International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2023.714.721

Research Article
Impact of Vitamin D Supplementation on Clinical Outcomes in Children with Asthma

Yan Wang, Wenqin Lao and Shunjuan Guo

Department of Pediatrics, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou 510260, China

Abstract

Background and Objective: Currently, childhood asthma incidence is rising, affecting children's growth and health. Vitamin D has multiple roles in the body's immune system, potentially closely linked to childhood asthma development. This study aims to discern the clinical efficacy of vitamin D supplementation as an intervention for children diagnosed with asthma. **Materials and Methods:** A cohort of 100 asthmatic children treated at The Second Affiliated Hospital of Guangzhou Medical University was included in this research. Using a randomized numerical table method, they were stratified into two groups: The study group (SG, n = 50, who received conventional asthma therapy coupled with vitamin D supplementation) and the control group (CG, n = 50, who were administered solely the conventional asthma treatment). Concurrently, 50 children diagnosed with non-asthmatic respiratory tract infections from the same period served as the case-control group (CCG). Pearson's analysis was utilized to evaluate the correlations between the serum 25-Hydroxy Vitamin D3 (25-OH-D3) concentrations of asthmatic children and their pulmonary function indices Forced Expiratory Volume in one second (FEV1) and Forced Vital Capacity (FVC) and the inflammatory marker IL-6. **Results:** The initial serum 25-OH-D3 levels in the SG and CG were notably inferior to the CCG ($p<0.05$). Post a three-month intervention, the SG demonstrated a marked elevation in serum 25-OH-D3 levels compared to the CG ($p<0.05$). During a 1 year follow-up, the SG displayed fewer exacerbations, reduced severity of episodes and fewer hospital admissions than the CG, with the disparities being statistically significant ($p<0.05$). After 3 months, the SG children exhibited superior FEV1 and FVC values and diminished IL-6 levels compared to the CG ($p<0.05$). **Conclusion:** Children with asthma tend to have significantly reduced serum 25-OH-D3 levels compared to their healthy counterparts. Proactive vitamin D supplementation appears promising in ameliorating these levels, offering a novel therapeutic avenue for asthma management.

Key words: Pediatric asthma management, 25-hydroxy vitamin D3, IL-6, vitamin D, correlation, clinical outcome

Citation: Wang, Y., W. Lao and S. Guo, 2023. Impact of vitamin D supplementation on clinical outcomes in children with asthma. Int. J. Pharmacol., 19: 714-721.

Corresponding Author: Yan Wang, Department of Pediatrics, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou 510260, China
Tel: +86–13143745156

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Bronchial asthma, colloquially referred to as asthma, is a persistent inflammatory ailment typified by its prolonged course, susceptibility to recurrence and migratory nature. It stands as the predominant chronic airway condition in pediatrics and has increasingly become a global public health concern[1,2]. Recent data indicate a marked surge in asthma's global prevalence. For instance, in China, the prevalence amongst children aged 0-14 was approximately 3.02% in 2020, a stark escalation from the rates observed in 2010[3]. Clinical surveillance underscores that sustained, recurrent asthma episodes can culminate in irreversible alterations to a child's airway structures. This leads to a steady deterioration in myriad lung function metrics and can drastically restrict physical activity, thereby impinging upon a child's physiological development and overall life quality[4,5].

Existing research posits that bronchial asthma emerges from a confluence of multifarious factors[6]. Although its precise etiology remains enigmatic, aberrant immune responses are presently the focal point of international asthma pathogenesis inquiries. Among these, the nexus between vitamin D and bronchial asthma has garnered significant scholarly attention[7]. Vitamin D, endowed with a plethora of physiological roles, modulates the body's immune response via both innate and adaptive mechanisms. Through its role in immune mediation, vitamin D has showcased therapeutic potential in specific diseases[8,9]. For instance, certain studies have corroborated vitamin D's capacity to recalibrate the Th1/Th2 immune disequilibrium, offering a preventive and therapeutic strategy against allergic conditions like asthma and even ameliorating the prognosis for patients with allergic ailments[10]. Furthermore, vitamin D has been implicated in mitigating the risk of respiratory infections stemming from bacterial or viral agents[11]. However, contemporary research elucidating the relationship between vitamin D and pediatric asthma remains somewhat limited.

