Bone mineral density in normal and asthmatic children

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Background: *The largest increase in bone mass occurs during childhood and adolescence. A subnormal bone mass is associated with increased risk of fracture. Bone mass is influenced by height, age, race, exercise, and stage of puberty. It is adversely affected by chronic disease states and corticosteroid use. We performed a cross-sectional study of bone density in children with moderate to severe asthma who were treated with inhaled corticosteroids, inhaled cromolyn, oral corticosteroids, or a combination of these, and we compared them with normal children.*
Methods: *A cross-sectional study of bone density, measured either by dual-photon or dual-energy absorptiometry, was performed on 97 normal white and 30 asthmatic white children, aged 5 to 18. Average daily calcium intake, height, weight, and Tanner stage were determined. The total daily and lifetime doses of inhaled corticosteroids in children with asthma were calculated. T tests, multiple regression, chi square analysis, and analysis of covariance were performed.*
Results: *No significant difference in bone density was demonstrated between children with asthma and normal control subjects. No measure (including calcium intake, Tanner stage, daily or lifetime inhaled corticosteroid dose, or duration of illness), except for height and age, provided a significant contribution to the explanation of bone density in children with asthma.*
Conclusion: *Children and adolescents with moderate to severe asthma, including those treated with inhaled corticosteroids, do not appear to have adversely affected bone mass. There was, however, the possibility of a type II error in this study because of the sample size. (J ALLERGY CLIN IMMUNOL 1994;94:490-7.)*

Key words: *Asthma, bone density, children, corticosteroids, absorptiometry, calcium*

Marked acceleration in skeletal growth and bone mass occurs in the prepubertal and pubertal years.[1-3] Peak bone density attained from childhood through early adult life may be a critical determinant for risk of fractures in adulthood.[4] Dietary calcium intake, exercise, age, race, height, and weight are factors known to affect bone mass; however, these factors account for less than half the variability in bone mass seen in adults.[5]

With the use of recently developed methods of determining bone density, several chronic diseases in children have been associated with suboptimal bone mass.[6, 7] Asthma is a common chronic illness in the pediatric age group: 5% to 10% of children have symptoms of asthma.[8, 9]

A new emphasis on asthma as an inflammatory disease indicates that medications with an antiinflammatory effect will be widely used,[10] even in patients with newly detected mild asthma.[11] Earlier

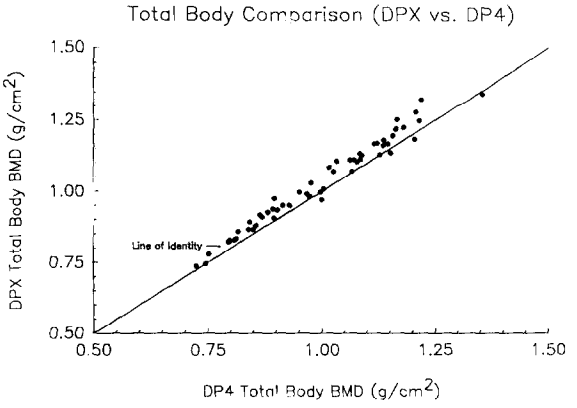

FIG. 1. Linear regression of DPA versus DPX (DEXA) scans in adult subjects. Unpublished data.

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TABLE I. Demographic data on subjects with asthma

Tanner stage		N	Mean age (yr) mean (95% C.I.)	Mean daily IS (μg/kg/day) mean ± SD	Mean daily IS (μg) mean (range)	Mean duration (mo) mean ± SD	Cromolyn + IS (no.)	IS only (no.)	Cromolyn only (no.)
1	Male	11	8.7 (4.6-12.8)	24.1 ± 18.1	620 (252-1200)	14.3 ± 13.2	5	5	1
	Female	5	7.6 (3.5-11.7)	24.6 ± 14.7	661 (220-1200)	26.4 ± 21.9	4	1	0
2	Male	4	11.6 (10.4-12.8)	7.2 ± 6.0	484 (168-1200)	27.0 ± 23.2	1	3	0
	Female	2	12.2 (12.0-12.4)	17.0 ± 7.2	800 (600-1000)	27.0 ± 12.7	2	0	0
3	Male	1	13.6	3.0	168	6.0	0	1	0
	Female	0	–	–	–	–	–	–	–
4	Male	2	15.6 (11.9-19.3)	8.0	504	84.0	0	1	1
	Female	1	14.1 (14.1)	13.9	800	24.0	0	1	0
5	Male	2	16.5 (16.3-16.7)	4.8 ± 0.7	426 (252-600)	54.0 ± 42.4	0	2	0
	Female	2	16.2 (14.2-18.2)	20.8 ± 0.6	1100 (1000-1200)	18.0 ± 8.5	2	0	0

IS, Inhaled steroids.

