Evaluating Bone Metabolism In Asthmatic Cases Using Inhaled Steroids

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Abstract

Background: Bronchial asthma is a chronic inflammatory disease in which eosinophils and different cells play a major role in pathogenesis, characterized by increased bronchial sensitivity of the airways. Topical steroids had been used to avoid long-term side effects of systemic steroids in asthma. The systemic effects of inhaled corticosteroids may be explained by the combined effects of many factors.

Objective: This study was performed to investigate the effects of inhaled steroids on bone mineralization and also on bone density.

Methods: Ninety-seven children divided into three groups, diagnosed with bronchial asthma and followed up in 2002 and 2003 at the GATA Haydarpasa Teaching Hospital were included in the study. Bone remodeling and destruction markers were used to examine the effects of inhaled steroids on bone metabolism.

Results: Comparisons between groups and among all three groups revealed no statistical differences in bone specific alkaline phosphatase (bALP), hydroxyproline (HP), carboxy-terminal telopeptide of type1 collagen (ICTP), calcium-creatinine ratio (Ca/GF), calcium (Ca) and phosphor (P) levels. Analysis of the groups in the study revealed that bone mineral density (BMD) scores were significantly higher in pubertal stage cases compared with those in the prepubertal stage.

Conclusion: No negative effect of inhaled steroid treatment on BMD was observed, and care must be taken over the use of the lowest dosage possible, especially in children, to keep respiratory functions and symptoms under control.

ABBREVIATIONS

bALP: Bone specific alkaline phosphatase
HP: Hydroxyproline
ICTP: Carboxy-terminal telopeptide of type1 collagen
Ca/GF: Calcium-creatinine ratio
Ca: Calcium
P: Phosphor
BMD: Bone mineral density
BMI: Body mass index
PTH: Parathormone
DS: Duration of sickness
DISU: Duration of inhaled steroid use
BD: Budesonide dose
INTP: Aminoterminal telopeptide of type I collagen

INTRODUCTION

Bronchial asthma is a lung disorder characterized by periodic attacks of wheezing alternating with periods of relatively normal breathing. The condition is caused by inflammation of the air passages in the lungs and affects the sensitivity of the nerve endings in the airways so they become easily irritated. Once the role of inflammation had been detected in asthma pathogenesis, it was determined that inflammation represented the main problem needing to be solved in management [1,2]. Topical steroids had been used to avoid long-term side effects of systemic steroids [3]. Well-

controlled, mild and moderate persistent asthma cases were observed after using these topical steroids [4,5]. However, it is still not known whether there are topical medication side effects that are inevitable in long-term medication using systemic steroids. Data regarding topical steroid safe dose ranges and the doses at which side effects are observed are limited [6].

Mineralization problems of growing bone tissue in childhood are seen more frequently and cause more serious problems in future life. Such problems in this period, if diagnosed early and with a proper approach and follow-up, can be treated without any damage occurring [7]. In this study, we investigated the side effects of long-acting inhaled steroids in childhood asthma on bone metabolism and bone mineral density.

METHODS

Ninety-seven children diagnosed with bronchial asthma and followed up in 2002 and 2003 at the GATA Haydarpasa Teaching Hospital were included in the study. The cases were divided into 3 groups. The first group consisted of 29 patients with mild and moderate persistent asthma scores, 10 girls and 19 boys, with ages ranging between 5 and 13 (7.52±2.1), receiving 100-600 mcg/day of budesonide over a period of 3-11 months (6.5±2 months). The second group consisted of 27 patients with mild and moderate persistent asthma scores, 13 girls and 14 boys, with ages ranging from 5-13 (7.2±2), receiving 300-600 mcg/day of budesonide over 13-84 (42.5±26.8) months. The third group consisted of 41 patients, 20 girls and 21 boys, aged between 4 and 14 (7.9±2.7), who received no long-acting inhaled or oral steroids but only short-acting beta-agonists when symptoms occurred. Bone remodeling and destruction markers were used to examine the effects of inhaled steroids on bone metabolism. Serum bone specific alkaline phosphatase (bALP) was analyzed as a marker of remodeling and carboxy-terminal telopeptide of type1 collagen (ICTP), the calcium-creatinine ratio (Ca/GF) and hydroxyproline (HP) were evaluated as bone destruction markers. Bone mineral density (Z-score) was measured from the lumbar zone (L1-L4) using Dual-Energy x-ray absorptiometry. SPSS for Windows 11.5 was used for statistical analyses of the data from this study.

