## Original article

# The critical level of vitamin D in childhood asthma

***Objectives:*** *Studies have suggested a significant link between vitamin D status and asthma. We sought to determine the cutoff level of25 hydroxy (25-OH) vitamin D that is significantly linked to asthma status in children.* ***Methods:*** *Our cross-sectional study comprised 90 asthmatic children, aged 2-18 years. They were evaluated clinically and classified according to asthma severity and control. Asthma control test (ACT) was performed in those aged above 4 years. Pulmonary functions were performed in cooperative children (n=59). Serum 25-OH vitamin D levels were measured by ELISA in all patients.* ***Results:*** *The study comprised 52 boys (57.7%) and 38 girls (42.3%) with mean age 7.03±4.36 years. Thirty-six patients (40%) had mild asthma, 37 (41%) moderate asthma and 17 (19%) had severe asthma. Forty-two patients (46.6%) had controlled asthma; 14 (15.6%) partially controlled and 34 (37.8%) had uncontrolled asthma. ACT score ranged: 11-26, with mean score: 18.9 ± 4.3 SD. Serum 25-OHvitamin D levels ranged between 2-48 ng/ml (mean± SD: 12.2 ± 9 ng/ml); levels were comparable among different grades of asthma severity (f= 1.975, p=0.145), while the uncontrolled asthma group showed the lowest levels (f=8.511, p <0.001). 25-OH vitamin D levels correlated positively with ACT score (r= 0.369, p= <0.001) but not with inhaled steroids doses or any of the pulmonary function parameters. A level of 7.5 ng/ml was associated with partial/complete uncontrol of asthma with 81 % sensitivity and 53 % specificity.* ***Conclusion:*** *25-OH vitamin D levels below 7.5 ng/ml are associated with poor asthma status in children.*

**Keywords:** Asthma, allergy, children, severity, inhaled steroids, 25 hydroxy vitamin D.

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## INTRODUCTION

Asthma is considered one of the most common causes of childhood emergency department visits, hospitalizations and missed school days[1]. There is growing evidence suggesting a link between vitamin D deficiency and asthma in children. Vitamin D was found to play an important role in pulmonary health by inhibiting inflammation, maintaining regulatory T cells and direct induction of innate antimicrobial mechanisms. Also, vitamin D was found to have multiple cytokine modulating effects through several different cells of the immune system. In addition, vitamin D shifts the balance of T lymphocyte response from Th1 phenotype to Th2 phenotype[2]. The role of vitamin D in lung development is well described[3]. Serum levels of 25-hydroxy (25-OH) vitamin D are considered the best circulating biomarker of vitamin D metabolic status and reflect contributions from all sources of vitamin D (i.e., diet and sun exposure)[4].

Studies on vitamin D and asthma in children have variable results[5-8]. We sought to investigate the relationship between vitamin D status and severity and control of bronchial asthma in a group of Egyptian asthmatic children and determine the critical level of vitamin D that is associated with poor asthma status. This is aimed to guide further studies using vitamin D supplementation as an adjuvant line in asthma management.

## PATIENTS AND METHODS

A cross sectional study was carried out, in the period from April 2012 to May 2014. The study comprised 90 Egyptian children aged 2-18 years, with physician diagnosed, persistent bronchial asthma (mild, moderate or severe) on controller therapy with or without other forms of allergy. They were enrolled consecutively from the Pediatric Allergy and Immunology Unit, Children's Hospital, Ain Shams University. The following patients were excluded from the study: patients with intermittent asthma, chronic lung disease other than bronchial asthma, patients receiving chronic steroid therapy for other reasons than asthma, non-compliant patients on no/irregular asthma controller therapy, subjects having inherited calcium or bone disease or having severe liver or kidney disease and patients receiving antiepileptic drugs or diuretics

## STUDY METHODS

***Clinical evaluation:***

Detailed medical history was recorded including: duration of asthma disease, frequency of asthma exacerbations, daytime and night time symptoms, vitamin D supplementation, average dose of inhaled steroids and/or systemic steroids in the month before enrollment and compliance on treatment. The dose of inhaled steroids was considered low, moderate or high according to Global Initiative for Asthma (GINA) [9]. Clinical examination was performed including detailed chest examination for the presence of respiratory distress, wheezes, chest infections and/or deformities, in addition to complete systematic examination.

