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Association of vitamin D levels and asthma exacerbations in children and adolescents: Experience from a tertiary care center

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Abstract

The role of vitamin D as an immunosuppressant and anti-inflammatory has been studied previously for different pathologies in different populations globally. Relationships between serum vitamin D levels and its effect on asthma exacerbations in the adolescent asthma population are not well studied in this region. Therefore, this study was conducted to determine the vitamin D status in pediatric and adolescent asthma patients, and its association with asthma exacerbations. A retrospective study was conducted at The Aga Khan University Hospital from 2016 to 2020. Children and adolescents who were diagnosed and admitted with acute asthma exacerbations and who had at least one measurement of 25 hydroxy-vitamin D (25 OHD) were included in the study. Serum vitamin D levels were documented for enrolled patients and their past 2-year data was analyzed for asthma exacerbations, mean length of stay per admission, and admission plus length of stay at High Dependency Unit. 114 patients were included in the study. 41 patients (35.96%) were found to be Vitamin D deficient, 38 patients (33.3%) were Vitamin D insufficient, and 35 patients (30.7%) were labeled as Vitamin D sufficient. The average number of exacerbations per year was significantly high in Vitamin D deficient group (2.82±1.11) in comparison with insufficient (2.05±0.92) and sufficient groups (1.37±0.59) ($p<0.001$). Vitamin D deficiency is related to an increased number of annual asthma exacerbations, length of stay per admission, and admission into High Dependency Unit (HDU).

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Introduction

The incidence and prevalence of asthma remains high in children worldwide [1]. Although multiple environmental and genetic factors contribute towards this condition, there is increasing evidence supporting the association between vitamin D deficiency and childhood asthma, in terms of prevalence [1-4]. Aside from vitamin D's functions of calcium absorption and bone mineralization, current literature suggests that vitamin D plays a role as an immune system regulator, with its deficiency contributing towards immunologically-based diseases such as asthma [5,6]. Vitamin D has been shown to promote regulatory T cells, which in turn inhibit Th2 responses, airway inflammation and airway hyperresponsiveness, all components of the pathophysiology of asthma [6,7]. It has also been found to enhance the efficacy of corticosteroids, playing an important role in asthma treatment [8]. Various studies among different populations suggest that vitamin D deficiency is associated with increased asthma severity, and contributes to increased rates of asthma exacerbations and hospital admissions among children [7,9-12]. Other studies have even explored the use of vitamin D as part of treatment for asthma exacerbations [13,14].

Serum vitamin D levels and its impact on acute asthma exacerbations in children and adolescents are not well explored in this region. Children that experience asthma exacerbations are at greater risk for future exacerbations regardless of disease severity and con-

trol, contributing to morbidity and mortality [15]. Therefore, the aim of this study is to establish the vitamin D status in pediatric asthmatic patients and determine its association with asthma exacerbations, length of stay (LOS) in hospital for each exacerbation, as well as admission into the High Dependency Unit (HDU) and LOS in the HDU. We hypothesize that a higher rate of acute asthma exacerbations is present among patients with lower vitamin D values. The aim of this study is to determine the association of vitamin D levels and asthma exacerbation in children with asthma.

Methods

A retrospective study was conducted at The Aga Khan University Hospital, Karachi, Pakistan. The study duration was from January 2016 to December 2020. We selected children and adolescents aged 6-18 years who were diagnosed and admitted with acute asthma exacerbations and had had at least one serum measurement of 25 hydroxy-vitamin D (25 OHD) levels during the study period. Serum Vitamin D levels were documented for every patient and their data for the past 2 years was analyzed for number of asthma exacerbations, mean LOS per admission, and length of stay at High dependency unit. Patients were categorized into three groups: i) vitamin D sufficient, ii) vitamin D insufficient, and iii) vitamin D deficient groups. Patients with serum 25 OHD concentrations <20 ng/ml were labeled as vitamin D deficient, and those with serum 25 OHD concentrations between 20 and 29.9 ng/ml were categorized as vitamin D insufficient, and patient with serum 25 OHD concentrations ≥30 ng/ml were labeled as vitamin D sufficient.

