

Peripheral Bone Status In Children With Asthma Evaluated By Digital X-Ray Radiogrammetry

H Mentzel, J Mainz, M Schäfer, A Malich, J Boettcher, W Kaiser

Citation

H Mentzel, J Mainz, M Schäfer, A Malich, J Boettcher, W Kaiser. *Peripheral Bone Status In Children With Asthma Evaluated By Digital X-Ray Radiogrammetry*. The Internet Journal of Radiology. 2005 Volume 5 Number 1.

Abstract

Objective: Loss of bone mass is a known possible complication in children with asthma. We evaluated the applicability of digital X-ray radiogrammetry (DXR), which estimates cortical bone mineral density (DXR-BMD) for quantification of cortical demineralisation in children with asthma.

Study design: 17 children (9f, 8m; mean age 11.3 years) underwent DXR measurements for calculation of DXR-BMD and metacarpal index (DXR-MCI) using the Pronosco X-posure system (V.2, Sectra Pronosco A/S, Vedbaek, Denmark) on the base of radiographs of the non-dominant left hand. The results were compared to a regional age and gender matched reference data base and correlated to asthma severity and use of inhaled corticosteroids.

Results: DXR-BMD was between 0.34 and 0.57g/cm² (median 0.41; SD 0.06) in asthmatic children compared to a range from 0.39 to 0.59g/cm² (median 0.41; SD 0.06) in the reference population. DXR-MCI was between 0.27 and 0.58 in asthmatics compared to a range from 0.33 to 0.46 in controls. The Z-scores for DXR-BMD were reduced for more than -1 SD in 4 asthmatics (23.5%) and the Z-Score for DXR-MCI was reduced in 6 patients (35.3%). The correlation between DXR-BMD and the dose of inhaled glucocorticoids for at least 6 months and asthma severity was significant ($p < 0.05$).

Conclusion: Digital X-ray radiogrammetry performed on radiograms on the non-dominant left hand may be sensitive to assess osteopenia in children with asthma.

INTRODUCTION

Asthma is the most frequent chronic disease during childhood in developed countries, and airway inflammation is a central characteristic of this disease [6]. Chronic inflammation is a well known cause of growth retardation and other metabolic effects such as a reduction of bone mineral density. Inhaled corticosteroids (ICS) are first line anti-inflammatory therapy in asthma management [17]. The increasing use of ICS to treat asthma is based on their dose-dependent effectiveness in decreasing bronchial reactivity and airway inflammation, leading to improved asthma control with fewer side effects than with oral steroids [1]. Studies in adults suggest that doses of inhaled corticosteroids greater than 800µg/day are associated with decreased bone mass [9]. But, a meta-analysis about the impact of long-term inhaled corticosteroids in patients with asthma showed no significant changes in bone mineral density (BMD)[8]. Possible systemic side effects of corticosteroids in children are also matter of discussion.

Adrenal suppression and growth retardation have been reported in children receiving 400 µg/day of either budesonide or beclomethasone dipropionate [4]. A reduced bone mass in prepubertal asthmatic children receiving high doses of inhaled corticosteroids was described by using dual energy X-ray absorptiometry (DXA). Another study reported normal BMD values in asthmatic children treated with moderate to high doses of inhaled corticosteroids by using quantitative computed tomography (QCT)[19].

However, as all osteodensitometrical techniques and systems have been developed and validated solely in adults, their scientific value and clinical applicability in children have yet to be fully evaluated [20]. In this preliminary pilot study, a new technique for the estimation of bone density in children – Digital X-ray radiogrammetry – was used to determine whether cortical bone mass is reduced in asthmatic children and to analyze the influence of a therapy with inhaled corticosteroids.