RESULTS

No statistical difference between age, gender, weight, height, body mass index (BMI) and Tanner scores was determined among the groups (p>0.05) (Tables I and II). Duration of sickness, length of inhaled steroid use and budesonide dose distribution among the groups are given in Table III.

Figure 1

Table I: Demographic features of groups.

		Group I	Group II	Group III	Intergroup p level
Age (years)		7.52±2.11	7.22±2.01	7.9±2.77	(p=0.718)
Gender	Female	10 (34%)	13 (48%)	20 (49%)	(p=0.44)
	Male	19 (66%)	14 (52%)	21 (51%)	
Weight (kg)		25.59±7.29	24.44±7.57	26.44±9.09	(p=0.694)
Height (cm)		121.93±12.26	119.74±12.84	122.44±14.42	(p=0.706)
BMI (kg/m^2)		16.84±1.76	16.61±2.22	17.1±2.03	(p=0.611)

BMI: Body mass index

Figure 2

Table II: Tanner score distribution among groups.

Tanner Score	GROUP 1	GROUP 2	GROUP 3	TOTAL	Intergroup p level
Score I	23	24	28	75	(p=0.49)
Score II	5	2	8	15	
Score III	1	1	4	6	
Score IV	0	0	1	1	
TOTAL	29	27	41	97	

Figure 3

Table III: Duration of sickness, length of inhaled steroid use and budesonide dose distribution among the groups.

Mean ± SD	Group I	Grup II	Grup III	Intergroup p level
Duration of sickness (months)	36.14±24.99	50.37±21.6	32.63±21.81	(p=0.005)
Duration of inhaled steroid use (months)	6.52±2.03	42.52±26.87	-	(p=0.0001)
Budesonide dose (mcg)	342.93±114.58	446.67±94.62	-	(p=0.0001)

Comparisons between groups and among all three groups revealed no statistical difference in Z-scores (p>0.05) (Table IV). Analysis of the groups in the study revealed that Z-scores were significantly higher in pubertal stage cases compared with those in the prepubertal stage (p<0.05) (Table V). Comparisons between groups and among all three groups revealed no statistical differences in bALP, HP, ICTP, Ca/GF, Ca and P levels (p<0.05) (Table VI).

Statistical correlations were investigated among Z-scores and duration of sickness (DS), duration of inhaled steroid use (DISU) and budesonide dose (BD) parameters. No correlation was determined between Z-score and DS, DISU and BD (Table VII).

Figure 4

Table IV: Z-score distributions by group.

	Mean ± S.D	Intergroup p Level	Groups Compared	p
Group I	-0.74±0.55	0.19	Groups I – II	0.504
Group II	-0.99±0.74		Groups I – III	0.97
Group III	-0.72±0.60		Groups II – III	0.098

Figure 5

Table V: Z-score distribution in prepubertal and pubertal cases

Z-score	No. of cases	Mean ± S.D	Intergroup p Level
Prepubertal (Tanner score)	75	-0.85±0.692	(p<0.05)
Pubertal (Tanner scores II, III and IV)	22	-0.23±0.827	

Figure 6

Table VI: Relation of factors positively correlated with Z-scores.

		bALP	HP	ICTP	Ca/GF	PTH	Ca	P
Group I		196.9±76.8	137.8±58.1	676.2±174.6	0.06±0.04	37.7±14.8	9.85±0.4	4.89±0.4
Group II		198.0±68.8	133.8±65.7	634.0±244.6	0.08±0.05	42.0±11.0	9.74±0.5	4.69±0.5
Group III		193.1±68.8	138.9±53.2	646.4±220.1	0.09±0.06	43.2±13.3	9.58±0.5	4.68±0.5
p	Groups I – II	(0.999)	(0.629)	(0.577)	(0.305)	(0.45)	(0.122)	(0.217)
	Groups I – III	(0.975)	(0.761)	(0.343)	(0.119)	(0.05)	(0.037)	(0.110)
	Groups II – III	(0.963)	(0.422)	(0.861)	(0.522)	(0.208)	(0.729)	(0.854)
	Between groups	(0.956)	(0.720)	(0.654)	(0.266)	(0.065)	(0.100)	(0.251)

bALP: Bone alkaline phosphatase, HP: Hydroxyproline, ICTP: Carboxy-terminal telopeptide of type 1 collagen, Ca/GF: Calcium/creatinine ratio, PTH: Parathormone, Ca: Calcium, P: Phosphorus.

