EDITORIAL REVIEW

Vitamin D and asthma

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Purpose of review
Asthma is a disease that continues to carry a significant health burden on humanity. Vitamin D is thought to play a role in many chronic diseases as it may possess immunomodulatory properties. This article will review the role of vitamin D regulation on the immune system and its potential implication in the pathophysiology of asthma.

Recent findings
Vitamin D receptors are present on many cells in the body, specifically peripheral blood mononuclear cells. Vitamin D has been shown to regulate the balance of several pro-inflammatory and anti-inflammatory responses in the immune system. Studies have suggested that prenatal vitamin D intake has an effect on childhood wheezing and asthma. Additionally, vitamin D may play a role in asthma exacerbations, and recent evidence also suggests its importance in steroid resistant asthma.

Summary
Vitamin D has a complex role on the immune system and its regulation of various aspects of immunity has allowed speculation on its potential role in asthma. However, the net effect of vitamin D on the immune system and its role in asthma still remains unanswered. More research needs to address the diagnostic and therapeutic implications vitamin D may have in the future of asthma management.

Keywords
airway hyperresponsiveness, asthma exacerbations, immune system, steroid resistance, vitamin D

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Introduction

Asthma is a prevalent disease worldwide that has significant social and financial burden on the individuals affected [1,2]. It is associated with high morbidity and mortality, especially in the adult population. As a result, national and global efforts have been implemented to reduce asthma prevalence, mortality, and morbidity [3,4]. Management of asthma includes multiple modalities and a step-up approach in its pharmacotherapy has been suggested. Increasing evidence demonstrates that vitamin D deficiency plays a role in chronic diseases including asthma [5]. This review will discuss vitamin D and its involvement with asthma.

Vitamin D deficiency

Vitamin D deficiency was once thought to be eradicated with dietary supplementation and adequate treatment of rickets with ultraviolet radiation. However, vitamin D deficiency remains an under-recognized disorder in the modern day and is prevalent even in countries that have adequate sunlight exposure and dietary supplementation [6,7]. Vitamin D is acquired by exposure to sunlight or through the diet. Some foods naturally contain vitamin D, such as oily fish (salmon and mackerel). Other sources include fortified foods, mostly dairy, bread products, and supplements. Additionally, many factors determine an individual's vitamin D status including age, sex, latitude, skin pigmentation, clothing use, medication, obesity, and dietary habits [7,8]. Vitamin D from sunlight or diet is hydroxylated in the liver to form 25-hydroxyvitamin D [25(OH)D] [9]. A second hydroxylation occurs primarily in the kidney to form 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], the biologically active form of vitamin D. The major circulating form of vitamin D is 25(OH)D and low levels define vitamin D deficiency [10]. Several criteria have been described to define appropriate serum levels of vitamin D including the level associated with maximal suppression of the circulating parathyroid hormone concentrations, greatest calcium absorption, highest bone mineral density (BMD), reduced rates of bone loss, reduced rates of falling, and reduced fracture rates [11]. However, there is no consensus on what optimal levels should be. Most experts agree that vitamin D deficiency is defined as a 25(OH)D level of less than 20 ng/ml and insufficiency at levels between 21 and 29 ng/ml. The desirable vitamin D concentration has been recommended to be above 30 ng/ml [12•]. However, optimal vitamin D levels may in fact be higher than what has been previously recommended, closer to 40 ng/ml [13].

Vitamin D and the immune system

The identification of vitamin D receptors (VDRs) on antigen presenting cells (APCs) such as macrophages and dendritic cells has linked vitamin D to the immune system [14]. An autoimmune role has also been speculated as vitamin D has been shown to have effects on immune cells including T lymphocytes, B lymphocytes, and dendritic cells, as discussed in several published reviews [15,16,17•]. A paracrine role for $1,25(OH_2)D_3$ has been proposed with the discovery that peripheral blood mononuclear cells release enzymes related to the activation and degradation of the active form of vitamin D. Specifically, T cells have been shown to metabolize $25(OH)D_3$ to $1,25(OH_2)D_3$ [18]. The mechanism of action of vitamin D has been linked to the binding of $1,25(OH_2)D_3$ to VDRs. This complex attaches to vitamin D responsive elements within the promoter region of vitamin D responsive genes, thereby influencing the rate of RNA polymerase II-mediated transcription [19]. The affiliation of asthma to gene variants has been an ongoing investigation and the reproducibility was recently reviewed [20]. Several studies have reported associations between the vitamin D receptor and asthma. Poon *et al.* [21] and Raby *et al.* [22] used family-based cohorts and discovered an association between VDR variants and the presence of asthma and atopy. However, two other studies could not confirm these findings [23,24]. Bossé *et al.* [25] has proposed that the effect of vitamin D may additionally involve other genes in the pathway of $1,25(OH_2)D_3$ synthesis. In the animal model, mice bred without VDRs did not develop experimental asthma and had mild airway inflammation. Furthermore, these VDR knockout mice did not develop airway hyperresponsiveness despite having a strong T helper (Th) 2 response [26].

