International Journal of Contemporary Pediatrics
Basavanagowda T et al. Int J Contemp Pediatr. 2021 Apr;8(4):672-677
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20211075

Original Research Article

Effect of inhaled corticosteroids on bone mineral density in asthmatic children

Thanuja Basavanagowda, Savitha Mysore Ramaraj*

Department of Pediatrics, Mysore Medical College and Research Institute, Mysuru, Karnataka, India

Received: 12 January 2021
Revised: 20 February 2021
Accepted: 05 March 2021

***Correspondence:**
Dr. Savitha Mysore Ramaraj,
E-mail: drsavithamr@gmail.com

ABSTRACT

Background: There is a rise in prevalence of asthma world-over. This study was undertaken as there are controversies regarding the effect of long term inhaled-corticosteroids (ICS) on bone mineral density (BMD).
Methods: Asthmatic children belonging to 5-18 year age-group as per the global initiative for asthma guidelines (GINA) guidelines, who were on ICS for a minimum period of 6 months were studied. This study was conducted at a tertiary-care teaching hospital in Mysuru. 60 asthmatic children were compared with 60 non-asthmatic controls. Dual-energy x-ray absorptiometry at 6 sites was used for estimating the BMD and vitamin D levels were measured.
Results: 0.771±0.114 g/cm^2 was the mean total BMD among children on low dose ICS, while it was 0.613±0.192 and 0.564±0.104 g/cm^2 respectively for those on medium and high dose ICS, with p value of 0.026. Children on low dose ICS did not have any impact on BMD, while 18.9% of those on medium and high dose ICS had a reduced total BMD. Trochanteric region was a useful predictor site for monitoring BMD in children on long term ICS with 38.7% and 68.9% being affected when on ICS for 6-12 months and more than 12 months respectively (p=0.018).
Conclusions: The ICS of medium and high dose, for a duration of more than 6 months had a reduced total BMD. However, no effect was seen with low dose. Trochanter is a useful site for long term monitoring of BMD in children. There was no correlation between vitamin D levels and control of asthma.

Keywords: Childhood asthma, Dual energy x-ray absorptiometry, Steroids, Vitamin D

INTRODUCTION

Asthma is the most common chronic respiratory illness affecting children worldwide. According to the global initiative for asthma guidelines (GINA), asthma is defined as: respiratory symptoms- wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity with variable expiratory airflow limitation.[1] The patho-physiological mechanism of inflammation and atopy has driven inhaled corticosteroids (ICS) to become the cornerstone of asthma therapy.[2] ICS are the most effective controller drugs because of multiple mechanisms of action, including anti-inflammatory, reduction of airway responsiveness, reversal of b_2 receptor down-regulation and prevention of airway remodelling. Even low dose of ICS is known to reduce mortality in asthma and the benefits are seen within 2-3 weeks of starting therapy.[1,3]

The WHO global estimate of asthmatics is 300 million. 10% of the asthmatics worldwide are from the Indian subcontinent.[4] The prevalence of asthma in India has been on the rising trend from 5% in 2002 to 7.3% in 2008 and 10.3% in 2010.[5-7] The prevalence of asthma in children ranges from 3-38%.[4] Due to the rising disease burden, early initiation and appropriate use of ICS therapy gains importance. However, there have been widespread, long-standing concerns regarding systemic adverse-events and impact on bone metabolism. There are studies which have shown that, high dose steroids can be associated with

decreased BMD.[8,9] On the other hand, some cross-sectional studies have shown no detrimental effects of ICS on BMD.[10,11] As per the current literature, the safety profile of long-term therapy with ICS is better than frequent bursts of oral corticosteroids on bone mineral accretion.[12] Adequate nutritional intake of calcium and vitamin D is supposed to reduce the long-term effects of corticosteroids on BMD. Hence, it is necessary to understand the interplay of ICS on bone metabolism and bone mineral density. In view of these conflicting results, this study was taken up to look into the effect of long-term ICS therapy on BMD in asthmatic children.

METHODS

Study design

The design of the study was cross sectional.

Source of data

The study was conducted at asthma clinic of Cheluvamba hospital in Mysuru, a teaching tertiary care hospital attached to Mysore Medical College and Research Institute. Children aged between 5-18 years diagnosed to have asthma according to GINA guidelines and have been on regular ICS therapy for a duration of at least 6 months formed the study subjects.[1] Non-asthmatic children admitted for other non-critical illnesses formed the control group. The study was conducted over a period of 12 months from June 2019 to June 2020.

