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Bone Mineral Density in Children Treated With Daily or Periodical Inhaled Budesonide: The Helsinki Early Intervention Childhood Asthma Study

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ABSTRACT: In a double-blind, randomized study, 136 children, 5–10-y-old, with newly detected persistent asthma received budesonide (BUD) 400 μg twice daily for 1 mo and thereafter 200 μg twice daily for 5 mo. Thereafter, 50 children were treated with BUD 100 μg twice daily, whereas 44 children used BUD as needed for 1 y; an additional 42 children received disodium cromoglycate (DSCG). Asthma exacerbations were treated with BUD for 2 wk in a dose of 400 μg twice daily in all groups. In this secondary analysis, bone mineral density (BMD) of the lumbar vertebrae was measured before and after the 18-mo treatment. Compared with DSCG, regular BUD treatment resulted in a significantly smaller increase in BMD (0.023 *versus* 0.034 g/cm^2; $p = 0.023$) and height (7.75 *versus* 8.80 cm; $p = 0.001$). Periodic treatment did not affect BMD. No intergroup differences were observed when BMD data were adjusted for changes in height. Daily BUD treatment in prepubertal children may slow down the increment in BMD and standing height. This was not observed in children receiving BUD periodically after the initial regular BUD treatment. The correlation between height and BMD suggests that following children's height might afford an estimation of inhaled corticosteroid effects on bone. **(*Pediatr Res* 68: 169–173, 2010)**

Inhaled corticosteroids (ICS) are recommended first-line treatment for all patients with persistent asthma (1). Systemic exposure to corticosteroids can suppress bone formation and increase bone resorption resulting in loss of bone mass and risk of fractures (2). Also, in children, the use of oral steroids has been associated with a dose-dependent increase in fracture risk (3). Case-control studies, too, have identified an increased risk of fractures with high doses of ICS (4,5), particularly in elderly patients (6). Therefore, there has been some concern that the use of ICS as long-term asthma maintenance therapy in children could have a detrimental effect on bone mineral density (BMD) and risk of fractures.

A recent Cochrane systematic review found that low to moderate doses of ICS did not affect BMD or risk of fractures in adults (7). However, it is not possible to extrapolate findings from adults to children. Bone mass in children is also influenced by height, age, race, exercise, presence of chronic illnesses, and especially the stage of puberty (8).

The clinically most important outcome for the effects of ICS on bone is an increased risk of fractures. This is not easy to study, particularly, in children in randomized prospective trials. The use of biochemical markers is restricted to describe bone metabolism, but BMD has been used as a surrogate marker of an increased susceptibility to fractures. In this respect, BMD has some power to predict fractures (9). Therefore, prospective, randomized, long-term (>12 mo) controlled trials using clinically relevant doses of ICS with adjustment for confounders and with BMD as an endpoint seem to be the best way to assess the risk of clinically important adverse effects of ICS on the bone (8).

There are a few prospective, randomized, long-term (≥12 mo) controlled clinical trials assessing the effects of ICS on bone in children (10–13). Two cross-sectional database reviews have assessed fracture risk in children treated with ICS (14,15). Both groups concluded that ICS use does not increase the risk of fractures in children. However, the reviewed studies included both prepubertal and pubertal children up to the age of 17 y, which may have caused confounding results.

An observational study in asthmatic children receiving budesonide (BUD) for 3–6 y did not show differences in BMD compared with control children (16). A decade later, the same authors reported that treatment with BUD at a mean daily dose of 350 μg for a mean of 14 y (mean accumulated dose, 1775 mg; range, 227-8760 mg) did not adversely affect BMD in adulthood in these children with asthma (Pedersen S, Agertoft L 2009 Peak bone mineral density (BMD) in children with asthma treated for a mean of 14 y with inhaled budesonide. 2009 European Respiratory Society Congress, 12–16 September, 2009, Vienna, Austria, Abstract P1212). Pubertal development with its burst of anabolic steroids is considered a major biologic factor promoting bone formation.

