

Short communication

Longitudinal evaluation of bone mass in asthmatic children treated with inhaled beclomethasone dipropionate or cromolyn sodium

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Inhaled corticosteroids are recommended as first-line therapy in patients with moderate to severe asthma. The use of these agents in the milder form of asthma is controversial because of their potential adverse effects, especially in growing children. We investigated 49 asthmatic children (38 treated with beclomethasone dipropionate (BDP) at a daily dose of 276 ± 125 $\mu\text{g/day}$ and 11 treated with cromolyn sodium (CS) at a daily dose of 30 ± 10 mg/day) for 7.4 months, with bone-mass measurements at baseline and after the treatment period. Evaluation of changes in cortical and trabecular bone mass (bone mineral density [BMD]; m/cm^2) was performed by absorptiometry at the proximal forearm and at the lumbar spine, respectively. Furthermore, to correct for bone size changes due to growth, we calculated volumetric BMD (VOL-BMD; mg/cm^3). At the end of the treatment period, the children who had received regular inhaled BDP had grown as well as children treated with CS, from 120 ± 1.4 to 123 ± 1.3 cm and from 118 ± 3.2 to 120.3 ± 2.8 cm, respectively. No children showed deviation from their percentile level of growth. Trabecular and cortical BMD increased after 7 months of follow-up in both groups to the same extent. When BMD was adjusted for body size (VOL-BMD; mg/cm^3), bone mass was found not to have changed after BDP or CS treatment course within and between the two groups.

**L. C. Martinati³, F. Bertoldo²,
E. Gasperi², P. Fortunati¹,
V. Lo Cascio², A. L. Boner¹**

¹Department of Pediatrics, University of Verona, Verona; ²Istituto di Semeiotica e Nefrologia Medica, University of Verona, Verona; ³Istituto Pio XII, Misurina, Italy

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Attilio Boner, MD
Clinica Pediatrica
Policlinico Borgo Roma
37134 Verona
Italy

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The development of fiberoptic bronchoscopy and the application of cellular and molecular biologic techniques have led to the recognition that chronic airway inflammation is a characteristic feature even in patients with mild asthma (1–3).

Inhaled corticosteroids are considered first-line therapy in asthmatic patients, but the use of these agents in the milder form of asthma has heightened awareness of and debate on their potential adverse effects, particularly in growing children, and has renewed interest in re-evaluating their risk-to-benefit ratio (4). This debate has, on one hand, the potential to promote the use of inhaled corticosteroids in the mild form of asthma and, on the other, the potential to decrease their use in patients

with the moderate form of the disease because of the fear of side-effects.

Several recent studies have documented dose-dependent alterations in biochemical markers of bone turnover with the use of inhaled corticosteroids (5). Since the functional and clinical significance of these alterations remains to be clarified, objective measures of skeletal maturation, including evaluation of linear growth and bone mineral density (BMD), would be of more value.

For this reason, we evaluated prospectively the effects of 7-month treatment with beclomethasone dipropionate (BDP) on bone mass in prepubertal asthmatic children. The same group was previously described in a cross-sectional study, in which we

Table 1. Demographic and clinical data (mean $\pm$ SD)

	CS group	BDP group
<i>n</i>	11	38
Age (years)	6.3 $\pm$ 2.6	6.4 $\pm$ 1.8
Height (cm) (mean $\pm$ SD)	118 $\pm$ 10.6	120 $\pm$ 8.6
Weight (kg) (mean $\pm$ SD)	25.2 $\pm$ 3.1	27.2 $\pm$ 4.2
Mean daily dose	30 $\pm$ 10	276 $\pm$ 125
	(mg/day)	(μ g/day)

did not find any difference in bone mass between the group of children treated with BDP and the group of children treated with cromolyn sodium (CS) (6).

Material and methods

Subjects

A total of 49 (40 boys and nine girls) prepubertal (Tanner's scale 1) children between 5 and 11 years of age (mean age 6.3 $\pm$ 1.9 years), with frequent episodic or perennial asthma, were included in the study. All subjects with chronic illness other than asthma, excessive exercise programs, or eccentricities in diet were excluded from the study. The informed consent of the parents was obtained, and the study was approved by the local ethics committee.

Treatment group

Thirty-eight subjects (30 boys and eight girls; 6.4 $\pm$ 1.8 years of age) were followed for a treatment period with BDP of 7.4 $\pm$ 2 months at a dosage of 150–700 μ g/day (mean 276 $\pm$ 125 μ g/day).