Exclusion criteria for study and control groups

Children with prior bone disease or fractures, vitamin D supplementation, diseases affecting vitamin D absorption (such as chronic liver and kidney diseases), immobility for more than 2 weeks in past 12 weeks were excluded from the study. Study subjects who had received more than 3 courses of oral corticosteroids in the past 1 year were also excluded.[12] Subjects of control group who had received any form of steroids in the past were excluded.

After obtaining approval by the institutional ethical committee and informed consent from parents/caregivers of the participants, detailed history and examination including height and weight assessment, details of ICS use: type of ICS, dose, duration, rinsing of mouth after ICS use and use of spacer was taken. Dose of steroids was categorized as low dose, medium dose and high dose based on GINA guidelines.[1] BMD was measured by whole body dual energy x-ray absorptiometry (DXA) based on fan beam technology using lunar prodigy. BMD was measured in various regions including the lumbar spine, total femur, neck of femur, Ward's triangle, trochanter, and total body in all the subjects included in the study. The units were expressed in g/cm^2 and Z scores. Z score less than -1 was taken as osteopenia.[13] The patient factors which affect the value including height, weight, gender, ethnicity were taken into consideration.[13] BMD of hip, spine and femur was compared to the Caucasian data base (as Asian database was not available for paediatric age group up to 18 years). Total body BMD and composition was compared with Asian database.

Serum 25 hydroxy vitamin D [25 (OH) D] levels was measured by enzyme linked immunosorbent assay (ELISA). Serum 25 (OH) D levels were interpreted according to the Indian academy of pediatrics (IAP) guidelines as: more than 20 ng/ml being sufficient, 12-20 ng/ml as insufficient and less than 12 ng/ml as deficient.[14]

Statistical analysis

Based on the reported prevalence of childhood asthma in the locality of 17.4% with 10% allowable error at 5% alfa level, 80% power, the sample size was calculated to be 60 in each of study and control groups, using the formula:

$$n = z^2 2pq/d^2$$

Where n=sample size, z=1.96, p=prevalence, $q = 1 - p$, d=10% margin of error.[15] Data was analysed using statistical package for the social sciences (SPSS) version 25. Differences and associations were interpreted statistically significant at $p<0.05$.

RESULTS

Among a total of 60 subjects in both study and control group, there were 39 (65%) male and 21 (35%) female children. Most of the subjects belonged to 5-9 year age group (48.3%) and least were in the age group of 13-18 years (16.7%). 25% of the study subjects gave a positive family history of asthma, 16.6% had associated allergic rhinitis and 10% had allergic conjunctivitis.

The mean BMD of the asthmatics was lower than that of the controls in all the regions measured, but, no statistically significant difference was noted (Table 1). The mean total BMD in the study subjects on low, medium, and high dose ICS therapy showed that with increase in dose of ICS, the mean BMD decreased and this difference was statistically significant (p=0.026). The mean value of total BMD in both medium dose and high dose ICS was lower among study subjects when compared to controls and these observations were statistically significant (p value of 0.001 and 0.0005 respectively) (Table 2). However, there was no statistically significant difference in the mean total BMD value among subjects on low dose ICS group when compared with controls. 12 (38.7%) of the 31 study subjects on ICS therapy for 6-12 months and 20 (68.9%) of 29 study subjects on inhaled steroid therapy for more than 12 months had a low trochanteric BMD. This difference was statistically significant (p=0.018) (Table 3). This infers that among all the sites, trochanteric region is the best site for monitoring and detection of low BMD, especially in those who are on long-term ICS therapy.

11.7% of the study subjects were on low dose of ICS, all of whom were well controlled. 58.3% of the asthmatics in our study were on medium dose of ICS therapy, among whom, 77.14% were well controlled. 30% of the subjects were on high dose ICS and among them, 55.56% were not well controlled. These observations were statistically significant (p=0.008), indicating that most asthmatics can be well controlled with low to medium dose of steroids. Of the 16 subjects who did not rinse their mouth after ICS use, low BMD was observed in 11 (68.75%) in trochanteric region, Ward's triangle and total femur, and 10 (62.5%) in the region of neck of femur. However, there was no statistical significance (p=0.148, 0.056, 0.148 and 0.07 respectively).