PATIENTS AND METHODS

PATIENTS

The patient population consisted of participants from the pediatric pulmonology outpatient clinic of an university hospital. Inclusion criterion was the diagnosis of asthma according to the American Thoracic Society [3]. Patients, who received a conventional radiograph of the non-dominant left hand for the evaluation of the skeletal maturation which is known to be retarded in some children with chronic diseases were enclosed in this retrospective cross-sectional study. The study population consisted of 17 children and adolescent patients (9 girls, 8 boys; age range from 6.4 years to 16.75 years; median age 11.3 years). The 17 consecutively sampled hand radiographs were used for the analysis of cortical DXR-BMD. Exclusion criteria were visible fractures of the investigated forearm, immobilisation, further diseases which may alterate the BMD. Local ethics committee was informed about the character of the study and approved to the study design.

RADIOGRAPHS

Conventional radiographs of the non-dominant left hand were performed for the evaluation of skeletal maturation. The use of the left hand was based on the fact that the original Greulich and Pyle atlas used the left hand. The radiographs were obtained in a single centre. Standardized radiographs of the left hand in posteroanterior projection (PA) were taken on a single film (Kodak Trimax Regula 400) using the following parameters: MPG 80 as X-ray device (General Electric, Milwaukee, USA), filter 1.0 mm aluminium 0.1 mm copper, film focus distance 1 m, small focus 0.6, tube voltage 45 kV, exposure 3.2 – 4 mAs.

DIGITAL X-RAY RADIOGRAMMETRY

The Pronosco X-posure system™ (version V.2, Sectra Pronosco A/S, Vedbaek, Denmark) was used to determine DXR-BMD and the metacarpal index (DXR-MCI) based on digital radiogrammetry (Figure 1).

Figure 1

Figure 1: The DXR-system consists of a scanner with a resolution of 300dpi (approximately 5.5lp/mm) and a computer with dedicated software.



Although the algorithm for the calculation of DXR-BMD (g/cm^2) has previously been published more in detail [22], we describe the process briefly. The radiographs of the left hand were scanned and automatically analyzed by the system. The system itself checked the quality of the scanned images. The involved computer algorithms automatically defined regions of interest (ROIs) around the narrowest parts of the metacarpals II, III, and IV and determined the outer and inner edges of the cortical bone parts. The average cortical thickness and bone width were assessed for these metacarpals. Assuming a cylindrical shape of the metacarpal bone the averaged cortical volume per area (VPA) was calculated. The DXR-BMD was computed on the basis of the VPA with a minor correction for porosity. Porosity was the fraction of the cortical bone that was not occupied by compact bone which is described by the local intensity minima (holes) found in the cortical part of the bone relative to the entire cortical area. The metacarpal index (DXR-MCI), expressed the mean cortical thickness normalized with the mean outer bone diameter (width). The scanning process and the analysis took 5 min for each patient.

DATA ANALYSIS

The DXR-results were expressed as the mean and standard deviation (SD). The normality of the data was checked using the Kolmogorov-Smirnov test. The evaluated DXR data were corrected for growth parameters and analyzed according to a regional database of healthy German Caucasian children and adolescents [14]. The data were compared to age and sex matched children and an individual standard of deviation (SD) was calculated for each subject. The results from bone densitometry are usually expressed as a relative value compared with those of young adults of the

same gender which is known as the T-score. In children it is not recommended to use the T-score because children show growth and bone development. Instead in children it is necessary to compare the evaluated BMD with healthy gender-, age-, and race-matched controls which can be expressed as Z-score. The Z-score will be defined as a standard deviation (SD) of the measured BMD in relation to the mean for the child's age and sex. The Z-score will be calculated using the following formula: $(\text{BMD patient} - \text{BMD control}) / \text{SD control}$. Z-scores could be evaluated for DXR-BMD and the DXR-MCI.

Statistical analysis was performed using the Statistical Package of Social Sciences (SPSS version 12.0, Chicago, IL, USA). The aim was testing the null hypothesis that there were no difference between patients with asthma and normal volunteers. The significance level was set to $p < 0.05$ (unpaired t-test). The findings of digital radiogrammetry were correlated to the clinical parameters (inhaled corticosteroid exposure, asthma severity, patients age, patients skeletal age, BMI).