We have previously reported the effects of continuous and periodical use of inhaled BUD on growth of prepubertal children

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Abbreviations: BMD, bone mineral density; **BMC,** bone mineral content; **BUD,** budesonide; **CV,** coefficient of variation; **DSCG,** disodium cromoglycate; **DXA,** dual energy x-ray absorptiometry; **ICS,** inhaled corticosteroid; **ICTP,** carboxyterminal telopeptide of type I procollagen; **PINP,** aminoterminal propeptide of type I procollagen; **SGA,** small for GA

with mild, persistent asthma (17). Continuous BUD was associated with fewer exacerbations and better asthma control. Standing height velocity was normalized during low-dose BUD treatment within 1 y of commencement of treatment. However, the height velocity increased more rapidly during periodical use of BUD than during the low-dose BUD treatment, suggesting catch-up of the initial loss in standing height.

As a secondary part of this same study, we here report results on BMD and markers of bone metabolism in relation to growth.

METHODS

Subjects. Children aged 5–10 y with newly detected mild asthma participated in a partly double-blind, randomized, parallel-group, single-center 18-mo study (17). Children with chronic diseases other than asthma that could influence the performance of the study or interpretation of study results were excluded. Children with a history of inhaled, nasal or oral corticosteroid use during the last 2 mo before the study were also excluded. The total cumulative doses of previously used ICS must not have exceeded 36 mg, 12 mg of nasal corticosteroids or oral doses equivalent to 200 mg of prednisolone. Children not in Tanner stage I at first visit and in stage >II at the end of the study as well as SGA children without a catch-up growth within 2 y of life were excluded in the BMD and growth analysis.

Study design and treatment. Children were randomized in balanced blocks into three treatment groups, two double-blind arms, and one open-treatment arm: 1) continuous budesonide (BUD/BUD, 400 μg twice daily for 1 mo, 200 μg twice daily for 2–6 mo, 100 μg twice daily for 7–18 mo; 2) budesonide/placebo (BUD/PLA), identical treatment as in Group 1 during months 1–6, but thereafter placebo for 7–18 mo; and 3) disodium cromoglycate (DSCG) 10 mg three times daily for 1–18 mo. The two BUD treatments were double-blinded in administration; DSCG was given by open label. BUD was administered *via* the dry powder inhaler, Turbuhaler, and DSCG *via* a pressurized metered dose inhaler. Exacerbations in all three groups were treated with BUD 400 μg twice daily for 2-wk period. This means that children in the BUD/PLA group received only periodic treatment with BUD during months 7–18 in case of an asthma worsening. Children with frequent exacerbations (frequent defined as a time interval of ≤2 mo between two exacerbations) could in addition receive oral theophylline (Theo-Dur, AstraZeneca, Södertälje, Sweden) for 6 wk in a daily dose of 10–15 mg/kg body weight. If this additional therapy was insufficient, the children received treatment with oral prednisolone and were excluded from the study.

Assessments. Each morning and evening throughout the study, the children measured their peak expiratory flow (PEF) and the peak inspiratory flow through the inhaler using a portable data storage spirometer (Vitalograph Ltd, Buckingham, UK) (17). Thereby adherence to twice daily treatment could be recorded.

At baseline and after treatment for 18 mo, the patients had measurement of BMD. Height was recorded before treatment and thereafter every third month with a stadiometer (Holtain Ltd, Crymych, UK) following a standardized procedure. The median value of three measurements was recorded. Tanner stage (sexual maturation) was scored at enrolment and at the end of the study.

BMD was assessed by dual energy x-ray absorptiometry (DXA), in lumbar vertebrae 1–4 using Hologic QDR 1000 densitometer (Hologic Inc., Waltham, MA) (18). Only one radiologist performed and analyzed all DXA measurements. A single device at the University Central Hospital of Helsinki was used. Quality control was maintained by daily scanning of an anthropomorphic spine phantom. The coefficient of variation (CV) for the DXA technique in adults has been reported to be 0.9% for lumbar spine (19). In children, the CV was not determined, because it was considered unethical to repeatedly expose them to x-rays. The unit contains a bottom-mounted x-ray source that releases a tightly collimated photon beam of altering energy (70 and 140 keV) that passes sequentially from the source through an internal reference standard and through the patient to a detector. Children were scanned in supine position during 5–8 min including 2–4 min of radiation time. Projected area (cm^2) and bone mineral content (BMC, *i.e.* grams of hydroxyapatite) were measured for vertebrae L-1 through L-4. The BMC value was divided by the surface area for each vertebra giving its BMD [grams per square centimeter (g/cm^2)]. The mean value of the four vertebrae gave the BMD of each child. BMD was also expressed as *Z*-scores.

