

MORBIDITY/MORTALITY

Vitamin D deficiency and adult asthma exacerbations

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Abstract

Objectives: There is growing evidence indicating a connection between vitamin D deficiency and the severity of asthma exacerbations. This study seeks to assess the relationship between vitamin D deficiency and the number and severity of asthma exacerbation in adults. **Methods:** A retrospective analysis was conducted in 92 patients being treated for asthma at the University of New Mexico Adult Asthma Clinic. Serum 25-hydroxyvitamin D3 levels were analyzed in adults with mild to severe persistent asthma. Using multi-variant modeling, the relationship was examined between serum vitamin D levels and the odds of asthma exacerbations ranging in severity from moderate to severe over the span of five years. **Results:** This study demonstrates that vitamin D sufficiency was significantly associated with a decreased total number of asthma exacerbations (incidence rate ratio [IRR]: 0.61, 95% confidence interval [CI]: 0.44–0.84, $p=0.002$), decreased total severe asthma exacerbations (IRR: 0.41, 95% CI: 0.24–0.72, $p=0.002$) and decreased emergency room visits (IRR: 0.42, 95% CI: 0.20–0.88, $p=0.023$). **Conclusion:** Vitamin D deficiency may be linked to the risk of severe asthma exacerbations in adults.

KeywordsAnalysis, deficient, FEV₁, hospitalization, preventative, sufficient, severity**History**

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Introduction

The prevalence of asthma has increased at an alarming rate over the past three decades [1]. Though this growth has recently plateaued, according to the Center for Disease Control, over 26 million adults in the United States still suffer from asthma, with almost 50% of these patients experiencing significant asthma exacerbations [2]. As the number of newly diagnosed asthmatics rises, the cost of caring for these patients also increases. In 2012, the annual direct healthcare cost in the United States for asthma was approximately \$50 billion; with indirect costs (i.e. lost productivity) leading to another \$5.9 billion dollars, for a total of \$56 billion dollars [3]. The majority of these costs are from severe asthmatics that make up 5–15% of the asthma population but account for more than 50% of the healthcare utilization and cost [4]. All of these combined factors have spurred researchers to evaluate modifiable factors that can improve asthma outcomes.

Twenty-five hydroxyvitamin D₃, henceforth to be referred to as vitamin D, has received a considerable amount of attention recently as its role in multiple chronic diseases has come to light. Vitamin D deficiency has been implicated in conditions ranging from multiple sclerosis and depression to chronic obstructive pulmonary disease (COPD) and asthma

[5–7]. The role of vitamin D in asthma is being explored extensively. Many studies in children are evaluating vitamin D deficiency and the development of asthma, as well as its role in the immunomodulation of airways and steroid sensitivity [8–11]. However, only a few studies have been performed in the adult population. This study examines an adult asthmatic population with varying degrees of asthma severity and analyzes the effect of vitamin D deficiency on the number and severity of asthma exacerbations.

Methods

A retrospective analysis was performed of 340 patients in the University of New Mexico (UNM) Adult Asthma Clinic. Patients who had a vitamin D level measured during the time they were enrolled in the clinic were then identified and selected from this cohort. Patients with confounding diagnoses (such as severe COPD and cystic fibrosis) were excluded. Patients who had no vitamin D levels measured were also excluded. The remaining 92 patients were included in this analysis.

The serum level of 25-hydroxyvitamin D₃ was used as a biomarker for vitamin D metabolic status and to reflect contributions from all sources of vitamin D (i.e. diet and sun exposure) [12,13]. Twenty-five hydroxyvitamin D₃ was chosen, as this is the vitamin D metabolite produced in the skin during ultra violet exposure and also the metabolite most commonly prescribed for vitamin D replacement (cholecalciferol) [13]. Measurements of vitamin D were obtained quantitatively using liquid chromatography and tandem mass

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spectrometry produced by Waters® (Walters Corporation, Milford, MA). The test, analyzed in TriCore Reference Laboratories® (Albuquerque, NM), measures vitamin D2 and D3 levels individually and then gives a total result. For the purpose of this study, only the vitamin D3 level was used.

Vitamin D levels were categorized into sufficient (>30 ng/mL) and deficient (<30 ng/mL). This level was chosen after a review done by Bischoff-Ferrari et al. demonstrated that health outcomes, including bone density, fracture risk and colorectal health, showed significant improvement at 30 ng/mL [15]. Though there is no specific research looking at the optimum vitamin D level for respiratory health, 30 ng/mL has been accepted as a reference point for vitamin D sufficiency in asthma studies [14]. Vitamin D levels were drawn by primary care providers, independent of the patients' asthma status. For this reason, multiple vitamin D levels were obtained at the primary care providers' discretion. All vitamin D levels obtained for the patient during the study period were assessed. Patients were deemed sufficient if over 50% of their vitamin D levels were greater than 30 ng/mL.

