Received: 29 May 2023 | Revised: 24 December 2023 | Accepted: 15 April 2024

DOI: 10.1002/hsr2.2086

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Evaluation of vitamin D deficiency and low bone mass in children with asthma in fars province: A case-control study

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Abstract

Background and Aims: Asthma is a chronic inflammatory pulmonary disease which affects 10%–20% of children and adolescents. Inhaled corticosteroids (ICS) is one of its most effective therapies. The effect of systemic corticosteroids on decreasing bone mineral density (BMD) was investigated and proved in children; however, the influence of ICSs on bone density has still remained unclear. This study evaluates the bone mineral density of children and adolescents with asthma in southern Iran and the associated factors, for example, amount of used inhaled steroid.

Method: This case-control study enrolled 41 children and adolescents (aged 8–18 years) with asthma and their age and gender-matched controls in 2019–2020. Serum Calcium, phosphate, vitamin D, and bone mineral density were measured. Their physical activity, sun exposure, and fracture history were evaluated subjectively.

Results: Lumbar BMD and BMD Z-score in patients showed no significant difference with controls ($p = 0.23$, $p = 0.73$). Also, it showed that there was no significant difference in biochemical studies, growth, and bone densitometry parameters between patients who used ICSs for less than 3 months/year corticosteroid therapy compared to those with equal or more than 3 months/year usage. Prevalence of vitamin D deficiency was 28% and 8% in the controls and patients, respectively ($p = 0.005$).

Conclusion: The present study showed that 9.46% of children and adolescents with asthma had low bone mass for chronological age, and it is not significantly higher than normal population. Dosage of inhaled steroid did not associate with osteoporosis in these patients. Prevalence of vitamin D deficiency in patients was lower than normal population, probably due to receiving vitamin D in their routine follow-ups.

KEYWORDS

asthma, bone density, child, vitamin D deficiency

Soheila Alyasin and Fateme S. Sadeghi contributed equally to this study.

1 | INTRODUCTION

Asthma is a chronic inflammatory pulmonary disease that affects both children and adults. Its prevalence among children aged 6–18 years varies between 10% and 20%. Inhaled corticosteroids (ICSs) is one of the most effective therapies which prevent asthma exacerbations.[1] The effect of systemic corticosteroids on decreasing bone mineral density (BMD) was investigated and confirmed in children[2,3]; however, the effect of ICSs on bone density has still remained unclear.[4] Some previous reports showed that prolonged treatment with inhaled steroids in children and adolescence with moderate to severe asthma did not have adverse effects on the bone mineral density.[5–8] However, few studies showed that children with asthma had lower total body BMD,[9,10] and BMD reduction in these patients depends on age,[11] dose of inhaled corticosteroid used in these children,[12] and genetic factors.[13] Zieck et al. showed that using inhaled corticosteroids was not associated with increased fracture risk in children with asthma.[4]

Difference in the results of studies about the association of using inhaled steroid on the BMD in children data and lack of sufficient related data in middle East prompted us to do this study. We evaluated the prevalence of vitamin D deficiency and bone mineral density of children and adolescents with asthma in Fars province, located in southern Iran; we also investigated the associated factors like steroid dosage.

2 | MATERIALS AND METHODS

This case-control study enrolled 41 children and adolescents with asthma and followed in the Imam Reza Asthma clinic affiliated to Shiraz University of Medical Sciences, located in Shiraz, Fars province in southern Iran, 2019–2020. Sample size calculated according to the inaloo et al.[14] study from an alpha error of 0.05, a beta error of −0.99, and power of 1 with relative risk reduction of 10% in all-causes mortality. So, at least 29 subjects should be included for this study which is measured using the below formula.

$$n = \frac{(Z_{1-\alpha/2}\sqrt{2\bar{p}\bar{q}} + Z_{1-\beta}\sqrt{p_1q_1 + p_2q_2})^2}{(\delta)^2},$$