At baseline and after treatment for 6, 12, and 18 mo, blood and urine samples were collected for determination of markers of bone formation and degradation, *i.e.* serum osteocalcin (20) and aminoterminal propeptide of type I procollagen (PINP) (21) as markers of bone formation and carboxyterminal telopeptide of type I procollagen (ICTP) (22) and urinary deoxypyridinoline (23) as markers of bone resorption. The urinary result was corrected by dividing deoxypyridinoline (nmol/L) with creatinine concentration (mmol) of the sample and expressed as U-deoxypyridinoline/creatinine. The intra and interassay CVs were 4.5–6.2% and 4.1–8.9% for serum osteocalcin, 2.4–3.5% and 2.7–6.7% for serum PINP, 3.8–7.3% and 2.5–8.0% for serum ICTP, and 1.4–5.3% and 7.3–14.2% for urinary deoxypyridinoline (24).

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) and was approved by the local Ethics Committee. Written informed consent was obtained from each patient's parent(s) or legal guardian and from the patient.

Statistical analysis. The sample size was determined by power calculations for morning PEF rates (17). The changes in BMD and height from baseline to end of treatment were compared between the three treatment regimens with an additive ANOVA model with fixed factors treatment and sex and using baseline as a covariate. Clinical chemistry and urine variables were compared between treatments using a similar but multiplicative ANOVA model, *i.e.* data were log transformed before analysis. The ratio of changes in BMD over changes in height was compared between treatments with an additive ANOVA model with fixed factors treatment and sex. Here, the changes are expressed as changes per cm grown.

Comparisons for months 1–6 were made between the combined BUD groups and the DSCG group; comparisons at 12 and 18 mo were made between the three groups. All tests were two-sided, and p values <0.05 were considered statistically significant.

RESULTS

Patient demographics. The baseline characteristics of the study population are shown in Table 1. Based on symptoms and lung function tests, the majority of the patients had mild persistent asthma (1). Only a few children had used ICS earlier in life and nobody during the 2-mo period preceding study entry.

Performance of the study. Figure 1 shows the flow of the patients during the study. A total of 178 children were randomized and 176 received allocated treatment. Of these, 142 had BMD measurements before and after the study. Patients withdrawn from the study (Fig. 1) did not have BMD measurements at the time of withdrawal. The primary analysis of growth and bone used this completer population not fulfilling some prespecified exclusion criteria; *i.e.* children with a birth length less than −2 SD and with no catch-up within the first 2 years, children with Tanner stage II at entry or Tanner stage III at the last visit. Six such children were excluded, two in each treatment group. Two additional children had one missing value each on BMD. The analysis population thus consisted of 136 children. Table 2 shows the mean doses of BUD used in the three treatment groups. A total of 364 exacerbations in 133 children were treated with 2-wk courses of BUD: 81 in the BUD/BUD group, 121 in the BUD/PLA group, and 162 in the DSCG group. Three exacerbations in three children

Table 1. *Baseline characteristics of the patients*

Treatment group	Continuous budesonide	Budesonide/ placebo (periodic budesonide)	Disodium cromoglycate
No. of patients	50	44	42
Age (yrs)	6.9 (5–10)	6.7 (5–9)	7.0 (5–10)
Male (%)	60	66	50
BMD (g/cm^2)	0.62 (0.50–0.77)	0.61 (0.53–0.74)	0.61 (0.45–0.76)
BMC (g)	19.4 (12–33)	18.3 (13–26)	19.0 (10–32)
Bone area (cm^2)	31 (22–47)	30 (22–41)	31 (20–45)
Height (cm)	129 (110–158)	125 (106–143)	127 (107–147)
Weight (kg)	29 (19–51)	27 (17–49)	28 (16–52)

Values are means with range in parentheses, unless otherwise stated.

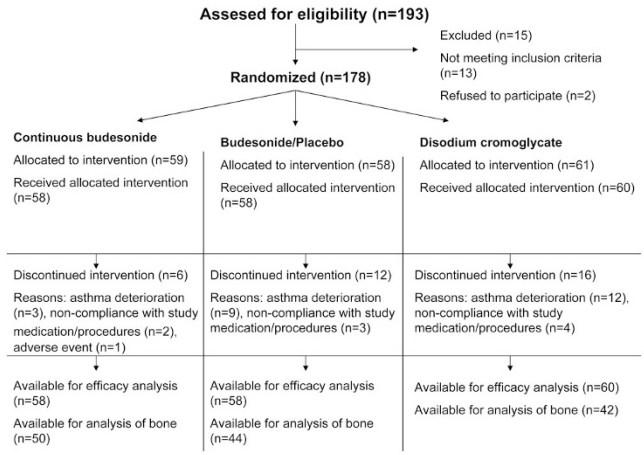

Figure 1. Flow chart of the patients.

