinic, Ain- Shams University, aged 4 to 10 years old and compared to 40 healthy age- and sex - matched control group.

Results: Among the 40 asthmatic children; 29 out of 40 (72.5%) had mild persistent asthma, 6 children (15%) with moderate persistent asthma and 5 patients (12.5%) had severe asthma. No significant differences were found in measured growth parameters between patients and controls and also no significant difference among the different asthma severity subgroups ($p=0.093$, $p=0.295$, $p=0.357$). The bone age of asthmatic children was significantly lower than the controls ($p=0.034$). Also, a significantly higher difference between the chronological age and the bone age among patients compared to controls ($p\text{-value}=0.044$). Patients were categorized into group A and group B according to presence and absence of delay in bone age (Group A; with normal bone age, group B; with delayed bone age). Delayed bone age was more prevalent in the patient groups (66.7% in the ICS group and 60.7% in the ICS + oral corticosteroids (OCS) compared to the control group (27.5%).

Conclusion: Asthmatic children were found to have delayed bone age and growth parameters. While ICS were essential for symptoms control, their use, particularly in combination with oral corticosteroids, had negatively impacted growth.

Keywords: Bronchial asthma, bone age, growth parameters, inhaled corticosteroids, Egyptian children.

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INTRODUCTION

Asthma is one of the most common chronic diseases in children, with significant impact on the overall quality of life, growth, and long-term development.¹ Asthma has a global prevalence of around 10% in children, and in Egypt there is a prevalence reaching 8.2% among Egyptian children aged 3 to 15 years.^{2,3}

Child growth is internationally recognized as an important public health indicator for monitoring nutritional status and health. Growth in children with asthma is a critical concern, as the disease and

its treatment can influence physical development. Chronic inflammation and frequent exacerbations can lead to poor appetite, increased energy expenditure, and reduced physical activity, all of which may contribute to growth impairment.⁴

Poorly controlled, severe asthma is associated with recurrent hospitalizations, sleep disturbances, and psychological stress, leading to more significant growth deficits than inhaled corticosteroids (ICS) use, emphasizing the importance of maintaining good disease control for overall development.⁵

Inhaled corticosteroids represent the mainstay in asthma management, while systemic corticosteroids might be used in asthma exacerbations.⁶ There have been contradictory results concerning the impact of asthma and its treatment on children growth, where some studies found a significant impact of asthma severity and corticosteroids use on children's growth aspects,⁷ while other studies denied this relation.⁸

The periodic anthropometric measurements e.g. height, weight, BMI, and bone age help identify deviations from normal growth early on, which is particularly important in asthmatic children.⁹

The study aimed to assess the bone age and growth parameters in children with bronchial asthma in comparison to healthy controls and to investigate the impact of asthma severity, control, and asthma treatment on the childhood growth parameters.

METHODS

This was a cross-sectional controlled study, conducted on 40 asthmatic children, aged 4 to 10 years old, recruited from the Pediatric Allergy, Immunology and Rheumatology Clinic, Children's Hospital, Ain-Shams University, and followed up in Pediatric Endocrinology Clinic and compared to 40 healthy age - and - sex matched control group, recruited from the Pediatric Outpatient Clinic, in the period from July 2023 till January 2024. An informed consent was obtained from the legal guardians before enrollment in the study. This study was approved from the local ethical committee of Ain Shams University, with approval number MS 432/2023.

Children having any chronic illness other than bronchial asthma like immunodeficiency or autoimmune disorders or chronic gastrointestinal disorders were excluded from the study. Patients on long term corticosteroids/immunosuppressive treatment for any condition other than bronchial asthma and those with known endocrinal disorders that affects skeletal growth like growth hormone deficiency, hypothyroidism or with known congenital musculoskeletal disorders or with short stature due to other causes were also excluded from the study.

Study Tools:

All included patients were subjected to:

Detailed medical history taking for demographic data, disease duration, asthma symptoms, frequency of asthma exacerbation, hospitalization for asthma per year, the associated comorbidities (respiratory infections, obesity, gastroesophageal reflux), other

reported allergic disorders, and family history of allergy. Therapeutic history also included asthma treatment whether systemic or ICS therapy, its dose, preparation, and duration. Asthma severity and asthma control were assessed according to the Global Initiative for Asthma (GINA) report 2023.⁶

Thorough clinical examination: Complete general and systemic examination was performed for asthmatic children with special emphasis on the assessment of respiratory signs of asthma and the presence of asthma exacerbation. Control children were subjected to a comprehensive medical examination children selected from the Pediatric Outpatient Clinic presented with acute minor illnesses. Both patients & controls were subjected to anthropometric assessment; weight was measured in kilograms (to the nearest 100 grams) using an electronic digital scale and its accuracy was periodically verified using reference weights, and height was measured in cm (measured to the nearest mm) with the subjects standing bare feet with the back against the gauges and feet on the weighing platform. Weight for height was plotted on growth curves and SDS of weight for height was calculated, height for age SDS.¹⁰ Body Mass Index (BMI): was calculated using the formula ($BMI = \text{wt}/\text{height in m}^2$). BMI SDS was calculated and assessed according to the age and sex specific reference values.^{11, 12}

Laboratory investigations:

Complete blood picture to check the absolute eosinophilic count (AEC), Erythrocyte Sedimentation Rate (ESR), renal and liver function tests, thyroid function tests using immunoassay methods.