Vitamin D replacement was analyzed by tracking prescriptions for various vitamin D preparations (cholecalciferol and ergocalciferol). The success of vitamin D replacement was not formally analyzed in the scope of this research as replacement was performed by primary care providers independent of the asthma clinic providers; however, a sub-analysis was made of patients receiving vitamin D replacement therapy during the study period. Patients with an initially low vitamin D level who received vitamin D replacement therapy and subsequently developed normal levels were deemed sufficient. Patients whose vitamin D levels remained below 30 ng/dL, despite receiving vitamin D replacement therapy, were deemed deficient. Sensitivity testing of the final results was performed which confirmed vitamin D supplementation did not confound the over all results of the study. Further details of this are described in the results section of this article. No differentiation was made between vitamin D insufficiency and deficiency.

The frequency of moderate and severe asthma exacerbations was then analyzed in this patient population. Asthma exacerbations were defined as events that were troublesome to patients causing a loss of asthma control, with symptoms more than two days a week, increased need for rescue medication or increased nocturnal awakenings that prompted a need for a change in treatment. Exacerbations were categorized as moderate (events that cause loss of asthma control and prompt a need for a change in treatment) or severe (events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as intubation or death from asthma). Per clinic protocol, moderate asthma exacerbations were identified by worsening symptoms for greater than two consecutive days, increased use of short acting beta agonists, a decrease in peak flow below 80% of the patient's personal best and/or similar decrease in forced expiratory volume in one second (FEV_1). These exacerbations were treated with a standard course of prednisone (40 mg/four days, 30 mg/three days and 20 mg/three days) in conjunction with baseline asthma treatment. Asthma exacerbations were not treated solely with an increase in inhaled corticosteroid

dosing as this is not supported in the National Asthma Education and Prevention Program (NAEPP) guidelines [16]. Moderate asthma exacerbations were calculated by identifying outpatient prescriptions and refills of prednisone bursts. Mild asthma exacerbations that were treated with an increase in albuterol use only could not be included due to the retrospective nature of this study. As brief episodes of more frequent albuterol use did not lead to an increase in albuterol prescriptions and as patients did not seek medical attention (clinic visits, urgent care visits or emergency room [ER] visits), no reliable method for collecting information on increased albuterol use for mild exacerbations was available in the electronic medical record.

Severe exacerbations were sub-classified into ER visits, hospitalizations, intensive care unit (ICU) admissions and intubations for asthma. Each severe exacerbation was counted only once and categorized by the final outcome of that exacerbation (i.e. an exacerbation that began as an ER visit but ended in an ICU admission was counted as an ICU admission). All data including but not limited to patient characteristics, treatment methods, laboratory values and outcomes were extracted from the electronic medical record and were rechecked for completeness.

The diagnosis of asthma was made by a pulmonologist per NAEPP guidelines [16]. Spirometry was performed for patients during enrollment in the clinic and when clinically indicated (i.e. worsening symptoms and change in therapy). Spirometry met the American Thoracic Society standards for acceptability and reproducibility. Patients were categorized as having mild to severe persistent asthma and were receiving standard of care treatment according to their asthma severity based on NAEPP guidelines. After the initial data collection, the database was de-identified. All subsequent analysis was made from the de-identified database. Approval for the study was obtained from the Human Resources Protections Office at UNM.

Statistical analysis

All statistical analysis was made using the SAS 9.3 program. The association between binary vitamin D levels and patient characteristics was evaluated. Statistical significance was assessed using Chi Square Tests or Fisher Exact Tests for categorical variables (including gender, smoking, asthma severity, inhaled corticosteroids, long acting beta-2 agonists, other asthma medications [tiotropium, albuterol and montelukast], prednisone and vitamin D supplementation) and using two-sided tests for continuous variables (age, body mass index [BMI] and FEV_1). Poisson regression models controlling for vitamin D supplementation and asthma severity were used to evaluate the associations between vitamin D levels and outcome measures. Statistical significance was assessed using Wald tests.

Results

A retrospective analysis of 92 patients attending the UNM Adult Asthma Clinic was performed, evaluating for a correlation between vitamin D levels and healthcare utilization. A summary of the patient population and characteristics is listed in Table 1. Patient characteristics were analyzed,

Table 1. Baseline patient characteristics.

