Allergol Immunopathol (Madr). 2013;41(2):102–107

Allergologia et immunopathologia

www.elsevier.es/ai

ORIGINAL ARTICLE

# Bone mineral density and associated parameters in pre-pubertal children with asthma treated with long-term fluticasone propionate

E. Ozkaya[a,*], E. Çakır[b], S. Uzuner[c], U. Erenberk[c], M.R. Dundaröz[c]

[a] Department of Pediatrics, Division of Pediatric Allergy, Bezmialem Vakif University, Istanbul, Turkey
[b] Department of Pediatrics, Division of Pediatric Pulmonology, Bezmialem Vakif University, Istanbul, Turkey
[c] Department of Pediatrics, Bezmialem Vakif University, Istanbul, Turkey

Received 11 October 2011; accepted 3 December 2011
Available online 8 March 2012

**KEYWORDS**
Asthma;
Bone mineral density;
Children;
Fluticasone propionate

**Abstract**
*Aims:* The primary aim of the objective of the study was to determine the effects of long-term treatment with the recommended dose of inhaled fluticasone propionate spray usage on bone mineral status in children with asthma.
*Methods:* This cross-sectional, case–control study was of 270 pre-pubertal children with asthma, who had used inhaled fluticasone propionate at a mean daily dose of 200 μg (range: 200–350 μg) for at least 5 years. The bone mineral density (BMD) of the lumbar spine was measured by dual-energy X-ray absorptiometry (DEXA). The results were compared to untreated controls ($n = 200$), who were newly diagnosed children with asthma without any corticosteroid treatment.
*Results:* The 270 study patients (175 males) were aged between 6 and 13 years. The average age (±SEM) was $9.2 \pm 0.6$ years, and the mean (±SEM) steroid dosage used was $183.3 \pm 57.0$ μg daily, with $236.5 \pm 17.2$ g total steroid use during treatment. Between the study and the control groups, no significant difference was observed in BMD ($p > 0.05$).
*Conclusion:* The findings suggest that long-term periodical treatment for 5 years with inhaled fluticasone propionate, 100 μg twice daily, in children with asthma revealed no negative effect on bone mineral density by using DEXA.


## Introduction

Asthma is the most common chronic childhood disease and has shown an apparent increase in recent years.[1] Asthma prevalence, although still high, has stabilised or even decreased in certain western high-prevalence regions.[2,3] National Guidelines (USA), recommend that adults and

* Corresponding author.
*E-mail address:* minozkaya@yahoo.com (E. Ozkaya).
*URL:* http://www.bezmialem.edu.tr (E. Ozkaya).

0301-0546/$ – see front matter © 2011 SEICAP. Published by Elsevier España, S.L. All rights reserved.
doi:10.1016/j.aller.2011.12.007

children with asthma receive daily inhaled corticosteroids (ICS) as first-line treatment.[2,3] The systemic bioavailability of inhaled corticosteroids is determined by the amount of drug delivered and subsequently absorbed by the lungs and the amount of drug absorbed from the gastrointestinal tract.[4] In contrast to intranasal steroids, with ICS there is a high degree of deposition in the oropharynx, nasal cavity, followed by mucociliary clearance to the throat and, eventually, to the gastrointestinal tract, and absorption from the mucosal surface can contribute up to 50% systemic bioavailability of the ICS.[5] The low frequency of side effects observed after long-term use of ICS is suggestive of the well-established safety of ICS, however, there should be careful monitoring of systemic side effects of ICS, especially in patients undergoing long-term or life-time treatment, such as treatment in children with asthma.[6] Glucocorticoid-induced osteoporosis or reduced bone mineral density (BMD) has been reported with low-dose (5–10 mg/d) orally or with high-dose inhaled corticosteroids[7]; the number of studies concerning the effects of inhaled fluticasone propionate (FP) on the mineral status of bone is limited and results are also conflicting.[8,9] Although large studies have reported that there was no substantial risk of ICS on bone metabolism in children with asthma,[10–12] there are no new data available for the long-term intermittent use FP administration and its effects on bone metabolism in the children. This study assessed the BMD and the associated parameters in children with asthma treated for at least 5 years with intermittent inhaled corticosteroid FP, and compared the findings with those of children with asthma who had never received treatment with corticosteroids. The following questions will be addressed by our study: are children with asthma using FP at decreased BMD and adverse effect on associate parameters and if so, how large is the risk compared with subjects not using this drug? Does the risk vary according to the dose or duration of FP use?