***Pulmonary function Tests:***

Pulmonary functions were evaluated for cooperative patients aged above 5 years (n=59), with special emphasis on peak expiratory flow (PEF) using the expiratory flowmeter and forced expiratory volume in the first second of forced expiration (FEV1) using the dynamic spirometer (Master Screen IOS; Jaeger, Höchberg, Germany), considering the best of 3 efforts starting with full force vital capacity (FVC) maneuvers. FEV % was also recorded for each patient (the ratio between FEV1 and FVC). The spirometer was calibrated for each subject with a 3-L syringe (Cardinal Health, Dublin, Ohio). The FVC maneuvers were carried out with the child standing and wearing a nose clip. Pulmonary function tests were performed and interpreted according to the standards of European Respiratory Society and the American Thoracic Society[10].

***Asthma grading:***

Enrolled patients were classified into mild, moderate or severe asthma and into controlled, partially controlled or uncontrolled asthma according to GINA[9].

***Asthma control test (ACT) scoring*** was carried out at the time of enrollment for cooperative subjects above the age of 4 years. A score of 19 or less was interpreted as uncontrolled asthma[11].

***Laboratory investigations included:***

Serum level of 25 25-OH vitamin D was detected in all enrolled subjects by ELISA technique using the 25-OH Vitamin D (total) ELISA kits, DRG International, Inc., USA. Results were expressed in terms of ng/ml, 25-OH vitamin D levels below 20 ng/mL were considered deficient[12].

***Statistical methods:***

Results were tabulated and analyzed by IBM computer using SPSS (statistical program for social science version 15). Data were normally distributed. Quantitative variables were described as mean and standard deviation and qualitative variables as number and percentage. Analysis of variance [ANOVA] was used to analyze the differences between group means (variation among and between groups). Correlations among numerical variables were tested using the Spearman rank correlation. The correlation coefficient (Spearman rho) was interpreted according to Hinkle et al., 2003[13]. Chi-square (x2) was used to determine whether there is a significant difference between the expected frequencies and the observed frequencies in one or more categories. Receiver-operating characteristic (ROC) curve analysis was used to examine the predictive value of 25-OH vitamin D level for asthma uncontrol as defined by GINA. A p value $\leq 0.05$ was considered significant.

***Ethical considerations:***

The study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964 as revised in 2008 and the study protocol gained approval from the local Ethical Committee of the Pediatric department, Faculty of Medicine, Ain Shams University. An informed consent was obtained from the care givers of enrolled children before enrollment in the study, with preservation of patients' anonymity.

## RESULTS

Clinical and epidemiological data of enrolled children are demonstrated in table 1. Their mean age was 7.03±4.36 years. Four patients had history of acute asthma exacerbation in the past 3 months. Only three children were on oral vitamin D supplementation at time of enrolment. Asthma

control test was done in 90 patients and its score ranged from 11-26, with mean score: 18.9 ± 4.3 SD. All patients were on inhaled corticosteroid therapy at time of enrollment. Results of pulmonary functions are shown in table 1. A normal pattern was found in 23 patients (39%), an obstructive pattern in 27 (46%) and a mixed obstructive and restrictive pattern in 9 patients (15%).

Serum 25-OHvitamin D levels ranged between 2-48 ng/ml (mean± SD: 12.2 ± 9 ng/ml); levels were comparable among different grades of asthma severity (f= 1.975, *p*=0.145) (figure 1). According to asthma control, the uncontrolled group showed the lowest levels of serum 25-OHvitamin D (f=8.511, *p*<0.001) (figure 2).

Although serum 25-OH vitamin D levels were noticed to be the lowest among patients with mixed obstructive and restrictive patterns of pulmonary functions (mean ± SD: 7.56±6.1 ng/ml) in comparison to normal (mean ± SD: 11.2± 6.5 ng/ml) and obstructive patterns (mean ± SD: 11.7± 8 ng/ml), yet, the difference between the 3 groups did not reach statistical significance (f=1.178, *p*=0.31).

Similarly, patients who were receiving low dose inhaled steroids (n= 29, 32.2%), versus those receiving moderate dose (n= 53, 59%) and high dose (n= 8, 8.8%), had comparable serum 25-OHvitamin D levels (mean± SD: 10.48±9.03, 14.11±13.76, 16.13±10.64, respectively) with no significant difference in between (f=1.098, *p*=0.338).