Control group

Eleven asthmatic children (10 boys and one girl), age-matched with the BDP group (mean age, 6.3 $\pm$ 2.6 years), receiving CS were followed as controls.

No subject had received treatment with systemic corticosteroids during the study period. All subjects used inhaled β_2 -agonists when needed. The demographic data of the groups are reported in Table 1.

Growth measurement

The children's height was measured at each visit with a Harpenden stadiometer (Holtain Limited, Crymych, Dyfed, UK) by a single observer. Three measurements were taken, and the mean was calculated. If one measurement was discrepant, the entire procedure was repeated.

At the beginning and at the end of the study, the pubertal stage of the children was assessed.

Bone mass measurements

Bone mass was measured as previously described (6) at the nondominant radius by dual-photon absorptiometry (Osteograph 1000; NIM, Italy) at the proximal one-third of the radius (exclusively cortical bone) and expressed as areal density (Rad-BD; mg/cm²). *In vivo*, the coefficient of variation (CV=SD/mean) was 0.89%.

The BMD (mg/cm²) of L2-L4 vertebrae in the anteroposterior scan (AP-BD) and of L3 in the lateral scan (LAT-BD) was assessed by dual x-ray absorptiometry (DXA, Sophos L-XRA). The instrument is equipped with a rotating detector, which permitted anteroposterior and lateral scans with the subject lying supine. This reduces the variance induced by repositioning the subject. The CV was 1.3% for the AP scan and 3.6% for the LAT scan.

The lateral scan of the lumbar spine allows a more selective measurement of the trabecular-rich vertebral body than the anteroposterior scan, which excludes the cortical bone of the posterior elements. This increases the sensitivity to detect trabecular bone loss, such as that induced by corticosteroid treatment (7, 8). Rad-BD, AP-BD, and LAT-BD represent areal density (mg/cm²) rather than true volume density (mg/cm³) and are functions of the bone size. Thus, differences in areal bone density measurements in growing children may reflect an increase in bone volume rather than of true bone density (9). Therefore, we calculated true density (VOL-BD, mg/cm³), as previously described (6).

Statistics

Statistical analysis was performed by nonparametric methods; the Wilcoxon signed rank test for paired data and the Mann-Whitney U-test for independent samples. A *P* value lower than 0.05 was considered significant. Linear correlation was performed when indicated.

Results

The mean of height and weight for boys and girls was not different from those of the reference population, and all subjects were between the 5th and 90th percentiles for height and weight (Table 1). The standard deviation of a single height measurement was 0.08 cm. Boys and girls were not different for height, weight, and body mass index (BMI; kg/m²) within each group. Therefore, we

Table 2. Height and bone mineral density (BMD) at forearm and lumbar spine in 38 asthmatic children treated with beclomethasone dipropionate (BDP) and in 11 asthmatic children treated with cromolyn sodium (CS). Table shows mean ($\pm$ SD) values in two groups at baseline and after 7-month follow-up, mean differences between two groups, and 95% confidence intervals of differences (CI 95%). A) Baseline values; B) follow-up after 7 months

	Baseline			
	BDP group	CS group	Mean differences	CI (95%)
Height (cm)	120 $\pm$ 1.4	118 $\pm$ 3.2	1.26	-0.84 3.37
BMD forearm (mg/cm ²)	429.2 $\pm$ 10.4	434.2 $\pm$ 14.3	-5.20	-16.6 6.29
BMD AP lumbar (mg/cm ²)	569.3 $\pm$ 12.6	558.7 $\pm$ 28.9	12.51 ^a	-1.87 26.91
BMD LL lumbar (mg/cm ²)	479.1 $\pm$ 5.2	476.9 $\pm$ 28.3	-0.06	-17.02 16.89
BMD volume (mg/cm ³)	148.1 $\pm$ 5.9	147.3 $\pm$ 10.5	0.73	-3.81 5.28
B				
	After 7 months			
	BDP group	CS group	Mean differences	CI (95%)
Height (cm)	123.0 $\pm$ 1.3**	120.3 $\pm$ 2.8*	1.51	-0.45 3.47
BMD forearm (mg/cm ²)	464.6 $\pm$ 7.3**	462.5 $\pm$ 16.0**	2.94	-8.63 14.52
BMD AP lumbar (mg/cm ²)	608.7 $\pm$ 14.0**	579.7 $\pm$ 30.7*	25.9 ^b	5.41 46.47
BMD LL lumbar (mg/cm ²)	487.3 $\pm$ 12.9*	481.7 $\pm$ 31.6*	0.40	-34.2 35.09
BMD volume (mg/cm ³)	150.3 $\pm$ 4.8	149.7 $\pm$ 7.9	1.26	-3.13 5.67

** P <0.001; * P <0.02 vs baseline values by Wilcoxon signed rank test; ^a P <0.02, ^b P <0.001 between groups by Mann-Whitney test.

analyzed boys and girls pooled together in each group.