$$p_1 = 27.6\% \; \delta = |p_2 - p_1|,$$

$$p_2 = 76.7\% \; \bar{p} = \frac{P_1 + P_2}{2}.$$

Patients aged 8–18 years with asthma who had been diagnosed with asthma and receiving treatment for at least 1 year before the study were included. Patients were excluded if they had other pulmonary comorbidities, malignancies, metabolic bone diseases, diabetes mellitus, chronic renal failure, active or passive smoking, and using some medications that affect bone metabolism like anticonvulsants, oral corticosteroids, antiviral, antifungal, and thyroid hormones. In addition, patients who had not received corticosteroid within the past year were excluded from study as well. Patients were classified based on whether they had an asthma attack in the last 3 months and used inhaled steroids during those attacks. Patients who had an asthma attack and using inhaler steroids in less than the last 3 months were included in the low-dose group in the study, and patients who had an asthma attack and using inhaler steroids for more than 3 months in the last year were included in the high-dose group. the frequency of their inhaled steroid use during those attacks also were recorded. Finally, two patients did not follow the study protocol, and 39 patients participated in this study to the end.

Thirty-nine age- and gender-matched healthy controls were randomly selected from a previous cohort study performed for evaluating the Iranian children's bone mass in this region.[15] All participants and their parents signed the informed consent form after discussing the aim and method of the study.

2.1 | Biochemical studies

Five milliliters of venous blood samples were taken after 8-h overnight fasting. Serum calcium (Ca), phosphorous (P), and alkaline phosphatase (ALP) were assessed by colorimetric method with Biosystem SA, auto analyzer. Serum 25-hydroxy vitamin D (25OHD) was measured by Cobas 411, using electrochemiluminescence method. this study conducted during autumn2020 and winter 2021. None of the patients and controls had used vitamin D supplement 3 weeks before the blood sampling.

2.2 | Bone mineral density

The Hologic system dual-energy X-ray absorptiometry (DXA) (Discovery QDR) was used to measure the lumbar spine (L1–L4) bone mineral density. Low bone mass (LBS) was defined as BMD Z score of −2 or lower than the expected range for age according to the International Society for Clinical Densitometry (ISCD). The coefficient of variation was 0.5% for the lumbar spine BMD in our center, according to the twice BMD measurements on the same day as the 10 patients, and the precision errors were calculated using the root mean square method.

2.3 | Anthropometrics, sun exposure, physical activity, and pubertal stage

Height and weight were measured according to standard scales and wall-mounted meters, when the patients wore light cloths without chose. Body mass index (BMI) was calculated through the standard formula:

BMI (kg/m^2) = weight (kg)/[height(m)]^2.

Pubertal stage was evaluated based on tanner standard classification. A written questionnaire was gathered from the parents

related to physical activity, sun exposure, previous fracture history, and calcium intake. We divided the children into two groups of physical activity, whether they performed physical activities fewer or more than 3 days per week. Also, patient's exposure to the sun was divided into sufficient and insufficient: ≥30 min/day versus <30 min/day sun exposure, subjectively.

2.4 | Statistical analysis

The statistical package for the social sciences (SPSS) software version 22 (SPSS Inc.) was used to analyze the data. Descriptive data were shown as mean ± SD (standard deviation), frequency, and percentage.

Normality of data distribution was checked using the Kolmogorov–Smirnov test. Chi-square test and Fisher exact test were used to compare the qualitative data, and the student *t*-test test and Mann–Whitney test was used for comparison of the quantitative data between the two groups. Variables with a univariate analysis *p*-value of less than 0.2 were entered in the multivariable analysis. Multiple linear regression analysis was used to determine the independent factors related to LBS in the lumbar area. *p*-Value less than 0.05 was considered as statistically significant.

2.5 | Results

A total of 78 individuals (39 children with Asthma and 39 controls) participated in the present study. The patients' mean age was 10.87 ± 2.9 years, and 71.8% of them were male. Descriptive data of patients as compared with the controls are showed in Table 1. Children with asthma had higher serum vitamin D level ($p < 0.001$) and higher BMI percentile ($p = 0.03$). Lumbar BMD and BMD Z-score in patients had no significant difference with controls ($p = 0.23$, $p = 0.73$).

Prevalence of vitamin D deficiency was 28% and 8% in the controls and patients, respectively ($p = 0.005$). Prevalence of LBS for chronological age was 6.76% and 9.46% in the controls and patients, respectively ($p = 0.76$). Table 2 shows the characteristics of patients who underwent corticosteroid therapy for less than 3 months/year compared to those equal or more than 3 months/year; the results showed no significant difference in biochemical studies, growth, and DXA (Dual-energy X-ray absorptiometry) parameters in both groups. Prevalence of vitamin D deficiency was 10.26% and 5.13% in patients with less than 3 months/year ICS therapy and those with more than 3 months/year ICS therapy, respectively ($p = 0.13$). Prevalence of LBS for chronological age was 7.69% and 10.26% in patients with <3 months/year ICS therapy and ≥3 months/year ICS therapy ($p = 0.48$).