The purpose of this study was to investigate the clinical efficacy of vitamin D supplementation as an intervention for children diagnosed with asthma and analyze the correlation between pulmonary function, inflammatory indices and serum 25-OH-D3 concentrations in children with asthma.

MATERIALS AND METHODS

General information: From September, 2021 to June, 2023, 100 asthmatic children treated at The Second Affiliated Hospital of Guangzhou Medical University were enlisted for this study. These participants were categorically allocated into two groups using a randomized numerical table: The study group (SG, n = 50, subjected to standard asthma treatment coupled with vitamin D supplementation) and the control group (CG, n = 50, receiving only the standard asthma treatment). Simultaneously, an additional 50 children diagnosed with non-asthmatic respiratory infections during this interval served as the healthy control group (CCG). Prior to commencement, this investigation secured approval from the ethics committee of The Second Affiliated Hospital of Guangzhou Medical University. Written informed consent from the subjects' guardians was also obtained.

Inclusion criteria:

- All participants fulfilled the diagnostic stipulations for asthma as articulated in the "Guidelines for the Diagnosis and Treatment of Asthma in Children"[12]
- Comprehensive clinical data was available for all participants
- Age bracket for participants ranged from 6 to 14 years
- All participants were eligible for pulmonary function evaluations

Exclusion criteria:

- Presence of restrictive ventilatory dysfunction
- Concurrent psychiatric disorders
- Consumption of vitamin AD within the preceding three months
- Existing immunodeficiency or metabolic disorders
- Concurrent rickets
- Concomitant pulmonary abnormalities or congenital airway malformations
- Intake of immunomodulators or glucocorticosteroids in the past month

Intervention method: The CG group was administered conventional asthma treatment, specifically inhaled albuterol sulfate aerosol (manufactured by GlaxoSmithKline Australia Pty Ltd., 100 µg/snap, approval number: H20160660). During acute exacerbation periods, dosages varied from 1.25-2.5 mg 2-3 times daily. Furthermore, Budesonide suspension inhalation (produced by AstraZeneca Pty Ltd., 1 mg specification, approval number: H20140475) was prescribed at 1 mg/dose 2-3 times daily. This treatment persisted for a minimum of 3-6 months, contingent upon individual patient progress.

The SG group, in addition to the aforementioned regimen, was provided with children's chewable calcium Vitamin D tablets (produced by A&Z Pharmaceutical Inc., 300 mg/tablet specification, approval number: GuoDiQiZhiJ20140153). One tablet was administered daily over a three-month span.

Observation indicators and evaluation criteria: Post-fasting, 5 mL blood samples were procured from the antecubital vein of participants, subsequently centrifuged for 15 min at 2000 r min^{-1} post a 2 hrs resting period. The resulting serum was stored at -80°C. Upon completion of sample collection, the serum was uniformly assayed for 25-OH-D3 levels utilizing a reagent kit sourced from Shanghai Jianglai Bio-Technology Co. Ltd., following the kit's explicit guidelines. Disparities in serum 25-OH-D3 levels among the SG, CG and CCG groups were assessed pre-treatment. Additionally, the serum 25-OH-D3 levels of SG and CG groups were contrasted both pre-treatment and post the three-month treatment period.

Lung functionality, specifically FEV1 and FVC indices, of participants in the SG and CG groups was gauged pre-treatment using the MasterScreen PFT spirometer (Jaeger, Hoechberg, Germany). A Pearson correlation analysis was employed to discern relationships between serum 25-OH-D3 concentrations and pulmonary function indices in the aforementioned groups.

The IL-6 levels in the SG and CG groups were ascertained pre-treatment via enzyme-linked immunosorbent assay. Furthermore, a Pearson correlation analysis illuminated potential associations between serum 25-OH-D3 concentrations and inflammatory markers in these groups.

A 1 year post-treatment follow-up of the SG and CG groups was executed, focusing on comparative metrics of attack frequency, attack severity and hospitalizations. At the three-month mark, differences in FEV1, FVC and IL-6 concentrations between the two groups were also assessed.

Statistical analysis: Data compilation and analysis were facilitated using SPSS 28.0. Count data were represented as rate (%) and evaluated using the χ^2 Test. Measurement data were expressed as Means±Standard Deviations (Mean±SD) and subjected to the t-test. Pearson test managed the correlation analyses, with statistical significance accepted at $p<0.05$.