## Subjects and methods

### Study design

We conducted a prospective case control study among 270 children diagnosed with mild-to-moderate asthma from the authors' Pediatric Allergy-Pulmonology outpatient clinic who were enrolled consecutively between May 2010 and December 2011. The diagnosis and severity of asthma were defined according to American Thoracic Society (ATS),[13] guidelines. Children were defined as asthmatic according to the following criteria: (a) recurrent episodes of at least one symptom of asthma, including cough, wheezing, breathlessness, and chest tightness; (b) an improvement of at least 12% in baseline forced expiratory volume in one second (FEV 1) after bronchodilator use; (c) a total serum IgE level of over 52 IU/ml determined by direct chemiluminescence, and a positive skin test for at least one allergen. Informed consent was given by the family of the patients.

### Study population

A total of 320 children who had received periodical inhaled FP for $\geq$5 years were included in the present study to investigate BMD and associated parameters. 270 patients gave informed consent after the explanation of the study. Subjects who had received periodical inhaled FP with a documented diagnosis for asthma for $\geq$5 years, as defined by ATS, were included in the present study investigating bone mineral status and associated parameters. The children had been seen at our out-patient Pediatric Allergy-Pulmonology clinic at least every 3–4 months for 5 years at the time of the present study. The following recordings were always made at each visit; number of hospital admissions due to acute asthma during the previous 3 months; age; height; weight; use of concurrent medicine; dose of inhaled FP; and inhalation device. Between clinic visits, changes in FP or other allergic medications were always made under the supervision of the clinic so that transient changes in treatment during periods of increased asthma symptoms were recorded. Furthermore, adjustments of the dose of inhaled FP were made based upon the assessment of clinical control of the disease in order to treat the child with the minimal effective dose. These recording made it possible to accurately calculate the average dose of exogenous corticosteroid during the previous 5 years and the accumulated dose of FP. Compliance with the asthma medication was checked at each visit by asking the child and family about their compliance and by checking inhalation skills and medication level. Finally, the child was given an inhaler at the clinic whenever the inhaler strength was changed. In such situations, the child was asked to return to clinic for another visit 2–3 months later and to bring the inhaler at that visit. These measures allowed an assessment of compliance by measuring the number of doses taken (weighing canister (pressurised metered dose inhaler (pMDI); Flixotide inhaler® 50 μg, or 125 μg, pMDI, GlaxoSmithKline, UK)) or by counting the number of doses left (Flixotide Diskus® 100 μg or 250 μg, GlaxoSmithKline, UK) in relation to the prescribed dose. We identified all prescriptions for FP that had been filled by cases in the last 5 years before and studied the risk of current extra exposure to FP. To investigate the exposure to FP according to dose, we calculate the average daily dose of FP by dividing the total quantity (in micrograms) by the days of supply for that prescription. Participants had not received specific immunotherapy, and none of them had allergic rhinitis requiring chronic use of nasal or systemic corticosteroids, but even those having allergic rhinitis symptoms were included to the study.

We have included 200 newly diagnosed children with mild to moderate asthma to the control group in order to obtain a sufficient number of patients for comparison. None of these newly diagnosed children had ever received oral, inhaled or nasal corticosteroids for >2 weeks.

