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Vitamin D deficiency and level of asthma control and severity in an adult population in Morocco

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analysis and interpretation; IAR critically reviewed the manuscript for important intellectual content and provided revisions to the manuscript; HEO provided overall supervision and guidance throughout the study and critically reviewed the manuscript for important intellectual content. All the authors have read and approved the final version of the manuscript and agreed to be held accountable for all aspects of the work.

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Abstract

Vitamin D plays a critical role in immune modulation, with implications for the severity and control of asthma. The study included 174 asthmatic patients aged 18-65 whose serum 25(OH)D₃ levels and their relationship with asthma severity, control, and lung function were assessed. The prevalence of hypovitaminosis D was 64%, with 36.3% of patients having normal levels, 29.8% insufficient, and 33.9% deficient. Lower vitamin D levels were significantly associated with increased asthma severity ($p=0.04$) and poorer asthma control ($p=0.03$). Patients with severe asthma had mean 25(OH)D₃ levels of 24.1 ± 11.8 ng/mL, compared to 32.5 ± 13.1 ng/mL in patients with non-severe asthma. Controlled asthma was linked with higher vitamin D levels (28.3 ± 12.5 ng/mL) compared to partially controlled (24.7 ± 10.8 ng/mL) and uncontrolled asthma (23.3 ± 12.1 ng/mL). A non-significant trend was observed toward reduced Forced Expiratory Volume in One Second (FEV₁) in vitamin D-deficient patients. Vitamin D deficiency is significantly associated with asthma control level and severity, underscoring the need for further research on the therapeutic potential of vitamin D in asthma management.

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Introduction

Asthma is one of the most common chronic diseases and constitutes a major public health issue worldwide. It is characterized by chronic inflammation of the airways, associated with bronchoconstriction and bronchial hyperreactivity.¹ For most patients, long-term maintenance therapy achieves satisfactory disease control. However, some patients do not achieve optimal asthma control, even with high-dose treatment. This group of patients with severe and poorly controlled asthma is at high risk of severe exacerbations and asthma-related mortality.

A new hypothesis suggests a link between insufficient levels of vitamin D (25(OH)D) and asthma. Vitamin D exerts various effects on the innate and adaptive immune systems, which could play a key role in the primary prevention of asthma, as well as in reducing its morbidity and the severity of its exacerbations.^{2,3} Concurrently, vitamin D deficiency is increasingly recognized in the general population, a phenomenon largely attributed to changes in diet, lifestyle, and behaviour.⁴

The relationship between asthma and vitamin D status has been studied in many articles.^{2,3,5} More specifically, low serum vitamin D levels have been associated with the severity of asthma. In asthmatic patients, vitamin D deficiency is associated with poor asthma control and decreased lung volumes.⁵ The number of asthma attacks and the need for emergency therapy are also increased in this group of patients. This suggests that physicians need to treat patients

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actively. In future studies, vitamin D supplements might have an important role in the treatment of asthma. Further studies are needed to shed light on this relationship.

The aim of the current study is to determine, using a prospective cohort, the prevalence of 25(OH)D insufficiency and deficiency in adult asthmatic patients and its potential relationship with asthma severity and control parameters.

Materials and Methods

Study design

A prospective cross-sectional study was conducted at the pneumology department of Rabat.

Study population and samples

The study included 174 asthmatic patients who were being followed up in pulmonary consultation. Inclusion criteria comprised adults over 18 years of age with confirmed asthma, as evidenced by a reversible obstructive ventilatory defect on spirometry. Exclusion criteria included non-compliant patients or those facing difficulties using inhalation devices, individuals receiving vitamin D supplementation, pregnant women, and those who declined to participate in the study. All patients provided written informed consent prior to taking part in the study.

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Data collection

Various parameters were collected for each patient, including age, gender, duration of asthma, Forced Expiratory Volume in One Second (FEV₁), clinical parameters of asthma control, atopy (allergic rhinitis and total Immunoglobulin E, IgE, levels), and background treatment. Asthma control was evaluated based on Global Initiative for Asthma (GINA) 2023 criteria over a four-week period. Severe asthma was defined as requiring GINA stage 4 or 5 treatment to maintain symptom control.

