



Vitamin D and asthma: current perspectives

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Purpose of review

To review the current evidence on the relationship between vitamin D and asthma.

Recent findings

The rising morbidity and tremendous socioeconomic burden of asthma have prompted efforts to seek modifiable environmental and nutritional factors that contribute to the asthma epidemic. The association between low levels of vitamin D and asthma has been supported by many, but not all observational and epidemiologic studies. Recently, several controlled clinical trials have been undertaken to explore the effect of vitamin D supplementation on asthma control and respiratory tract infections. While some trials support the beneficial role of vitamin D supplementation in reducing asthma severity in children, several trials have found no beneficial role in adults.

Summary

Given the high prevalence of vitamin D insufficiency in children and adults worldwide and recent randomized controlled trials of vitamin D in asthma, supplementation with vitamin D cannot be recommended as adjunctive therapy for asthma.

Keywords

asthma, exacerbations, immunomodulation, respiratory tract infections, vitamin D

INTRODUCTION

There has been considerable interest in the role of vitamin D in the pathogenesis of asthma and allergic diseases over the past decade. In fact, some of the common biological and sociological risk factors for vitamin D insufficiency have also been implicated in the development of asthma, such as non-Hispanic black ethnicity [1,2], higher latitude [3] and obesity [4,5]. The association between the status of vitamin D and asthma has been extensively investigated [6,7⁸]. Although many aspects of the association are still awaiting clarification, the information retrieved from these studies is of clear significance in helping develop better preventive and therapeutic strategies for asthma management.

METABOLISM OF VITAMIN D

While humans acquire 10% of vitamin D from natural foods and fortified dairy products, most vitamin D originates from epidermal 7-dehydrocholesterol which is converted to vitamin D₃ (cholecalciferol) by solar ultraviolet B radiation. The photochemically synthesized cholecalciferol is subsequently transported to liver where

hydroxylation catalyzed by CYP27A1 (25-hydroxylase) leads to the formation of 25-hydroxyvitamin D₃ [25(OH)D₃], the predominant form of circulating vitamin D [9]. Further hydroxylation of 25(OH)D₃ by CYP27B1 (1 α -hydroxylase) yields the biologically active 1, 25-dihydroxyvitamin D₃ [1,25(OH)₂D₃]. All physiological actions of vitamin D are dependent on the engagement of vitamin D receptor (VDR) by 1,25(OH)₂D₃ in the cytoplasm. Upon ligand binding, the activated VDR is translocated into the nucleus where it forms a heterodimer with the retinoid-X receptor (RXR). The VDR–RXR complex is able to bind the vitamin D response elements in the promoter region, thereby regulating the transcription of vitamin D-responsive genes.

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KEY POINTS

- Population-based studies show inconsistent data on the correlation between inadequate vitamin D status and asthma due to the heterogeneous nature of the disease and various confounding variables. Epidemiologic evidence suggests that vitamin D insufficiency or deficiency is related to increased asthma morbidity.
- Vitamin D has prominent immunomodulatory functions by enhancing antimicrobial peptide production and affecting the activities of different immune effector cells (T_H2 , T_H17 and Treg). It also attenuates the inflammatory responses induced by respiratory viral infections.
- Several clinical trials have not uniformly shown the protective effects of vitamin D supplementation on asthma control. Thus, vitamin D replacement as an adjunctive therapy for asthma is currently not recommended.

Although $1,25(OH)_2D_3$ synthesis is classically considered to occur in the proximal tubules of kidney, extrarenal expression of the 1α -hydroxylase has been observed in a variety of other cell types including airway epithelium [10] and many of those in the immune system such as dendritic cells, macrophages and lymphocytes [11–13], resulting in the production of locally active vitamin D. Similarly, as a member of nuclear receptor superfamily, VDR is expressed almost ubiquitously throughout human tissues and cell types [14]. These salient features of vitamin D signaling enables it to exert actions beyond bone metabolism, likely in paracrine and intracrine manners [15].