RESULTS

The DXR-system recognized the metacarpals of all 17 patients and the DXR-BMD could be calculated successfully in all of these patients. The evaluated DXR-BMD was in the range from 0.34 and 0.57 g/cm² (median 0.41, SD 0.06) in asthmatic patients and in the range from 0.39 to 0.59 g/cm² (median 0.41, SD 0.06) in the reference population. DXR-MCI showed values between 0.27 to 0.58 (median 0.34, SD 0.07) in asthmatic patients and reached from 0.33 to 0.46 (median 0.36, SD 0.04) in controls. The distribution of osteodensitometric parameters using DXR is listed in Table 1. Compared to controls the DXR-BMD was not significantly reduced in young asthmatics ($p = 0.18$). There was also no significant difference between the DXR-MCI in asthmatics and controls ($p = 0.35$).

Figure 2

Table 1: Clinical characteristics of the study group

	Asthmatic Children
Patients (f/m)	17 (9/8)
Age (range)	11.3 (6.4-16.75)
Skeletal Age (range)	10.5 (4.0-16.0)
Asthma severity score (2/3)	8/9
Inhalative Corticosteroids yes/no	17/0
Height (cm; range)	148.0 (113-179)
Weight (kg; range)	44.0 (18-64)
Body Mass Index (kg/m ² ; range)	19.22 (14.1-24.8)

In patients with asthma the median Z-score for the DXR-BMD was -0.23 (range from -2.68 to +0.60) in comparison

to the local reference data. After correction for skeletal maturation the median Z-Score of DXR-BMD was -0.55 (range from -1.70 to +0.60). The median Z-Score of DXR-MCI in asthmatics was -0.77 (range from -2.3 to +2.4) after correction for skeletal age. According to the chronological age one patient (5.9 %) showed a Z-score of DXR-BMD in the level of osteoporosis (Z-Score < -2.5 SD), 5 patients (29.4 %) revealed a Z-score according to osteopenia (Z-Score between -1.0 to -2.5 SD), and 11 patients (64.7 %) were in the normal range (Z-Score > -1.0 SD). After correction for skeletal maturity no patient showed osteoporosis, 4 patients revealed osteopenia (23.5 %), and 13 patients were in the normal level (76.5 %). After correction for bone age 6 patients (35.3 %) showed reduced DXR-MCI values corresponding to osteopenia (Z-Score between -1.0 and -2.5 SD) and in 11 patients DXR-MCI was in the normal range (64.7 %). Without correction for skeletal maturation one patient showed a reduced DXR-MCI corresponding to osteoporosis (Z-Score < -2.5 SD) and 7 patients showed osteopenia (Z-Score between -1.0 and -2.5 SD).

There were no significant correlations between the DXR-parameters (DXR-BMD and DXR-MCI) and asthma severity. Regarding inhaled corticosteroids (ICS) our data revealed a significant correlation of 0.56 between DXR-BMD and the ICS-dose applied for at least 6 months with a medium daily dose of 271 µg fluticasone-propionate equivalent ($p < 0.05$). Table 3 demonstrates the correlations between the DXR-parameters and the clinical characteristics (calendarly age, body weight, body mass index).

Figure 3

Table 2: Radiogrammetrical measurements in children with asthma

N = 17	Asthmatic patients	References
	Median (SD)	Median (SD)
DXR-BMD (g/cm ²)	0.41 (0.06)	0.40 (0.01)
<i>DXR-BMD</i> Z-Score Skeletal Age	-0.55	
DXR-MCI	0.34 (0.07)	0.36 (0.04)
<i>DXR-MCI</i> Z-Score Skeletal Age	-0.77	
Cortical thickness	0.12 (0.02)	
Porosity	3.30 (1.14)	

Figure 4

Table 3: Association between DXR-parameters and clinical characteristics in the study group of children with asthma

N = 17	DXR-BMD Patients	DXR-MCI Patients
Exposure of inhaled glucocorticoids	0.56*	0.31
Asthma severity	0.30	0.13
Skeletal age	0.86**	0.71**
Calendarly age	0.72**	0.57*
Height	0.68**	0.73**
Weight	0.56**	0.52*
BMI	0.18	0.06

** p < 0.01

* p < 0.05.

