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Corresponding Author
G. Chaitra,
Department of Pediatrics, Siddaganga Medical College Research Institute, Tumkur, Karnataka, India

Author Designation
[1]Associate Professor
[2,4]Assistant Professor
[3]Senior Resident

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Serum Calcium and Vit D in Children with Asthma on Long Term High Dose Inhaled Bedizened

[1]H.C. Madhu, [2]Sumanth H. Patil, [3]N. Sowmya and [4]G. Chaitra
[1-4]Department of Pediatrics, Siddaganga Medical College Research Institute, Tumkur, Karnataka, India

ABSTRACT
There are numerous tests to evaluate bone mineralization. The biochemical tests include serum vitamin D and parathyroid hormone (PTH)., markers of bone formation like osteocalcin, bone specific alkaline phosphates and serum carboxy terminal propeptide of type 1 collagen, and markers of bone resorption like plasma tartarate resistant acid phosphates, urinary deoxy-pyridinolline cross linked telopeptide of type 1 collagen, deoxy-pyridolline and urinary hydroxyproline. Children with asthma (diagnosed in accordance to GINA guidelines) in the age group of 7-17 years who have been receiving high dose Budesonide (≥400µg/day in 6-11 years and ≥800µg/day in more than 11 years) for at least ≥2 years were enrolled as cases. The mean serum calcium level among the cases was found to be 9.2±0.6mg/dl against a normal reference range of 8.5-10 mg/dL. All except one participant had normal serum levels of calcium. The mean serum vitamin-D level was found to be 55.7±16.0nmol/L against a normal reference range of 40-145nmol/L. Five patients were found to be vitamin-D deficient. Vitamin-D deficiency status was not found to be different in subjects with low BMD when compared to subjects with normal BMD. The mean serum PTH level was found to be 44.0±25.2 pg/mL against the reference range of 14-75pg/ml. One subject was found to have high PTH level along with low vitamin-D level.

INTRODUCTION

Asthma is a complex disease marked by chronic airway inflammation and a history of respiratory symptoms such as wheezing, chest tightness, coughing and shortness of breath that vary in duration and intensity, along with variable expiratory airflow limitation[1]. Though asthma has a low case fatality rate, recurrent exacerbations are a major cause of school absenteeism in children. Asthma is one of the most widespread chronic diseases that affects around 339 million people across the globe, as per the World Health Organization[2]. According to the World Health Organization, there were 417, 918 fatalities and 24.8 million DALYs lost worldwide due to asthma in 2016[2]. It causes a considerable burden of disease, leading to both untimely death and reduced quality of life, among all age groups worldwide. Its prevalence is on an increasing trend, especially in the paediatric age group[3]. Inhaled corticosteroids (ICS) have been the standard first line of treatment of asthma for quite some time. For the treatment of chronic asthma, ICS remain the most effective anti-inflammatory medications[1]. Asthma mortality and morbidity have been reduced with the use of ICS[4]. ICS therapy has brought about reduction in symptoms, improvement in lung function, decreased degree of bronchial hyper responsiveness and reduced number of exacerbations, thereby improving the quality of life of asthmatic patients' manifold. Bedizened is one such ICS that has been commonly in use in the treatment of asthma. ICS are used because of their anti-inflammatory and immunomodulatory properties. ICS appear to reverse components of asthma-induced structural alterations (airway remodeling), such as increased bronchial wall vascularity. Corticosteroids are known to cause a wide array of adverse effects attributable to their systemic actions such as suppression of hypothalamo- pituitary -adrenal (HPA) axis, hindering growth velocity, adrenal insufficiency, osteoporosis, skin thinning, cataracts, glaucoma, etc[5]. Although ICS have a better safety profile than their systemic counterparts, their regular use is believed to be associated with some systemic adverse effects. One such effect which is of concern is the effect of ICS on bone mineral accretion. Corticosteroids adversely affect the functioning of osteoblast and osteoclasts, thereby leading to decreased calcium accretion in bone, increase in bone resorption and bone calcium loss[6], thereby leading to reduced bone mineral density (BMD) and increased risk of fractures. There are numerous tests to evaluate bone mineralization. The biochemical tests include serum vitamin D and parathyroid hormone (PTH)., markers of bone formation like osteocalcin, bone specific alkaline phosphates and serum carboxy terminal propertied of type 1 collagen and markers of bone resorption like plasma tartarate resistant acid phosphates, urinary deoxy-pyridinolline cross linked telopeptide of type 1 collagen, deoxy-pyridolline and urinary hydroxyproline. Dual energy x-ray absorptiometry (DEXA), quantitative CT (QCT) and quantitative ultrasonography are among some of the radiological procedures used to quantify bone mineralization (QUS). Among these, DEXA is the most popular and time-saving method. Bone mineral content and density are calculated using this technique, which makes use of the high sensitivity of calcium in absorbing X-rays. It is the investigation of choice to assess BMD because of its high precision, low cost, short scanning time and most importantly less radiation exposure[7,8].

MATERIALS AND METHODS

Place of Study: Department of Pediatrics.

Study Design: Cross sectional observational study.

Sample Size Calculation: In a previous study by Harris *et al.,* it was observed that the mean value of spinal density in asthmatic patients taking high dose ICS was 0.71±0.09. Taking this value as reference, the minimum required sample size with estimate to be within 3% as margin of error and 5% level of significance., a total of 35 patients will be required to complete the study.

Inclusion Criteria: Children with asthma (diagnosed in accordance to GINA guidelines) in the age group of 7 to 17 years who have been receiving high dose Budesonide (≥400µg/day in 6-11 years and ≥800 µg/day in <11 years) for at least ≥2 years were enrolled as cases.