Radiological study:

Plain X-ray posterior-anterior (PA) view of the left hand and wrist was done to assess the bone age and was compared to age matching Greulich's Atlas.¹² The hand radiographs are quite safe to obtain as the effective dose of radiation received during each exposure is between 0.0001-0.1 mSV. This dose is less than 20 minutes of natural background radiation, or the amount of radiation received by an individual on a 2-minute transatlantic flight.¹³

Statistical Analysis

Data were collected, revised, coded, and entered to the Statistical Package for Social Science (IBM SPSS) version 27. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data found non-parametric. Categorical variables were presented as number and percentages. The comparison between groups

regarding qualitative data was done by using Chi-square test. The comparison between two groups with quantitative data and parametric distribution was done by using independent t-test while with non-parametric distribution was done by using Mann-Whitney test. The correlation between the parameters was examined using Spearman's correlation coefficient (Spearman's rho). Receiver-operating characteristic (ROC) curve analysis is used to examine the discriminative value of biomarkers. The probability of <0.05 used as cutoff point for significant tests. The p-value was considered significant (S) if $p\text{-value} < 0.05$, non-significant (NS) if $p\text{-value} > 0.05$ and highly significant (HS) if $p\text{-value} < 0.01$.

RESULTS

The study included 40 children with asthma, 20 females (50%) and 20 males (50%). Their age ranged from 4 to 10 years with a mean $\pm$ SD of 8.24 ± 1.68 with a mean (SD) age at onset of 3.46 ± 1.21 years and a mean (SD) disease duration of 4.71 ± 1.74 years. Most patients experienced daytime and nighttime symptoms a median of 2 days per week, with a monthly symptom frequency of median 6 days. Among the studied patients, 20 cases (50%) had uncontrolled asthma, while 12 cases (30%) were partially controlled and 8 patients (20%) were controlled. Asthma severity over the past month was mild in 29 cases (72.5%), moderate in 6 cases (15%), and severe in 5 cases (12.5%) of patients. The mean (SD) annual exacerbation rate was 2.45 ± 0.88 episodes, with a mean (SD) of 1.65 ± 0.86 hospitalizations per year. Gastro-esophageal reflux disease (GERD) was the only comorbidity reported in only one case (2.5%). Allergic rhinitis was the most frequent associated allergic condition found in 30 cases (75%), followed by skin allergies in 6 cases (15%) and gastrointestinal allergy in only one case (2.5%). A family history of asthma was reported in 11 patients (27.5%).

Both asthmatic patients and controls were comparable in age distribution, the male sex was slightly higher in the control group with no statistical significance ($p\text{-value} = 0.260$). The asthmatic children had lower weight for height SDS ($p\text{-value} = 0.308$) but with no statistical significance and significantly lower bone age ($p = 0.034$) compared to controls with a higher prevalence of delayed bone age, 25 cases (62.5%) in patients versus 11 subjects (27.5%) in controls ($p\text{-value} = 0.002$). The gap between chronological and bone age was significantly larger as well in the patients group with a median of 1.5 years versus 0.5 year in controls ($p\text{-value} = 0.044$). The weight for

height SDS, the height for age SDS and body mass index standard deviation scores (SDS) didn't show statistically significant difference between patients and controls ($p = 0.308$, $p = 0.981$, $p = 0.173$ respectively) No significant differences were found in height-for-age SDS and BMI SDS ($p\text{-value} = 0.981$, 0.173 respectively) (Table. 1).

Comparisons within the patient group according to bone age (normal vs. delayed):

Asthmatic patients were subdivided according to the bone age into two groups: group A (patients with normal bone age) included 15 patients (37.5%) and group B (patients with delayed bone age) including 25 patients (62.5%) (Table 2).

Group B showed a significantly lower BMI (16.41 ± 2.22 vs. 17.47 ± 2.07 , $p\text{-value} = 0.030$) and BMI SDS (0.19 vs. 0.65 , $p = 0.014$) compared to Group A. However, the other studied anthropometric parameters showed no significant difference between both groups (Table 2).

The type of ICS preparation differed significantly; 22 cases out of 25 children (88%) received fluticasone propionate alone had lower mean bone age versus 3 cases (12%) received fluticasone propionate/salmeterol combination (Group B) ($p\text{-value} = 0.04$). The other treatment-related factors, such as the duration and daily dose of ICS, and other asthma medications, including oral corticosteroids (OCS), and leukotriene receptor antagonists (LTRAs) showed no significant differences between the two studied groups (Table 3).

Effect of Asthma Control and Severity on Growth parameters and Bone Age:

The 40 asthmatic patients were categorized based on their level of asthma control, in accordance with the Global Initiative for Asthma (GINA) guidelines; controlled asthma group included 8 patients (20%), 12 (30%) had partially controlled asthma and 20 (50%) had uncontrolled asthma.