Table 2. *Mean daily doses of budesonide, μg/day (range), during the study*

Period	Continuous budesonide	Budesonide/ placebo	Disodium cromoglycate
0- to 6-mo period	468.5 (454.2–800.0)	468.5 (454.2–800.0)	63.3 (0.0–417.6)
7- to 18-mo period	223.4 (200.0–423.8)	32.6 (0.0–487.0)	62.6 (0.0–288.9)

had to be treated with oral steroids, and these children were withdrawn from the study. Adherence to treatment, based on the data storage spirometer results, was ~90% in the beginning of the study but decreased to a level of ~60% by the end of the study.

Bone mineral density. The results of the statistical analysis of changes in BMD given both as g/cm^2 and as *Z*-scores are shown in Table 3. A statistically significantly larger increase in BMD was found for both parameters in the DSCG than in the BUD/BUD group. The increase in BMD was intermediate in the BUD/PLA group. Calculated as grams per square meter, the mean increment in BMD was 3.7% in the BUD/BUD group, 4.8% in the BUD/PLA group, and 5.5% in the DSCG group. The mean increments in BMC were 14.4, 14.9, and 16.2% (no significant differences between the groups) and 10.4, 9.4, and 10.3% in bone area (no significant differences between the groups) in the respective treatment groups.

After treatment for 6 mo, there was a statistically significant difference in changes in height between BUD-treated (combined group) and DSCG-treated children. After 12 and 18 mo, there were significant differences between all three groups when compared two by two.

At baseline, there was a statistically significant correlation between BMD and height ($n = 175$; $r = 0.325$; $p < 0.001$). There was also a statistically significant correlation between BMD and height for the 136 BUD-treated patients during the study ($r = 0.333$; 95% CI 0.173–0.475; $p < 0.001$). The increase in BMD adjusted for the increase in height showed no significant differences between the groups (Table 4). This suggests that the differences in change in BMD could be explained by the change in growth. Numerically the ratio (slope) was smallest in the BUD/BUD group. No significant differences in body mass index were observed between treatment groups at any time point. The results of the clinical chemistry measurements are shown in Figure 2. Statistically significant differences between the combined BUD group and the DSCG group were seen on all four parameters after the 6-mo treatment. No statistically significant differences were found at the end of the study except between BUD/BUD and DSCG on serum ICTP ($p = 0.036$; Fig. 2).

DISCUSSION

This study reporting BMD in children with asthma is part of a previously reported, double-blind, randomized, 18-mo study that compared regular and periodical BUD treatment strategies (18). Regular use of high-dose BUD followed by low dose afforded better asthma control and fewer exacerbations than periodic use of BUD given only at times of exacerbations. Standing height velocity was normalized during low-dose BUD treatment. The height velocity increased, however, more rapidly during periodical use of BUD than during the low-dose BUD treatment, suggesting catch-up of the initial loss in standing height (17). The effects we report on BMD in this secondary analysis are the result of BUD treatment because only three patients required oral steroids for exacerbations. Consequently, in this study, use of oral steroids cannot have influenced the BMD results of children with worsening asthma. A limitation of our study is, however, that it only lasted for 18 mo. In a long-term study, the number of exacerbation requiring high-dose BUD might have increased. The main reason for not prolonging the study period was to avoid any influence of puberty on BMD and height.