Vitamin D status is usually determined by measuring the serum level of $25(OH)D_3$. Although there is a lack of consensus on the desirable vitamin D level, in general, vitamin D deficiency is defined as level of $25(OH)D_3$ below 20 ng/ml, and vitamin D insufficiency is designated with levels fall in a range of 21–29 ng/ml according to the Institute of Medicine (IOM) report [16,17]. However, it should be recognized that the current definitions of vitamin D inadequacy are based on the effects of vitamin D on the calcium metabolism and bone mineralization. Whether these cut-off levels are applicable to other physiological actions of vitamin D remains unknown.

ASSOCIATION BETWEEN VITAMIN D AND ASTHMA

Owing to the considerable heterogeneity of asthma and various outcome measures and confounders, observational studies exploring the linkage between low vitamin D status and asthma in both adults and children have not been consistent [8^{••}].

In a population-based study, Niruban *et al.* [18[•]] reported that vitamin D-deficient patients were more likely to have current asthma than those with higher $25(OH)D_3$ levels. By contrast, no such association was observed by other cross-sectional adult studies [19,20[•]]. Similar studies [21,22,23[•],24] of children and adolescents failed to identify the correlation as well. Interestingly, a survey of 1213 Canadian children aged 6–12 years showed that both low (≤ 20 ng/ml) and high (≥ 30 ng/ml) levels of serum $25(OH)D_3$ were related to increased risk of recurrent wheeze and reduced rate of changes in lung function, suggesting a nonlinear association of vitamin D status with immune response and respiratory disease [25].

Longitudinal studies have also yielded contradicting results. Large prospective adult studies [26,27[•]] in northern Europe showed no correlation between baseline serum $25(OH)D_3$ levels and incident asthma at the follow-up. By contrast, an inverse relationship was found between the vitamin D levels and incident asthma at older ages in children [28,29], implying that vitamin D may help shape the development of respiratory and immune systems. Tolppanen *et al.* [30], however, reported that serum $25(OH)D_3$ levels were positively associated with risk of wheezing, but not with asthma.

Vitamin D deficiency appears to be a significant risk factor for all-cause mortality in adults with asthma [31]. Inadequate vitamin D status may be connected to increased asthma severity. A number of asthma studies in adults demonstrated lower vitamin D levels are associated with worse asthma control [32], more asthma exacerbations, emergency department (ED) visits and hospitalizations [33,34[•],35–37], increased airway hyper-responsiveness (AHR) and reduced corticosteroid responsiveness [37], whereas Devereux *et al.* [19] reported in a case-control study that there was no relationship between asthma severity and serum $25(OH)D_3$ concentrations in adult patients with mild-to-moderate asthma and vitamin D deficiency. Similarly, most of the available data are consistent in the beneficial role of vitamin D in disease severity and control in asthmatic children [38[•]]. Vitamin D insufficiency or deficiency in this population is associated with more asthma exacerbations [39–41], ED visits or hospitalizations [42] and corticosteroids use [40,41,43,44[•]]. These observations are in accordance with the ability of vitamin D to act synergistically with glucocorticoids to control the immune response [45].

In both children and adult patients with asthma, serum $25(OH)D_3$ levels positively correlated with lung function according to some studies [32,37,39,40,45–47], but not others [19,27[•]]. Wu *et al.* [48] evaluated 1024 asthmatic children enrolled in

the Childhood Asthma Management Program (CAMP). In comparison with vitamin D-sufficient children, those who were vitamin D-deficient had less improvement in prebronchodilator forced expiratory volume in 1 second (FEV₁) over the course of 1 year when treated with inhaled corticosteroids [48].

The programming effect of vitamin D on the development of childhood allergic diseases and asthma has been assessed by a number of prospective birth cohort studies. The concentration of 25(OH)D₃ assayed in neonatal cord serum or in maternal circulation during pregnancy commonly serves as a surrogate marker for the extent of prenatal exposure to vitamin D. The finding that lower vitamin D status *in utero* may not increase the risk of asthma in offspring has been demonstrated by studies in which the cord blood [49,50,51[■],52[■]] and the maternal 25(OH)D₃ levels [53–56,57[■]] were measured. Of note, a correlation between increased risk of asthma hospitalization and high maternal 25(OH)D₃ concentration (≥ 50 ng/ml) was observed in patients who were followed into their adulthood [58[■]], raising the concern for worse asthma control associated with excessive prenatal vitamin D exposure. However, the lack of longitudinal determination of vitamin D status and inadequate adjustments for all confounding variables in these observational studies [38[■],59] has made it challenging to fully understand the impact of vitamin D on asthma pathogenesis during early life.

