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

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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 systemTM (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 relativ 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: (BMD patient – BMD control)/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/cm^2 (median 0.41, SD 0.06) in asthmatic patients and in the range from 0.39 to 0.59 g/cm^2 (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/m²; 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-proprionate equivalent ($p<0.05$). Table 3 demonstrates the correlations between the DXR-parameters and the clinical characteristics (calendary age, body weight, body mass index).

Figure 3

Table 2: Radiogrammetrical measurements in children with asthma

N = 17	Asthmatic patients Median (SD)	References Median (SD)
DXR-BMD (g/cm²)	0.41 (0.06)	0.40 (0.01)
DXR-BMD Z-Score Skeletal Age	-0.55	
DXR-MCI	0.34 (0.07)	0.36 (0.04)
DXR-MCI 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**
Calendary 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 parathyreoid 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-proprionate 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 benefitial for the consecutive improvement of the muscle-bone-unit [23]. This is one possbile 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 ± 253.35 µg/m^2/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 routineously 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 detectaed 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.

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