Table 3 is a summary of the results of regression analysis of the factors associated with serum vitamin D in patients. It was shown that vitamin D level of our patients did not depend to age, gender, BMI percentile, puberty, physical activity, sun exposure, and duration of steroid therapy ($R^2 = 0.937$). Table 4 displays the result of regression analysis of the factors associated with lumbar BMD-Z score in patients. It was shown that lumbar BMD-Z score of our patients did not depend to age, gender, BMI percentile, puberty, physical activity, sun exposure, dental caries, vitamin D level, and duration of steroid therapy ($R^2 = 0.330$). In addition, Table 5, which shows the results of regression analysis of the factors associated with the number of fracture episodes during ICS therapy in patients, it was showed that fracture episode during asthma treatment in our patients did not depend to age, gender, BMI percentile, puberty, physical activity, sun exposure, dental caries, calcium, phosphor, vitamin D level and duration of steroid therapy reveals no significant associated factor ($R^2 = 0.301$).

TABLE 1 General characteristics of patients and control group and the related comparisons.

Variable	Control group	Patients	*p*-Value[a]
Age (years)	10.97 ± 2.79	10.87 ± 2.89	0.79
Calcium (mg/dL)	9.98 ± 0.49	8.75 ± 1.03	0.05
Phosphorous (mg/dL)	4.14 ± 0.58	3.9 ± 0.8	0.06
Alkaline phosphates (IU/L)	417 ± 156	325 ± 130	0.47
25OHD (ng/mL)	19.26 ± 6.69	31.25 ± 16.59	<0.001
Height (cm)	142.87 ± 14.1	144.95 ± 17.41	0.68
Weight (kg)	36.87 ± 12.61	39.87 ± 16.04	0.46
Body mass index (BMI) (kg/m^2)	17.54 ± 2.68	18.52 ± 3.88	0.26
BMI percentile (%)	46.84 ± 25.56	53.63 ± 34.62	0.03
Lumbar bone mineral density (BMD) (g/cm^2)	0.61 ± 0.14	0.59 ± 0.14	0.23
Lumbar BMD Z-score	−1.04 ± 1.01	−1.1 ± 1.01	0.73
Sun exposure (%)	Insufficient 33.3% Sufficient 66.7%	Insufficient 35.9% Sufficient 64.1%	0.81
Physical activity (%)	Insufficient 28.2% Sufficient 71.8%	Insufficient 33.3% Sufficient 66.7%	0.43
Puberty (%)	Prepubertal 48.6% Early pubertal 40% Late pubertal 11.4%	Prepubertal 23.1% Early pubertal 53.8% Late pubertal 23.1%	0.07
Sex (%)	Male 71.8% Female 28.2%	Male 71.8% Female 28.2%	>0.99

[a]Chi-square test and Fisher exact test were used to compare the qualitative data, and the student *t*-test test and Mann–Whitney test was used for comparison of the quantitative data between the two groups.

TABLE 2 General characteristics of patients who used corticosteroid (CS) for less than 3 months/year compared to those who used it for at least 3 months/year and their related comparisons.

Variable	Less than 3 months/year CS	≥3 months/year CS	*p*-Value[a]
Age (years)	11.09 ± 3.38	10.4 ± 2.02	0.79
Calcium (mg/dL)	8.22 ± 1.16	8.5 ± 0.81	0.46
Phosphorous (mg/dL)	3.88 ± 0.95	3.92 ± 0.56	0.54
Alkaline phosphates (IU/L)	317 ± 149	341 ± 101	0.46
25OHD (ng/mL)	31.4 ± 20.58	30.3 ± 8.52	0.40
Height (cm)	145.2 ± 19.2	144.5 ± 15.45	0.88
Weight (kg)	42.06 ± 19.18	36.83 ± 10.05	0.75
Body mass index (BMI) (kg/m^2)	18.98 ± 4.42	17.94 ± 3.01	0.16
BMI percentile (%)	55.95 ± 36.02	50.06 ± 36.03	0.52
Lumbar bone mineral density (BMD) (g/cm^2)	0.61 ± 0.16	0.56 ± 0.11	0.35
Lumbar BMD Z-score	−0.93 ± 0.87	−1.33 ± 1.21	0.45

[a]Chi-square test and Fisher exact test were used to compare the qualitative data.