	All patients (n = 92)	Vitamin D sufficient (n = 36)	Vitamin D deficient (n = 56)	p Value
Age (years)	55 (24–85)	51.5 (24–78)	56 (26–85)	0.095
Gender				
Male	24 (26%)	10 (27.7%)	14 (25%)	0.7671
Female	68 (73.9%)	26 (72.2%)	42 (75%)	
Race/ethnicity ^a				
White	49 (53.2%)	19 (52.7%)	30 (53.5%)	0.4527
Hispanic	31 (33.6%)	15 (41.6%)	16 (28.5%)	
African American	4 (4.3%)	1 (2.7%)	3 (5.3%)	
Native American	3 (3.2%)	1 (2.7%)	2 (3.5%)	
2 + races	4 (4.3%)	0 (0%)	4 (7.1%)	
BMI ^a	35.7 (18.2–52.2)	33.6 (18.2–48.02)	36.1 (19.0–52.2)	0.1056
Smoking				
Yes	14 (15.2%)	4 (11.1%)	9 (16%)	0.1059
No	57 (61.9%)	27 (75%)	30 (53.5%)	
Former	21 (22.8%)	5 (13.8%)	17 (30.3%)	
FEV ₁ , liters	2.52 (0.70–4.75)	2.37 (0.70–4.45)	2.28 (1.19–4.75)	0.4711
Asthma severity				
Mild	8 (8.6%)	4 (11.1%)	4 (7.1%)	0.6483
Mild persistent	23 (25%)	7 (19.4%)	16 (28.5%)	
Moderate persistent	39 (42.3%)	16 (44.4%)	23 (41%)	
Severe persistent	22 (23.9%)	9 (25%)	13 (23.2%)	
Reversibility ^a				
Yes	28 (30.1%)	11 (29.7%)	17 (30.3%)	
No	15 (16.3%)	8 (22.2%)	7 (12.5%)	
Vitamin D supplementation				
Yes	28 (30.4%)	8 (22.2%)	20 (35.7%)	0.0142
No	47 (51%)	25 (69.4%)	22 (39.2%)	
Formerly	17 (18.4%)	3 (8.3%)	14 (25%)	

FEV₁: forced expiratory volume in one second and BMI: body mass index.

p Values in this chart represent the statistical value of the group identified (i.e. race). Each variable was analyzed separately and then the group as whole was analyzed for statistically significant differences between vitamin D sufficient and deficient groups.

Results are expressed as medians (interquartile ranges) for continuous variables and numbers of subjects (percentage of group) for categorical variables.

^aInformation is missing on some subjects for race/ethnicity (n = 1), BMI (n = 5), reversibility (n = 49).

Table 2. Asthma treatment and severity stratified by vitamin D sufficiency and deficiency.

Treatment modalities	Vitamin D sufficient	Mild (n = 4)	Mild persistent (n = 7)	Moderate persistent (n = 16)	Severe persistent (n = 9)
Asthma medications					
Inhaled corticosteroids		1 (25%)	7 (100%)	16 (100%)	9 (100%)
Long acting beta-2 agonist		0 (0%)	6 (85.7%)	9 (56.2%)	9 (100%)
Oral prednisone (daily)		0 (0%)	0 (0%)	2 (12.5%)	3 (33.3%)
Supplemental medications					
Albuterol		4 (100%)	5 (71.4%)	13 (81.2%)	9 (100%)
Leukotriene receptor antagonist		0 (0%)	3 (42.8%)	2 (12.5%)	3 (33.3%)
Tiotropium		0 (0%)	0 (0%)	0 (0%)	3 (33.3%)
Ipratropium		0 (0%)	0 (0%)	2 (12.5%)	6 (66.6%)
Omalizumab		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treatment modalities	Vitamin D deficient	Mild (n = 4)	Mild persistent (n = 16)	Moderate persistent (n = 23)	Severe persistent (n = 13)
Asthma medications					
Inhaled corticosteroids		0 (0%)	15 (93.7%)	21 (91.3%)	13 (100%)
Long acting beta-2 agonist		0 (0%)	13 (81.2%)	18 (78.2%)	12 (92.3%)
Oral prednisone (daily)		0 (0%)	0 (0%)	3 (13%)	5 (38.4%)
Supplemental medications					
Albuterol		2 (50%)	14 (87.5%)	21 (91.3%)	11 (84.6%)
Leukotriene receptor antagonist		1 (25%)	5 (31.2%)	12 (52.1%)	7 (53.8%)
Tiotropium		0 (0%)	0 (0%)	1 (4.3%)	1 (7.6%)
Ipratropium		0 (0%)	0 (0%)	3 (13%)	2 (15.3%)
Omalizumab		0 (0%)	0 (0%)	0 (0%)	1 (7.6%)