TABLE II. Multiple regression analysis

	Group 1		Group 2		Groups 1 and 2		Subjects with asthma	
R^2	Girls (n = 41)	Boys (n = 21)	Girls (n = 19)	Boys (n = 16)	Girls (n = 60)	Boys (n = 37)	Girls (n = 10)	Boys (n = 20)
Height vs TBD	0.757	0.862	0.711	0.805	0.737	0.833	0.658	0.816
Age vs TBD	0.743	0.806	0.676	0.863	0.705	0.813	0.685	0.747
Height vs spine	0.651	0.816	0.731	0.820	0.674	0.812	0.672	0.661
Age vs spine	0.697	0.696	0.691	0.860	0.655	0.7120	0.658	0.695

Abbreviations used
DEXA: Dual-energy absorptiometry
DPA: Dual-photon absorptiometry
RDA: Recommended daily allowance
TBD: Total bone density

and more routine use of cromolyn sodium and/or inhaled corticosteroids is now being stressed, especially in patients with moderate symptoms.[10, 11] Oral corticosteroid therapy has well known side effects, including detrimental effects on bone growth in children.[12] The use of inhaled corticosteroids in children with asthma may be associated with decreased bone formation, as reflected in diminished serum osteocalcin levels in children receiving inhaled corticosteroids.[13] A recent report suggested, however, that lowered serum osteocalcin levels might be directly related to having asthma and not to a specific therapy.[14]

A preliminary study in pediatric patients with mild to moderate asthma demonstrated no significant difference in bone density compared with normal subjects.[15] We therefore sought to determine, in the pediatric age group, the effect of moderate to moderate-severe asthma on bone density, a sensitive marker of longitudinal bone formation. In addition, we attempted to determine whether medication, including inhaled steroids and other measured clinical parameters of asthma severity, influenced bone density.

METHODS

The protocol was approved by the institutional review board of Creighton University. The study subjects comprised three groups. All children were recruited from within a 50-mile radius of the greater Omaha metropolitan area. Recruitment methods for the nonasthmatic children included appeals in the campus newsletter. Asthmatic subjects were predominately patients of one physician or were recruited by appeals to allergists in the medical community. All subjects with chronic illnesses other than asthma, family history of osteoporosis, excessive exercise programs, menstrual irregularities, or eccentricities in diet were excluded. All subjects were within the 10th and 90th percentile for height and weight.

TABLE III. Total and regional bone densities in studied subjects

Mean (95% CI)	Group 1 and 2 control subjects		Group 2 control subjects		Subjects with asthma	
	Male	Female	Male	Female	Male	Female
N	37	60	16	19	20	10
Age (yr)	10.7 (4.0-17.4)	12.2 (5.7-18.7)	10.3 (4.2-16.4)	11.7 (5.2-18.2)	10.9 (4.3-17.7)	10.9 (3.1-18.7)
Height (cm)	143.8 (105.1-181.7)	147.1 (116.0-178.8)	144.3 (102.0-186.6)	146.5 (108.9-184.1)	147.0 (103.7-190.3)	141.4 (102.8-180.0)
Weight (kg)	40.2 (8.1-68.5)	43.4 (16.8-70.2)	42.9 (1.9-83.9)	43.2 (9.1-77.3)	47.0 (0.3-95.5)	39.8 (12.8-66.8)
TBD (gm/cm^2)	0.917 (0.639-1.195)	0.963 (0.665-1.261)	0.918 (0.636-1.200)	0.967 (0.634-1.300)	0.957 (0.700-1.214)	0.913 (0.646-1.180)
Spine (gm/cm^2)	0.811 (0.425-1.209)	0.920 (0.550-1.374)	0.837 (0.420-1.254)	0.948 (0.391-1.505)	0.888 (0.482-1.294)	0.864 (0.490-1.238)
Head (gm/cm^2)	1.631 (1.155-2.107)	1.809 (1.145-2.473)	1.600 (1.208-1.992)	1.768 (1.074-2.462)	1.694 (1.130-2.258)	1.628 (1.109-2.147)
Arms (gm/cm^2)	0.651 (0.422-0.880)	0.677 (0.550-1.374)	0.652 (0.418-0.888)	0.691 (0.419-0.963)	0.676 (0.468-0.884)	0.679 (0.477-0.881)
Legs (gm/cm^2)	0.911 (0.447-1.387)	0.962 (1.550-1.374)	0.914 (0.451-1.377)	0.977 (0.530-1.424)	0.954 (0.529-1.379)	0.902 (0.455-1.349)

Values are expressed as means with ranges in parentheses.