The pathophysiology behind asthma directly involves the host immune response which is driven by the balance between Th1 and Th2 cells, subsets of $CD4^+$ cells. Th1 cells are involved with cell-mediated responses and secrete interferon γ (IFN-γ), interleukin (IL)-2, and tumor necrosis factor α (TNF-α). Th2-associated cytokines IL-4 and IL-5 are involved with antibody-mediated immunity [16]. Asthma is driven by enhanced activity of Th2 cells which induce IgE production, and promote eosinophilic airway inflammation and airway hyperresponsiveness [27,28]. *In vitro*, T cells have been shown to be direct targets for $1,25(OH_2)D_3$ [29] and the effect of vitamin D on helper T cells has been investigated. Evidence has shown a five-fold increase in VDR expression occurring after activation of quiescent $CD4^+$ cells. $1,25(OH_2)D_3$ was found to inhibit the release of T helper cell-associated cytokines IFN-γ, IL-2, and IL-5 and increase the production of IL-4 [30]. The shift away from Th1 mediated responses towards Th2 mediated responses was also seen in a previously published study, explicitly with inhibited IFN-γ production and enhanced production of IL-4, IL-5, and IL-10 [31]. However, not all murine studies demonstrate the production of IL-4 after exposure to $1,25(OH_2)D_3$ [32]. Vitamin D has been shown to decrease production of IL-4 in bronchoalveolar lavage fluid and decrease the inflammatory response [33]. In another study, mice had decreased airway hyperresponsiveness and cellular responses of the airways after exposure to erythemal ultraviolet B irradiation [34]. In humans, $1,25(OH_2)D_3$ has been shown to inhibit IL-12 generated IFN-γ production and additionally inhibit IL-4 and IL-13 expression activated by IL-4 [35]. However, Matheu *et al.* [36] have shown that vitamin D can simultaneously enhance some Th-mediated cytokines and suppress others. Although these findings seem contradictory, the differences might be explained by the different effects of vitamin D on naïve and mature T cells [37]. The role of Th17 cells, which produce the cytokine IL-17, is also being investigated. The production of IL-17 has been reported to be inhibited by vitamin D [38]. This cytokine is involved in autoimmune disorders and inflammatory responses, but also plays a role in the host defense against certain extracellular bacteria and fungi. IL-17 may also be involved with asthma, specifically neutrophil-driven responses [39].

Vitamin D and asthma: the clinical correlations

Although there is continuing research published on the potential effects of vitamin D on the immune system, the exact role of vitamin D in asthma in the clinical setting is still being debated. An analysis of the Third National Health and Nutrition Examination Survey (NHANES III) demonstrated an association between serum vitamin D levels and respiratory infections. A correlation was further seen with patients with asthma and COPD suggesting that the role of vitamin D may be more significant in these populations [40]. Another population-based study suggests a strong relationship between serum concentrations of 25-hydroxyvitamin D, forced expiratory volume in 1 s (FEV1), and forced vital capacity, as lower pulmonary function is associated with vitamin D deficiency [41]. Reviews of diet and asthma and epidemiologic studies have discussed the potential effects of antioxidants and fatty acids; however, little has been said about supplementation with vitamin D [42–47]. The correlations seen amongst these variables are intriguing but the causal effects remain to be elucidated.