Exclusion Criteria:

- Children with any chronic illness in which bone mineralization could be affected (like chronic renal insufficiency, malabsorption syndromes, thyroid disorders, etc.).
- Children who have received <3 short courses (3-days) of systemic corticosteroids in the past 6 months.
- Children with malnutrition (BMI<-2SD as per WHO growth charts).
- Children with any features suggestive of clinical rickets.
- Family history of osteoporosis.
- Children who have taken supplements of calcium and vitamin D in the last 6 months.
- Children regularly taking any other drug which might affect bone mineralization (like loop diuretics, antiretrovirals, phenytoin, etc.).

Patient Enrollment: hildren with asthma who presented to the pediatric chest clinic in the age group of 7-7 years who have been receiving high dose Budesonide (≥00µg/day in 6-1 years and ≥800µg/day

in <11 years) for at least ≥2 years were enrolled for the study.

RESULTS AND DISCUSSIONS

Table 1: Baseline Descriptive Characteristics

Variable	Value
Age	11.6±3.0 (7-17)
Sex ratio (Male/female)	26/9
Duration of ICS (years)	3.4±1.6 (2-10)
Height (cm)	140.1±17.2 (110-173)
Weight (kg)	37.2±12.5 (20-72)
BMI (kg/m2)	18.5±2.8 (14.65-24.91)
Daily sunlight exposure (hours)	1.1±0.47 (0.5-2)
Daily intake of calcium (g)	0.78±0.16 (0.45-1.1)
Daily hours of exercise	0.6±0.3 (0-1)
Daily intake of vitamin D (IU)	415.2±103.6 (246-608)

Values depict numbers as mean±SD (range)

Out of the 35 study participants, 20 (57.1%) were aged between 7-11 years and 15 (42.9%) were aged between 12-17 years. Most of the cases (48.6%) were found to be in stage 1.

Table 2: SMR Staging of Study Population

Stage	Frequency	Percentage
Stage 1	17	48.6
Stage 2	5	14.3
Stage 3	7	20.0
Stage 4	6	17.1
Total	35	100.0

Table 3: Laboratory Investigations Including Secondary Outcomes

Variable	Mean±SD (Range)	Normal Values
Serum calcium levels (mg/dL)	9.2±0.6 (6.1-10.1)	8.5-10
Serum alkaline phosphatase (IU/L)	176.6±58.3 (54-302)	50-130
Serum phosphorus (mg/dL)	4.2±0.52 (2.8-5.5)	2.5-5.5
Serum vitamin D (nmol/L)	55.7±16.0 (20-97)	40-145
Serum PTH (ng/mL)	44.0±25.2 (7.8-134.2)	14-75

Thus BMD-LS was found to be significantly low in the study population. Vitamin-D deficiency status was assessed in subjects with low BMD and subjects with normal BMD and no significant difference was found in the two groups.

Table 4: Low BMD and Vitamin-D Deficiency Status

Parameter	Vitamin-D deficiency found in subjects with Low BMD	Vitamin-D deficiency found in subjects with normal BMD	P value
BMD-WB	1 out of 3 (33.33%)	4 out of 32 (12.5%)	0.42
BMD-LS	1 out of 9 (11.1%)	4 out of 26 (15.4%)	0.81

Chi-square analysis, p values-not significant

Asthma is a chronic inflammatory condition that affects both adults and children. Its prevalence has been seen increasing globally bringing about significant morbidity and mortality. There is a substantial body of evidence that suggest ICS are effective at controlling symptoms, improving lung function and reducing acute exacerbations. Therefore, ICS are considered the gold standard first-line preventative therapy and are widely recommended in national and international guidelines[9]. Long-term ICS use may be associated with adverse effects such as decreased bone mineral density, cataract, fractures and reduction in growth velocity in children. Concerns surrounding these potential harms may have a negative effect on ICS adherence, thus exposing patients to poorer asthma control and a potentially higher risk of needing oral corticosteroids for acute exacerbations. Hence, this study was planned to evaluate whether bone mineral density is affected by the use of long-term ICS in asthma. We evaluated 35 subjects of asthma (aged 7 to 17 years), receiving long term high dose inhaled Budesonide (Dose: ≥400µg/day in 6-11 years and ≥ 800µg/day in more than 11 years, Duration: ≥2 years) in detail with history, clinical examination and laboratory investigations which included DEXA scan (for BMD) and biochemical parameters such as serum calcium, phosphorus, alkaline phosphatase, vitamin-D and PTH levels. The primary objective of the study was to measure the BMD using DEXA scan in the study participants and compare the results with the normative data available for Indian pediatric population[10]. The mean serum calcium level among the cases was found to be 9.2±0.6mg/dl against a normal reference range of 8.5-10mg/dL. All except one participant had normal serum levels of calcium. The mean serum vitamin-D level was found to be 55.7±16.0 nmol/L against a normal reference range of 40-145 nmol/L. Five patients were found to be vitamin-D deficient. Vitamin-D deficiency status was not found to be different in subjects with low BMD when compared to subjects with normal BMD. The mean serum PTH level was found to be 44.0±25.2pg/mL against the reference range of 14-75pg/ml. One subject was found to have high PTH level along with low vitamin-D level. Therefore not many deviations in parameters of secondary objectives were observed in the current study. ICS might not be having any effect on these parameters.

CONCLUSION

The mean serum vitamin-D level was found to be 55.7±16.0nmol/L. The mean serum calcium level among the cases was found to be 9.2±0.6mg/dl. The mean serum PTH level was found to be 44.0±25.2pg/mL.

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