Blood samples were obtained from all patients to measure total 25-hydroxy vitamin D (25-OHD) levels (mcg/mL) using radioimmunoassay by chemiluminescence technique. Additionally, serum protein, calcium, and creatinine levels were assessed. Serum 25(OH)D levels were categorized as sufficient (≥ 30 ng/mL), insufficient (20-30 ng/mL), or deficient (< 20 ng/mL).

Data analysis

Statistical analysis was performed using SPSS.20 software. Descriptive statistics included mean and standard deviation for quantitative variables, and frequency and percentage for qualitative variables. Analytical statistics involved chi-square or Fisher's exact test for qualitative variables

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and Student's t-test for quantitative variables. Correlation, univariate, and multivariate logistic regression analyses were conducted, with $p < 0.05$ considered statistically significant.

Results

Subjects' characteristics

A total of 174 patients were included in the study, aged between 18 and 65 years, with a female predominance (60%). Among the patients, 57 had severe asthma, and 117 had non-severe asthma; 78 were classified as uncontrolled and 96 as controlled. The mean concentration of 25(OH)D₃ was 26.3 ± 11.2 ng/mL. The distribution of vitamin D levels revealed that 36.3% of patients had normal 25(OH)D₃ levels, 29.8% were vitamin D insufficient, and 33.9% were vitamin D deficient, indicating a hypovitaminosis D prevalence of 64% in our study. Table 1 presents the characteristics of the studied population.

25(OH)D levels, asthma severity, and asthma control

The serum levels of 25(OH) D were significantly associated with asthma severity ($p = 0.04$). Specifically, patients with severe asthma had lower mean 25(OH)D levels of 24.1 ± 11.8 ng/mL, compared to those with non-severe asthma with mean levels of 32.5 ± 13.1 ng/mL ($p = 0.04$). Additionally, the serum vitamin D levels varied according to asthma control status: controlled

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asthma had mean levels of 28.3 ± 12.5 ng/mL, partially controlled asthma had 24.7 ± 10.8 ng/mL, and uncontrolled asthma had 23.3 ± 12.1 ng/mL. This difference was statistically significant ($p=0.03$) (Figure 1).

Regarding the relationship between vitamin D concentrations and the number of medications required for asthma control, the mean serum vitamin D level was 28.5 ± 11.5 ng/mL in patients needing one or fewer medications, 26.5 ± 12.2 ng/mL in those requiring two medications, and 23.7 ± 11.9 ng/mL in patients needing three or more medications. However, this difference was not statistically significant ($p=0.12$) (Figure 2).

Relationship between vitamin D and Forced Expiratory Volume in One Second

Our analysis revealed that vitamin D insufficiency was associated with a decrease in FEV₁. Patients with serum vitamin D levels <30 ng/mL exhibited a mean FEV₁ of 2.3 ± 0.9 L, whereas those with vitamin D levels ≥ 30 ng/mL had a mean FEV₁ of 2.7 ± 1.1 L. Although there appeared to be a direct relationship between vitamin D levels and FEV₁ (regression coefficient =0.48; $r=0.03$), this relationship did not reach statistical significance.

Factors associated with 25(OH)D deficiency or insufficiency

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The analysis revealed that the mean age varied significantly according to vitamin D levels. Patients with vitamin D levels >30 ng/mL had a mean age of 42.4 ± 13.5 years, those with vitamin D insufficiency (20-30 ng/mL) had a mean age of 46.1 ± 16.4 years, and those with vitamin D deficiency (<20 ng/mL) had a mean age of 54.1 ± 13.8 years ($p=0.02$). Furthermore, there was a statistically significant difference in the frequency of asthma attacks, asthma severity, and asthma control based on vitamin D levels. However, no significant differences were found in gender, Body Mass Index (BMI), atopy (allergic rhinitis and total IgE levels), respiratory function, or the types and doses of prescribed therapies, including inhaled corticosteroids (Table 1).

Factors associated with asthma severity

When comparing a group of patients with severe asthma to another group with non-severe asthma, a multivariate analysis of risk factors for severe asthma was conducted. This analysis demonstrated that the likelihood of having severe asthma was 4.09 times higher in patients with insufficient vitamin D levels compared to those with sufficient levels ($p=0.03$) (Table 2).