including age, gender, self-identified race and ethnicity, smoking status and BMI. Asthma variables between the two groups were also analyzed, including severity, FEV₁ and reversibility. Other phenotypic factors such as IgE levels and exhaled nitric oxide were not included due to limited

measurements in this population seeking routine clinical care. The characteristics of the two groups were similar with the exception of vitamin D supplementation. Patients with vitamin D deficiency were more likely to be receiving vitamin D supplementation (in the form of cholecalciferol and less

Table 3. Asthma exacerbations in vitamin D sufficient group vs. vitamin D deficient group.

Asthma exacerbations	All patients (n = 92)	Vitamin D sufficient (n = 36 [39.7%])	Vitamin D deficient (n = 56 [60.2%])	p Value	95% CI
Exacerbations; all types	197	54	143	0.0024	[0.4–0.8]
Moderate	115 (58.3%)	38 (70.3%)	77 (53.8%)	0.1787	[0.5–1.1]
Severe	82 (41.6%)	16 (29.6%)	66 (46.1%)	0.0020	[0.2–0.7]
ER visits	44 (22.3%)	9 (16.6%)	35 (24.4%)	0.0227	[0.1–0.8]
Hospitalizations	24 (12.1%)	5 (9.2%)	19 (13.2%)	0.1486	[0.1–1.3]
ICU admissions	11 (5.5%)	2 (3.7%)	9 (6.2%)	0.338	[0.09–2.2]
Intubations	3 (1.5%)	0 (0%)	3 (2%)	1.00	[0]

ER: emergency room, ICU: intensive care unit and CI: confidence interval.

commonly ergocalciferol), which was the only confounding factor identified. Vitamin D deficiency was not associated with a decreased FEV₁, increase in asthma severity, increased BMI or with a particular race in this study.

The treatment received by the patients for their baseline asthma symptoms, stratified by vitamin D status is summarized in Table 2. An analysis of the treatment received by both vitamin D sufficient and deficient patients showed that the two groups were receiving similar therapy according to the severity of their asthma regardless of their vitamin D level.

From 2009 to 2013, this patient population suffered a total of 197 exacerbations needing a change in therapy, 82 of which were severe. The majority of these occurred in vitamin D-deficient patients. In this small adult patient population, vitamin D deficiency was associated with an increase in both the total absolute number and odds of asthma exacerbations, specifically the number of ER visits. Poisson regression models were used to investigate this data. This analysis revealed vitamin D sufficiency was significantly associated with decreased total asthma exacerbations (incidence rate ratio [IRR]: 0.61, 95% confidence interval [CI]: 0.44–0.84, $p = 0.002$), decreased total severe asthma exacerbations (IRR: 0.41, 95% CI: 0.24–0.72, $p = 0.002$) and decreased ER visits (IRR: 0.42, 95% CI: 0.20–0.88, $p = 0.023$). As vitamin D supplementation was identified as a potential confounding factor this was used as a covariate in the regression model. These results were statistically significant even after sensitivity testing correcting for vitamin D supplementation in both groups. A summary of these findings is listed in Table 3.

There was a trend toward increased hospitalizations, ICU admissions and intubations in the vitamin D-deficient population, but this did not reach statistical significance as the numbers of events were small. Particularly, intubations only occurred in the vitamin D-deficient population. A careful analysis of these two patient populations did not show significant difference in race, gender, smoking status, comorbid conditions or BMI. For this reason, specific testing to control for these variables was not performed. Vitamin D deficiency was found to be a risk factor for total asthma exacerbations and particularly severe asthma exacerbations independent of age, gender, asthma severity, comorbid conditions, medications, smoking status and BMI.

Discussion

Epidemiological studies performed over the past decade show a surge in vitamin D deficiency that parallels an increase in

the incidence of asthma [17]. Research continues in children to assess whether this finding indicates vitamin D deficiency plays a role in abnormal lung development and thus, a propensity to develop asthma [8]. Data thus far has yielded mixed results and currently, a direct causal relationship between vitamin D deficiency and asthma has yet to be established.