Age, sex, body height and weight, body mass index (BMI), family history of atopy, skin test and Tanner stage results were recorded for all study group participants. To avoid the confounding influence of some covariates, the following exclusion criteria were used in the present study: patients who have a Tanner stage level $\geq$II, >14 days treatment with systemic corticosteroids ever (both groups of children), topical corticosteroids ever applied to 25% of the body surface (both groups), additional non-atopic systemic disease (e.g., disorders of calcium metabolism, spine demineralisation, osteoarthritis, metabolic bone disease, anorexia, or obesity,) or injuries of the spine with risk of bone density loss

(e.g., prior fracture/immobilisation), and chronically using some supplements (e.g., anticonvulsants, non-dietary vitamin D, ketaconazole, hormone replacement therapy).

### Measures

BMD (g/cm$^2$) was measured using dual-energy X-ray absorptiometry (DEXA) (GE Lunar DPX Duo Bone Densitometer, Absolute Medical Equipment, Inc, Monsey, NY, USA). The densitometer was calibrated daily 30 min after turning the apparatus on. Quality control was performed using calibration standard and QC phantom. BMD scans of the AP lumbar spine/paediatric ($L_1$–$L_4$) vertebra were analysed using the World Health Organization criteria for bone mass,[14] and the International Society for Clinical Densitometry.[15] *Z* scores were calculated using the reference population provided by the manufacturer.

Morning venous blood samples were taken to assess osteocalcin, alkaline phosphatase (ALP), calcium, phosphorus, and cortisol levels. ALP, calcium, and phosphorus were analysed spectrophotometrically by a Mega Automatic analyser (Merck, Tempe, AZ, USA). Osteocalcin, intact parathyroid hormone (PTH), and cortisol samples were analysed using an Immulite chemoluminescence immunassay (Diagnostic Products Corp., Inc., LA, CA, USA).

### Ethical approval

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice and was approved by the local Ethics Committee.

### Statistical analysis

The sample size was determined by power calculation. Power analysis was conducted using the post hoc test (LSD) test. Power of the study was calculated as 0.45. SPSS program (v11.5, SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Signal intensities are given in arbitrary units with mean, standard deviation (SD), or standard error of the mean (SEM). General characteristics were analysed by an independent sample *t*-test or a Mann–Whitney test depending on the data and by Pearson chi-square test for categorical data. To investigate the relative importance of the variables associated with bone metabolism in relation to dependent factors and in cases of any confounding between them, they were fitted together using a multivariate linear regression model to control confounding factors and to determine which characteristics were independent of the total steroid dose of the children with asthma. A *p* value less than 0.05 or OR with a 95% confidence interval (CI) that did not include 1.00 was considered statistically significant.

## Results

A total of 470 children were studied: 270 in the FP group and 200 in the control group. The patients' characteristics are shown in Table 1. The ages of the 270 study patients (175 males) were between 7 and 10 (±SEM) 9.2 ± 0.6 years. The average (±SEM) follow-up time was 62.67 ± 9.86 months (range: 46–76 months). The mean total accumulated dose of FP for children in the study group 183.3 ± 57 μg daily, with 236.5 ± 17.2 g total steroid and the mean (±SEM) FP dose used was 183.3 ± 57.0 μg daily. All patients had positive skin test results for at least one allergy (Table 1).

The ages of the 200 control patients (115 males) were between 6 and 10 years. The average (±SEM) age was 8.8 ± 0.5 years, height was 133.4 ± 3.2 cm, and weight was 30.8 ± 1.4 kg. All patients had positive skin test results. The two groups were comparable with respect to age, height, and weight. The proportion of males was somewhat higher, and the mean duration of asthma at the time of the study was significantly longer in the FP group than in the control group.