RESULTS

Baseline clinical data assessment across the three children groups: The foundational clinical data, encompassing gender, age, height, weight, disease duration and disease severity grading for children in the three groups, were meticulously evaluated and juxtaposed. Analytical results demonstrated no marked disparities among these data across the groups, insinuating that the cohorts were statistically homogeneous ($p>0.05$), as detailed in Table 1.

Variation in serum 25-OH-D3 levels across the three children cohorts: Upon analysis, serum 25-OH-D3 levels in both the SG and CG cohorts were found to be notably diminished in comparison to the CCG cohort ($p<0.05$). These findings were elucidated in Table 2 and illustrated in Fig. 1.

Table 1: Comparison of the differences in baseline clinical data among the three groups of children

General clinical data	SG group (n = 50)	CG group (n = 50)	CCG (n = 50)	t/χ^2	p-value
Gender					
Male	29	30	28	0.132	0.716
Female	21	20	22		
Mean age (years)	9.23±2.15	9.93±2.05	9.31±2.23	0.523	0.167
Average height (cm)	126.98±13.51	127.55±12.59	126.98±13.65	0.639	0.557
Average weight (kg)	26.65±7.12	27.86±7.71	26.98±6.98	0.669	0.518
Mean duration of disease (years)	1.91±0.81	1.86±0.92	-	1.695	0.098
Disease severity					
Mild	14	10	17	0.447	0.780
Moderate	26	27	23		
Severe	10	13	10		

Data are represented by Mean±SD or n (%), SG group: Study group, CG group: Control group and CCG: Case-control group

Table 2: Differential comparison of serum 25-OH-D3 levels among children in the three groups ($\bar{x}\pm s$)

Group	Number of cases	Serum 25-OH-D3 (μg L^{-1})
SG group	50	19.04±2.20[a]
CG group	50	20.40±1.54[a]
CCG group	50	53.02±3.19
F-value	-	29.536
p-value	-	<0.001

Data are represented by Mean±SD, SG group: Study group, CG group: Control group, CCG: Case-control group, F: Statistics of comparison among three groups and [a]$p<0.05$ compared with the CCG group

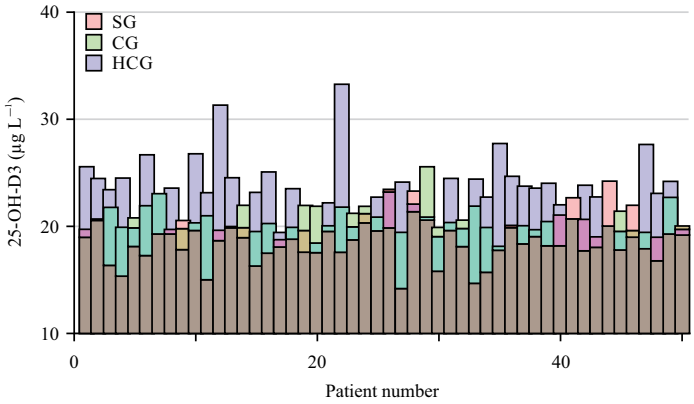

Fig. 1: Differential comparison of serum 25-OH-D3 levels among children in the three groups

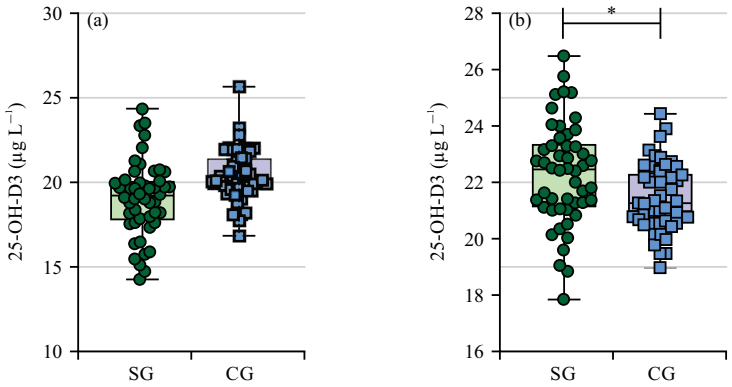

Fig. 2(a-b): Differential comparison of serum 25-OH-D3 levels between children in the SG and CG groups before treatment and after 3 months of treatment