No significant differences were found in the studied growth parameters (weight for height SDS, height for age SDS, and BMI SDS) across different asthma subgroups according to asthma control (uncontrolled, partly controlled and controlled group) $p\text{-value} = 0.597$, 0.647 and 0.929 respectively.

Furthermore, according to the level of asthma severity over the past month, 29 patients (72.5%) had mild asthma, 6 (15%) had moderate asthma and 5 (12.5%) had severe persistent asthma. The compared anthropometric measurements and bone age between the three studied subgroups showed no significant differences.

However, all 5 patients with severe asthma (100%) showed delayed bone age, compared with moderate asthma 4 cases out of 6 (66.7%) and mild asthma 16 out of 29 (55.2%) had delayed bone age. The median bone age difference also increased with severity, from one year in mild asthma to 1.5 years in moderate asthma and 2 years in severe cases, though these differences were not statistically significant.

Comparison of Treatment Groups with Controls:

Patients were classified into two subgroups based on their treatment regimen; patients on ICS alone (designated as Group 1) and those receiving combination of ICS and oral corticosteroids (OCS) during exacerbation (Group 2).

Comparison with the control group revealed no significant differences between the studied groups in terms of age, sex distribution, family history of allergic diseases, and the studied anthropometric

measurements. However, bone age showed significant differences, delayed bone age was highly significantly more prevalent in the treatment groups (8 out of 12 cases; 66.7% in the ICS group and 17 out of 28 cases; 60.7% in the ICS + OCS group) compared to the control group (11 out of 40 cases; 27.5%), with a $p=0.007$. , the bone age difference was significantly higher in the ICS (median: 2 years) and ICS + OCS (median: 1.5 years) groups compared to controls (median: 0.5 years), with a $p=0.004$ as shown in Table 4.

There was a non-significant difference between Group 1 and Group 2 as regards the asthma duration (p -value= 0.778), however, asthma severity over the last month was significantly higher in Group 2 (p -value= 0.039) with 6 cases (21.4%) in Group 2 compared to no cases (0%) in Group 1 having moderate asthma and 5 cases (17.9%) in Group 2 compared to no cases (0%) in Group 1 with severe asthma (p -value= 0.039).

Table 1. Demographic, anthropometric data and bone age of asthmatic patients and controls

	Patients n=40	Controls n=40	P-value
Age (years)			
Mean (SD)	8.24 ± 1.68	8.3 ± 1.69	0.877
Range	4 – 10	4 – 10	
Sex			
Female	20 (50%)	15 (37.5%)	0.260
Male	20 (50%)	25 (62.5%)	
Weight for height SDS			
Median (IQR)	-0.02 (-0.47 - 0.38)	0.26 (-0.83 - 0.67)	0.308
Range	-2.45 – 0.7	-2.93 – 2.26	
Height for age SDS			
Median (IQR)	-0.41 (-1.12 - 0.45)	-0.37 (-1.33 - 0.55)	0.981
Range	-3.89 – 2.3	-3.13 – 3.1	
BMI			
Mean (SD)	16.56 ± 2.22	17.41 ± 2.1	0.083
Range	12.5 – 20.6	13.6 – 23.8	
BMI SDS			
Median (IQR)	0.21 (-0.79 - 1)	0.63 (-0.17 - 1.19)	0.173
Range	-3.22 – 2.43	-1.94 – 4.21	
Bone age (year)			
Mean (SD)	6.79 ± 2.13	7.76 ± 1.89	0.034
Range	2.5 – 11	3 – 11	
Bone age			
Normal	15 (37.5%)	29 (72.5%)	0.002
Delayed	25 (62.5%)	11 (27.5%)	
Difference between chronologic age and bone age			
Median (IQR)	1.5 (0.25 – 2)	0.5 (0 – 1)	0.044
Range	0.0 – 4.5	0 – 2.83	

BMI: Body mass index, IQR: Inter-quartile range, SD: Standard deviation, SDS: standard deviation score
 p -value > 0.05: Non-significant (NS); p -value < 0.05 : Significant (S); p -value < 0.01: Highly significant

Table 2. Comparison between Group A and Group B regarding anthropometric measurements

	Bone age		P-value
	Normal Group A n=15	Delayed Group B n=25	
Weight SDS			
Median (IQR)	-0.02 (-0.67-0.70)	-0.10 (-0.91 - 0.70)	0.386
Range	-1.72 - 2.31	-2.04 – 1.99	
Height SDS			
Median (IQR)	0.14 (-0.68 – 0.66)	-11. (-0.068 – 0.92)	0.949
Range	-3.05 – 1.53	-1.84 –1.70	
Weight for height SDS			
Median (IQR)	0.21 (-0.7 - 0.5)	-0.02 (-0.53 - 0.41)	0.529
Range	-2.14 - 1.77	-2.93 - 2.26	
Height for age SDS			
Median (IQR)	-0.66 (-1.77 - 0.25)	-0.1 (-0.82 - 0.74)	0.065
Range	-3.89 - 1.92	-3.56 - 3.1	
BMI			
Mean (SD)	17.47 ± 2.07	16.41 ± 2.22	0.030
Range	13.6 - 23.8	12.5 - 20.6	
BMI SDS			
Median (IQR)	0.65 (-0.14 - 1.19)	0.19 (-0.91 - 0.85)	0.014
Range	-1.57 - 4.21	-3.22 - 2.39	