Serum 25-OH vitamin D levels correlated positively with ACT scores (r= 0.369, *p*= <0.001) (figure 3), but not with age (r= -0.189, *p*= 0.074), average daily inhaled steroids (r= 0.204, *p*= 0.054) nor with pulmonary functions parameters, namely FEV1 (r= 0.207, *p*= 0.116), FEV % (r= 0.001, *p*= 0.991), FVC (r= 0.21, *p*= 0.11) and PEF (r= 0.185, *p*= 0.16).

According to serum 25-OHvitamin D levels, patients were classified into 2 groups: vitamin D deficient group (25-OHy vitamin D levels < 20 ng/ml) (n= 72, 80 %) and vitamin D non-deficient group (25-OHvitamin D levels ≥ 20 ng/ml) (n= 18, 20 %). Patients in both groups were comparable concerning the distribution of asthma severity ($x^2$= 0.197, *p*=0.906) and pulmonary function pattern ($x^2$= 0.268, *p*= 0.874) but they were significantly different in terms of asthma control ($x^2$= 12.164, *p*=0.002) with higher percentage of uncontrolled cases (n=32; 44.4 %) among the vitamin D deficient group versus the non-deficient one (n=2; 11.1%).

The vitamin D deficient and non-deficient groups were further compared in terms of their ages, ACT scores, pulmonary function parameters and the average daily doses of inhaled steroid and the 2 groups were found to be comparable except in the ACT test score which was significantly lower among the vitamin D deficient group (table 2).

Serum 25-OH vitamin D levels of the controlled asthma group versus the partially controlled and the uncontrolled groups were plotted in a ROC curve. Levels below 8.5 ng/ml were associated with uncontrolled asthma with sensitivity 69 % and specificity 66.7 %; positive predictive value 67.65%; and negative predictive values 68.37% (AUC: 0.743; Std error: 0.052; p<0.001, with 95 % confidence interval) (figure 4). A lower serum 25 OH vitamin D cut off level of 7.5 ng/ml could predict asthma uncontrol with a better performance: sensitivity 81 %, specificity 53%, positive predictive value 63.3%; and negative predictive value 73.6%. Patients with 25-OH vitamin D levels at or below 7.5 ng/ml had significantly lower FVC and ACT in comparison to those having levels above 7.5 ng/ml with f= 4.763, p= 0.03 and f=11.62, p< 0.001 respectively. Other parameters namely FEV1, FEV %, PEF and average daily dose of inhaled steroids were all comparable in both groups (p= 0.121, 0.888, 0.604 and 0.079 respectively).

**Table 1.** Epidemiological and clinical data of enrolled patients

| Parameter | Classification | Number | Percentage |
|---|---|---|---|
| Gender | Boys | 52 | 57.7 % |
| | Girls | 38 | 42.3 % |
| Allergic manifestations | Asthma | 90 | 100% |
| | Allergic rhinitis | 9 | 10% |
| | Atopic dermatitis | 10 | 11% |
| | Urticaria/angioedema | 3 | 3% |
| Family history of allergy | Positive | 41 | 46% |
| | Negative | 49 | 54% |
| Asthma severity | Mild | 36 | 40 % |
| | Moderate | 37 | 41 % |
| | Severe | 17 | 19 % |
| Asthma control | Controlled | 42 | 46.6 % |
| | Partially controlled | 14 | 15.6 % |
| | Uncontrolled | 34 | 37.8 % |
| Pulmonary function tests | Normal | 23 | 39 % |
| | Obstructive | 27 | 46 % |
| | Mixed obstructive and restrictive | 9 | 15 % |
| Inhaled steroid dose Parameter | Low | 29 | 32.2 % |
| | Moderate | 53 | 59 % |
| | High | 8 | 8.8 % |