(a) Difference in serum 25-OH-D3 levels between children in the SG and CG groups before treatment was not statistically significant (p>0.05) and (b) serum 25-OH-D3 levels in the SG group were higher than that of children in the CG group after treatment (p<0.05) and *p<0.05

Comparative analysis of serum 25-OH-D3 levels in the SG and CG cohorts pre and post treatment: Before treatment, there was no discernible difference in the serum 25-OH-D3 concentrations between the SG and CG groups (p>0.05) (Fig. 2a). Remarkably, post the three-month treatment duration, SG children exhibited elevated serum 25-OH-D3 levels relative to their CG counterparts (p<0.05) (Fig. 2b). Moreover, both groups witnessed an enhancement in their serum 25-OH-D3 levels compared to the initial pre-treatment measurements (p<0.05) (Table 3).

Correlation between serum 25-OH-D3 concentrations and pulmonary function indices (FEV1 & FVC) in asthmatic children: A Pearson correlation analysis discerned a pronounced positive correlation between the serum 25-OH-D3 levels and both FEV1 (r = 0.3365, p<0.0001) (Fig. 3a) and FVC (r = 0.3649, p<0.0001) (Fig. 3b) lung function indices in asthmatic children.

Relationship between serum 25-OH-D3 levels and inflammatory marker IL-6 in asthmatic children: Pearson correlation analytics highlighted a significant inverse correlation between serum 25-OH-D3 concentrations and the inflammatory marker IL-6 (r = -0.2923, p<0.0001), as demonstrated in (Fig. 4).

Variation in episode count, disease severity and hospitalizations between SG and CG cohorts: Upon a year of observation, children in the SG cohort reported fewer episodes (Fig. 5a), milder disease manifestations (Fig. 5b) and reduced hospitalizations (Fig. 5c) when juxtaposed against the CG cohort. These findings were statistically significant (p<0.05) (Table 5).

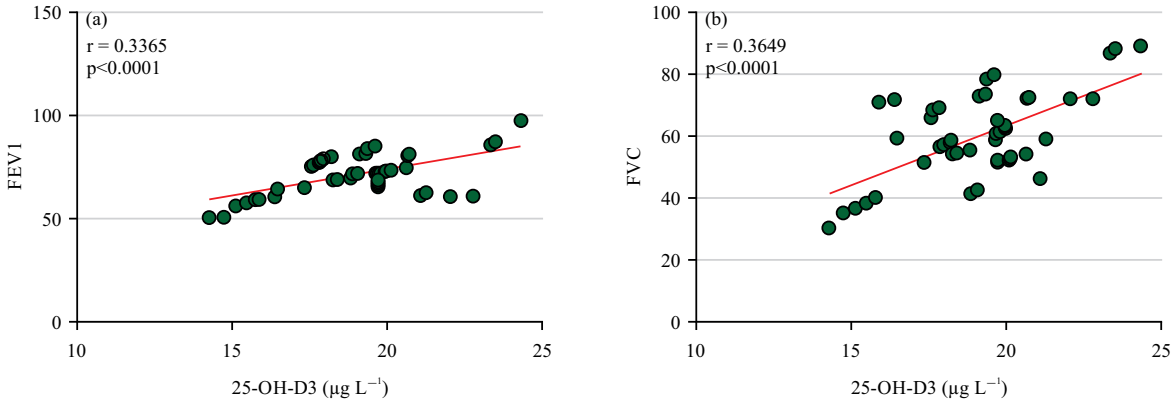

Fig. 3: Correlation between serum 25-OH-D3 level and its lung function indexes FEV1 and FVC in asthmatic children
Serum 25-OH-D3 level in asthmatic children showed significant positive correlation (r = 0.3365, p<0.0001) with its lung function indexes FEV1 and FVC (r = 0.3649, p<0.0001)