BMI: Body mass index, IQR: Inter-quartile range, SD: Standard deviation, SDS: Standard deviation score
 p-value > 0.05: Non-significant (NS); p-value < 0.05 : Significant (S); p-value < 0.01: Highly significant

Table 3. Comparison between Group A and Group B regarding treatment received

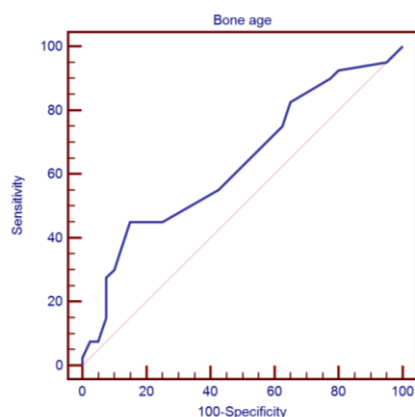
	Bone age		P-value
	Normal Group A n=15	Delayed Group B n=25	
Inhaled Corticosteroid (ICS)			
Duration (years)			
Mean (SD)	3.87 ± 1.3	3.78 ± 1.43	0.849
Range	1 – 5	1 – 6	
Preparation			
Fluticasone 125 mcg	9 (60%)	22 (88%)	0.040
Fluticasone/ salmeterol 125/25 mcg	6 (40%)	3 (12%)	
Dose received /day			
Medium dose 250 mcg	12 (80%)	19 (76%)	0.769
High dose 500 mcg	3 (20%)	6 (24%)	
Oral corticosteroid (OCS)			
(Prednisolone)			
No	4 (26.7%)	8 (32%)	0.722
Yes	11 (73.3%)	17 (68%)	
Duration (days)			
Median (IQR)	5 (1 - 5)	5 (1 - 5)	0.725
Range	1 – 5	1 – 5	
Frequency/year			
Median (IQR)	2 (1 - 3)	2 (1 - 3)	0.664
Range	1 – 3	1 – 5	
Use of other allergy medications			
LTRAs	9 (60%)	12 (48%)	0.649
Antihistamines	1 (6.7%)	1 (4%)	

ICS: Inhaled Corticosteroid, IQR: Inter-quartile range, LTRAs: Leukotriene receptor antagonists,
 OCS: Oral corticosteroids, SD: Standard deviation

Table 4. Comparison between treatment groups and controls as regards demographic data, anthropometric measurements and bone age

	Control group n=40	Group 1 Treatment group on ICS n=12	Group 2 Treatment group on ICS and OCS during exacerbation n=28	P-value
Age (years)				
Mean (SD)	8.3 ± 1.69	8.25 ± 1.42	8.23 ± 1.8	0.971
Range	4-10	6-10	4-10	
Sex				
Female	15 (37.5%)	5 (41.7%)	15 (53.6%)	0.416
Male	25 (62.5%)	7 (58.3%)	13 (46.4%)	
FH of other allergic disease				
No	37 (92.5%)	10 (83.3%)	25 (89.3%)	0.642
Yes	3 (7.5%)	2 (16.7%)	3 (10.7%)	
Weight SDS				
Median (IQR)	0.46 (-0.67 – 0.94)	-0.19 (-0.35 – 0.06)	-0.27 (-0.91 – 0.30)	0.085
Range	-1.72– 2.31	-1.07 – 1.99	-2.04 – 1.99	
Height SDS				
Median (IQR)	0.45 (-0. 63 – 1.01)	-0.20 (-0.85 – 0.75)	-0.37 (-1.06 – 0.62)	0.242
Range	-3.05 – 1.70	-1.24 – 1.44	-1.84 – 1.53	
Weight for height SDS				
Median (IQR)	0.26 (-0.83 - 0.67)	0.2 (-0.4 - 0.36)	-0.07 (-0.47 - 0.42)	0.579
Range	-5.19	-2.08	-3.15	
Height for age SDS				
Median (IQR)	-0.37 (-1.33 - 0.55)	-0.68 (-1.95 - 0.5)	-0.37 (-0.99 - 0.45)	0.817
Range	-6.19	-5.38	-5.34	
BMI				
Mean (SD)	17.41 ± 2.1	17.13 ± 2.86	16.32 ± 1.89	0.295
Range	13.6 - 23.8	13.2 - 20.6	12.5 - 19.8	
BMI SDS				
Median (IQR)	0.63 (-0.17 - 1.19)	0.65 (-0.88 - 1.4)	0.2 (-0.73 - 0.89)	0.28
Range	-6.15	-4.69	-5.45	
Bone age (year)				
Mean (SD)	7.76 ± 1.89	6.67 ± 2.1	6.84 ± 2.18	0.103
Range	03-Nov	03-Nov	2.5 - 11	
Bone age				
Normal	29 (72.5%)	4 (33.3%)	11 (39.3%)	0.007
Delayed	11 (27.5%)	8 (66.7%)	17 (60.7%)	
Bone age difference				
Median (IQR)	0.5 (0 - 1)	2 (0 - 3)	1.5 (0.5 - 2)	0.004
Range	0 - 2.83	0 - 3	0 - 4.5	

BMI: Body mass index, FH: Family history, ICS: Inhaled corticosteroid, IQR: Inter-quartile range, OCS: Oral corticosteroids, SD: Standard deviation, SDS: Standard deviation scores

**Figure 1.** Receiver operating characteristic curve (ROC) for bone age to discriminate between patients' group and control group.