TABLE IV. Comparison of group 2 control subjects and patients with asthma

Tanner stage		Group 2 control subjects		Patients with asthma		
		N	Mean % RDA Ca^{++}	N	Mean % predicted FEV_1	Mean % RDA Ca^{++}
All	Male	16	116 (39-159)	20	95 (56-157)	124 (81-202)
	Female	19	83 (38-148)	10	78 (54-142)	90 (43-191)
1	Male	9	115 (64-159)	11	100 (78-157)	126 (88-202)
	Female	9	78 (38-145)	5	66 (54-96)	97 (43-191)
2	Male	4	131 (75-158)	4	93 (81-118)	132 (92-150)
	Female	1	64	2	79 (72-86)	98 (91-104)
3	Male	0	–	1	79	97
	Female	2	126	0	–	–
4	Male	3	98 (39-159)	2	86 (56-116)	124 (114-134)
	Female	4	84 (60-99)	1	58	55
5	Male	0	–	2	93 (80-106)	116 (81-151)
	Female	3	72 (63-79)	2	116 (91-142)	84 (81-87)

Values expressed as means with ranges in parentheses.
FEV_1, Forced expiratory volume in 1 second.

Group 1

Sixty-two nonasthmatic white children, 21 boys and 41 girls, between the ages of 5 and 18, were studied with either dual-photon absorptiometry (DPA) (model DP4; Lunar Radiation, Madison, Wis.) from 1988 to 1989, or dual-energy x-ray absorptiometry (DEXA) (Lunar DPX) since 1989. DEXA involves a lower radiation dose compared with DPA. Total and regional bone densities could be determined from the same DPA or DEXA scan. Calcium intake and pubertal status (except menstrual status) were not determined in normal subjects in group 1.

Group 2

Thirty-five normal white children, 17 boys and 18 girls, ages 6 to 16, without significant medical histories,

Subjects with asthma (inhaled steroids)	
Male	**Female**
15	9
10.6	10.4
(4.2-17.0)	(2.7-17.9)
145.7	139.5
(102.7-188.7)	(100.3-178.7)
43.2	38.9
(6.8-79.5)	(10.8-67.1)
0.932	0.912
(0.705-1.159)	(0.638-1.186)
0.847	0.868
(0.542-1.150)	(0.473-1.261)
1.613	1.600
(1.229-1.995)	(1.076-2.130)
0.660	0.678
(0.472-0.848)	(0.464-0.892)
0.931	0.900
(0.517-1.345)	(0.428-1.372)

were studied between August and December 1992. Total and regional bone densities could be determined from the same DEXA scan. A 4-day calcium intake diary was completed, and evaluations of average daily calcium intake and the percent recommended daily allowance (RDA) of calcium intake were determined by a registered dietician. Pubertal status was determined by physical examination performed by one physician.

Group 3

Thirty children with moderate to moderate-severe asthma, 20 boys and 10 girls, ages 5 to 16, were studied from August to December 1992. All subjects with asthma had DEXA scans. Children with asthma met current National Heart, Lung, and Blood Institute guidelines for severity.[10] All were receiving daily medication, including inhaled corticosteroids, inhaled cromolyn sodium, or combinations of inhaled cromolyn and inhaled corticosteroids; several were dependent on oral corticosteroids (Table I). Because different inhaled corticosteroid preparations were used by the subjects, the actual total daily dose in micrograms for each inhaled product was calculated and also expressed as micrograms per kilogram, as well as total daily dose in micrograms. The total lifetime dose of inhaled corticosteroid was determined and expressed in milligrams. A 4-day calcium intake diary, identical to that for group 2, was completed. The physical examination, Tanner stage determination, and pulmonary function test were performed by one physician.