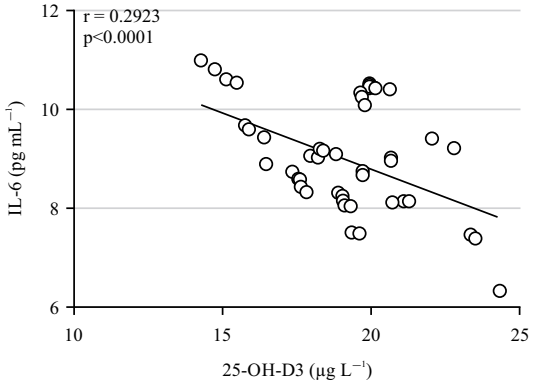

Fig. 4: Correlation between serum 25-OH-D3 level and its inflammatory indicator IL-6 in asthmatic children
Both serum 25-OH-D3 level and its inflammatory indicator IL-6 in asthmatic children showed significant negative correlation (r = -0.2923, p<0.0001)

Table 3: Differential comparison of serum 25-OH-D3 levels between children in SG group and CG group before treatment and after 3 months of treatment

Group	Number of cases	Serum 25-OH-D3 level before treatment (μg L $^{-1}$)	Serum 25-OH-D3 level after 3 months of treatment (μg L^{-1})
SG group	50	19.04±2.20	22.01±1.68[a]
CG group	50	20.40±1.54	21.68±1.17[a]
t	-	0.653	2.365
p-value	-	0.449	0.021

Data are represented by Mean±SD, SG group: Study group, CG group: Control group, t: Difference of quantitative indicators between SG group and CG group and [a]p<0.05 when compared with the same group before treatment

Table 4: Differences in the number of seizures, severity of illness and hospitalization between children in the SG and CG groups

Group	Number of cases	Number of episodes	Severity	Number of hospitalizations
SG	50	1.02±0.20	0.31±0.10	0.30±0.09
CG	50	1.99±0.46	0.40±0.11	0.98±0.16
t	-	6.326	5.116	4.016
p-value	-	0.000	0.000	0.000

Data are represented by Mean±SD, SG group: Study group, CG group: Control group and p<0.05 indicates statistical significance between the two groups

Disparities in pulmonary function and IL-6 concentrations post three months of treatment: After a three-month treatment span, children in the SG cohort demonstrated superior FEV1 and FVC values and diminished IL-6 concentrations relative to the CG cohort (p<0.05, Table 5).