TABLE 3 Analysis of the factors associated with vitamin D level in patients.

Variables	Beta	*p*-Value[a]	Std. error
Age (years)	−0.62	0.43	4.51
Gender	0.05	0.83	9.33
Body mass index (BMI) percentile (5)	−0.72	0.06	0.17
Puberty	0.01	0.97	5.68
Physical activity	0.02	0.91	7.69
Sun exposure	−0.2	0.84	10.91
History of fracture	−0.38	0.24	12.73
Duration of steroid therapy	0.12	0.54	6.77
Lumbar z-score	−0.45	0.43	9.28

[a]Results of multiple linear regressions of the factors associated with vitamin D level in patients, conducted by Enter method (R^2 = 0.937).

3 | DISCUSSION

The present study revealed that 9.46% of children and adolescents with asthma had LBS for their chronological age (LBMC), which was not significantly higher than the normal population. Also, prevalence of LBMC in patients who used ICS for more than 3 months/year was not higher than those who used it for less than 3 months/years.

TABLE 4 Analysis of the factors associated with Lumbar bone mineral density (BMD) Z-score in patients.

Variables	Beta	*p*-Value[a]	Std. error
Gender	0.056	0.83	0.586
Age (years)	−0.617	0.26	0.195
Body mass index (BMI) (k/m^2)	0.367	0.25	0.083
Puberty	0.668	0.27	0.471
Physical activity	−0.311	0.20	0.514
Sun exposure	−0.200	0.47	0.585
History of fracture	−0.269	0.25	0.605
Duration of steroid therapy	0.123	0.55	0.511
Dental caries	−0.281	0.28	0.665
Calcium (mg/dL)	−0.052	0.85	0.283
Phosphorous (mg/dL)	−0.083	0.76	0.339
Vitamin D level (ng/mL)	−0.032	0.88	0.014

[a]Results of multiple linear regressions of the factors associated with Lumbar BMD Z-score level in patients, conducted by Enter method (R^2 = 0.330).

TABLE 5 Analysis of the factors associated with fracture episodes during Asthma treatment.

Variables	Std. error	Exp (B)	*p*-Value[a]
Gender	1.859	0.156	0.31
Age (years)	0.269	1.149	0.60
BMI (kg/m^2)	0.253	0.681	0.13
Sun exposure	1.962	0.220	0.44
Physical activity	1.408	0.917	0.95
Lumbar Z-score	0.668	0.762	0.68
Vitamin D (ng/mL)	0.042	1.072	0.09
Phosphorous (mg/dL)	1.165	1.090	0.94
Calcium (mg/dL)	0.811	0.495	0.38
Duration of steroid therapy	0.023	0.988	0.60

[a]Results of multiple linear regressions of the factors associated with fracture episodes during Asthma treatment conducted by Enter method (R^2 = 0.301).

Prevalence of vitamin D deficiency in patients was lower than normal population, probably due to receiving vitamin D in their routine follow-ups. In addition, we showed that lumbar BMD-Z score and fracture episodes in patients did not depend on the duration of using ICS and severity of asthma.

In 1997, Boot et al. showed that children with asthma had lower total body BMD after using inhaled corticosteroids for 3–8 years.[9] After that, Hams et al. showed a reduced bone mass in prepubertal asthmatic children receiving high dose of ICS (more than 400–800 µg/day).[10] Kelly et al. showed that multiple oral

corticosteroid usage during treatment of asthma could produce a dose-dependent reduction in bone mineral density in children with asthma.[12] In addition, Monadi et al. showed that BMD reduction during inhaled corticosteroid therapy was dependent on the age of patients; the youngers were at greater risk of BMD loss.[11] On the other hand, many previous studies showed that using inhaled corticosteroid therapies in children with asthma was not associated with LBS or fractures.[4–8] Agertoft et al. investigated total body BMD of the children with asthma treated for 3–6 years with continuous inhaled budesonide and showed no significant decline in BMD, and gender; also, the duration of asthma was not affected in this regard.[8] Similar to these results, Bahceciler et al. showed that BMD of children with asthma treated for about 13 months with continuous inhaled budesonide was not different from those who had never been treated with ICSs.[7] In addition, Griffiths et al. showed that high-dose inhaled fluticasone propionate for a duration more than 6 months did not change the biochemical markers of bone metabolism or total BMD in children with asthma.[6] Similar results were observed in Turpeinen et al. and Kinberg et al.'s studies.[5,16]