As stated previously, bone mass was measured before 1989 by dual-energy photon absorptiometry (DPA). Scans performed after 1989 used DEXA. A comparison of total bone density (TBD) measured by the two methods in our laboratory showed a linear correlation, with slopes differing by 2.7% (Fig. 1); thus, DPA results obtained before 1989 (16 subjects in group 1) were adjusted to be equivalent to the DEXA measurements.

Statistical analysis was performed with t tests, chi square analysis, multiple regression, and analysis of covariance.[16] A p value of 0.05 or less was considered significant. R^2 was determined by squaring the multiple R obtained by multiple regression. R^2 is also called coefficient of determination.

RESULTS

Comparison of groups 1 and 2

The normal children were divided into two groups, based on the dates of the bone mass determination (see Methods section), and a comparison of the two control groups was undertaken. Group 1 included 62 children (Table II), ages 5 to 18, studied from 1988 to 1991. Group 2 included 35 normal children (Table II), ages 6 to 16, studied in 1992 with DEXA.

According to multiple regression analysis, in group 1 height explained (R^2) 86% of the variance of TBD for boys and 76% for girls; in group 2 height explained 81% of TBD for boys and 71% for girls (Table II).

Analysis of covariance was performed to compare the TBD of the two control groups, with a separate analysis for each gender. The two control groups were not significantly different, based on a comparison of the slopes, elevation, or residual variances of the TBD (dependent variable) versus height or age (separate independent variables) regression lines for boys or girls. The control groups could therefore be combined for a comparison with the asthmatic groups.

Combined control groups

When a multiple regression analysis was applied to the group of 97 normal children (Table II), height explained 83% of the TBD variance for boys and 74% for girls. Age was considered a confounding variable for height, and a separate multiple regression analysis was performed with age as an independent variable (Table II). No other measure provided any additional significant contribution to variation in TBD, including Tanner stage or percent RDA of calcium.

The regional bone density data for the 97 normal subjects are included in Table III. Group 2 normal children had a 4-day calcium intake and

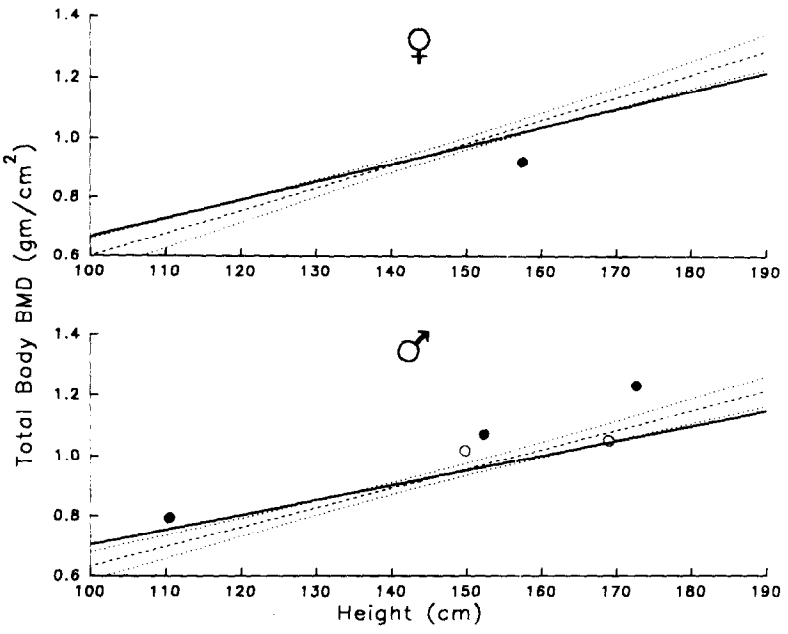

FIG. 2. Mean and 95% confidence limits *(dashed lines)* for normal boys and girls. The *solid line* represents the line of best fit for children with asthma receiving inhaled corticosteroids for height versus TBD. *Solid circles* represent oral and inhaled corticosteroids; *open circles* represent inhaled cromolyn sodium and are included as incidental data points.

Tanner stage determination. The results of this additional information are shown in Table IV.

Asthmatic groups

The demographic information on the 30 asthmatic children is shown in Table I. In the 28 children receiving inhaled corticosteroids, the mean total dose of inhaled corticosteroid was 606 μg/day with a range between 168 and 1200 μg/day. Most subjects were in Tanner stage 1 or 2. According to a chi square analysis, there was no difference in the Tanner stage distribution between group 2 normal subjects and children with asthma. A comparison of the total and regional bone density between children with asthma and group 2, and combined normal subjects is seen in Table III. Six children were receiving daily therapy of inhaled cromolyn (two) or oral steroids plus inhaled steroids. These six asthmatic children were not included in the covariance analysis.