Regardless of its role in the pathogenesis of asthma, there is growing evidence that vitamin D deficiency worsens existing asthma [14,18]. Vitamin D receptors are found in abundance on T cells that inhabit the respiratory epithelium and vitamin D plays an important immunological role in the body's natural defense against respiratory infections. Science et al. described a decrease in respiratory tract infections in vitamin D-sufficient children and adolescents regardless of their asthma status [19]. Increased susceptibility to respiratory viral infections could be one reason why vitamin D-deficient asthmatics appear to have an increased number of severe exacerbations, as viral infections are the most common cause of exacerbations [20]. Multiple studies have shown a direct relationship between the degree of vitamin D deficiency and a decrease in FEV₁ [11,14,18,21] though this was not reproduced in this patient population. Data also indicates that vitamin D deficiency plays a role in the steroid resistance seen in severe asthmatics, one of the main reasons for failure of asthma treatment [10,11,21,22]. A cross sectional study performed by Chambers et al. showed low vitamin D levels corresponded with decreased Foxp3 Treg cells, thought to play a role in steroid responsiveness [9]. Sutherland et al. sought to determine the effect of vitamin D levels in glucocorticoid responsiveness in asthmatics. Performing a cross sectional ancillary study, they analyzed patients with severe persistent asthma and found that low vitamin D levels were associated with a decrease in lung function and glucocorticoid sensitivity [20]. A composite of all these factors likely explains why vitamin D deficiency appears to have a deleterious effect on asthma.

Brehm et al. found that children with vitamin D deficiency were more likely to have severe asthma exacerbations as compared to their vitamin D-sufficient counterparts [14]. However, until now, no such studies have been performed in adults. To our knowledge, this study is the first to analyze asthma exacerbations in adults of all degrees of asthma severity with vitamin D deficiency. These findings show an increase in all asthma exacerbations and especially severe asthma exacerbations in the vitamin D-deficient population, consistent with the findings of Brehm et al. This suggests

that vitamin D deficiency may be a modifiable risk factor for the severity of asthma exacerbations. This study did not reproduce findings seen in other studies showing a correlation between vitamin D deficiency and obesity or reduced FEV₁. This was surprising considering the substantial data connecting obesity with not only vitamin D deficiency but asthma severity as well. This may be due to the relatively small study size and the characteristics of this specific patient population. The majority of patients in this study (~80%) are overweight or obese regardless of their vitamin D level, and this may have influenced the ability to detect any statistical differences between overweight vs. normal weight patients.

This study does have several weaknesses. First, it is a retrospective analysis of a small group of asthmatic patients seeking specialty care and may not represent the general asthma population seen in primary care clinics. It should be noted that asthmatics who attend a specialty asthma clinic tend to have difficulty to control disease and their attendance in such a clinic generates certain biases. The data were collected from a single center without taking into consideration that the patient population may have sought care elsewhere; therefore some data may be missing. There were not vitamin D levels measured on all the patients in the original population of 340 patients, which limits the data pool. Many patients had multiple vitamin D levels, and this study was unable to assess the significance of brief variations in vitamin D levels and their impact on asthma exacerbations. The time of the year that the vitamin D levels were drawn was not taken into account. New Mexico has a significantly higher percentage of ultraviolet (UV) light exposure when compared to other areas of the United States [23]. This could influence vitamin D production and levels though it is difficult to assess if the increase UV exposure nullifies seasonal variations typically seen in vitamin D levels.

These patients were seen in a subspecialty clinic and treated by pulmonologists with close follow-up; however, there was no way to assure individual patient compliance with asthma treatment retrospectively. Patients received asthma education, an action plan and were able to demonstrate appropriate inhaler technique on each visit.

Another hypothesis to consider regarding the prevalence of vitamin D deficiency in this population is the potential for reverse association. As symptomatic asthmatics may avoid physical activity or be limited by allergies, their disease may prevent them from engaging in outdoor activities. It could be hypothesized then that the presence of asthma is causal of vitamin D deficiency and not vice versa. One would expect with this theory that more severe asthmatics would have lower vitamin D levels, and this was not shown in the analysis of this patient population. Furthermore, the cause of vitamin D deficiency is likely multifactorial and cannot be explained exclusively by limited sun exposure.

Conclusion

This study suggests that vitamin D deficiency could be a modifiable risk factor for severe asthma exacerbations. Larger randomized controlled studies are needed to corroborate these results and verify if they can be applied to the general adult asthma population. Vitamin D replacement therapy could be

an inexpensive way to decrease severe asthma exacerbations, thereby reducing overall asthma treatment costs and improving the quality of life for asthmatic patients.

Declaration of interest

Authors have no conflicts of interests to disclose.

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