In the present study, we showed that neither BMD nor fracture risk in children with asthma treated with ICSs for more than 6 months was different from the healthy controls. Similar to our study, Loke et al. showed that using inhaled corticosteroids for more than 12 months in patients with asthma was not associated with harmful effects on fractures or BMD.[17]

Zeick et al. also studied children with asthma and revealed that inhaled corticosteroid was not associated with fracture risk in these patients.[4] The difference between previous studies might be, to some extent, due to difference in patient selection. In our study, we had a very rigid selection criterion in an attempt to exclude the patients with chronic obstructive pulmonary disease, smoking, and those with other chronic inflammatory diseases. One of the important factors was smoking (passive or active) which has a harmful effect on bone mineral density and fracture risk.[18] Another explanation is that treatment with inhaled corticosteroid could reduce chronic inflammation and decrease the need for using oral corticosteroids during asthma exacerbations; hence, it might have a positive impact on BMD.[17] Inhaled corticosteroids may allow the patients to have more active life by controlling the disease. Therefore, increasing physical activity in these patients could have positive effect on BMD.[19] The last important factor is the genetic. New biologic pathways were suggested that a gene module and several genes can play possible roles in the pathogenesis of glucocorticoid-induced derangement in BMD. Lee et al identify an important gene module composed of 199 genes showed a significant association with the BMD Z score in both childhood and adult asthmatic patients.[20]

The present study, like any other research, has some strengths that was specifically investigating the bone mineral density and fracture risk in asthmatic children of southern in Iran. It also had some limitations. First, we evaluated the sun exposure and physical activity using a subjective method; hence, it could have some personal errors. Another limitation of our study was that we could not evaluate the effect of different inhaled corticosteroids separately because of our limited sample size that could affect the statistical analysis. Moreover, it is better to check vitamin D level with HPLC (High-performance liquid chromatography)-tandem mass spectrometry (HPLC-MS/MS) technology. More prolonged follow-up study and evaluating wrist or knee region BMD should be done to evaluate the effect of inhaled steroids on BMD more precisely.

4 | CONCLUSION

The present study showed that 9.46% of children and adolescents with asthma had LBS for chronological age, and it is not significantly higher than normal population. Also, we showed that lumbar BMD of these patients was not associated with the amount of inhaled corticosteroids. It seems that using inhaled corticosteroids in children with asthma did not affect the BMD. Prevalence of vitamin D deficiency in patients was lower than normal population, probably due to receiving vitamin D in their routine follow-ups.

4.1 | What's known?

Inhaled corticosteroids is one of its most effective therapies. The effect of systemic corticosteroids on decreasing bone mineral density was investigated and proved in children; however, the influence of ICSs on bone density has still remained unclear.

4.2 | What's new?

Lumbar bone mineral density of these patients was not associated with the amount of inhaled corticosteroids. Using inhaled corticosteroids in children with asthma did not affect the bone mineral density.

AUTHOR CONTRIBUTIONS

Soheila Alyasin: Conceptualization; methodology; resources; supervision; validation; visualization. **Fateme S. Sadeghi**: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; writing—original draft; writing—review and editing. **Forough Saki**: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; validation; visualization; writing—original draft; writing—review and editing. **Mohamadhosein Dabaghmanesh**: Methodology; resources; supervision; validation.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the finding of this study are available from the corresponding author upon a reasonable request. The data are not publicly available due to privacy of ethical restriction.

ETHICS STATEMENT

Shiraz University of Medical Science Ethics Committee and vice-chancellor of research approved the study with the code of IR.SUMS.MED.REC.1399.312. All participants and their parents signed the informed consent form after discussing the aim and method of the study. We have done this study in Shiraz Endocrinology and Metabolism Research Center.

TRANSPARENCY STATEMENT

The lead author Forough Saki affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: Alyasin S, Sadeghi FS, Saki F, Dabaghmanesh M. Evaluation of vitamin D deficiency and low bone mass in children with asthma in fars province: a case-control study. *Health Sci Rep*. 2024;7:e2086. doi:10.1002/hsr2.2086