Asthmatic children compared with control subjects

The mean and 95% confidence limits for height versus TBD for the 97 normal children are shown in Fig. 2, and age versus TBD is shown in Fig. 3. The individual total bone mass for the 24 children with asthma receiving inhaled steroids is plotted against the regression curve with 95% confidence limits for the control subjects. The analysis of covariance (comparison of regression lines) revealed no difference between normal boys and boys with asthma or between normal girls and girls with asthma in slope, elevation, or residual variances for the corresponding regression lines (Figs. 2 and 3).

Total and regional bone densities were compared between the 97 normal children and the children with asthma. There was no significant difference in the ages, as determined by *t* test analysis. There was no significant difference between the children with asthma and control subjects for any bone density measurement, for either boys or girls (Table III) as determined by *t* test analysis. It is important to mention that there is a large probability for committing a type II error. Use of the age range of 5 to 18 years increases the standard deviation of the measured bone mineral density. To reasonably exclude a type II error in comparing normal subjects with patients with asthma receiving inhaled steroids, with an α coefficient of 0.05 (two-tailed), a β coefficient of 0.2, and a power of 80% it would be necessary to study over 1000 male control and asthmatic subjects and at least 125 female control and asthmatic subjects.

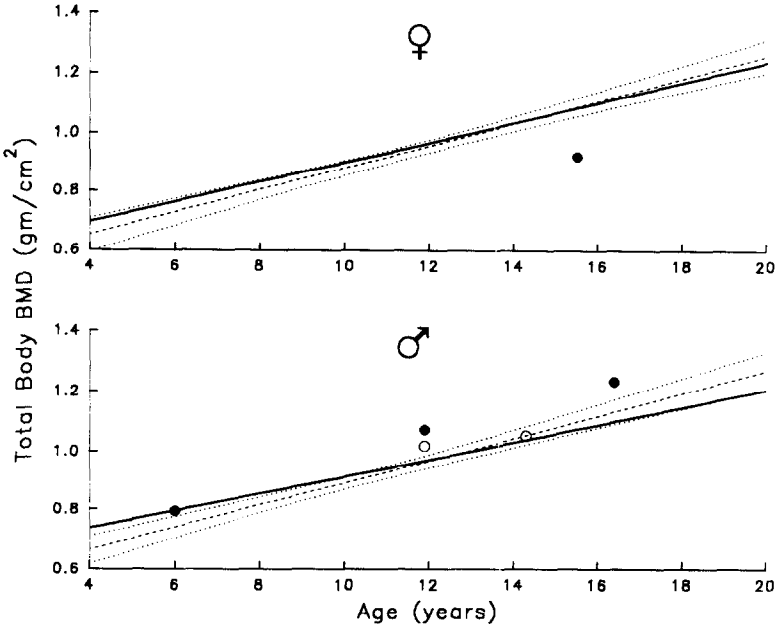

FIG. 3. Mean and 95% confidence limits *(dashed lines)* for normal boys and girls. The *solid line* represents the line of best fit for children with asthma receiving inhaled corticosteroids for age versus TBD. *Solid circles* represent oral and inhaled corticosteroids; *open circles* represent inhaled cromolyn sodium and are included as incidental data points.

Multiple regression was determined for the 30 children with asthma, with age and height used in separate analyses. Height explained 82% of variance in TBD for boys with asthma and 66% for girls with asthma. Age also significantly explained (R^2) the variance in TBD, and the results are shown in Table II. No measured independent variable, including daily (micrograms per kilogram per day), lifetime inhaled corticosteroid dose, calcium intake, percent predicted forced expiratory volume in 1 second, duration of asthma, or Tanner stage, was able to significantly explain the dependent variables of TBD or spine density in patients with asthma beyond what was identified by age or height (Table II).