### BMD parameters and fluticasone treatment

Although we found lower levels for mean basal serum cortisol and osteocalcin and higher levels for phosphorus, ALP, and PTH in the study group, there were no statistically significant differences between the two groups for these parameters ($p > 0.05$). The *Z* scores and the BMD results of the two groups were also similar ($p > 0.05$) and comparable with the control group ($p > 0.05$, Table 2). Additionally,

**Table 1** Patient characteristics of the study and control groups of children with asthma.

| | Fluticasone group | Control group | *p* value |
|---|---|---|---|
| Number of patients | 270 | 200 | |
| Age, mean (yrs) | 9.2 ± 0.6 | 8.8 ± 0.5 | 0.420 |
| Male (%) | 175 (64) | 115 (61) | 0.550 |
| Height, mean (cm) | 135.0 ± 3.8 | 133.4 ± 3.2 | 0.430 |
| Weight, mean (kg) | 30.4 ± 1.2 | 30.8 ± 1.4 | 0.160 |
| Skin prick test positivity to at least one allergen, no. of patients | 270 | 200 | |
| IgE (kU/l) | 418.7 ± 34 | 455.6 ± 41.5 | 0.234 |
| Symptoms duration, mean (yrs) | 6.5 ± 0.7 | 2.2 ± 0.4 | 0.19 |
| BMI (kg/m$^2$) | 14.52 ± 3.02 | 15.33 ± 2.10 | 0.460 |
| FEV1 (% predicted) | 88.50 ± 16.20 | 82.55 ± 17.30 | 0.260 |

BM: body mass index
Values are given as mean ± standard error of the mean.

**Table 2** Comparison of some bone metabolism associated parameters between two groups.

| Parameters | Fluticasone group ($N = 270$) | Control group ($N = 200$) | $p$ value |
|---|---|---|---|
| *BMD ($g/cm^2$)* | $0.76 \pm 0.72$ | $0.60 \pm 0.50$ | 0.35 |
| *Z score (no.of patients, %)* | | | |
| >−1.0 | 195 (72) | 120 (71) | 0.31 |
| −1> Z <2.0 | 65 (24) | 45 (26) | |
| >2 | 10 (4) | 6 (3) | |
| *Calcium (mg/dl)* | $9.02 \pm 0.4$ | $9.5 \pm 0.30$ | 0.19 |
| *Phosphorus (mg/dl)* | $4.2 \pm 0.8$ | $4.9 \pm 0.3$ | 0.68 |
| *ALP (IU/l)* | $410 \pm 211.5$ | $390.4 \pm 188.7$ | 0.38 |
| *PTH (pg/ml)* | $19.9 \pm 0.5$ | $18.2 \pm 0.3$ | 0.63 |
| *Osteocalcin (ng/ml)* | $76.6 \pm 21.8$ | $80.5 \pm 27.5$ | 0.75 |
| *Cortisol ($\mu g/dl$)* | $9.2 \pm 1.64$ | $9.8 \pm 1.90$ | 0.60 |

BMD: bone mineral density; ALP: alkaline phosphatase; PTH: parathyroid hormone.
Values are given as mean ± standard error of the mean.

the authors assessed the body height, weight, and BMI-associated standard deviation scores separately for the two groups. Although lower scores for all parameters were found in FP-treated children, none of the comparisons reached statistical significance (Table 1). Finally, a possible association of the BMD results and FP treatment was analysed. There was no correlation between the BMD scores and associated parameters and the accumulated or current dose of FP (Table 3). The number of times per week that the children participated in sports activities was the same in both groups (1.25 fluticasone, and 1.40 control), respectively.

## Discussion

The assessment of possible systemic side effects of long-term inhaled corticosteroid treatment is a central issue in paediatrics, as corticosteroids are prescribed to more patients with asthma and for longer periods of time than ever before.[16] Currently available ICSs, beclamethasone dipropionate (BDP), budesonide (BUD), flunisolide (FLU), FP, mometosone furoate (MF), and ciclesonide (CIC) differ from each other in terms of their systemic absorption, volume of distribution, half-life, and the extent of systemic bioavailability.[4,5] The systemic bioavailability of the inhaled corticosteroids is determined by the amount of the drug delivered and subsequently absorbed by the lungs and the amount of drug absorbed from the gastrointestinal tract.