IMMUNOMODULATORY ROLE OF VITAMIN D

By promoting inflammation and tissue remodeling, T-helper 2 (T_H2) cells play a central role in orchestrating the immune responses to allergens in the airway. T_H2 polarization is facilitated by CD11c⁺ myeloid dendritic cells which express CYP27B1 and VDR, and are therefore subjected to vitamin D regulation [60,61]. In principle, 1,25(OH)₂D₃ down-regulates the expression of surface major histocompatibility complex (MHC)-II and co-stimulatory molecules (CD80 and CD86) while enhancing interleukin (IL)-10 and programmed cell death ligand (PDL)-1 production [62–64]. In this way, vitamin D prevents the maturation of dendritic cells, inhibits T-cell activation and maintains a tolerogenic phenotype [63,65]. However, the effect of vitamin D on T_H2 cells does not seem to be unidirectional despite its evident suppression of dendritic cell activities. Some studies have demonstrated that the vitamin D status correlated negatively with T_H2 skewing, AHR and eosinophilia [66,67[■]], whereas others have shown the induction of T_H2 response by vitamin D, implying an increased risk for asthma [68,69]. Interestingly, elevated levels of IgE

and T_H2 cytokines were observed concomitantly with diminished airway eosinophilia and AHR in VDR-knockout mice [70]. These divergent results underline the pleiotropic effects of vitamin D on the adaptive immune system. In the setting of asthma, counteracting mechanisms may be simultaneously engaged by vitamin D to influence airway inflammation.

A significant negative correlation between serum IL-17 and vitamin D levels was seen in asthmatic children [71]. Further study discovered that 25(OH)D₃ *in vitro* not only decreased T_H17 cytokine synthesis (IL-17A and IL-23), but also impaired T_H17 differentiation likely by arresting the maturation of dendritic cells [72]. Similarly, 1,25(OH)₂D₃, but not dexamethasone, reduced IL-17A and IL-22 levels when incubated with peripheral blood mononuclear cells (PBMCs) of patients with moderate-to-severe asthma [73].

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There are several lines of evidence indicating that vitamin D may dampen the airway inflammation by modulating regulatory T (Treg) cell activities. Serum 25(OH)D₃ levels in asthmatic patients correlated positively with the frequency of Treg cells in bronchoalveolar lavage [74] and with Forkhead box P3 (Foxp3) expression in PBMCs [75]. In addition, *in vitro* data demonstrated that 1,25(OH)₂D₃ promoted Foxp3 and cytotoxic T-lymphocyte-associated protein (CTLA)-4 production [74,76,77] and up-regulated glucocorticoid receptor expression in human CD4⁺ T cells [78]. In keeping with these findings, vitamin D supplementation led to a significant increase in IL-10 levels and the abundance of circulating Treg cells in asthmatic mice, which partly accounted for the reduced airway inflammation [79].

In addition, vitamin D may play a role in respiratory tract infections, leading to exacerbations in asthma. Asthmatic patients with very low serum 25(OH)D₃ levels (<10 ng/ml) had a higher risk of upper respiratory tract infection compared with those who were vitamin D-sufficient [80]. The levels of sputum human cathelicidin antimicrobial peptide (hCAP18) were significantly lower in asthmatic patients than in control individuals, which may predispose asthmatic patients to infections [81]. It is known that the synthesis of hCAP18 and its active

cleavage product LL-37 is induced by vitamin D and is dependent on the cellular CYP27B1 activity [82,83]. Repletion of vitamin D in patients with vitamin D deficiency resulted in a significant increase of Toll-like receptor-2 (TLR2), which activated the production of hCAP18 [84]. However, Xiao *et al.* [81] noted an inverse relationship between hCAP18/LL-37 levels and pulmonary function in asthmatic patients. This finding, in conjunction with the ability of hCAP18/LL-37 to chemoattract eosinophils and stimulate the release of cysteinyl leukotrienes in the airway, may argue for a rather pro-inflammatory role of hCAP18/LL-37 induced by vitamin D [85].