The best cut off value for bone age between patients' group and control group was ≤ 6 years with sensitivity of 45.0%, specificity of 85.0% and AUC of 0.634 (Fig.1).

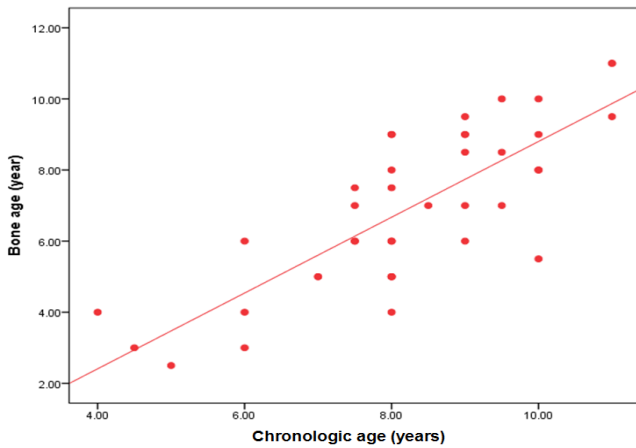


Figure 2a. Correlation between bone age and chronologic age of patients group

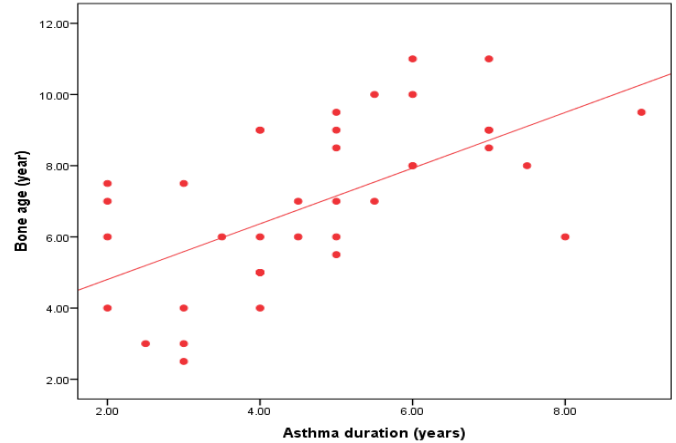


Figure 2b. Correlation between bone age and asthma duration of patients group

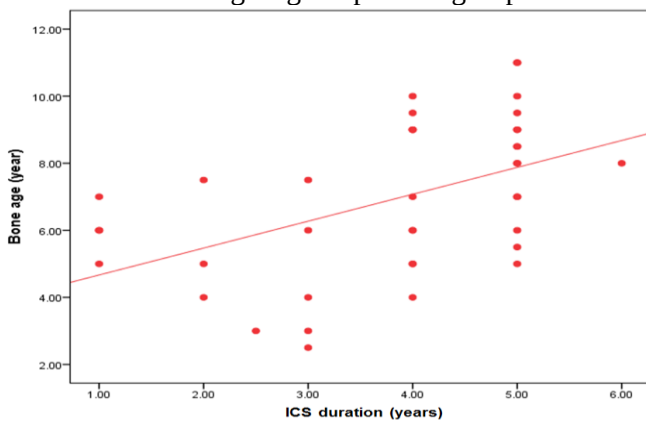


Figure 2c. Correlation between bone age and ICS duration of patients group

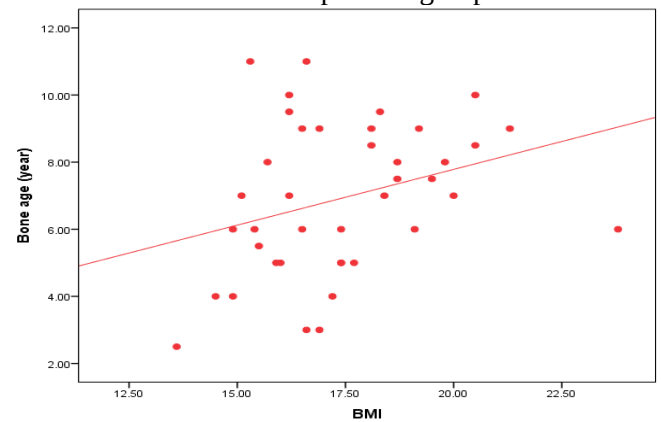


Figure 2d. Correlation between bone age and BMI of patients group

Correlation studies showed a significant positive correlation between the bone age and each of the chronologic age, asthma duration, duration of ICS and the BMI with p- values= 0.000, 0.000, 0.001 and 0.038 respectively).