Diagnosis of asthma was established according to Global Initiative for Asthma (GINA) guidelines: i) identifying characteristic episodic respiratory symptoms such as wheezing, shortness of breath, chest tightness or cough, and ii) documented variable expiratory airflow limitation [16]. This includes spirometry with bronchodilation, of which an increase of FEV_1 >12% after administration of a bronchodilator is indicative of asthma [16]. Serum IgE levels also aided the diagnosis [17].

Patients admitted with bronchopneumonia, bronchiolitis, upper airway obstruction and previously diagnosed with chronic lung disease, cystic fibrosis, tuberculosis, congenital cardiac diseases and immune deficiency syndrome were excluded from the study.

Asthma exacerbation, as defined by the American Thoracic Society (ATS) and European Respiratory Society (ERS), is a deterioration in symptoms and/or lung function, and/or an increase in rescue bronchodilator use, for at least two days. If no hospital admission or Emergency Department (ED) visit is required, it will be classified as moderate exacerbation, whereas an admission or ED visit, along with oral corticosteroid treatment for at least three days, is classified as severe exacerbation [15].

All patients in different groups were further studied and compared for their use on controller medications for the past 6 months from their first documented exacerbation during study period. This included use of oral montelukast therapy, inhaled corticosteroids (inhalers or nebulization) and long acting beta agonist (inhalers). This provided the distribution of different patients in three groups according to GINA guidelines and described their management plan, as seen in Figures 1 and 2. With evolving changes in guidelines, the defined steps to control symptoms for each patient were different for different years and were not uniform (Figures 1 and 2). For our study purpose and to create uniformity in labelling steps, we have chosen 2020 GINA guidelines [18].

Statistical analysis

The data were analyzed using IBM Corp. released 2013, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA. Continuous variables were expressed as mean and standard deviation, while categorical variables were described as frequency and percentages. The ANOVA test was used for means and Chi-square test was used for categorical data to assess significant difference the groups. A p-value ≤0.05 was considered significant, with a type I error of 5%.

Results

A total of 114 patients with asthma, who were admitted for exacerbation, fulfilled the eligibility criteria for the study duration. Forty-one (41) patients (35.96%) were found to be vitamin D deficient, 38 patients (33.3%) were found to be vitamin D insufficient, while 35 patients (30.7%) were vitamin D sufficient. The frequencies of patients with failure to thrive and short stature were significantly different between the three groups (p=0.00). The average duration in years of asthma diagnosis was similar between the three groups of patient and unrelated to the vitamin D status (p=0.54). Age was also unrelated to vitamin D status (p=0.71). Demographic details of asthmatic patients divided based on vitamin D levels, including the use of specified medications for asth-

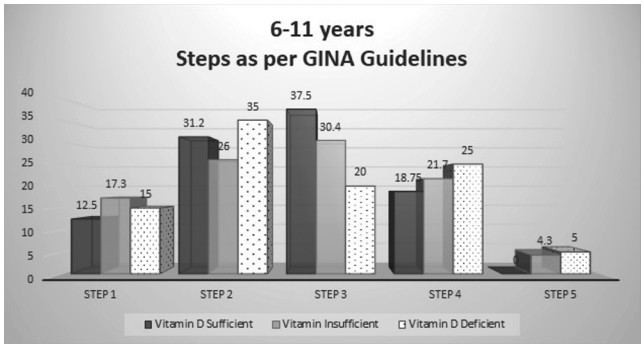

Figure 1. Vitamin D groups and GINA guideline steps of management (6 to 11 years).

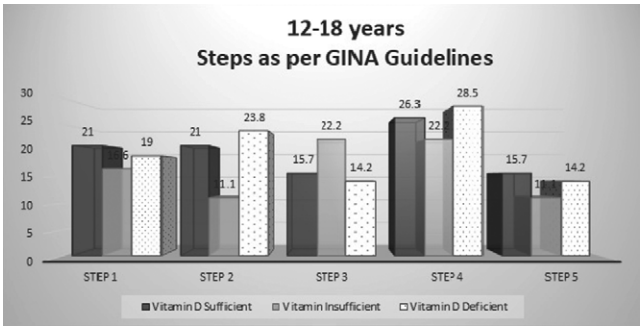

Figure 2. Vitamin D groups and GINA guideline steps of management (12 to 18 years).

ma, are presented in Table 1. Mean asthma exacerbations per year were significantly high (2.82±1.11) in vitamin D deficient groups in comparison with insufficient (2.05±0.92) and sufficient (1.37±0.59) groups (p<0.001). There was a statistically significant difference (p<0.001) in the average LOS per hospital admission between the three groups, with the vitamin D deficient group having the longest stay (3.56±1.14), vitamin D sufficient having the shortest stay (1.74±0.95), and vitamin D insufficient having an intermediate between these two groups (2.50±0.83). The number of HDU admissions showed a statistically significant difference between the three groups (p=0.01), as well as the average LOS at the HDU (p<0.001). These findings are presented in Table 2.