The IL-4 and IL-13-producing invariant natural killer T (iNKT) cells have been identified in the lungs of patients with moderate-to-severe asthma [86]. Interestingly, in VDR-knockout mice, the production of IL-4, IL-5, IL-13, IL-17 and AHR was significantly attenuated likely due to defects of vitamin D-dependent iNKT cell development [87]. These data seem to point toward an adverse effect of vitamin D on asthma by iNKT-mediated mechanisms. However, it remains unclear if the same notion applies to human asthma [88].

EFFECTS OF VITAMIN D ON AIRWAY STRUCTURE

In airway epithelial cells, the constitutive expression of 1α -hydroxylase leads to the local production of $1,25(\text{OH})_2\text{D}_3$, the basal level of which is maintained by the low abundance of the inactivating 24-hydroxylase [10]. When administered to human bronchial epithelial cells infected by human rhinovirus (HRV), $1,25(\text{OH})_2\text{D}_3$ had no direct effect on HRV replication, but induced histological changes of the epithelium toward squamous metaplasia [89]. Similar studies [90,91] of epithelial infections by influenza A (H1N1) and RSV showed inability of vitamin D to restrain these viruses; however, the production of various inflammatory cytokines was significantly suppressed after the vitamin D treatment. Therefore, although vitamin D does not offer direct control of viral replication, it may decrease disease severity by inhibiting the inflammatory responses and resultant airway injury.

Vitamin D inhibits the epithelial–mesenchymal transition by attenuating the transforming growth factor (TGF)- β -mediated epithelial cell invasiveness [92], suggesting a protective effect on airway remodeling. In children with corticosteroid-resistant asthma, increased airway smooth muscle (ASM) mass was associated with lower serum $25(\text{OH})\text{D}_3$ levels, worse lung function and more asthma symptoms [40]. On the contrary, in-vitro and murine

studies have shown that vitamin D was capable of impeding ASM proliferation [93–95], alleviating detrimental changes of airway structure [96] and inhibiting production of mediators of inflammation and remodeling [95,97]. These data together provide evidence for the beneficial role of vitamin D in mitigating airway remodeling in asthma.

THERAPEUTIC ROLE OF VITAMIN D IN ASTHMA

Given the disagreement on the relation between vitamin D and asthma, randomized controlled clinical trials are important to clarify the causality of association and to establish the effect of vitamin D replacement on the clinical outcomes and pathogenic characteristics of asthma.

In a double-blinded, place-controlled randomized trial by Urashima *et al.* [98], 430 school-age children were randomized to receive vitamin D_3 1200 IU/day or placebo for 4 months during the winter season. It was found that the vitamin D_3 group had fewer influenza A infections than the placebo group. Of note, in a small subset of children with asthma, vitamin D_3 supplementation led to a significantly lower rate of exacerbation than placebo, although the prevalence of asthma was low and the vitamin D status was not determined in this cohort [98]. Similarly, the favorable role of vitamin D in preventing asthma exacerbation was supported by a smaller trial which showed asthmatic children taking low-dose vitamin D_3 (500 IU/day) and inhaled budesonide had a significantly lower rate of exacerbation than those taking budesonide and placebo after 6 months [99]. These data are consistent with observational studies which showed that vitamin D deficiency may increase the risk of asthma exacerbations in children and that vitamin D may potentiate the effect of corticosteroids.

Whether vitamin D_3 intervention improves airway inflammation in asthmatic patients was investigated by de Groot *et al.* [100]. Forty-four adult patients with sputum eosinophilia or neutrophilia were randomized to receive a single dose of long-acting vitamin D_3 (400 000 IU) or placebo. It was demonstrated that vitamin D_3 treatment did not significantly alter sputum neutrophil or eosinophil counts compared to placebo after 9 weeks, although a within-group analysis showed vitamin D_3 treatment resulted in a reduction, but only in those with severe sputum eosinophilia [100].