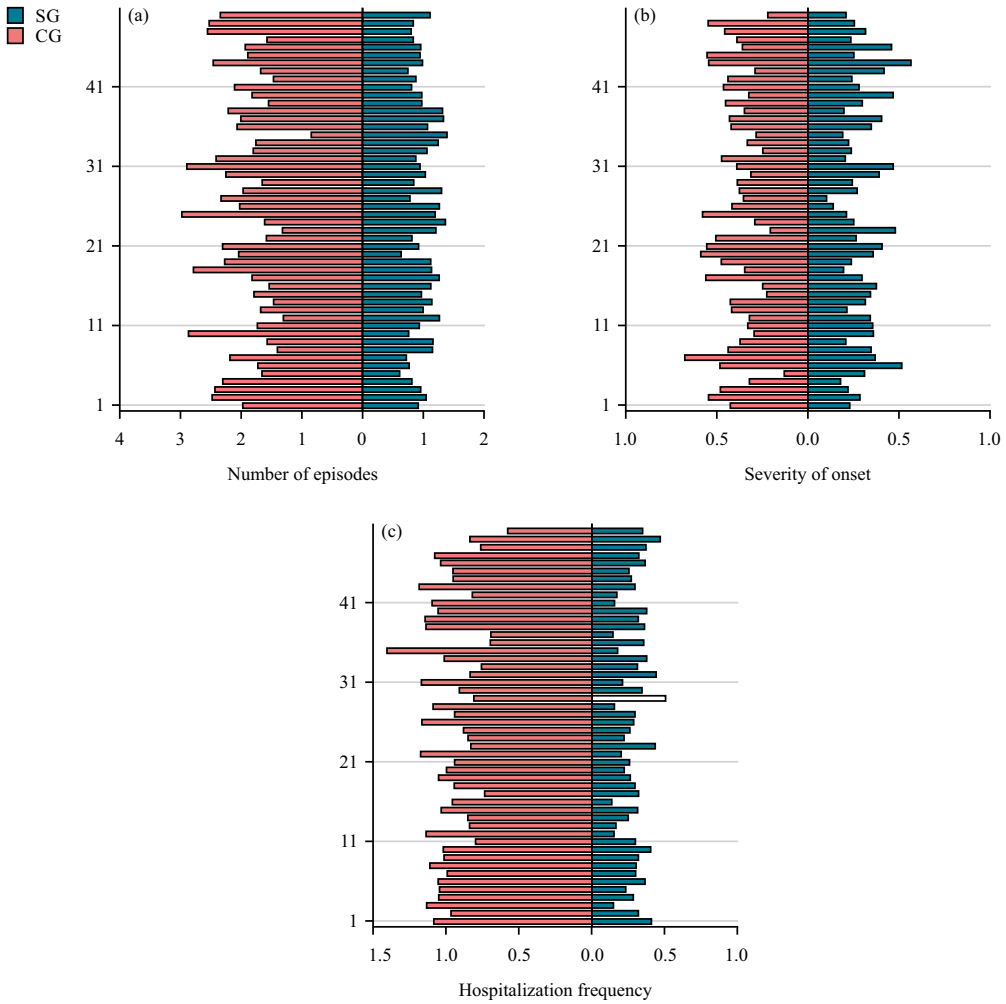

Fig. 5: Differences in the number of seizures, severity of onset and number of hospitalizations between children in the SG and CG groups

Table 5: Differences in lung function and IL-6 levels between the two groups of children at 3 months of treatment

Group	Number of cases	FEV1 (L)	FVC (%)	IL-6 (pg mL^{-1})
SG	50	3.62±0.51	95.63±2.15	98.56±10.11
CG	50	3.29±0.49	90.11±1.98	114.89±12.51
t	-	5.663	2.326	3.625
p-value	-	0.000	0.021	0.011

Data are represented by Mean±SD. FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, IL-6: Interleukin-16, SG: Study group, CG: Control group and $p<0.05$ indicates statistical significance between the two groups

DISCUSSION

This study found that serum 25-OH-D3 levels in children with asthma were significantly lower than those in healthy children and that proactive supplementation of vitamin D could increase serum 25-OH-D3 levels and ameliorate asthma symptoms in children with asthma.

At present, the etiological mechanisms underpinning childhood bronchial asthma remain elusive. Clinical interventions for bronchial asthma predominantly target symptomatic alleviation and diminution of recurrent episodes. However, recurrent episodes induce remodeling of the airway structure in asthmatic children, subsequently impairing their respiratory function[13,14]. Though hormone-based pharmaceuticals are efficacious in ameliorating the clinical manifestations in asthmatic children, they exhibit limited impact on airway remodeling. Recently, in-depth research into 25-OH-D3 has posited that vitamin D levels may be

intricately linked to asthma progression. It has been observed that attenuated serum vitamin D concentrations are commensurate with escalated asthma symptom severity. Thus, enhancing the clinical manifestations of asthmatic children via vitamin D supplementation appears a promising therapeutic avenue[15,16].

In this investigation, an analytical journey was embarked upon, scrutinizing the evolution of clinical manifestations and outcomes in asthmatic children post-vitamin D supplementation, leveraging a control group for enhanced insights. The findings revealed that serum 25-OH-D3 levels in asthmatic children (both SG and CG cohorts) were markedly reduced in comparison to children in the CCG group, who had non-asthmatic respiratory infections. Notably, intergroup variations in serum 25-OH-D3 concentrations between SG and CG cohorts were not statistically profound. However, post-vitamin D administration, children in the SG cohort exhibited elevated serum levels, surpassing their CG counterparts. This suggested a potential association between serum vitamin D concentrations and the severity of asthmatic conditions. A comprehensive meta-analysis executed by Wang's ensemble[17] involving a substantial dataset (5,711 asthmatic children and 21,561 non-asthmatic children) accentuated that children diagnosed with asthma had considerably diminished serum 25-OH-D3 levels. Moreover, the recidivism rate for asthmatic children receiving vitamin D therapy was substantially lower than their placebo-administered peers (18.4 vs 35.9%, $p = 0.002$). These observations by Wang's team resonate profoundly with the findings presented in the present study.