During the study, BMD increased in all treatment groups. However, the regular use of budesonide (BUD/BUD) resulted at the end of the study in a statistically significantly smaller increment in BMD than DSCG calculated as g/cm^2 and *Z*-score. The increase in BMD (g/cm^2) in the group receiving periodical BUD after the first 6 mo (BUD/PLA group) was not statistically different from the other two groups. The incre-

Table 3. *The changes in lumbar bone mineral density during 18 months shown as g/cm^2 and Z-scores in children in the three treatment groups*

		ΔBMD (g/cm^2)			ΔZ-score		
Treatment comparisons	*N*	Δ	95% CI	*p*	Δ	95% CI	*p*
BUD/BUD	50	0.023	0.017, 0.029		−0.29	−0.38, −0.20	
BUD/PLA	44	0.029	0.022, 0.036		−0.16	−0.26, −0.06	
DSCG	42	0.034	0.027, 0.041		−0.13	−0.23, −0.04	
B/BUD–B/PLA		−0.006	−0.015, 0.003	0.200	−0.13	−0.26, 0.00	0.052
B/BUD–DSCG		−0.011	−0.020, −0.002	0.022	−0.16	−0.29, −0.02	0.021
B/PLA–DSCG		−0.005	−0.014, 0.005	0.319	−0.03	−0.17, 0.11	0.700

Table 4. *The increment in height and in BMD adjusted by the increment in height*

Treatment comparisons	*N*	ΔHeight (cm)			ΔBMD/ΔHeight (1000g/cm^3)		
		Δ	95% CI	*P*	Δ	95% CI	*p*
BUD/BUD	50	7.75	7.34, 8.17		2.99	2.25, 3.73	
BUD/PLA	44	8.18	7.73, 8.63		3.59	2.80, 4.39	
DSCG	42	8.80	8.35, 9.25		3.75	2.95, 4.55	
B/BUD–B/PLA		−0.42	−1.03, 0.18	0.170	−0.60	−1.68, 0.47	0.271
B/BUD–DSCG		−1.05	−1.66, −0.44	0.001	−0.76	−1.85, 0.33	0.172
B/PLA–DSCG		−0.63	−1.26, 0.01	0.053	−0.16	−1.29, 0.97	0.784

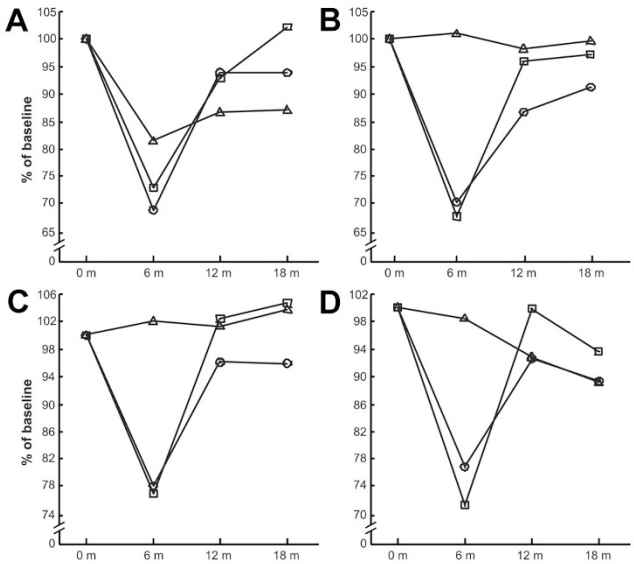

Figure 2. Changes in serum osteocalcin (*A*), serum PIPN (*B*), serum ICTP (*C*), and urinary deoxypridinoline (*D*) in three treatment groups, ○, BUD/BUD; □, BUD/placebo; and △, DSCG. Statistically significant differences between the combined BUD group and the DSCG group were seen on all four parameters after the 6-mo treatment.

ments in mean BMC resemble the changes in BMD between the groups although these changes were not statistically significant. Instead, the increments in mean bone areas were on the same level between the groups suggesting that BMC might be the driver of the differences in BMD. When corrected for growth data, the differences in BMD data disappeared. Children discontinuing the study prematurely did not have BMD measurements when withdrawn from the study.

After high-to-moderate dose BUD treatment for 6 mo, all four markers of bone metabolism were significantly reduced compared with the DSCG group. At the end of the study, when BUD had been administered in a low dose or periodically, no significant differences were observed between the groups in bone formation markers; serum PINP and osteocalcin. ICTP, the serum marker of bone resorption, was slightly lower in children receiving BUD regularly compared with the DSCG group. However, no significant differences were observed in urine deoxypyridinoline, another marker of bone resorption. Therefore, this finding of decreased ICTP remains unclear. These findings in markers of bone metabolism describe the actual bone turnover after the 18-mo treatment and not the net results in BMD and standing height. The rapid increase in the levels of bone markers during the periodic and regular low-dose BUD suggests a tendency toward normal age dependent bone metabolism.