Discussion

This study highlights a significant association between vitamin D levels in pediatric asthmatic patients and acute asthma exacerbations. 35.69% of patients were vitamin D deficient, 33.3% of patients were vitamin D insufficient, and 30.7% were vitamin D sufficient. The average number of asthma exacerbations per year was significantly high in the vitamin D deficient group (2.82±1.11) as compared to the insufficient and sufficient groups (p<0.001). Average LOS per admission for exacerbation patients was significantly different between the groups (p<0.001), with the longest stay among Vitamin D deficient patients (3.56±1.14). Number of HDU admissions and average length of stay at HDU also showed significant differences (p=0.01, p<0.001).

In this study, asthmatic patients that were vitamin D insufficient and deficient had levels <30 ng/mL. Esfandiar *et al*. presented similar findings, in which 73.9% of a group of children with asthma were vitamin D deficient [3]. Another study conducted in Korea also found that 86% of asthmatic children showed vitamin D deficiency, whereas 28% of non-atopic children had deficient levels [2]. Further, the current study revealed that 34.21% of children in the vitamin D insufficient group failed to thrive and approximately 28.94% of children had short stature. There was a significant difference for these aspects among the three categories of vitamin D status (p=0.00). This indicates that nutritional status may be an important factor in defining vitamin D statuses in children and adolescents with asthma. Serum vitamin D levels are influenced by environmental factors such as age, body fat, amount of melanin, and time spent outdoors, which is why this current study examined failure to thrive and stature [6]. However, the findings in the current study are different than other studies, which found no significant difference in BMI between their control and asthmatic group, while another found that vitamin D insufficiency was associated with a higher BMI [2,9].

In this study, it is evident that the average number of asthma exacerbations in the group with vitamin D deficiency were significantly high in comparison with the vitamin D insufficient and sufficient groups. These results are consistent with previous studies, including Gupta et al, who found that lower vitamin D levels were associated with an increased number of asthma exacerbations in children, and increased disease severity [19]. A study by Brehm *et al*. conducted in Puerto Rico concluded that vitamin D insufficiency was associated with higher odds of greater than or equal to one severe asthma exacerbation in the prior year [odds ratio (OR), 2.6; 95% confidence interval)CI), 1.5–4.9; p=0.001] [10]. A similar study in Costa Rica corroborates these findings, with a reduced number of hospitalizations as vitamin D levels increased [12].

Table 1. Demographic details (n=114).

Variables	Vitamin D sufficient	Vitamin D insufficient	Vitamin D deficient	p-value
Patient, n (%)	35 (30.7%)	38 (33.3%)	41 (35.96%)	
Age (years)	9.76 ±3.49	11.31±2.95	10.74 ±2.19	0.71
Male:Female	1.6:1	1.4:1	1.8:1	
Failure to thrive (weight for age−2SD), n (%)	10 (28.57%)	13 (34.21%)	19 (46.34%)	0.00
Short stature (height less than−2SD), n	7 (20%)	11(28.94%)	16(39.02%)	0.00
Mean serum 25 OH vitamin D value (ng/ml)	60.5±2.52	26.28±1.86	9.89±2.03	0.00
Average duration on diagnosis with asthma (years)	5.46±1.39	4.98±1.84	5.71±2.17	0.54
Use of montelukast	30 (85.71%)	34 (89.47%)	40 (97.56%)	0.73
Use of inhaled Steroids	20 (57.57%)	25 (65.78%)	35 (85.36%)	0.02
Use of inhaled LABA	11(31.42%)	18 (47.36%)	21(51.21%)	0.04

LABA, long-acting bronchodilator inhaler.

Table 2. Outcome variables and comparison between groups.