15% of the study subjects and 11.7% of the controls had vitamin D deficiency and this difference was statistically not significant. 35% and 38.3% of the respective groups had vitamin D insufficiency and these differences were also statistically insignificant. 50% of each group had normal vitamin D levels indicating that there is no statistically significant difference between study and control groups with respect to vitamin D levels (p=0.843). Among 30 study subjects who had normal vitamin D levels, 66.7% had good control and 33.3% did not. Of the 30 subjects with low vitamin D levels, 22 (73.3%) had well controlled asthma compared to 8 (26.7%) who did not. These observations however were statistically not significant (p=0.513). Of the 30 study subjects with low vitamin D levels, 6 (20%) were on low dose, 18 (60%) were on medium dose and 6 (20%) were on high dose steroids. In those with normal vitamin D levels, 1 (3.3%) was on low dose, 17 (56.7%) were on medium dose and 12 (40%) were on high dose steroid therapy.

However, these observations were not statistically significant (p=0.06) (Table 4) indicating that the dose of steroids does not significantly affect vitamin D levels. Out of 31 subjects who were on ICS for 6-12 months, 45.2% had low and 54.8% had normal vitamin D levels. Of the 21 study subjects on steroid therapy for 6-12 months, 42.9% had low and 57.1% had normal levels. Of the 8 subjects on steroid therapy for more than 24 months, 87.5% had low vitamin D levels and 12.5% had a normal value. These observations were statistically insignificant (p=0.073) (Table 5) indicating that duration of steroid therapy does not significantly affect the vitamin D levels.

Table 1: Area wise mean bone mineral density among study and control groups.

BMD regions	Study group, mean (SD) (g/cm^2)	Control group, mean (SD) (g/cm^2)	P value
Neck of femur	0.715 (0.135)	0.739 (0.122)	0.310
Ward's triangle	0.664 (0.129)	0.704 (0.126)	0.091
Trochanter	0.572 (0.104)	0.608 (0.112)	0.076
Total femur	0.690 (0.135)	0.731 (0.137)	0.102
Lumbar	0.701 (0.184)	0.722 (0.181)	0.540
Total	0.610 (0.170)	0.620 (0.140)	0.766

Table 2: Mean total bone mineral density levels compared with dose of inhaled steroids.

Dose of steroids	Mean±SD total BMD (g/cm^2)		P value
	Study subjects	Control group	
High dose	0.564±0.104	0.731±0.137	0.001
Medium dose	0.613±0.192		0.0005
Low dose	0.771±0.114		0.4610

Table 3: Comparison of area wise bone mineral density with the duration of steroid therapy.

Duration (month)	NOF		Troch		Ward's		Total femur		Lumbar		Total BMD	
	L	N	L	N	L	N	L	N	L	N	L	N
6-12	12	19	12	19	13	18	13	18	11	20	6	25
>12	14	15	20	09	16	13	19	10	16	13	4	25
Total	26	34	32	28	29	31	32	28	27	33	10	50
P value	0.454		0.018		0.305		0.067		0.125		0.563	

NOF=neck of femur; Troch=trochanter; Ward's=Ward's triangle; Lumbar=lumbar spine; L=low BMD; N=normal BMD

Table 4: Comparison of vitamin D levels with dosage of steroids.

Vitamin D (ng/ml)	Low dose (%)	Medium dose (%)	High dose (%)	Total	P value
<20	6 (20)	18 (60)	06 (20)	30	0.06
>20	1 (3.3)	17 (56.7)	12 (40)	30	

Table 5: Comparison of Vitamin D levels with the duration of steroid therapy.

Vitamin D (ng/ml)	6-12 months (%)	12-24 months (%)	>24 months (%)	P value
<20	14 (45.2)	09 (42.9)	7 (87.5)	0.073
>20	17 (54.8)	12 (57.1)	1 (12.5)	
Total	31	21	8	

DISCUSSION

This was a cross sectional study of 60 asthmatic children and 60 age-and-sex matched non-asthmatic controls belonging to the age group of 5-18 years, conducted at asthma clinic of a tertiary care hospital in Mysuru.

The mean BMD values in all the regions (including total BMD, trochanter, Ward's triangle, neck of femur, total femur and lumbar spine) in this study was higher in control group than the study subjects, though this difference was statistically not significant. The mean total BMD in medium and high dose ICS groups was significantly lower compared to controls but not so in low dose steroid group. The present study has found trochanteric region to be an important site in monitoring the BMD in asthmatic children on long term ICS therapy. More studies are required to re-affirm these observations. Most asthmatics can be well controlled with low to medium dose of steroids.

There was no significant difference between study and control groups with reference to vitamin D levels. Vitamin D levels were not found to have any association with degree of control of asthma. Dose and duration of steroid therapy did not have any significant impact on vitamin D levels.