To further elucidate the association between serum 25-OH-D3 levels and the condition of asthmatic children, a Pearson analysis was executed, focusing on the relationship between serum 25-OH-D3 concentrations and pulmonary function indices as well as inflammatory markers in these children. The results unveiled a direct correlation between serum 25-OH-D3 levels and pulmonary function metrics of FEV1 and FVC. Conversely, an inverse correlation was identified with the inflammatory marker IL-6. Subsequent observations indicated that post-treatment, children in the SG group exhibited enhanced FEV1 and FVC compared to the CG group, while their IL-6 concentrations were diminished. In an exploration by Aierken's team[18], involving 43 asthmatic children, a positive correlation was discerned between the children's serum IL-6 and their immunoglobulin levels and duration of asthma. In contrast, vitamin D concentrations are inversely correlated with asthma duration. This suggests a potential interplay between vitamin D and IL-6 levels. However, this team did not delve deeper into this connection. Litonjua[19] study proposed that vitamin D plays a pivotal role in mitigating recurrent asthma episodes in children. Vitamin D supplementation appeared to attenuate exacerbation risks in asthmatic children with serum 25-OH-D3 levels below 10 ng mL^{-1}, while also refining their pulmonary function metrics.

This research, along with prior studies, bolsters the theoretical underpinning of the present study. It is postulated that vitamin D might modulate asthma's pathology via several mechanisms.

By enhancing serum IL-10 levels via the up-regulation of Foxp3 by Treg cells, vitamin D elicits an immunosuppressive effect, subsequently ameliorating the clinical manifestations in asthmatic children[20].

Vitamin D plays a role in the airway remodeling observed in asthmatic children[21]. The proliferation of airway smooth muscle cells, a pivotal structural element inducing airway remodeling, can be suppressed by vitamin D, which mitigates the cell transition from the G0/G1 to the S-phase, ultimately reducing airway remodeling and improving clinical manifestations.

Furthermore, vitamin D impedes the secretion of fibroblast-derived fibers[20]. Investigations have corroborated that asthmatic children possess an elevated count of fibroblasts in their airways compared to their healthy counterparts[22]. The fibroblast counts correlate with their pulmonary function and vitamin D can diminish the expression of α-SMA at both the gene and protein levels, refining the airway remodelling process.

While this study underscored the potential benefits of vitamin D in ameliorating the clinical symptoms of asthmatic children through a comparative lens, it is not devoid of limitations. These include a relatively brief follow-up duration, limited data sources and a modest sample size. The long-term ramifications of extended vitamin D supplementation and any potential adverse reactions warrant further exploration. Continued comprehensive research will be instrumental in illuminating novel strategies and insights for pediatric asthma management.

CONCLUSION

Asthmatic children exhibit a notable reduction in serum 25-OH-D3 levels compared to the healthy children. Proactive vitamin D supplementation can increase the serum 25-OH-D3 levels in asthmatic children, which could be considered as a new direction for asthma treatment, with the potential for significant practical application. A large-scale, multi-center prospective study will be conducted in the future to offer new insights and references for the treatment of asthmatic children.

SIGNIFICANCE STATEMENT

Currently, clinical research on the relationship between vitamin D and pediatrics primarily focuses on the impact of vitamin D deficiency on children's immunity and calcium absorption. However, there is limited research on the correlation between vitamin D and the condition of children with asthma. The present study demonstrated that vitamin D deficiency may have a promoting effect on childhood asthma and proactive supplementation of vitamin D is likely to help improve the condition of children with asthma. This provides new ideas and measures for the clinical treatment of children with asthma and also provides a theoretical reference for further research.