** N: Number*

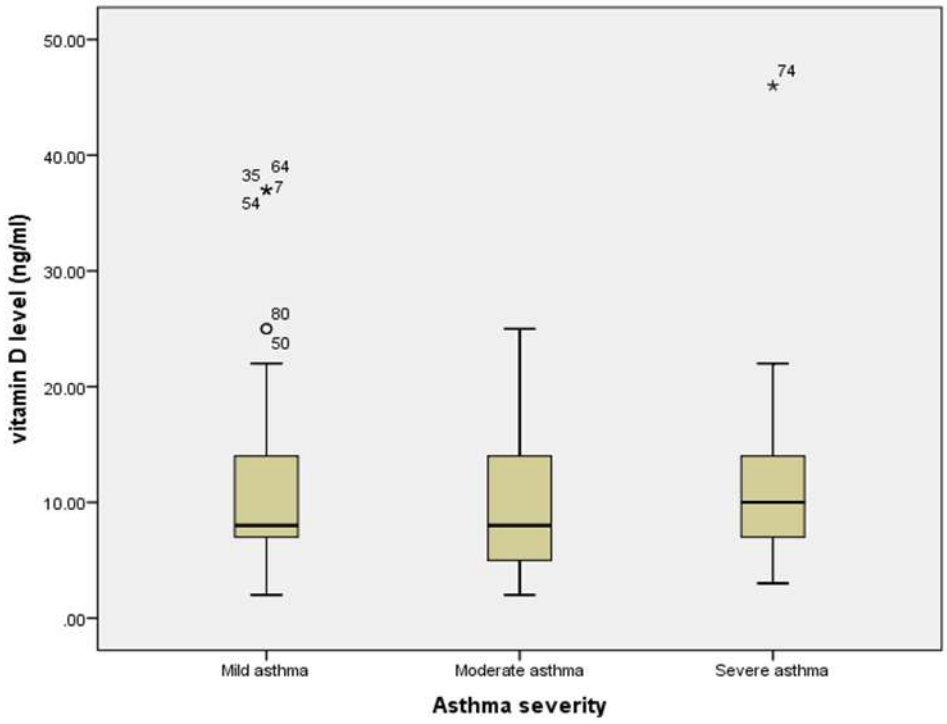


**Figure 1.** Variation of serum 25-OH vitamin D level with asthma severity

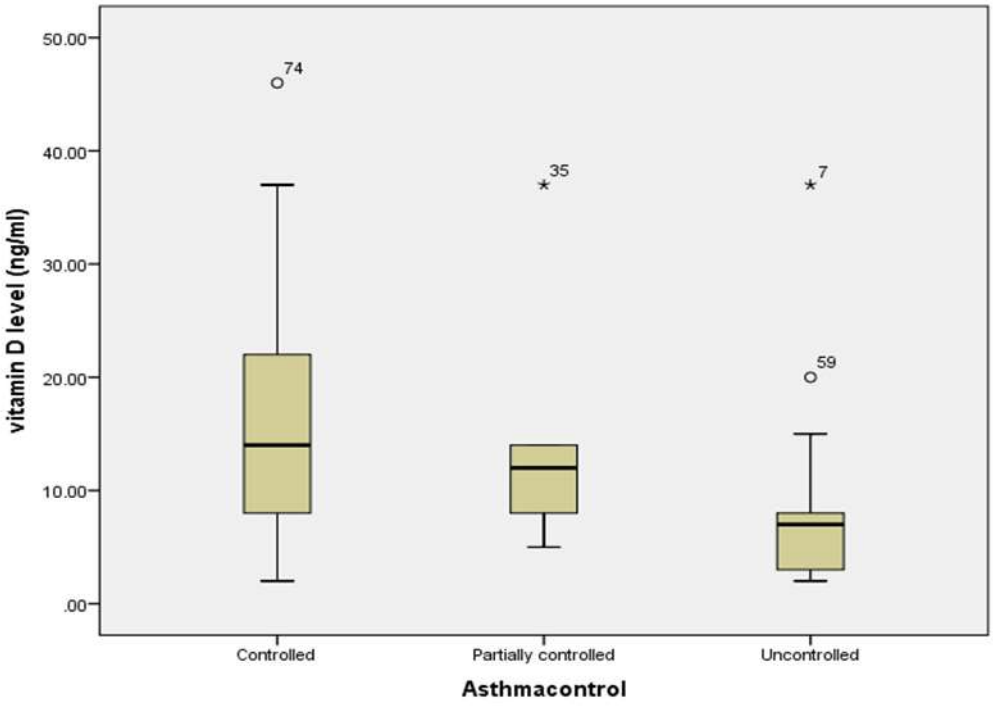


**Figure 2.** Variation of serum 25-OH vitamin D level with asthma control

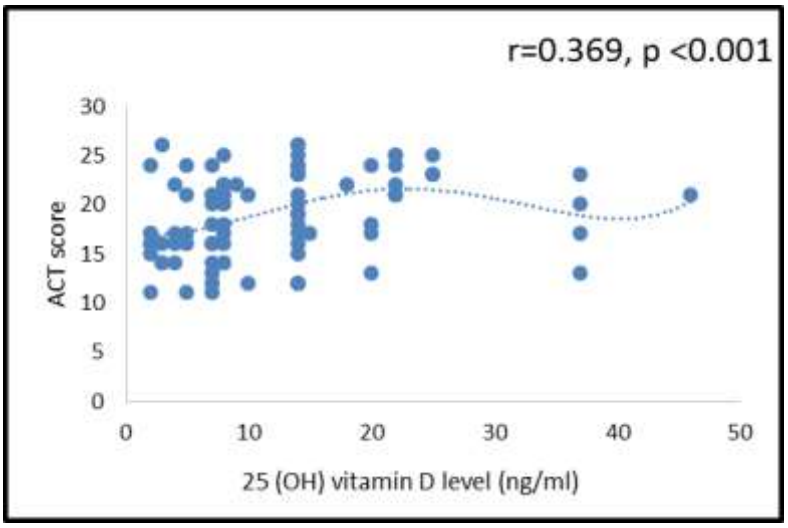


**Figure 3.** Correlation between serum 25-OH vitamin D levels and ACT score

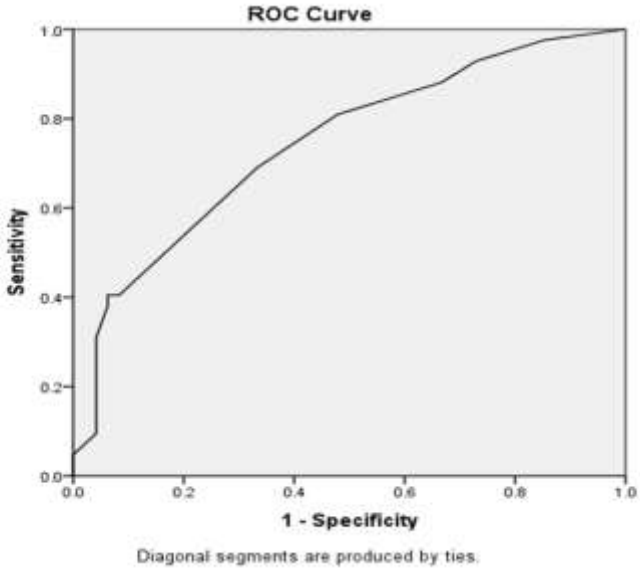


**Figure 4.** ROC curve for serum 25-OH vitamin D levels among controlled versus partially/un-controlled asthmatic patients

**Table 2.** Correlation between DHR & CD11b and CD11b & CD62L in control.

| Parameter | Vitamin D deficient | Vitamin D Non-deficient | f | *p* |
|---|---|---|---|---|
| Age (years) | 7.2 ± 4.2 | 5.9 ± 3.7 | 1.39 | 0.241 |
| ACT score | 18.47 ± 4.3 | 20.8 ± 3.8 | 4.54 | 0.03 |
| PEF (L/S) | 70.9 ± 15.4 | 75.3 ± 10.4 | 0.73 | 0.398 |
| FVC (L/S) | 90.71±11.81 | 94.5±9.32 | 0.907 | 0.345 |
| FEV% | 92.3 ± 15.6 | 90.3 ± 10.4 | 0.178 | 0.674 |
| FEV 1 (L/S) | 83.7 ± 13.2 | 85.5 ± 6 | 0.173 | 0.679 |
| Average daily inhaled steroid (ug/day) | 224.6±118.9 | 280 ± 158.2 | 2.77 | 0.1 |
| Frequency of uncontrolled asthma n (%) | 33 (44.4%) | 2 (11%) | $x^2$= 12.164 | 0.002 |

*FEV 1: forced expiratory volume 1; FVC: forced vital capacity; FEV% = FEV 1/FVC; PEF: peak expiratory flow; L/S: liter per second*

## DISCUSSION

This study showed that 80 % of our Egyptian asthmatic children had vitamin D deficiency (levels below 20 ng/ml). Sunny countries and non-white populations are reported to have lower vitamin D levels and higher incidence of asthma in comparison to the white populations[14,15]. Darker skin pigmentation, seasonal and atmospheric factors, with avoidance of sun exposure, all add to decreased cutaneous vitamin D synthesis[16]. Vitamin D deficiency in asthmatic children has been observed in several controlled studies and vitamin D deficient children were found to have significantly higher incidence of asthma[17-19]. A few observational studies suggested association between low serum 25-OH vitamin D levels and poor asthma control and reduced lung function in children[20-22], whereas some other studies had reported adverse impact of vitamin D on asthma[5, 23].