**Table 3** Estimates of total steroid dose effect of variables associated with bone metabolism status of the children with asthma through logistic regression ($N = 270$).

| | OR | 95% CI |
|---|---|---|
| BMD | 1.2 | 0.40–3.20 |
| ALP | 0.9 | 0.50–1.80 |
| PTH | 1.3 | 0.91–2.81 |
| Osteocalcin | 1.6 | 0.95–3.82 |
| Cortisol | 0.8 | 0.70–2.76 |

BMD: bone mineral density; ALP: alkaline phosphatase; PTH: parathyroid hormone; CI: confidence interval.

A meta-analysis of comparative clinical trials demonstrated half dose of FP (as compared to BUD and BDP) was numerically superior in four of them when compared with BUD and BDP. Therefore, despite the difficulties with standardisation, the trials suggest that when using pMDI, FP is more effective than BDP and BUD.[17] Studies using oral dosing of labelled and unlabelled drug have demonstrated that the oral systemic bioavailability of FP is negligible (<1%), primarily due to incomplete absorption and pre-systemic metabolism in the gut and liver; the systemic availability of FP will equal lung deposition.[18] In contrast, the majority of the FP delivered is systemically absorbed. FP is said not to be metabolised locally in the lung. The drug is cleared rapidly by liver metabolism, with a total blood clearance equivalent to hepatic blood flow. Therefore, the fraction of drug inhaled contributes substantially to the systemic availability.[19] Lower bioavailability and extensively metabolism of FP than other corticosteroids, may partly explain the lack of bone associated side effects in our study.

The present study's results corroborate those reported in previously published studies of smaller groups of less well-characterised children for shorter periods of time with FP.[8,20] In the light of the current studies, there is no evidence that the long-term treatment of children with FP in low-medium doses is associated with reduction of BMD or with increased risk of osteoporosis.[21] However, changes in the in the total bone mineral content in children treated with high doses of BDP or BUD or FP have been recently documented during 12 months of treatment.[22]

The effects of exogenous corticosteroids on bone can be evaluated by biochemical markers of bone metabolism, BMD, or frequency of fractures.[23,24] The lumbar spine is the ideal site for DEXA scans because of its high content of metabolically active trabecular bone, its propensity for fractures as well as its sensitivity, and changes in the mineral density and bone size in growing children.[15,25]

The DEXA technique is very precise and delivers a low radiation dose to the patient. With the DEXA system used, which was a pencil beam system, it was also possible to determine the length of body segments with high accuracy and precision.[26] However, DEXA has disadvantages such as limited availability, high cost, exposure to ionising radiation

and limited accuracy in very obese individuals. Moreover, interpretation of DEXA results depends on the software or technology used even in the same device.[27–29]

The results showed no significant differences compared with control for effects on BMD after 5 years of treatment with FP inhaled spray. When designing the present study, the authors tried to avoid some of the problems of interpreting potential findings in the FP-treated children. This was achieved by restricting the study to well-characterised patients who were known to have never received systemic corticosteroids for >14 days, and by including a control group of children with asthma who had never received exogenous corticosteroids. In addition, the technicians who took measurements of BMD were blinded with respect to the treatment given in order to minimise any possible bias. The BMD results from this study corroborate those of Kemp et al.[30] and they are extended by showing that even the most commonly bioavailable formulation of fluticasone at a relatively high dose does not cause a reduction in BMD at the lumbar spine, the most appropriate and sensitive marker for the skeletal effects of systemic corticosteroid therapy. A cohort follow-up study, CAMP study, reported that long-term ICS use was associated with a small decrease in bone mineral accretion in males but not females, but no increased risk of osteopenia.[31] In contrast, Turpeinen et al.,[32] found that high to moderate dose inhaled BUD for 6 months resulted in a statistically significant decrease in BMD in prepubertal children with asthma. Additionally, they showed that this effect was, however, still measurable after 1 year of treatment with low-dose BUD.