Discussion

Vitamin D plays a crucial role in both innate and adaptive immunity, particularly through the activation of antimicrobial peptides such as cathelicidin. It modulates the actions of T

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lymphocytes (Th1 and Th2), reduces the release of pro-inflammatory cytokines by peripheral blood mononuclear cells and T cells, and increases the secretion of IL-10.³ The most compelling role of vitamin D in the pathophysiology of asthma lies in its ability to modulate the regulatory T cell response. The efficacy of corticosteroid therapy in asthma partly depends on this modulation and the increased secretion of IL-10.²

The effect of vitamin D can be observed on the airway function by genetic, epigenetic, and therefore, by immunological changes. Vitamin D receptor gene polymorphisms (FF genotype) have been reported to affect bronchial hyperresponsiveness in children, and vitamin D receptor gene polymorphisms may also affect the development of allergic diseases.⁶ There are also epigenetic gene expression manner changes with vitamin D.⁷ Hypermethylation in the promoter region of various genes was identified in asthmatic patients.

Our study revealed a prevalence of hypovitaminosis D of 67%, which is consistent with the widespread vitamin D deficiency reported in developing countries by Arabi *et al.*⁸ Although female sex and obesity are known risk factors for vitamin D insufficiency,⁹ our study found no significant relationship between these factors and vitamin D levels. Hereditary differences, such as genetic polymorphisms involved in cholesterol synthesis, hydroxylation, and vitamin D transport, may explain variations in vitamin D levels among populations living at the same latitude. Despite Morocco being a sunny region, factors such as clothing habits, sunscreen use, and sun avoidance contribute to this deficiency even among healthy individuals. These findings

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highlight the importance of examining lifestyle behaviors and habits influencing vitamin D levels in different populations.

Several cross-sectional and observational studies have demonstrated a relationship between vitamin D deficiency and atopic symptoms, including rhinitis, asthma, atopic dermatitis, and food allergies. Additionally, maternal vitamin D status during pregnancy could affect the subsequent development of allergic diseases in their children, suggesting a complex relationship between vitamin D and atopy.¹⁰ However, results regarding the association between vitamin D levels and atopic biomarkers such as IgE, eosinophilia, IL-4, and IL-5 remain contradictory. Seasonal variations, differential sun exposure according to latitude, and allergen exposure behaviours may influence these outcomes. In our study, no significant association was found between vitamin D levels and certain allergy markers such as total IgE and allergic rhinitis.

In recent years, many studies have been conducted on the relationship between asthma and vitamin D. These studies are designed in two groups: clinical trials conducted on patients with asthma and studies examining the association between asthma and vitamin D. Forty-nine clinical trials in patients that were conducted in 31 years between 1989 and 2020 were examined in a study, which included 3128 patients, it was concluded that vitamin D supplementation significantly reduced the risk of asthma attacks and the use of steroids, and that it increased FEV₁ values.¹¹ In a cross-sectional study of 3,629 people, it was concluded that 25(OH)D insufficiency was significantly associated with increased asthma risk; in addition, there was a

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20% increase in the odds of asthma in every 10 nmol/L decrease in 25(OH)D.¹² Furthermore, the development and progression of asthma are expected to be different in children with sufficient vitamin D levels compared to those with insufficiencies.

The association between vitamin D levels, asthma severity, and poor control found in our study aligns with several published studies. This association is thought to be mediated through vitamin D's immunomodulatory effects, particularly its role in regulating inflammatory pathways within the airways. Korn *et al.* concluded that vitamin D deficiency is associated with asthma severity, control, lower FEV₁, higher BMI, elevated exhaled nitric oxide, and eosinophilia in sputum.⁵ Similarly, Smarah *et al.* linked vitamin D deficiency with asthma control, the number of treatments, and age.¹³ Montero-Arias *et al.* also found associations with asthma severity, hospitalization or emergency visits during the year, and FEV₁.¹⁴ These findings reinforce the potential impact of vitamin D deficiency on asthma severity and control.

The significant correlation between vitamin D levels and asthma control status highlights the potential role of vitamin D supplementation as an adjunctive therapy in achieving optimal asthma management. Several studies have proposed that vitamin D supplementation may improve asthma control by reducing airway inflammation and enhancing lung function. Based on expert opinion, a suggested dose for individuals with adequate vitamin D intakes is 600 to 1000 IU of vitamin D₃/day, which equals 15 to 25 mcg/day, while the supplementation of 400 to 1000 IU (10 to 25 mcg) of vitamin D daily is also recommended for infants, children, and adolescents between 0 to 18 years.¹⁵ However, conflicting findings exist in the literature

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regarding the effectiveness of vitamin D supplementation in improving asthma outcomes, warranting further investigation into its therapeutic potential.