The nonsignificant ICS effect on BMD in our study when corrected for growth data are in accordance with a previous report in 49 children treated with beclomethasone dipropionate or DSCG for 7 mo in an open, nonrandomized study (25). When BMD was adjusted for body size, bone mass was found not to have changed after either treatment within or between the groups. It thus appears that following height velocity of children with asthma treated with ICS is good enough for following the risk for adverse effects during long-term treatment with ICS. As previously shown, BUD had a dose-dependent effect on linear growth in the study (17).

The Childhood Asthma Management Program (CAMP) comparing the effects of BUD 400 μg/d with nedocromil 16 mg/d over 4–6 y in 5–12-y-old children (n = 1041) did not find a difference in BMD between the groups (13). A cross-sectional analysis of baseline data in the CAMP study found no significant effect of previous ICS use on BMD (26). The analysis of the CAMP data (13) was, however, an intention-to-treat analysis that would not have identified outliers with low rates of bone accretion. Some children also reached puberty during the study. The CAMP protocol also allowed use of prednisone bursts for exacerbations and introduction of open label ICS for worsening asthma. Multiple oral steroid bursts were found to produce a dose-dependent reduction in BMC and increased risk for osteopenia. ICS use had the potential for reducing bone mineral accretion in boys progressing through puberty, but this risk was considered to be outweighed by the ability to reduce the amount of oral steroids used in these children (27).

To the best of our knowledge, this study is the second long-term randomized, double-blind study evaluating the effects of high-dose ICS, followed by low-dose ICS in prepubertal children. The results in this study could further be compared with periodical ICS therapy and nonsteroidal therapy (DSCG). Our study protocol therefore differs in several aspects from that of the first long-term study reported by Visser *et al.* (12). They did not found differences in BMD between the two fluticasone propionate regimens but no comparison with healthy controls or asthmatic children not receiving ICS therapy were included. The results are therefore difficult to compare.

Markers of both bone formation and bone resorption can be easily measured and several studies have evaluated the influence of ICS on them (4–7,15,26–28). Overall, the results have been reassuring indicating minimal effects of ICS. Doses of ICS

producing good asthma control in the majority of patients have not been associated with detectable effects on these markers (29) whereas subtle changes have sometimes been reported with high dose ICS. As an example, Boot *et al.* (30) did not find differences in mean osteocalcin, PICP, and ICTP levels between asthmatic children treated with ICS and controls. In contrast, Akil *et al.* (28) found a significant decrease in osteocalcin and increase in ICTP levels compared with pretreatment values in a study in 22 asthmatic children. Also, in the study comparing high-dose with low-dose fluticasone propionate, significant initial reductions in osteocalcin and PINP levels were noticed without a difference in effect on BMD (12). In our study, high-dose BUD for 6 mo resulted in a clear decrease in both markers of bone formation and degradation. The changes were much larger than the intra and interassay CVs. During subsequent low-dose treatment, all mean values, except ICTP, returned to baseline. Complete normalization occurred in the group receiving periodic treatment with BUD. In simple terms, an elevation of all markers could occur when there is increased bone turnover without net loss or gain in bone mass, whereas a reduction of all markers, which is normally seen with low doses of oral corticosteroids or high doses of ICS, could signify a reduction in bone turnover leading to a reduction of the age-dependent increase in BMD and standing height. It is also clinically more relevant to consider the net effect of bone formation and bone resorption (31). When markers of formation and resorption, as in our study, decrease to the same extent, a real bone loss may possibly not occur.

Our findings suggest that inhaled BUD may induce a slight but statistically significant decrease in BMD in prepubertal children with asthma. This effect seems to be linked to the 6-mo initial treatment with high to moderate doses of BUD. The effect was, however, still measurable after 1 y of treatment with low-dose BUD. As a correlation exists, although not applicable on an individual level, between BMD and risk of fractures, we believe that our findings related to BMD are of clinical importance. The observed decrease in height velocity was in line with the changes in BMD. Between periodic BUD and DSCG treatments, no significant differences in decrease were observed, neither for BMD nor for standing height. The correlation between height and BMD suggests that following children's height might afford an estimation of ICS effects on bone. A clinically important observation is that treatment with ICS should always aim at the lowest effective dose that keeps the patient in good asthma control, thereby the risk of adverse events is minimized.

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