Studies of biochemical markers of bone metabolism such as serum osteocalcin may have potential as indicators of the long-term effects of corticosteroids but are less indicative than DEXA regarding the potential for cumulative effects over a five-year period. In this study, serum osteocalcin values were not statistically different between the two groups. The serum osteocalcin values were highly variable and may not be reliable or predictive of other systemic effects of ICSs.[33,34] It is unclear whether the individual markers of systemic effects of corticosteroids correlate with each other or which is the most sensitive and predictive of problems in other organ systems. The results of the present study for serum osteocalcin level were not predictive of the changes in the skeletal BMD measurements in children who had used five-year intermittent FP in children with asthma.

Suppression of the hypothalamic-pituitary-adrenocortical (HPA)-axis is one of the methods used to determine if exogenous steroids have potentially negative effects. Reviewing the types of studies and methods used to measure the HPA axis is beyond the scope of this study; however, the authors studied serum cortisol levels in both study and control groups. Serum levels of cortisol in the morning (as in this study) and 24-h urine excretion are methods for the detection of the treatment-induced inhibition of HPA axis. Single plasma cortisol values in the morning (before dose), as used in this study, provide a momentary value only, conclusion regarding the cortisol pattern over 24 h cannot be drawn. However, as the values are gathered at the same time in both groups, they are comparable in each individual. It can be concluded that endogen cortisol production is active and that the children treated with FP do not show statistically different values from the reference values of the controls. The use of 24-h urinary cortisol provides a more reliable index of the HPA-axis function, as it is not affected by the circadian variations in cortisol secretion.[35] Treatment with low or moderate doses ($\leq$400 $\mu$g in children) of ICS is usually not associated with suppression of the HPA axis in children.[36] There have been reports of symptomatic adrenal insufficiency in children on chronic ICS treatment. Most of these children were treated with high doses of inhaled FP.[37,38] In this study, our patients only received conventional doses of FP.

The authors found no significant changes in other biochemical markers of bone metabolism such as serum calcium, phosphorus, ALP, and PTH. Moreover, they did not have the opportunity to evaluate serum procollagen peptide I levels, another important marker for bone metabolism because of a lack of measurement technique. Dietary calcium intake is another important point to be discussed. Some authors think that decreased BMD may be partly related with low calcium intake necessary for the maintenance of adequate calcium, while vitamin D intake is thought to be helpful to control the negative side effects of the ICS on bone turnover.[39–41]

## Conclusion

In conclusion, long-term periodical usage of inhaled FP at an average daily dose 200 $\mu$g for over 5 years has no statistically significant negative effects on BMD at the lumbar spine in pre-pubertal children with asthma. The markers of bone formation and resorption failed to reveal differences in treated and untreated asthma. The results of this study add to the body of evidence supporting the safety of long-term FP use in children with asthma.

## Conflict of interest

The authors have no conflict of interest to declare.

## References

1. Asher I. The International Study of asthma and Allergies in Childhood (ISAAC). N Z Med J. 2008;121:117–8.
2. Barraclough R, Devereux G, Hendrick DJ, Stenton SC. Apparent but not real increase in asthma prevalence during the 1990s. Eur Respir J. 2002;20:826–33.
3. Martinez FD. Trends in asthma prevalence, admission rates, and asthma deaths. Respir Care. 2008;53:561–5.
4. National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma. Full report 2007. Available online at www.nhlbi.nih.gov./guidelines/asthma/asthgdln.pdf [last accessed 05.09.07].
5. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated 2008. Available on line at www.ginasthma.org/guidelineitem.asp.I1=2&l2=1&intld=60 [last accessed 09.02.09].
6. Derendorf H, Hochhaus G, Meibohm B, Mollman H, Barth J. Pharmacokinetics and pharmacodynamics of inhaled corticosteroids. J Allergy Clin Immunol. 1998;101:S440–6.
7. Sweetman S, editor. Martindale: the complete drug reference. London: Pharmaceutical Press; 2007 [electronic version].