The effect of vitamin D on lung function was also evaluated in small randomized trials. In one study [101], vitamin D_3 (14 000 IU/week) did not alleviate AHR in children despite a substantial elevation of serum $25(\text{OH})\text{D}_3$ levels after 6 weeks.

Interestingly, in a proof-of-concept study, Nanzer *et al.* [102[■]] reported that calcitriol [1,25(OH)₂D₃] as an add-on therapy to prednisolone for 4 weeks significantly improved the lung function in adults with corticosteroid-resistant asthma, indicating a rapid effect of calcitriol on augmenting corticosteroid responsiveness.

In the Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma (VIDA) clinical trial, 408 patients with vitamin D insufficiency or deficiency on inhaled corticosteroids were randomized to receive add-on therapy with placebo or high-dose vitamin D₃ (100 000 IU loading dose followed by 4000 IU/day) for 28 weeks. The time to the first treatment failure (primary outcome), rate of first asthma exacerbation or overall exacerbation rate did not differ between vitamin D₃ and placebo groups, although the overall dose of inhaled corticosteroids to maintain asthma control was slightly lower in those taking vitamin D₃ [103[■]]. Interestingly, in the subset of patients who achieved vitamin D sufficiency (>30 ng/dl), vitamin D resulted in a significant 43% reduction in asthma exacerbations. Each 10 ng/ml increase in serum 25(OH)D concentrations with vitamin D was associated with a reduction in the overall rate of treatment failures [hazard ratio 0.88, 95% confidence interval (CI) 0.78–0.99, *P*=0.04] and overall rate of exacerbations (hazard ratio 0.80, 95% CI 0.67–0.96, *P*=0.02). Treatment with vitamin D₃ had no significant effect on lung function, AHR, asthma control, quality of life or sputum eosinophilia.

Furthermore, the recently completed Vitamin D₃ Supplementation in Adults with Asthma (ViDiA) trial evaluated the effect of vitamin D₃ repletion on asthma exacerbation and upper respiratory infection. There was no significant difference in the time to severe exacerbation or upper respiratory infection with vitamin D compared with placebo [104[■]]. Overall, both of these large controlled trials in adults with asthma suggest that vitamin D supplementation in the presence of vitamin D insufficiency does not improve asthma control, and thus argue against vitamin D₃ supplementation as an efficacious therapeutic strategy, regardless of the distinct fashion of drug administration, baseline vitamin D status and length of treatment in these studies.

Taken together, although vitamin D supplementation may have a role in lowering the risk of asthma exacerbation in children [105], further studies are needed. No robust evidence is available to support its use as an effective adjunctive therapy for asthma control in other clinical settings. In addition to the variability of study design and confounders, there are several notable factors which may have obscured the beneficial effects of vitamin D in the studies. For instance, it is not clear whether the level of vitamin

D achieved in these trials represents the ideal vitamin D levels for lung disease. Determining the optimum vitamin D threshold is crucial to avoid an undesirable outcome of supplementation, given the proposed U-shaped association between vitamin D status and immune responses [106]. Moreover, while the total serum 25(OH)D₃ concentration has been uniformly accepted as an indicator of vitamin D status, it may be of more clinical significance to measure the free bioavailable 25(OH)D₃, the level of which is influenced by a genetic polymorphism in the vitamin D binding protein gene [107[■]]. Lastly, it has been alternatively hypothesized that low vitamin D status is the consequence rather than the cause of inflammatory disorders, calling into question the vitamin D replacement in treating these diseases [108].

CONCLUSION

Our understanding of how vitamin D exerts its actions on immune cells and the airway has advanced tremendously over the past decade. The highly prevalent but modifiable status of vitamin D inadequacy and the favorable safety profile with this supplement have made it an attractive therapeutic option in treating asthma. However, in light of the considerable complexity and heterogeneity of asthma pathogenesis, it is not surprising to see a great deal of inconsistency in the available data with respect to the protective effect of vitamin D. It thus remains premature to advocate vitamin D replacement in asthmatic patients beyond what has been recommended by the current guidelines. Future randomized controlled studies may help better define the optimum dosage and length of treatment and identify specific endotypes of asthma that are potentially responsive to the supplementation.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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