Variables	Vitamin D sufficient (n=35)	Vitamin D insufficien (n=38)	Vitamin D deficient (n=41)	p-value
Mean asthma exacerbation per year	1.37±0.59	2.05±0.92	2.82±1.11	<0.001
Average LOS per admission	1.74±0.95	2.50±0.83	3.56±1.14	<0.001
Number of HDU admissions, n (%)	10 (28.56%)	17(44.7%)	26(63.41%)	0.01
Average length of stay at HDU	1.2±0.42	2.17±0.80	2.76±1.03	<0.001

LOS, length of stay; HDU, high dependency unit.

Furthermore, table 1 shows that there is a statistically significant difference regarding the use of inhaled corticosteroids among the three groups (p=0.02), with the greatest use among the vitamin D deficient group (85.36%). Use of long-acting bronchodilator inhaler (LABA) also showed a significant difference (p=0.04), with the vitamin D deficient group utilizing it the most (51.21%). This is in line with a previous study conducted in Costa Rica, which also found a statistically significant association between serum vitamin D levels and inhaled steroids [12]. Similarly, a different study analyzing vitamin D levels in asthmatic children found a significant association between increased inhaled corticosteroids use, oral corticosteroids use, and total steroid dose with lower vitamin D levels [20]. These findings, including in the current study, may suggest that low vitamin D levels increase asthma severity, thereby increasing the need for pharmacological treatment such as inhaled and oral steroids, as also concluded in other studies [20]. Although corticosteroid therapy proves beneficial to asthmatic patients, various laboratory studies suggest that long-term glucocorticoid therapy can eventually result in vitamin D deficiency, due to increased activity of 24-hydroxylase, which is responsible for degrading vitamin D metabolites [21,22]. On the other hand, oral administration of vitamin D has been shown to enhance and potentiate the anti-inflammatory function of corticosteroids in asthmatics, and even reverse glucocorticoid resistant asthma [23].

Asthma exacerbations are known to contribute to mortality, with one of the most common risk factors in children being viral infections (>80%), such as rhinovirus [15,24]. Vitamin D is known to increase the production of cathelicidin in macrophages, enhancing antimicrobial activity, and also supports antiviral responses in respiratory epithelial cells, protecting against a major cause of exacerbations [6,13]. Vitamin D has also been shown to inhibit TH17 cytokine production and enhance the action of inhaled corticosteroids, as well as enhance the production of IL-10 as an anti-inflammatory [14,19].

While this study did not explore the rate of exacerbation after vitamin D supplementation, current literature explores the therapeutic use of vitamin D to control or improve symptoms of asthma attacks. A Cochrane systematic review evaluating trials with administration of vitamin D concluded that participants given vitamin D experienced fewer asthma attacks needing treatment with oral steroids, the average number of attacks per person per year went down from 0.44 to 0.28, and the risk of a hospital visit for an acute asthma attack was cut in half [14]. A similar meta-analysis also concluded that vitamin D reduced the rate of exacerbations, as well as the proportion of people having at least one exacerbation requiring an emergency department visit or hospital admission [13].

The limitations of this study include the lack of a control group present without asthma to compare the vitamin D levels of asthmatic patients to. Further, asthmatic patients were not classified based on severity similar to previous studies [4]. Seasonal changes and sun exposure affecting vitamin D levels were not accounted for in this study. Lastly, based on the study design, it could not be established whether low vitamin D levels led to asthma and exacerbations, or whether the asthma itself led to low serum levels in this cohort. A previous study exploring various inflammatory conditions found that serum vitamin D levels decreased after an inflammatory insult, which may suggest that asthmatic inflammation itself can lead to decreased vitamin D levels [25]. Other studies hint at low vitamin D, such as from lack of sun exposure, contributing to the pathogenesis of asthma, due to its involvement in lung maturation and surfactant production, and downregulation of the immune response [26]. Further studies are needed to discern this relationship.

Conclusions

This study supports the hypothesis of lower vitamin D levels contributing to a higher rate of asthma exacerbations in adolescents. Timely and constant vitamin D supplementation can help in reducing the frequency and severity of exacerbation in asthma patients. Further prospective research can explore the effects of vitamin D supplementation in reducing exacerbations and asthma severity in children.