DISCUSSION

Bronchial asthma is the most common chronic respiratory condition of childhood worldwide and good asthma care extends beyond providing medication to improve outcomes.¹⁴ Nevertheless, the goal of different therapeutic approaches is not only to treat the disease, but to improve patients' quality of life and inhibit the long-term consequences of childhood asthma.¹⁵ An essential factor in assessing the overall health of children with asthma is monitoring their growth parameters, including bone age, a critical biological indicator of maturity frequently used in clinical practice.¹⁶

The age of patients in our study ranged from 4 to 10 years with a mean (SD) of 8.24 ± 1.68 years with an equal male and female distribution. This result is

comparable to previous studies that reported a higher prevalence of asthma in male children as observed by *Alahmadi et al., 2019*¹⁷ in their systematic review that included 12 studies in Saudi Arabia. Likewise, *Dharmage et al., 2019*¹⁸ demonstrated that pre-pubertal boys had a higher asthma incidence, prevalence, and hospitalization rate than girls of the same age. The difference might be explained by the small number of the studied cases in our study compared to other studies or difference in socioeconomic levels in different countries with exposure to different asthma triggers.

Asthmatic children in our study, although maintaining normal weight ranges for their age, exhibited a lower median (IQR) weight for height SDS -0.02 ($-0.47 - 0.38$), compared to the controls 0.26 ($-0.83 - 0.67$) with a p-value 0.308. This aligns with findings from *Evans et al., 2019*¹⁹ who studied 95 racially and ethnically diverse children with persistent asthma from low-income urban communities in the USA and reported that these children generally consumed poor-quality diets.

The low weight observed among the asthmatic children in our study is likely influenced by the disease itself, which directly impacts their nutritional status. Moreover, the frequent asthma exacerbations and recurrent hospitalizations increase their vulnerability to infections, adversely affecting their quality of life, overall health, and physical growth. There were no significant differences as regards height SDS, height-for-age SDS, BMI, or BMI SDS between asthmatic children and the control group. These findings are consistent with a study conducted by *Nasrin et al., 2019*²⁰ who reported no differences in height and BMI between asthmatic and non-asthmatic children. However, *Van der Voort et al., 2012*²¹ observed that growth measurements including both weight and height were reduced in the studied asthmatic children compared to controls, highlighting the potential variability in outcomes across different populations and settings.

Notably in our study, the mean bone age of asthmatic patients 6.79 ± 2.13 years was significantly delayed than that of the control group 7.76 ± 1.89 years, with a greater disparity observed between chronological age and bone age in patients compared to controls with a p-value 0.044. The percentage of delayed bone age was 62.5% in patients compared to 27.5% in controls with a p-value 0.002. Chronic inflammation in asthma may interfere with growth and bone development by disrupting hormones, which are crucial for skeletal maturation. Additionally, the use of corticosteroids, a common asthma treatment, could suppress growth and impair bone formation. Asthmatic patients may also experience nutritional deficiencies, particularly in calcium and vitamin D, due to dietary restrictions or poor absorption caused by the chronic condition. Moreover, other factors such as reduced physical activity, and socioeconomic conditions may also contribute to these findings. This was in coherence with *Zhang et al., 2019*²² who reviewed 37 articles on asthmatic children and reported that asthma, particularly in severe or uncontrolled cases, can temporarily impair growth. Similarly, in an earlier study in Egypt, *Zayed and Abdelhady, 2014*⁷ found a significant decrease in growth measurements, specifically bone age among asthmatic children compared to controls. Additional mechanisms contributing to growth restriction in asthmatic children have been proposed, including the chronic hypoxia, the diminished lung function, and recurrent infections.²³

The delay in bone age was more prevalent in group B; 25 patients (62.5%) versus 15 patients

(37.5%) who had normal bone age within the same group. Group B patients had highly significant more delayed bone age than group A with p-value=0.002. There were no significant differences between both studied groups in terms of demographic data or disease characteristics, including asthma duration, severity level, control status, and the frequency of exacerbations or hospitalizations. As far as we know, one of the most important factors implicated in the impaired growth of asthmatic children and adolescents is ICSs treatment. Interestingly, a significantly higher percentage of patients with delayed bone age were on Fluticasone propionate 125 mcg (88%) compared to those on Fluticasone propionate/salmeterol 125/25 mcg (12%). This could suggest a potential association between the use of Fluticasone propionate and a greater reduction in bone age, warranting further investigation. As for the use of Fluticasone propionate/salmeterol, which was found to be more frequently received by patients with normal bone age compared to those with delayed bone age (40% versus 12%, respectively). The addition of LABA to ICS in fluticasone propionate/salmeterol which is a recommended step-up in treatment for asthmatic patients with persistent symptoms and/or risk of exacerbations, this strategy does not only decrease the dose of ICS used, which is likely linked to the delayed bone age, but also improves asthma symptom control, lung function and decreases the risk of exacerbations.²⁴ Hence, the delayed bone age could be attributed to the higher systemic absorption of fluticasone, in Fluticasone propionate as well as its potentially stronger local effect on growth suppression compared to the combination therapy in Fluticasone propionate/salmeterol.