Figure 7

Table VII: Correlation between Z-score and DS, DISU and BD

	DS	DISU	BD
	Z-score		
r	.155	.115	-.054
p	.128	.397	.695

DS: Duration of sickness, DISU: Duration of inhaled steroid use, BD: Budesonide dose

DISCUSSION

Bronchial asthma is a chronic inflammatory disease in which eosinophils and different cells play a major role in pathogenesis, characterized by increased bronchial sensitivity of the airways. Following the realization of the important role played by inflammation in pathogenesis, inhaled steroids became the drug of choice in the treatment of chronic asthma. Data show that after inhaled steroid treatment the frequency and progression of symptoms decrease, and vital capacity and quality of life improve.

The security problem of long-acting inhaled steroids is an important issue, and one on which there is still no consensus. Childhood is the period of the fastest growth and development. The skeletal system occupies an important place in systems that grow rapidly in this period. Bone tissue is produced on the one hand and resorbed on the other, and this cycle continues on a lifetime basis. Steroids affect this cycle by impairing various stages within it [8].

Studies on the effects of inhaled steroids on bone metabolism fall into two groups. One group examined bone metabolism biochemical markers that occur during bone formation and resorption, the other group evaluating the effects on bone mineral density [9].

Bone metabolism indicators are the biochemical main products that appear during bone production and destruction and that can be determined in body fluids. Widely used bone production indicators in scientific studies are total alkaline phosphatase (ALP) measured in serum, bone specific alkaline phosphatase (bALP), osteocalcin, carboxy terminal propeptide type 1 collagen (PICP) and aminoterminal propeptide type 1 collagen (INTP). Bone destruction indicators include tartrate resistant acid phosphatase observed in serum and pyridinoline/deoxypyridinoline observed in urine, carboxy-terminal telopeptide of type 1 collagen (ICTP), aminoterminal telopeptide of type 1 collagen (INTP), calcium/creatinine levels and hydroxyproline (HP) [10,11]. Bootsma et al. demonstrated that serum bALP levels are not affected by inhaled fluticasone and beclomethasone dipropionate in asthmatic adults [12].

Sorva et al. determined no difference between bALP values at 0, 1 and 5 months in a longitudinal study of 27 asthmatic children who received inhaled beclomethasone dipropionate [10]. Hoekx et al. reported no change in bALP levels when they used budesonide and beclomethasone at a dosage of 800 mcg/day and fluticasone at a dosage of 400 mcg/day for 6 months [11]. There was no statistical difference between ICTP levels in our groups. Consistent with the literature, short- and long-term use of moderate and low dose inhaled steroids have no negative effect on bone remodeling.

ICTP is a destruction product indicating c-telopeptides entering the bloodstream as a result of bone matrix type 1 collagen destruction. An increased level in urine reveals collagen destruction. Kannisto et al. reported an approximate 21% decrease in ICTP in asthmatic children receiving 500 mcg/day of fluticasone, normalizing in the fourth month at 200 mcg/day [13]. ICTP levels in the study did not change in asthmatic children who received budesonide. Kerstenj et al. reported no difference between PICP and ICTP levels in

patients receiving 800 mcg/day of beclomethasone dipropionate 2.5 years before and after follow-up [14].

In a study by Wolters et al. in which they divided asthma cases into two groups, giving one group 2.5-5 mg of oral prednisolone and the other 200-400 mcg/day of inhaled budesonide, the authors reported no change at the end of two weeks with budesonide, but determined a reduction in serum osteocalcin levels, a destruction marker, and urinary HP proportionate to dosage in the group receiving oral steroids. They concluded that short-term low dose oral steroid treatment reduced bone turnover and recommended low dose prednisolone as preferable to 800 mcg/day of budesonide in order to avoid this [15]. Martinati et al. determined PTH, bALP and ICTP levels before their study, in the first and second months, and in the first month after treatment in 39 children with seasonal allergic rhinitis who received 200-400 mcg/day of beclomethasone dipropionate over a two-month period, and reported no difference between the levels [16]. Ali et al. reported an HP/creatinine rate increase in the early period of high dose (200 mcg/day) beclomethasone dipropionate treatment [17]. In our study, there was no statistical difference between ICTP, HP and Ca/GF levels as a destruction marker in our groups.