The limitations of our study include the potential for reverse causality, where severe asthma could lead to vitamin D insufficiency due to limited physical activity and outdoor exposure. Other confounding factors may exist, such as smoking, sun exposure, lifestyle, and potential environmental variables. Furthermore, our monocentric design limits the generalizability of our results to other populations. A multicentric study would be necessary to confirm these observations and better understand the underlying mechanisms.

Conclusions

Our study provides evidence of the implication of vitamin D deficiency in asthma severity, control, and lung function. While our findings support the notion that vitamin D supplementation may hold promise as adjunctive therapy in asthma management, additional well-designed clinical trials are needed to elucidate the therapeutic efficacy and optimal dosing regimens of vitamin D in asthma. Moreover, future research should explore the underlying mechanisms driving the observed associations and identify potential biomarkers to guide personalized vitamin D supplementation strategies in asthma patients.

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Table 1. Patients' characteristics.

Characteristics	All patients (n=174)	25(OH)D level in serum			p-value
		>30 ng/mL (n=63)	20-30 ng/mL (n=51)	<20 ng/mL (n=60)	
Age (years), mean \pm SD	48.1 \pm 15.7	42.4 \pm 13.5	46.1 \pm 16.4	54.1 \pm 13.8	0,02
Gender (female), n (%)	105 (60)	39 (37)	30 (29)	36 (34)	0,87
BMI >30 Kg/m ² , n (%)	72 (41)	21 (29)	30 (42)	21 (29)	0,79
Allergic rhinitis n (%)	135 (77,6)	42 (31)	48 (36)	45 (33)	0,54
Total IgE (UI/mL)	254.4 \pm 32.8	198.8 \pm 28.6	238.6 \pm 34.2	215.9 \pm 35.4	0,33
FEV ₁ (%), mean \pm SD	72.9 \pm 18.3	81.6 \pm 14.5	73.7 \pm 18.4	68.4 \pm 18.5	0,07
FEV ₁ /FVC, mean \pm SD	69.7 \pm 5.4	71.2 \pm 4.9	68.6 \pm 5.7	69.9 \pm 5.3	0,53
Asthma attacks, n (%)	36 (20,7)	6 (16,7)	12 (33,3)	18 (50)	0,004
Severe asthma, n (%)	57 (32,7)	6 (10,5)	21 (36,8)	30 (52,7)	0,02
Uncontrolled asthma, n (%)	78 (45)	15 (19)	27 (35)	36 (46)	0,01

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ICS high dose, n (%)	147 (84,5)	45 (30,7)	48 (32,6)	54 (36,7)	0,23
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SD, Standard Deviation; BMI, Body Mass Index; IgE, Immunoglobulin E; FEV₁, Forced Expiratory Volume in One

Second; FVC, Forced Vital Capacity; ICS, Inhaled Corticosteroid.

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Table 2. Multivariate analysis of potential risk factors for severe asthma.

Covariate	Odds ratio	95% Confidence Interval	p-value
FEV ₁ (%)	0,99	[0,97-1,02]	0,98
Vitamin D insufficiency	4,09	[1,32-22,52]	0,03
BMI (Kg/m ²)	1,05	[0,98-1,13]	0,38
Age (years)	0,99	[0,96-1,03]	0,69
High dose ICS	3,72	[0,47-29,90]	0,21
Female sex	1,57	[0,40-6,15]	0,52

BMI, Body Mass Index; FEV₁, Forced Expiratory Volume In One Second; ICS, Inhaled Corticosteroid.