Similarly, *Axelsson et al., 2019*²⁵ studied the effects of various ICS on bone age to identify those with the least negative impact. Their analysis of six randomized controlled trials (RCTs) involving 1,199 children in Sweden suggested that the drug molecule and delivery device could influence growth effects in children with persistent asthma, specifically Fluticasone appeared to inhibit growth at equivalent doses. In contrast, *Tao et al., 2012*²⁶ conducted a study on 73 asthmatic children treated with Fluticasone 125 mcg for one year and found no significant effect on bone age. In another study, *Pruteanu et al., 2014*²³ reviewed 10 trials involving 3,394 children with mild to moderate asthma and concluded that newer ICS molecules, including ciclesonide, fluticasone, and mometasone, showed no significant impact on growth over one year.

These findings highlight the complexity of ICS effects on growth and the importance of considering specific drug properties and devices when prescribing for pediatric asthma. However, there were no significant differences between both groups regarding the duration, dosage, or frequency of ICS use. It is noted that even in spite of the use of oral steroids there was no remarkable effect. Bigger sample size should be applied to further confirm such finding.

In our cohort, a significant correlation was found between the bone age and several clinical, anthropometric and laboratory parameters. Notably, bone age showed a strong positive correlation with chronologic age with a p-value 0.000, highlighting that the expected progression of bone growth aligns with actual age in this patient population. Similarly, significant positive correlations were found with asthma duration and the duration of ICS use with p-value 0.000 and 0.001 respectively, suggesting that the prolonged duration of chronic disease and its treatments may influence skeletal maturation. This association may reflect the cumulative impact of systemic inflammation and treatment on growth and development. This aligns with *Mainz et al., 2009*²⁷ who observed in his study that prolonged asthma duration has been associated with altered skeletal maturation, particularly in children with severe asthma or long-term corticosteroid use. Additionally, *Zayed and Abdelhady, 2014*⁷ reported that long-term ICS use has been found to significantly influence bone age progression, supporting the correlation observed between ICS duration and bone age. Contrarily, a RCT by *Roux et al., 2003*²⁸ found no significant effect of ICS duration on bone mineral density (BMD) or skeletal maturity among children with asthma when prescribed at standard doses, challenging the idea that short-term use impacts bone age. On the other hand, the duration of oral corticosteroid used in our study population did not exhibit any significant correlation with bone age. This suggests that short-term or intermittent use of oral corticosteroids may have a minimal impact on bone growth, particularly when compared to long-term ICS use. The Childhood Asthma Management Program (CAMP) study, demonstrated that repeated short courses of oral corticosteroids reduced bone mineral accretion in a dose-dependent manner, especially in boys, which contrasts with the lack of correlation reported in our study.²⁹

Additionally, in our study an inverse but non-significant correlation was found between the bone age and the frequency of asthma exacerbations.

Although, no significance was reached but this raises the possibility that more frequent disease exacerbations may impede skeletal maturity, potentially due to the longstanding systemic inflammation. Similarly, *Mainz et al., 2009*²⁷ reported that frequent asthma exacerbations in children have been indirectly linked to delayed bone age due to systemic inflammation, consistent with the observed trend toward an inverse correlation in our study. On the other hand, *Jung et al., 2014*³⁰ reported minimal impact of exacerbations or systemic inflammation on skeletal development, suggesting that exacerbation frequency may not reliably predict changes in bone age.

Of note, the anthropometric measures including weight SDS, height SDS and BMI showed positive correlations with bone age with p-value 0.669, 0.671 and 0.038 respectively, indicating that growth parameters are closely related to skeletal maturity. This was in agreement with *Bazargan et al., 2019*³¹ who reported in his study on asthmatic children, a significant positive correlation between bone age and anthropometric indices like height and weight but found variability in BMI correlations. He concluded that skeletal development generally aligns with anthropometric growth, supporting these positive correlations. However, no significant correlations were found with weight-for-height SDS and height-for-age SDS, suggesting that relative deviations in growth percentiles may not necessarily impact the pattern of skeletal development, these findings were consistent with that observed by *Zayed and Abdelhady, 2014*.⁷

In the present study, patients were subdivided according to the level of asthma control during the last month into controlled (20%), partly controlled (30%) and uncontrolled (50%) subgroups defined by GINA guidelines 2023. Comparison was done between the different subgroups as regards anthropometric measurements and bone age, with no significant differences identified. However, the median (IQR) weight SDS and height SDS were highest in the controlled group -0.10 (-0.35 – 0.38) and 0.32 (-0.33 – 0.92) compared to the other groups. The effective asthma management in the controlled group and hence, better asthma control may support optimal growth, likely by reducing systemic inflammation and improving the overall physical health. The medians of weight-for-height SDS, height-for-age SDS and BMI values were comparable across all groups. Moreover, no significant difference was observed in the bone age across asthma control groups. This was similar to the results of *Elnady et*

al., 2019³² where 128 Egyptian asthmatic children were evaluated and no significant differences were found between well-controlled and uncontrolled asthmatic children in terms of weight, height and BMI. However, a Brazilian study conducted by *Zacaron et al.*, 2019³³ including 266 asthmatic children found that more than half of the studied children had uncontrolled disease, and this impacted children growth.