8. Passalacqua G, Albano M, Canonica GW, Bachert C, Van Cauwenberge P, Davies RJ, et al. Inhaled and nasal corticosteroids: safety aspects. Allergy. 2000;55:16–33.
9. Ebeling PR, Erbas B, Hopper JL, Wark JD, Rubinfeld AR. Bone mineral density and bone turnover in asthmatics treated with long-term inhaled or oral glucocorticoids. J Bone Miner Res. 1998;13:1283–9.
10. Altintas DU, Karakoc GB, Can S, Yilmaz M, Kendirli SG. The effects of long term use of inhaled corticosteroids on linear growth, adrenal function and bone mineral density in children. Allergol Immunopathol. 2005;33:204–9.
11. Mainz JG, Sauner D, Malich A, John S, Beyermann H, Mentzel HJ, et al. Cross-sectional study on bone density-related sonographic parameters in children with asthma: correlation to therapy with inhaled corticosteroids and disease severity. J Bone Miner Metab. 2008;26:485–92.
12. Roux C, Kolta S, Desfougères JL, Minini P, Bidat E. Long-term safety of fluticasone propionate and nedocromil sodium on bone in children with asthma. Pediatrics. 2003;111:706–13.
13. Allen DB, Bielory L, Derendorf H, Dluhly R, Colice GL, Szefler SJ. Inhaled corticosteroids: past lessons and future issues. J Allergy Clin Immunol. 2003;112:S1–40.
14. Irwin RS, Richardson ND. Side effects with inhaled corticosteroids the physician's perception. Chest. 2006;130 S: 41–53.
15. American Thoracic Society. Standardization of spirometry: 1994 update. Am J Respir Crit Care Med. 1995;152:1107–36.
16. Genant HK, Cooper C, Poor G, Reid I, Ehrlich G, Kanis J, et al. Interim report and recommendations of the World Health Organization Task-Force for Osteoporosis. Osteoporos Int. 1999;10:259–64.
17. Baim S, Leonard MB, Bianchi ML, Hans DB, Kalkwarf HJ, Langman CB, et al. Official positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Pediatric Position Development Conference. J Clin Densitom: Assess Skelet Health. 2008;11:6–21.
18. Peters PS. Safety of inhaled corticosteroids in the treatment of persistent asthma. J Natl Med Assoc. 2006;98:851–61.
19. Van Boxtel CJ, Sheffer AL, editors. The pharmacokinetics of fluticasone propionate. Clin Pharmacokinet. 2000;39 Suppl.:1–54.
20. Barnes NC, Hallett C, Harris TA. Clinical experience with fluticasone propionate in asthma: a meta-analysis of efficacy and systemic activity compared with budesonide and beclomethasone dipropionate at half the microgram dose or less. Respir Med. 1998;92:95–104.
21. Thorsson L, Dahlström K, Edsbäcker S, Källén A, Paulson J, Wirén JE. Pharmacokinetics and systemic effects of inhaled fluticasone propionate in healthy subjects. Br J Clin Pharmacol. 1997;43:155–61.
22. Pedersen S. Clinical safety of inhaled corticosteroids for asthma in children: an update of long-term trials. Drug Saf. 2006;29:599–612.
23. Hopp RJ, Degan JA, Phelan J, Lappe J, Gallagher GC. Cross-sectional study of bone density in asthmatic children. Pediatr Pulmonol. 1995;20:189–92.
24. Visser MJ, van der Veer E, Postma DS, Arends LR, de Vries TW, Brand PL, et al. Side-effects of fluticasone in asthmatic children: no effects after dose reduction. Eur Respir J. 2004;24: 420–5.
25. Reilly SM, Hambleton G, Adams JE, Mughal MZ. Bone density in asthmatic children treated with inhaled corticosteroids. Arch Dis Child. 2001;84:183–7.