DISCUSSION

In this study we evaluated the clinical applicability of DXR in children with asthma. Our data revealed no significant correlation between the severity of asthma and the estimated DXR-BMD as well as DXR-MCI, but, this is limited by the inclusion of patients with only grade 2 or 3. There were no significant differences between the DXR-parameters in asthmatic children and in the local reference atabase which was in concordance to other studies in children which not demonstrated a deleterious effect of flutcasone propionate on bone density in children [7, 18]. Osteoporosis is a widely recognized complication of oral corticosteroid therapy in asthmatic adults [5]. Steroid-induced osteoporosis results from the inhibition of osteoblastic activity, increased bone resorption due to attenuated sex hormone secretion, and raised parathyroid hormone levels due to reduced renal and gastrointestinal calcium absorption [13]. While reduced BMD has been reported in asthmatic adults treated with inhaled corticosteroids also [10, 16], otherwise some studies in children suggest that these agents have no adverse effects on BMD measured by using dual energy X-ray absorptiometry (DXA)[7] or quantitative computed tomography (QCT) of the lumbar spine and the distal radius [19]. There are also reports of meta-analysis in adults about the impact of long-term inhaled corticosteroid therapy on bone mineral density which described no significant changes in BMD [8, 12]. Further studies described a dose-response relation between the cumulative ICS dose and BMD measured by DXA at the lumbar spine and the proximal femur in asthmatic adults [25]. A significant negative correlation between the dose of ICS and BMD was described in a study on prepubertal children with asthma [1]. In our study, there was only a positive significant correlation of DXR-BMD to the moderate dose of inhalative corticosteroids (fluticasone-propionate equivalent) which was applied in all children. These findings suggests the thesis that an adequate therapy in asthmatics allows these patients more physical activity which is beneficial for the consecutive improvement of the muscle-

bone-unit [23]. This is one possible reason for the development of an adequate peak bone mass also in asthmatic children with optimal therapy.

Given that skeletal maturation and bone density are dependent on the timing of puberty, analysis of bone mineral density was considered for bone age as well as for chronological age. It is well known, that skeletal age in children with chronic illness is often retarded. The Z-score compares the patients BMD with the mean BMD expected for the patients peers matched for age, gender, and race and is expressed as the number of standard deviations. The World Health Organization criteria for adults using Dual energy X-ray Absorptiometry (DXA) to define osteopenia in postmenopausal women as bone density between 1-2.5 standard deviations below the young adult mean and osteoporosis less than 2.5 standard deviations below the mean [11]. Currently, there exist no verified definitions for osteopenia and osteoporosis in children. In the present study we classified reduced bone mass with a Z-score less than -1 SD as osteopenia and severely reduced bone mass as a Z-score less than -2.5 SD. So, in our patients, the DXR-BMD Z-score was reduced at a level of < -1.0 SD in 23.5 % of the cases (4/17patients with asthma). Griffiths et al. [7] reported reduced BMD estimated by DXA in 16.2 % of their patients with asthma treated by prolonged ICS intake (mean dose $771.2 \pm 253.35 \mu\text{g}/\text{m}^2/\text{day}$).

In the present study, we evaluated the novel DXR technique. In children, digital radiogrammetry has a significant advantage over other techniques, because it uses a radiograph of the left hand which is routinely obtained in children who are suspected for disturbed skeletal maturation (e.g. growth retardation, oncologic patients, patients suffering from chronic inflammatory bowel diseases). Therefore, no additional radiation exposure is needed. Digital radiogrammetry (DXR) is a low-cost convenient method that has been effectively used for evaluation of several adults with reduced BMD [2, 14, 24]. There are also some reports about the use of DXR in children [14, 15, 20, 21]. Further advantages of the DXR method in comparison to other osteodensitometric methods are the missing influence of the operator because the positioning of the ROIs is automatically and the operator has no possibility to influence the localization. Furthermore, there is no influence of soft tissue thickness on BMD calculations. A drawback of DXR is that it is essentially a projectional technique in which bone mass is only assessed in two dimensions whereas bone growth takes place in three dimensions. Actually,