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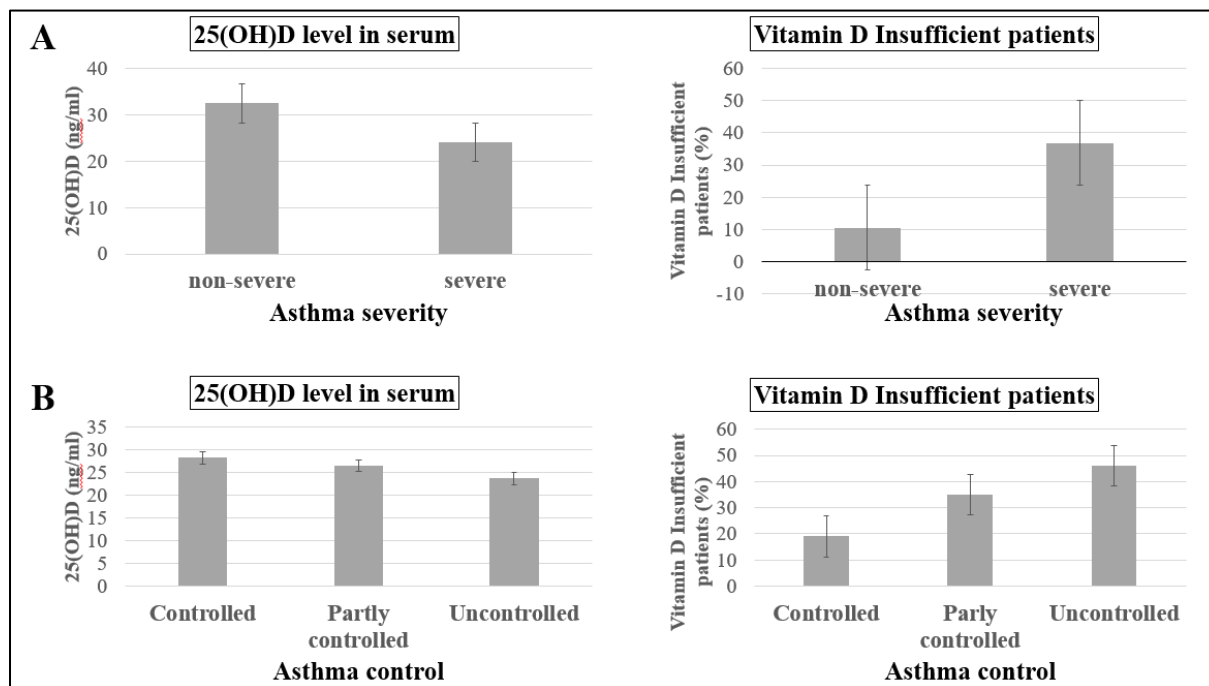


Figure 1. A) 25(OH)D level in serum, vitamin D insufficiency, and asthma severity. Left: 25(OH)D level in serum (mean \pm SD) stratified by asthma severity. Right: Percentage of vitamin D insufficient patients stratified by asthma severity. B) 25(OH)D level in serum, vitamin D insufficiency, and asthma control. Left: 25(OH)D level in serum (mean \pm SD) stratified by asthma control (GINA classification). Right: Percentage of vitamin D insufficient patients stratified by asthma control (GINA classification).

SD, Standard Deviation; GINA, Global Initiative for Asthma

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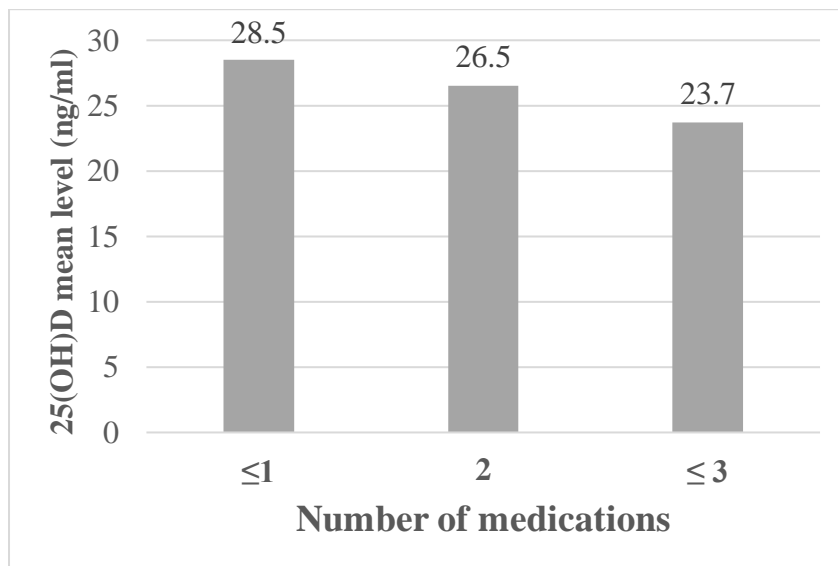


Figure 2. Relationship between the 25(OH)D level in serum and the number of treatments required to control asthma.

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