26. Braillon P, Chotel F. Bone mineral content and soft-tissue assessment in limb segments by dual energy X-ray absorptiometry: optimal scan speed and pixel size. J Clin Densitom. 2003;6:149–58.
27. Plank LD. Dual energy X-ray absorptiometry and body composition. Curr Opin Clin Nutr Metab Care. 2005;8:305–9.
28. Akil I, Yuksel H, Urk V, Onur E, Var A, Guvenc Y. Biochemical markers of bone metabolism and renal calcium excreation in the asthmatic patient treated with inhaled corticosteroids. Asthma Allergy Immunol (Turkish) 2004;31:5–10.
29. Jones CD, Laval-Jeantet AM, Laval-Jeantet MH, Genant HK. Importance of measurement of spongious vertabral bone mineral density in the assessment of osteoporosis. Bone. 1987;8:201–6.
30. Kemp JP, Osur S, Shrewsbury SB, Herje NE, Duke SP, Harding SM, et al. Potential effect of fluticasone propionate on bone mineral density in patients with asthma: a 2-year randomized, double-blind, placebo-controlled trial. Mayo Clin Proc. 2004;79:458–66.
31. Kelly HW, Van Natta ML, Covar RA, Tonascia J, Green RP, Strunk RC, et al. Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the childhood Asthma Management Program (CAMP) study. Pediatrics. 2008;122:e53–61.
32. Turpeinen M, Pelkonen AS, Nikander K, Sorva R, Selroos O, Juntunen-Backman K, et al. Bone mineral density in children treated with daily or periodical inhaled budesonide: the Helsinki Early Intervention Childhood Asthma study. Pediatr Res. 2010;68:169–73.
33. Rizzo MC, Solé D, Naspitz CK. Corticosteroids (inhaled and/or intranasal) in the treatment of respiratory allergy in children: safety vs. efficacy. Allergol Immunopathol (Madr). 2007;35:197–208.
34. Barnes NC. Safety of high-dose inhaled corticosteroids. Respir Med. 1993;87:27–31.
35. Breborowicz A, Niedziela M. Adrenal function in children with severe asthma treated with high-dose inhaled glucocorticoids: recommended screening tests in outpatient condition. J Pediatr Endocrinol Metab. 2007;20:781–9.
36. Sahiner UM, Cetinkaya S, Ozmen S, Arslan Z. Evaluation of adrenocortical function in 3–7 aged asthmatic children treated with moderate doses of fluticasone propionate: reliability of dehydroepiandrosterone sulphate (dhea-s) as a screening test. Allergol Immunopathol (Madr). 2011, doi:10.1016/j.aller.2010.06.005 [epub ahead of print].
37. Patel L, wales JK, Kibirige MS, Massarano AA, Couriel JM, Clayton PE. Symptomatic adrenal insufficiency during inhaled corticosteroid treatment. Arch Dis Child. 2001;85:330–9.
38. Drake AJ, Howells RJ, Shield JP, Prendiville A, Ward PS, Crowne EC. Symtomatic adrenal insufficiency presenting with hypoglicaemia in children with asthma receiving high dose inhaled fluticasone propionate. BMJ. 2002;324:1081–3.
39. Agertoft L, Pedersen S. Bone mineral density in children with asthma receiving long-term treatment with inhaled budesonide. Am J Respir Crit Care. 1998;157:178–83.
40. Johnston CC, Miller JZ, Slemenda CW. Calcium supplementation and increase in bone mineral density in children. N Eng J Med. 1992;327:82–7.
41. Gagnon L, Boulet LP, Brown J, Desrosiers T. Influence of inhaled corticosteroids and dietary intake on bone density and metabolism in patients with moderate to severe asthma. J Am Diet Assoc. 1997;97:1401–6.