quantitative computed tomography (QCT) presents the sole method for the evaluation of real bone mineral density. The DXR technology used in our study calculates only the cortical BMD. Consequently, the bone loss of the trabecular partition could be not detected by using DXR. However, the retrospective character of our study imposes limitations, and general conclusions have to be reserved to further studies with prospective character and a more extensive population.

In conclusion, our pilot study showed that DXR in a pediatric asthmatic population is able to detect alterations in cortical bone partitions with simultaneous assessment of skeletal maturation. Prospective longitudinal studies are necessary to reveal the role of DXR within the fields of pediatrics.

CORRESPONDENCE TO

Hans-J. Mentzel, MD Institute of Diagnostic and Interventional Radiology Department of Pediatric Radiology Friedrich-Schiller-University Jena Kochstraße 2 07745 Jena Germany e-mail: hans-joachim.mentzel@med.uni-jena.de phone: ++49 3641 935369 fax: ++49 3641 936767

References

1. Allen HD, Thong IG, Clifton-Bligh P, Holmes S, Nery L, Wilson KB. Effects of high-dose inhaled corticosteroids on bone metabolism in prepubertal children with asthma. *Pediatr Pulmonol* 2000; 29: 188-193
2. Böttcher J, Pfeil A, Lehmann G, Heinrich B, Malich A, Hansch A, Petrovitch A, Mentzel HJ, Hein G, Kaiser WA. Clinical trial for differentiation between corticoid-induced osteoporosis and periarticular demineralization via digital radiogrammetry in patients suffering from rheumatoid arthritis. *Z Rheumatol* 2004; 63: 473-482.
3. Colice GL, Burt J, Song J, Stampone P, Thompson PJ. Categorizing asthma severity. *Am J Respir Crit Care Med* 1999; 160: 1962-1967
4. Doull IJM, Freezer NJ, Holgate ST. Osteocalcin, growth, and inhaled corticosteroids: a prospective study. *Arch Dis Child* 1996; 74: 497-501
5. Drozdowska B. Skeletal status assessed by quantitative ultrasound at the calcaneus in females with bronchial asthma on prolonged corticosteroid therapy. *Maturitas* 2005; 16: 386-392
6. Gergen PJ, Mullally DI, Evans R. National survey of prevalence of asthma among children in the United States, 1976-1980. *Pediatrics* 1988; 81: 1-7
7. Griffiths AL, Sim D, Strauss B, Rodda C, Armstrong D, Freezer N. Effect of high-dose fluticasone propionate on bone density and metabolism in children with asthma. *Pediatr Pulmonol* 2004; 37: 116-121,
8. Halpern MT, Schmier JK, van Kerckhove MD, Watkins M, Kalberg CJ. Impact of long-term inhaled corticosteroid therapy on bone mineral density: results of a meta-analysis. *Ann Allergy Asthma Immunol* 2004; 92: 201-207
9. Ip M, Lam K, Yam L, Kung A, Ng M. Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids. *Chest* 1994; 105: 1722-1727
10. Israel E, Banerjee TR, Fitzmaurice GM, Kotlov TV, La Hive K, Le Boff MS. Effects of inhaled glucocorticoids on bone density in premenopausal women. *N Engl J Med* 2001; 345: 941-947
11. Kanis JA, Melton IJ, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. *J Bone Miner Res* 1994; 9: 1137-1141
12. Leone FT, Fish JE, Szeffler SJ, West SL. Systematic review of the evidence regarding potential complications of inhaled corticosteroid use in asthma: collaboration of American College of Chest Physicians, American Academy of Allergy, Asthma, and Immunology, and American College of Allergy, Asthma, and Immunology. *Chest* 2003; 124: 2329-2340
13. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. *Arch Intern Med* 1999; 159: 941-955
14. Malich A, Freesmeyer MG, Mentzel HJ, Sauner D, Boettcher J, Petrovitch A, Behrendt W, Kaiser WA. Normative values of bone parameters of children and adolescents using digital computer-assisted radiogrammetry (DXR). *J Clin Densitom* 2003; 6: 103 - 111
15. Mentzel HJ, John U, Boettcher J, Malich A, Pfeil A, Vollandt R, Misselwitz J, Kaiser WA. Evaluation of bone-mineral density by digital X-ray radiogrammetry (DXR) in pediatric renal transplant recipients. *Pediatr Radiol* 2005; 35: 489-494.
16. Packe GE, Robb O, Robins SP, Reid DM, Douglas JG. Bone density in asthmatic patients taking inhaled corticosteroids: comparison of budesonide and beclomethasone dipropionate. *J R Coll Physicians Lond* 1996; 30: 128-132
17. Rabinovitch N, Gelfand EW. New approaches to the treatment of childhood asthma. *Curr Opin Pediatr* 1998; 10: 243-249
18. Rao R, Gregson RK, Jones AC, Miles EA, Campbell MJ, Warner JO. Systemic effects of inhaled corticosteroids on growth and bone turnover in childhood asthma: a comparison of fluticasone with beclomethasone. *Eur Respir J* 1999; 13: 87-94
19. Reilly SM, Hambleton G, Adams JE, Mughal MZ. Bone density in asthmatic children treated with inhaled corticosteroids. *Arch Dis Child* 2001; 84: 183-184
20. van Rijn RR, van der Sluis IM, Link TM, Grampp S, Guglielmi G, Imhof H, Gluer C, Adams JE, van Kuijk C. Bone densitometry in children: a critical appraisal. *Eur Radiol* 2003; 13: 700-710
21. van Rijn RR, Grootfaam DS, Lequin MH, Boot AM, van Beek RD, Hop WC, van Kuijk C. Digital radiogrammetry of the hand in a pediatric and adolescent Dutch Caucasian population: normative data and measurements in children with inflammatory bowel disease and juvenile chronic arthritis. *Calc Tissue Int* 2004; 74: 342-350
22. Rosholm A, Hyldstrup L, Baeksgaard L, Grunkin M, Thodberg HH. Estimation of bone mineral density by digital X-ray radiogrammetry: theoretical background and clinical testing. *Osteoporos Int* 2001; 11: 961-969
23. Schoenau E. The "functional muscle-bone unit": a two-step diagnostic algorithm in pediatric bone disease. *Pediatr Nephrol* 2005; 20: 356-359
24. Ward KA, Cotton J, Adams JE. A technical and clinical evaluation of digital X-ray radiogrammetry. *Osteoporos Int* 2003; 14: 389-395
25. Wong CA, Walsh LJ, Smith CJ, Wisniewski AF, Lewis SA, Hubbard R, Cawte S, Green DJ, Pringle M, Tattersfield AE. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet* 2000; 355: 1399-1403

Author Information

Hans J. Mentzel, M.D.

Department of Pediatric Radiology, Institute of Diagnostic and Interventional Radiology, Friedrich-Schiller-University

Jochen Mainz, M.D.

Department of Pediatrics, Pediatric Pulmonology, Friedrich-Schiller-University

Max Schäfer

Department of Pediatric Radiology, Institute of Diagnostic and Interventional Radiology, Friedrich-Schiller-University

Ansgar Malich, M.D.

Department of Diagnostic Radiology, Suedharz-Hospital

Joachim Boettcher, M.D.

Department of Pediatric Radiology, Institute of Diagnostic and Interventional Radiology, Friedrich-Schiller-University

Werner A. Kaiser, M.D.

Department of Pediatric Radiology, Institute of Diagnostic and Interventional Radiology, Friedrich-Schiller-University