Baseline mean height was slightly but not significantly greater in the BDP group than in the CS group (Table 2A). All children grew as expected for normal growth (Table 2A and B).

The BDP-treated children increased in height from 120 $\pm$ 1.4 to 123 $\pm$ 1.3 cm (P <0.01), and the CS-treated children from 118 $\pm$ 3.2 to 120.3 $\pm$ 2.8 cm (P <0.02). The final height was not statistically different between the two groups.

At the beginning and at the end of the study, there were no significant differences between boys and girls in AP-BD, LAT-BD, VOL-BD, and Rad-BD within the groups. Therefore, the densitometric data were analyzed after being pooled in each group (Table 2A and B). Baseline Rad-BD, AP-BD, LAT-BD, and VOL-BD values in both groups were in the normal age-related range for healthy, nonasthmatic children. Furthermore, AP-BD was in good agreement with published normative data (9, 11-13).

At the end of the study, all the children were in prepubertal condition (Tanner's scale 1). At the baseline, there were no differences in pure trabe-

cular BMD (LAT-BD) and in cortical BMD (Rad-BD) between the two treatment groups. AP-BD was moderately higher in the BDP group than in the CS group, probably as an effect of slightly greater body size in the former group. In fact, when the areal density was corrected for the vertebral volume (VOL-BD), the two groups were comparable. After 7 months of follow-up, lumbar and forearm areal BMD showed a significant increase (Table 2A and B) in both groups, but after the adjustment for body size changes due to growth, there were no differences from baseline values within and between the groups.

In the BDP group, we did not find any correlation between BMD values and the mean or cumulative BDP doses. Furthermore, no correlation was found between height changes and BDP doses (data not shown).

Discussion

The technique used in our study is a very sensitive one to detect the impact of steroids on bone. In fact, corticosteroid-induced bone loss is more pro-

nounced in trabecular than cortical bone (14). There are few studies addressing the effect of inhaled corticosteroids on bone density in children with asthma (6, 15–17). All the cross-sectional studies showed the lack of effect of inhaled steroids on bone formation and resorption (6, 17). In our study, after 7.4 months of therapy, considering only the follow-up period, but really after a total of 14 months of treatment, considering also the period preceding the baseline, no significant bone loss was observed.

Cortical and trabecular bone areal density (Rad-BD and LAT-BD) in the BDP group was not apparently affected by inhaled corticosteroid, as no significant differences were observed with the control group after 7 months of follow-up. The final AP-BD in the BDP group was moderately but significantly higher than in controls. This was due partly to a moderately higher baseline value and also to a slightly greater final height in the BDP group. The negative impact of inhaled steroids on bone mass in growing children could be masked by the increase of bone size when bone mass is expressed as areal bone density (mg/cm^2); in fact, the correction of bone mineral content (mg) for projected area (cm^2) removes some, but not all, of the dependence on bone size. Therefore, areal bone density increases as bone volume increases. When mineral content was corrected completely for bone volume, VOL-BD in the BDP group showed no significant changes from baseline or from the CS group. Our data are in good agreement with true volumetric spinal bone density measured by quantitative computed tomography, showing no increase between 2 and 12 years in normal children (13, 18).

In our study, the children treated with BDP received inhaled steroids for the 7 months preceding the baseline observation. This might suggest that the bone mass could have been lost before the baseline observation, since it has been shown that, in patients taking systemic corticosteroids, the largest amount of bone loss occurs rapidly during the first few months of treatment (19). However, there were no differences in baseline bone-mass values between the two groups, and this reasonably excludes a negative impact on bone mass of the previous treatment period.

In conclusion, a low-dose regimen with inhaled steroid is safe in asthmatic children and is not associated with a reduction in BMD. However, further longitudinal studies are needed in children and young adults because peak bone mass density is reached in early adulthood, and it has been suggested that maximal peak bone mass density is probably the most clinically relevant outcome measure to assess when the influence of steroids on bones in children is studied (20). However, our preliminary results in prepubertal asthmatic children are reassuring.

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