To assess the impact of asthma severity on growth in our study, patients were again divided into three subgroups pursuant to the level of asthma severity during the last month. Resembling the comparison among subgroups as regards asthma control, the anthropometric measurements and bone age among the asthma severity subgroups did not show any significant difference. However, the median (IQR) weight SDS and median (IQR) height SDS were slightly lower in severe asthmatic cases compared to other cases. Furthermore, children with severe asthma had the lowest median BMI and the highest proportion of delayed bone age (100%) compared to mild and moderate subgroups. This suggests the impact of asthma severity on the different growth parameters. In agreement to our study, *Ismail et al.*, 2006³⁴ in his study in Alexandria divided children with asthma according to asthma severity to moderate and severe asthma, compared to control group as regards the skeletal growth parameters. They found no significant differences between asthmatic children and normal children as regards weight, height, BMI and skin fold thickness but a significant difference was identified between the two asthmatic groups (moderate and severe) and the controls in bone age, where the severe asthmatic cases had the lowest mean value.

Moreover, in the current study, patients were divided with respect to treatment received into a group on ICS only (Group 1) and another group on both ICS and OCS received during exacerbation (Group 2), both were compared to controls. No significant difference was observed in age or sex distribution as well as family history of allergic disorders among the two treatment groups and the control group. However, the percentage of family history of allergic diseases was higher in the treatment groups (16.7% in ICS group and 10.7% in ICS and OCS group) compared to the control group (7.5%). Similarly, no significant difference was found in the anthropometric measurements including weight SDS, height SDS, BMI, weight-for-height SDS, height-for-age SDS, or BMI SDS across the studied groups. Despite this finding, children receiving either ICS only or

combined therapy of ICS and OCS exhibited a lower median weight SDS -0.19 (-0.35 – -0.06) and -0.27 (-0.91 – -0.30) and height SDS -0.20 (-0.85 – 0.75) and -0.37 (-1.06 – 0.62) compared to controls. Interestingly, a significant delay in bone age was observed in both treatment groups compared to controls with a p-value= 0.007. Additionally, the bone age difference (the gap between chronological and bone age) was also significantly higher in the treatment groups compared to the control group with a p-value= 0.004. This supports the hypothesis of corticosteroids affecting growth velocity and skeletal development. *Nassar et al.*, 2024³⁵ in a cross-sectional study compared 90 children with moderate to severe asthma divided into three groups: Group I (ICS), Group II (OCS), and Group III (controls). The BMD was significantly reduced in children receiving OCS compared to ICS and controls. The ICS group showed minimal effects on BMD compared to controls.

Despite the notion that the delayed bone age could be a consequence of the asthma, rather than an adverse effect of ICS, this negative impact on growth can be minimized by using the minimum effective ICS dosage, decreasing the systemic availability of the drug through careful selection of the inhalation device and proper technique, the concomitant use of alternative anti-inflammatory agents and, appropriate choice of the ICS medication with least effect on growth. The impact of ICS on bone age and growth in children with asthma remains a subject of ongoing research. While some studies suggest minimal effects, others indicate potential concerns, particularly with prolonged or high-dose ICS use. Clinicians should carefully assess the benefits and risks of ICS therapy, considering individual patient factors and monitoring growth and bone health during treatment.

There are some limitations that have been encountered in this study. First, the study was conducted in a single center, there was a lack of generalizability. Second, the study was limited by the small sample size. Third, we cannot extrapolate a causal relationship due to the cross-sectional design. Finally, the genetic and familial variants were not studied and these parameters might have confounded the results.

Finally, we have to highlight that many confounders could be attributing to the different results like the diversity in dietary patterns, socioeconomic status and compliance to medications. There are also other familial factors

and multiple genetic variants that explain a large proportion of the heritability of height.³⁶

CONCLUSION

Asthmatic children were found to have delayed bone age and growth parameters. While ICS were essential for symptoms control, their prolonged use, particularly with oral corticosteroids, had negatively impacted growth. The strong correlation between bone age and factors like asthma duration, ICS use, and body measurements suggested that treatment, not just the disease, played a key role in growth patterns. These insights underscore the need for a more tailored approach to asthma treatment, balancing effective symptom control with strategies to mitigate potential growth suppression and ensure optimal long-term development.

AUTHORS CONTRIBUTION

NNT is the corresponding author, she put the study design, shared in clinical work, data analysis, interpretation of results, revision of all data in the study. She wrote the draft of the paper and approved the final version for submission. **ENT** performed the study through collecting cases, examination of patients, acquisition of data, and did the literature search. **SGM** shared in examination of patients, data collection and analysis, interpretation of results, revision of data in the study, shared in writing the paper draft.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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