The sex ratio in our study showed a male preponderance of 1.85:1, which is consistent with over all male preponderance found in other studies.[10,16-20] There is male preponderance in the early childhood. This disparity undergoes a gradual change and during adolescence, the prevalence in males reduces with a concurrent rise in the females to finally end with a female predominance during adult life – 9.6% in women compared to 6.3% in men.[21]

The mean total BMD values in present study was lower than the values seen in some other studies.[11,14,22] This could be because the study involves Asian population where the reference values are said to be lower.[23] In concordance with the present study, the mean total BMD was higher in the control group than the study group though none of the studies showed any statistical significance.[11,14,22] The lumbar spine BMD values in some studies range from 0.59 g/cm^2 to 0.88 g/cm^2.[10,11,17,18,23,24] The mean lumbar BMD in this study was 0.701 g/cm^2 which falls within the same range. There was no statistically significant difference between the study subjects and the control group in these studies, except the study by Allen et al where the study subjects were 48 but only 9 in the control group.[19] The present study concurred with the observation of no statistical difference between study and control groups with respect to the mean BMD values in the neck of femur.[17,25]

Unlike in the present study, where a statistically significant difference was noted between the study subjects on low versus high dose steroid therapy on mean total BMD, in the study by Bahceciler et al there was no statistical significance.[11] But in the said study, 52 study subjects (22 males, 30 females) were compared with 22 controls (10 males, 12 females) and the categorization into low and high dose therapy was based on a cumulative steroid dosage cut off of 102 mg. In the present study, this categorization was done as per the GINA guidelines 2020 and our study had better sample size and equal number of controls.[1]

Similar to our study, in the study by Kavitha et al there was no statistically significant difference between vitamin D levels and the control of asthma.[26] A wide variation can be seen in the vitamin D levels in the different studies. Unlike in the present study where the was no statistically significant difference between vitamin D levels and control of asthma, other studies have shown a statistical significance.[27,28] However, there was no clinical significance as both study subjects and control group had normal vitamin D levels in the Omole et al study while on the other hand, both the groups have low vitamin D levels in the study by Somashekar et al.[27,28]

Strengths of the study include comparison of BMD among asthmatics with age and sex matched non-asthmatic controls. BMD measurement in the study was done in several regions including trochanter, Ward's triangle, neck of femur, total femur, lumbar spine and total body, unlike most studies which have measured BMD in lumbar spine, neck of femur or whole body but not at the trochanter.

Limitations of the study are that skeletal age assessment and Tanner staging was not done. To compensate for the same, equal number of age and sex matched controls were used. Longitudinal follow-up of study subjects was not done to monitor for changes in BMD, as it was not a prospective study, however this issue was addressed by comparison of duration of steroid therapy with BMD.

CONCLUSION

Low dose inhaled corticosteroids were found to be safe with no impact on BMD, whereas, there was a significant reduction in BMD with medium-to-high dose ICS therapy for more than 6 months. Trochanter is a useful predictor site for monitoring effect of long term ICS on bone

metabolism. Neither was there an association between vitamin D levels and the control of asthma, nor with varying dose or duration of ICS therapy. Annual monitoring of BMD is recommended in children on long term medium-to-high dose ICS.

It is an established fact that long term oral corticosteroids impact the bone metabolism significantly. However, the effect of long term inhaled corticosteroids on bone mineral density is controversial. This study demonstrates that there is a significant reduction in BMD with long term medium and high dose ICS and emphasizes the safety of low dose ICS.

ACKNOWLEDGEMENTS

Authors would like to thank Dr. P. K. Vedanthan, International asthma services for their support for asthma clinic, Mysore alumni association for financial support and Dr. Praveen Kannan of Kannan diagnostic centre for support to get BMD by DXA