DISCUSSION

Attainment of peak bone density is achieved by late adolescence or early adulthood.[1-3] Several factors contribute to the variability in bone density seen in adults including dietary calcium intake, exercise, age, height, and weight.[5] Genetic factors,[17, 18] menstrual irregularities,[19] and race[20, 21] have also been shown to influence peak bone density. Chronic diseases in childhood have been associated with low bone density.[6, 22, 23]

Asthma, a common chronic disease of childhood, has repeatedly been shown to affect growth. Children with asthma eventually reach a normal height parameter but have a delay in the prepubertal growth spurt and onset of puberty.[24-29]

Asthma has recently been viewed as an inflammatory disease.[30-32] Earlier and more routine use of corticosteroids has been stressed.[10-11, 33-34] Oral corticosteroids have known effects on bone and childhood growth.[12, 33] Inhaled corticosteroids have been proven to be beneficial in the treatment of asthma,[34, 35] and their effect on linear growth has shown conflicting results. High-dose inhaled budesonide has been shown to decrease linear growth rates.[36, 37] Other preliminary studies have shown that other preparations may not affect linear growth.[38, 39] Inhaled corticosteroids in adults have been shown to affect markers of bone growth.[40-42]

Sorva et al.[13] noted decreased serum osteocalcin levels in children with asthma treated with inhaled budesonide at a dose of 800 μg/m². Konig et al.[14] also found a reduction in serum osteocalcin, but it was reduced equally in all children with asthma, regardless of treatment, including administration of inhaled beclomethasone at doses up to 800 μg/day. Decreased osteocalcin levels were thought to be an effect of asthma rather than of specific treatment. The authors also measured bone mineral density in eight children with

asthma receiving beclomethasone and in eight asthmatic control subjects.[14] There was no significant difference in whole-body mineral density.

We elected to use densitometry, an accurate, precise, reproducible, and safe means of measuring bone mineral density, in children with moderate to moderate-severe asthma who were receiving long-term daily medications, including inhaled corticosteroids. The mean daily dose of inhaled corticosteroids was 606 μg/day (range, 168 to 1200 μg/day). Our results showed that children with moderate asthma of both sexes did not demonstrate lower bone mineral density compared with normal subjects, nor was their bone density influenced by use of inhaled corticosteroids. Our results support the results of Konig et al.,[14] who observed no significant difference in bone density in children with severe asthma compared with normal children. We included subjects receiving various preparations of inhaled corticosteroids, but the total daily dose was expressed as micrograms per kilogram per day in multiple regression analysis to equalize the effect of each product.

Four asthmatic subjects, one girl and three boys, included in the study were receiving alternate-day oral steroids. The girl was a postpubertal 15-year-old who had been taking 2.5 mg of prednisone every other day for 7 years and had an inhaled corticosteroid dose of 1000 μg/day. As might be expected, her TBD was significantly lower than the 95% confidence limits (Fig. 1). Surprisingly, the boys had TBDs above the 95% confidence intervals of normal subjects. They included a prepubertal 6-year-old taking 15 mg of prednisolone every other day for 5 years with an inhaled corticosteroid dose of 400 μg/day, and a RDA of calcium of 202%; an 11-year-old in Tanner stage 2 taking 10 mg of prednisone every other day for 8 months, an inhaled corticosteroid dose of 1200 μg/day, and a RDA of calcium of 136%; and, a 16-year-old, postpubertal boy taking 16 mg of methylprednisolone every other day for 7 years, with an inhaled corticosteroid dose of 600 μg/day and an RDA of calcium of 81%. We have no explanation for these findings. The evaluation of additional subjects receiving oral corticosteroids with precise assessment of weight-bearing exercise and calcium intakes would be valuable.

With the use of multiple regression analysis, the ability (R^2) of height (or age) to explain TBD (or spine density) in asthmatic subjects was consistently lower than in normal control subjects (Table II), although not significantly (Table III). This was not explained by a difference in mean height, age, or Tanner stage distribution. Although there was no significant difference in bone density between children with asthma and control subjects, it is possible that a substantially larger number of subjects would be necessary to definitively conclude that inhaled steroids do not influence bone density in the pediatric population. An alternative approach might be to undertake a longitudinal observation of developing bone density in asthmatic children with significant disease who receive continuous medical treatment. The observation of diminished serum osteocalcin levels in children with asthma[13, 14] could suggest the potential for diminished bone density in selected individuals with long-standing asthma.

The use of bone densitometry may allow detection of suboptimal bone density in selected children with asthma who might be at particular risk. Such children might include those receiving long-term high-dose inhaled steroids,[43] children with steroid-dependent asthma, especially if accompanied by low calcium intakes, or children with asthma and severe food allergies. A child who may be at risk for diminished bone density before entering adulthood could thus be identified, allowing for therapeutic interventions, such as calcium supplementation, which has been shown prospectively to positively affect bone density in prepubertal children.[44, 45]

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