Studies have generally shown that the use of high dose inhaled steroids, in particular in the early period, has negative effects on bone metabolism. In our study we determined no difference between the shortest period (group 1) in which metabolic compensatory mechanisms can enter the equation and in which it is possible to refer to drug side effects, and between case groups using inhaled steroids at a low-medium dosage (group 2) for as long as a year compared with the control group (group 3) not using steroids in terms of effects on bone metabolism.

We investigated the effects of inhaled steroids on bone mineralization and also on bone density. Weight, height, age, pubertal status and parameters affecting bone mineral density must be carefully determined in studies based on bone mineral density [18,19]. There were no differences in age, sex or pubertal status in our study, and the conditions affecting bone mineral density were equalized, except for asthma and inhaled steroid medication, between the groups. Rib and vertebral fracture rate was 11% in asthmatic patients receiving systemic steroids, whereas no fractures were reported in the group not receiving them in one retrospective study [20].

Packe et al. reported low Z-scores in 20 severely asthmatic adults receiving 800 mcg/day of budesonide for one year, 13 of whom received systemic steroids at various times, compared with 17 mild asthmatic adults who did not receive steroids [21]. Packe reported that bone mineral density (BMD) decreased by 18% in a healthy control group not receiving steroids compared with 20 asthmatic adults receiving 1000-2000 mcg/day of BPD over three years [22]. Hanania et al. reported that BMD decreased in proportion to dose in asthmatic cases receiving 800 mcg/day of steroids over one year [23]. There has been some debate over these three studies; patients receiving inhaled steroids had also received systemic steroids previously. Case numbers were small, and severe asthmatic cases were included in the study groups whereas moderate asthmatic cases were included in the control groups. It is indicated that long-term and high dose inhaled steroid treatment reduced bone mineral density, as in systemic steroid treatment. Konig et al. reported similar bone mineral densities between moderate asthmatic patients not receiving steroids and 18 asthmatic children receiving 400-800 mcg/day of BPD for at least 6 months [24]. Hopp et al. determined no difference between healthy and asthmatic children receiving 200-450 mcg/day of inhaled steroids for 4-60 months, and concluded that these can safely be used in children [25].

In our study, we compared bone mineral densities between mild and moderate asthmatic cases receiving 342±114.5 mcg/day of budesonide for 6.52±2 months (group 1) and mild-moderate asthmatic cases receiving 446.67±94.6 mcg/day for 42.52±21.8 months. There were no differences between the groups. Independently of the groups, Z-scores were high in pubertal groups compared with prepubertal and pubertal cases. There were no statistical differences between the first and second groups in terms of duration of disease and inhaled steroid and dosage. We concluded that inhaled steroids, at the dosage and periods we used, had no negative effect on bone density or bone metabolism. We attributed this to our use of mild-moderate doses of inhaled steroids and to the fact that our cases were not severely asthmatic.

Calcium, phosphor, and parathormone levels were examined to evaluate the Ca-P metabolism in our study. Toogood et al. determined no difference between serum Ca and P levels in adult asthmatic patients receiving 2400 mcg/day of high dose budesonide over seven days' follow-up [26].

Sorve et al. established no difference between Ca and P levels in mild-moderate persistent asthma cases receiving inhaled steroids over two years in a cross-sectional study [27].

Akil et al. reported that biochemical markers of bone metabolism were not significantly different between controls and asthmatic children [28].

No increase in serum parathormone levels was observed in our study, and serum Ca and P levels were similar and within normal ranges in all three groups. Ca and P levels are of vital importance and are regulated by several control systems. In children with severe rickets and even many chronic diseases including this system, Ca and P levels are the last to be affected in those receiving oral steroids.

The systemic effects of inhaled corticosteroids may be explained by the combined effects of many factors. These effects may exhibit individual variations depending on the medication dosage received. These individual variations in sensitivity to inhaled corticosteroids may also have an effect in terms of effects on bone metabolism. In this study, no negative effect of inhaled steroid treatment on BMD was observed, and care must be taken over the use of the lowest dosage possible, especially in children, to keep respiratory functions and symptoms under control.

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