REFERENCES

1. Abul, M.H. and W. Phipatanakul, 2019. Severe asthma in children: Evaluation and management. Allergol. Int., 68: 150-157.
2. Hoch, H.E., P.R. Houin and P.C. Stillwell, 2019. Asthma in children: A brief review for primary care providers. Pediatr. Ann., 48: e103-e109.
3. Jabeen, U., F. Zeeshan, I. Bano, A. Bari and A.W. Rathore, 2018. Adherence to asthma treatment and their association with asthma control in children. J. Pak. Med. Assoc., 68: 725-728.
4. Fang, L., L. Yi-Ran and L. Lin, 2021. Effect of exercise rehabilitation on exercise capacity and quality of life in children with bronchial asthma: A systematic review [In Chinese]. Chin. J. Contemp. Padiatr., 23: 1050-1057.
5. Zhou, X.J., Z. Qin, J. Lu and J.G. Hong, 2021. Efficacy and safety of salmeterol/fluticasone compared with montelukast alone (or add-on therapy to fluticasone) in the treatment of bronchial asthma in children and adolescents: A systematic review and meta-analysis. Chin. Med. J., 134: 2954-2961.
6. Wang, Q., W. Zhang, L. Liu, W. Yang and H. Liu, 2019. Effects of physical therapy on lung function in children with asthma: Study protocol for a systematic review and meta-analysis. Medicine, Vol. 98. 10.1097/MD.0000000000015226.
7. Hufnagl, K., I. Pali-Schöll, F. Roth-Walter and E. Jensen-Jarolim, 2020. Dysbiosis of the gut and lung microbiome has a role in asthma. Semin Immunopathol., 42: 75-93.
8. Koefoed, H.J.L., A.M. Zwitserloot, J.M. Vonk and G.H. Koppelman, 2021. Asthma, bronchial hyperresponsiveness, allergy and lung function development until early adulthood: A systematic literature review. Pediatr. Allergy Immunol., 32: 1238-1254.
9. Ismailova, A. and J.H. White, 2022. Vitamin D, infections and immunity. Rev. Endocr. Metab. Disord., 23: 265-277.
10. Bikle, D.D., 2022. Vitamin D regulation of immune function. Curr. Osteoporos. Rep., 20: 186-193.
11. Bradley, R., J. Schloss, D. Brown, D. Celis and J. Finnell *et al*., 2020. The effects of vitamin D on acute viral respiratory infections: A rapid review. Adv. Integr. Med., 7: 192-202.
12. Cloutier, M.M., S.J. Teach, R.F. Lemanske and K.V. Blake, 2021. The 2020 focused updates to the NIH asthma management guidelines: Key points for pediatricians. Pediatrics, Vol. 147. 10.1542/peds.2021-050286.
13. Khramova, R.N., E.V. Tush, A.A. Khramov, D.Y. Ovsyannikov and K.S. Popov *et al*., 2020. Relationship of nutritional status and spirometric parameters in children with bronchial asthma. Mod. Technol. Med., 12: 12-23.
14. Akulenko, M.V. and N.I. Kosyakova, 2022. Energy status of lymphocytes in children with bronchial asthma of various severity in comparison with frequently Ill and healthy children. Bull. Exp. Biol. Med., 173: 723-729.
15. Ahmad, E.S., S.M. Diab, E.G. Behiry, S.E.B.E.S. El Bassyoni, S.R. Ishak and A. Ramadan, 2022. Autophagy-related 5 gene mRNA expression and ATG5 rs510432 polymorphism in children with bronchial asthma. Pediatr. Pulmonology, 57: 2659-2664.
16. Forno, E., L.B. Bacharier, W. Phipatanakul, T.W. Guilbert and M.D. Cabana *et al*., 2020. Effect of vitamin D_3 supplementation on severe asthma exacerbations in children with asthma and low vitamin D levels: The VDKA randomized clinical trial. JAMA, 324: 752-760.
17. Wang, Q., Q. Ying, W. Zhu and J. Chen, 2022. Vitamin D and asthma occurrence in children: A systematic review and meta-analysis. J. Pediatr. Nurs., 62: e60-e68.
18. Aierken, A., B. Yusufu and P. Xu, 2020. Correlation between asthmatic infants with rickets and vitamin D, inflammatory factors and immunoglobulin E. Exp. Ther. Med., 20: 2122-2126.
19. Litonjua, A.A., 2019. Vitamin D and childhood asthma: Causation and contribution to disease activity. Curr. Opin. Allergy Clin. Immunol., 19: 126-131.
20. Rosser, F.J., Y.Y. Han, E. Forno, L.B. Bacharier and W. Phipatanakul *et al*., 2022. Effect of vitamin D supplementation on total and allergen-specific IgE in children with asthma and low vitamin D levels. J. Allergy Clin. Immunol., 149: 440-444.e2.
21. Eigenmann, P., 2021. Comments on vitamin D and sensitization, asthma treatment, and lung function development. Pediatr. Allergy Immunol., 32: 1137-1140.
22. Majak, P., J. Jerzyńska, K. Smejda, I. Stelmach, D. Timler and W. Stelmach, 2012. Correlation of vitamin D with Foxp3 induction and steroid-sparing effect of immunotherapy in asthmatic children. Ann. Allergy Asthma Immunol., 109: 329-335.