References

1. Dharmage SC, Perret JL, Custovic A. Epidemiology of asthma in children and adults. Front Pediatr 2019;7:246.
2. Kim Y-R, Seo SC, Yoo Y, Choung JT. Are children with asthma in South Korea also associated with vitamin D deficiency? Environ Health Toxicol.2017;32:e2017005.
3. Esfandiar N, Alaei F, Fallah S, et al. Vitamin D deficiency and its impact on asthma severity in asthmatic children. Ital J Pediatr 2016;42:108.
4. Hatami G, Ghasemi K, Motamed N, et al. Relationship between vitamin D and childhood asthma: A case-control study. Iran J Pediatr 2014;24:710-4.
5. Al-Zayadneh E, Alnawaiseh NA, Ajarmeh S, et al. Vitamin D deficiency in children with bronchial asthma in southern Jordan: a cross-sectional study. J Int Med Res 2020;48: 300060520974242.
6. Lange NE, Litonjua A, Hawrylowicz CM, Weiss S. Vitamin D, the immune system and asthma. Expert Rev Clin Immunol 2009;5:693-702.
7. Adam-Bonci T-I, Cherecheș-Panța P, Bonci E-A, et al. Suboptimal serum 25-hydroxy-vitamin D is associated with a history of recent disease exacerbation in pediatric patients with bronchial asthma or asthma-suggestive recurrent wheezing. Int J Environ Res Public Health 2020;17:6545.
8. Litonjua AA. Vitamin D and childhood asthma: causation and contribution to disease activity. Curr Opin Allergy Clin Immunol 2019;19:126-31.
9. Brehm JM, Schuemann B, Fuhlbrigge AL, et al. Serum vitamin D levels and severe asthma exacerbations in the childhood asthma management program study. J Allergy Clin Immunol 2010;126:52-8.e5.
10. Brehm JM, Acosta-Pérez E, Klei L, et al. Vitamin D insufficiency and severe asthma exacerbations in Puerto Rican children. Am J Respir Crit Care Med 2012;186:140-6.
11. Havan M, Razi CH, Bulus AD, et al. Effects of 25 hydroxy vitamin D levels on the severity and asthma control in school age asthma patients. Arch Argent Pediatr 2017;115:336-42.
12. Brehm JM, Celedón JC, Soto-Quiros ME, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. Am J Respir Crit Care Med 2009;179:765-71.
13. Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. Lancet Respir Med 2017;5:881-90.
14. Martineau AR, Cates CJ, Urashima M, et al. Vitamin D for the management of asthma. Cochrane database Syst Rev 2016;9: CD011511.
15. Forno E, Celedón JC. Predicting asthma exacerbations in children. Curr Opin Pulm Med 2012;18:63-9.

16. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention 2021. Accessed: 20 Jan 2022. Available from: www.ginasthma.org
17. Rothe T, Spagnolo P, Bridevaux P-O, et al. Diagnosis and management of asthma – The Swiss Guidelines. Respiration 2018;95:364-80.
18. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention 2020. Available from: https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf
19. Gupta A, Sjoukes A, Richards D, et al. Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. Am J Respir Crit Care Med 2011;184:1342-9.
20. Searing DA, Zhang Y, Murphy JR, et al. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. J Allergy Clin Immunol 2010;125:995-1000.
21. Kurahashi I, Matsunuma A, Kawane T, et al. Dexamethasone enhances vitamin D-24-hydroxylase expression in osteoblastic (UMR-106) and renal (LLC-PK1) cells treated with 1α,25-dihydroxyvitamin D3. Endocrine 2002;17:109-18.
22. Dhawan P, Christakos S. Novel regulation of 25-hydroxyvitamin D3 24-hydroxylase (24(OH)ase) transcription by glucocorticoids: Cooperative effects of the glucocorticoid receptor, C/EBPβ, and the Vitamin D receptor in 24(OH)ase transcription. J Cell Biochem 2010;110:1314-23.
23. Xystrakis E. Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. J Clin Invest 2005;116:146-55.
24. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. J Allergy Clin Immunol 2010;125:1178-87; quiz 1188-9.
25. Reid D, Toole BJ, Knox S, et al. The relation between acute changes in the systemic inflammatory response and plasma 25-hydroxyvitamin D concentrations after elective knee arthroplasty. Am J Clin Nutr 2011;93:1006-11.
26. Litonjua AA. Childhood asthma may be a consequence of vitamin D deficiency. Curr Opin Allergy Clin Immunol 2009;9:202-7.