In our study, 25-OH vitamin D levels were comparable among different grades of asthma severity. However, as regards asthma control, 25-OH vitamin D was the lowest among patients with uncontrolled asthma and the levels correlated positively with ACT score. This supports the possible role of vitamin D in asthma control in children and might reflect the importance of 25-OH vitamin D monitoring and hence considering supplementation in deficient asthmatics regardless the degree of severity. The relationship between vitamin D and asthma severity and control is not fully understood, with inconsistent outcomes among different studies. For instance, some studies reported that children with poorly controlled refractory asthma had lower 25-OH vitamin D levels than those with moderately controlled or controlled asthma[21, 24]. An inverse relation between serum 25-OH vitamin D levels and asthma severity and exacerbations has been observed in a cross-

sectional study of 616 Costa Rican children[20]. Other studies failed to find a significant relation between vitamin D levels and asthma severity and control in children[25-29]. The different results among studies might reflect the differences among populations with respect to genetic, racial and environmental factor.

In our study, a cut off level for 25-OH vitamin D of 7.5 ng/ml could discriminate between controlled and partially/un-controlled patients which is different from the well-defined values for 25-OH vitamin D levels required for bone health (≥ 20 ng/ml)[12]. Different cut-off levels of 25-OH vitamin D in different disorders have also been reported. A 25-OH vitamin D level of 25 ng/ml could discriminate between Egyptian asthmatic adults (n=70) and healthy controls (n=20) with sensitivity of 80% and specificity of 85% [30], while a level of 17.23 ng/mL was observed in another study as a cutoff between a group of 30 Egyptian patients with alopecia areata versus 20 healthy controls[31]. In rheumatoid arthritis, 25-OH vitamin D levels of 12.3 and 17.9 ng/ml could predict high and low disease activity respectively in 102 adult patients from Saudi Arabia[32].

In our series, 25-OH vitamin D levels were comparable among different patterns of pulmonary dysfunction although they seemed to be lower among patients with mixed obstructive and restrictive pattern in comparison to normal and obstructive patterns. 25-OH vitamin D levels did not correlate with any of the pulmonary functions parameters, neither were there differences in pulmonary function parameters between vitamin D deficient (below 20 ng/ml[12]) and non-deficient groups. However, a 25-OH vitamin D level of 7.5 ng/ml seemed to be critical in our studied asthmatic children as below this level, both asthma control and FVC were found to be poor. ***Devereux et al.*** showed no association between vitamin D levels and pulmonary functions in 80 adult asthmatics in the UK[28]. A study evaluating 25-OH vitamin D levels in 1315 children, aged 5–18 years, found that those with insufficient vitamin D levels had significantly lower FVC and lower FEV1 on pulmonary function tests when compared to those with sufficient levels[33]. Also, among 1,024 children with persistent asthma treated with inhaled steroids a greater improvement of lung function over one year was noticed in children with vitamin D sufficiency versus deficiency[34]. Contrary to our findings, significant positive correlation between serum 25-OH vitamin D levels and pulmonary function parameters has been observed by several researchers[35-38]. In a pediatric randomized control trial, 500 units of vitamin D supplementation daily for 6 months showed decreased asthma exacerbation though vitamin D levels did not change before and after supplementation, while lung functions improved significantly[39].

We did not observe any significant relation between 25-OH vitamin D levels and the average daily doses of inhaled steroids. The relationship between inhaled steroid dose and 25-OH vitamin D level in asthmatic subjects is not clear with some studies supporting the role of vitamin D in decreasing the inhaled steroid requirements[7,24] while others denying this role[25,33].

Our study has some limitations, first, being a cross sectional one, besides, lung development and function and development of allergies were observed to be affected not only by the current vitamin D status but also by maternal and in-utero vitamin D levels[40] which was not investigated in our work.

**In conclusion**, our study demonstrated a significant relation between serum 25-OH vitamin D level and degree of asthma control in children with a level at or below 7.5 ng/ml being associated with poor asthma control and lower pulmonary functions. Further longitudinal randomized controlled studies are warranted for investigating the effect of vitamin D supplementation on asthma control. More insight onto the common polymorphisms in the vitamin D receptor and other genes in the vitamin D pathway and their relation to asthma severity and control is worthwhile.

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