Funding: The study was funded by research grant from Mysore Alumni Association
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Global Initiative for Asthma, Global Strategy for Asthma Management and Prevention. 2020. Available at: https://ginasthma.org. Accessed on 24 April 2020.
2. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. N Engl J Med. 2000;343(15):1054-63.
3. Sukumaran TU. Asthma training module (ATM), asthma by consensus (ABC) and asthma education. Indian Pediatr. 2011;48(6):433-5.
4. Kant S. Socio economic dynamics of asthma. Indian J Med Res. 2013;138(4):446-8.
5. Chakravarthy S, Singh RB, Swaminathan S, Venkatesan P. Prevalence of asthma in urban and rural children in Tamil Nadu. Nat Med J India. 2002;15(5):260-3.
6. Pakhale S, Wooldrage K, Manfreda J, Anthonisen N. Prevalence of Asthma Symptoms in 7th- and 8th-Grade School Children in a Rural Region in India. J Asthma. 2008;45(2):117-22.
7. Jain A, Vinod Bhat H, Acharya D. Prevalence of bronchial asthma in rural Indian children: A cross sectional study from South India. Indian J Pediatr. 2010;77(1):31-5.
8. Seibel MJ, Cooper MS, Zhou H. Glucocorticoid-induced osteoporosis: mechanisms, management and future perspectives. Lancet Diabetes Endocrinol. 2013;1:59-70.
9. Mortimer KJ, Harrison TW, Tattersfield AE. Effects of inhaled corticosteroids on bone. Ann Allergy Asthma Immunol. 2005;94:15-21.
10. Harris M, Hauser S, Nguyen TV, Kelly PJ, Rodda C, Morton J, et al. Bone mineral density in prepubertal asthmatics receiving corticosteroid treatment. J Paediatr Child Health. 2001;37:67-71.
11. Bahceciler NN, Sezgin G, Nursoy MA, Barlan IB, Basaran MM. Inhaled corticosteroids and bone density of children with asthma. J Asthma. 2002;39:151-7.
12. Fuhlbrigge AL, Kelly HW. Inhaled corticosteroids in children: effects on bone mineral density and growth. Lancet Respir Med. 2014;2:487-96.
13. Larry A, Binkovitz, Maria J, Henwood. Pediatric DXA: Technique and interpretation. Pediatr Radiol. 2007;37:21-31.
14. Khadilkar A, Khadilkar V, Chinnappa J, Rathi N, Khadgawat R, Balasubramanian S, et al. Prevention and treatment of vitamin D and calcium deficiency in children and adolescents: Indian Academy of Pediatrics (IAP) guidelines. Indian Pediatr. 2017;54(7):567-73.
15. Sanjana JM, Mahesh PA, Jayaraj BS, Lokesh KS. Changing trends in the prevalence of asthma and allergic rhinitis in children in Mysore, South India. Eur Respir J. 2014;44(58):1187.
16. 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;37:116-21.
17. Sidoroff VH, Ylinen MK, Kroger LM, Kroger HP, Korppi MO. Inhaled Corticosteroids and Bone Mineral Density at School Age: A Follow-up Study After Early Childhood Wheezing. Pediatr Pulmonol. 2015;50(1):1-7.
18. Boot AM, de Jongste JC, Verberne AA, Pols HA, de Muinck, Keizer-Schrama SM. Bone mineral density and bone metabolism of prepubertal children with asthma after long-term treatment with inhaled corticosteroids. Pediatr Pulmonol. 1997;24(6):379-84.
19. 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(3):188-93.
20. Kelly HW, Van Natta ML, Covar RA, Tonascia J, Green RP, Strunk RC. 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(1):53-61.
21. Kynyk JA, Mastronarde JG, McCallister JW. Asthma, the sex difference. Curr Opin Pulm Med. 2011;17(1):6-11.
22. Agertoft L, Pedersen S. Bone mineral density in children with asthma receiving long-term treatment

with inhaled budesonide. Am J Respir Crit Care Med. 1998;157(1):178-83.
23. Laura KB, Trevor H, Wang MC, Balasubramanian N, Robert M. Bone Mineral Acquisition in Healthy Asian, Hispanic, Black, and Caucasian Youth: A Longitudinal Study. JCEM. 1999;84(12):4702-12.
24. Tse SM, Kelly HW, Litonjua AA, Van Natta ML, Weiss ST, Tantisira K. Corticosteroid use and bone mineral accretion in children with asthma: Effect modification by vitamin D. J Allergy Clin Immunol. 2012;130(1):53-60.
25. Roux C, Kolta S, Desfougeres JL, Minini P, Bidat E. Long term safety of fluticasone propionate and nedocromil sodium on bone in children with asthma. Pediatrics. 2003;111(6):706-13.
26. Kavitha TK, Gupta N, Kabra SK, Lodha R. Association of Serum Vitamin D Levels with Level of Control of Childhood Asthma. Indian Pediatr. 2017;54(1):29-32.
27. Omole KO, Kuti BP, Oyelami OA, Adegbola AJ, Omole JO. Serum Vitamin D profile of Nigerian children with asthma: Association with asthma severity and control. Pediatr Pulmonol. 2018;53:544-51.
28. Somashekhar AR, Ashwini BP, Vanitha Gowda MN. Vitamin D Levels in Children with Bronchial Asthma. J Clin Diagn Res. 2014;8(10):4-75.

Cite this article as: Basavanagowda T, Ramaraj SM. Effect of inhaled corticosteroids on bone mineral density in asthmatic children. Int J Contemp Pediatr 2021;8:672-7.