The exact relationship between vitamin D and the development of asthma is under discussion. Some investigators have described vitamin D supplementation as being a cause of asthma [48]. A birth cohort in northern Finland reported that vitamin D supplementation in the first year of life increased the risk of atopy, allergic rhinitis, and asthma at age 31 years [49]. However, this study did not assess maternal vitamin D intake or childhood asthma and atopy. Another study has shown that pregnant women with higher levels of vitamin D are correlated with an increased risk for eczema in their infants at the age of 9 months and 9 years of age [50]. This study was limited by the sample size at follow-up, approximately 40% at 9 years of age. Other studies dispute the negative correlation between asthma and vitamin D, suggesting that vitamin D may have a preventive or protective effect on the disease. A birth cohort in Scotland showed children of mothers who had lower vitamin D intake had an increase in the risk of recurrent wheeze at age 5 years. However, there was no association with spirometry or exhaled nitric oxide concentration and patients were noted to have a borderline decrease in bronchodilator response [51]. A second epidemiologic study conducted in Boston showed similar results with an increase in maternal vitamin D intake associated with lower risk of recurrent wheeze at 3 years of age [52]. Another study has shown an inverse relationship between vitamin D intake from food and supplementation and the development of asthma and allergic rhinitis in children 5 years of age [53••]. A limiting factor to all these studies was the use of food frequency questionnaires and not serum levels of vitamin D. Further evaluation will need to be undertaken to clarify the exact role of vitamin D in the pathogenesis of asthma.

Vitamin D and asthma exacerbation

Viral respiratory infections are a common cause of asthma exacerbation in children and adults and respiratory infections have been associated with lower vitamin D levels [40]. The most common offenders in exacerbations have been reported to be rhinoviruses and coronaviruses [54,55]. Increasing evidence has implicated viruses as having more than an infectious role in respiratory disease. Rhinoviruses have been shown to enhance allergic airway inflammation in mice models [56]. In humans, rhinovirus infection induces airway inflammation, increases asthma exacerbation severity, and results in more severe infection in asthmatics when compared to normal subjects [57]. Rhinovirus illnesses that caused wheezing in infancy and childhood were more strongly associated with asthma development later in childhood [58]. The association of asthma in childhood with viral infections has been seen with respiratory syncytial virus infections as well [59]. A recent study demonstrated that vitamin D levels were inversely associated with total IgE and eosinophil count. Additionally, patients with higher vitamin D levels were associated with fewer hospitalizations in the prior year [odds ratio (OR) $= 0.05$, 95% confidence interval (CI) $= 0.004–0.71$, $P = 0.03$]. The study found that of the 616 Costa Rican children evaluated, 28% had insufficient levels of vitamin D, which demonstrates that hypovitaminosis is present in areas that are considered to have adequate sun exposure. This same study suggests an association between increased vitamin D levels and a decreased need for anti-inflammatory medications [60••].

Vitamin D and asthma control

Airway inflammation is a key component in asthma and inhaled glucocorticoids are the most effective anti-inflammatory medication for asthma. A subset of asthma patients are labeled glucocorticoid resistant, defined as poor clinical response with treatment with high-dose oral glucocorticoid. This group of asthma patients have less than a 15% improvement in airway obstruction (FEV1) after a 14-day course of prednisolone 15 mg/day in patients who have greater than 15% improvement in FEV1 with an inhaled β-2 agonist [61]. Steroid resistance has additionally been linked to chronic airway remodeling [62]. The molecular mechanisms of glucocorticoid resistance are complex and multifactorial. One described process includes the reduction in regulatory T cells (Tregs). These cells suppress the activation of the immune response that causes airway inflammation and airway hyperresponsiveness. On a cellular level, dendritic cells present allergens and activate Th2 cells. Tregs express inhibitory cytokines IL-10 and TGF-β to suppress Th2 cells directly or via action on dendritic cells [63]. There is evolving evidence that vitamin D increases the production of regulatory T cells [64,65]. Increasing information specifically suggests a role of these cells in steroid-resistant asthma. $CD4^+$ cells from steroid-resistant patients do not produce IL-10 after stimulation with dexamethasone [66]. Vitamin D has been shown to promote Tregs to produce IL-10 alone [67] and also in the presence of dexamethasone [68]. Xystrakis *et al.* [69] demonstrated that vitamin D induces Treg cells to secrete IL-10 in steroid-resistant patients that have impaired induction of IL-10 by glucocorticoids alone. However, a recent study did not replicate these previous findings *in vitro*, as exposure to glucocorticoid did not enhance peripheral blood mononuclear cells to produce IL-10 [70••]. Further evidence suggests that vitamin D alters human airway smooth muscle expression of chemokines, and may additionally inhibit expression of a steroid-resistant gene [71••].

Another mechanism of glucocorticoid resistance involves glucocorticoid receptors and the ability to regulate inflammatory gene expression. Activated glucocorticoid receptors can directly associate with glucocorticoid receptor elements to activate expression of anti-inflammatory genes. Alternatively, they can inhibit inflammatory gene expression by action on cytokine transcription factors. Glucocorticoid receptors phosphorylation can be ligand dependent and be induced in a mitogen-activated protein kinase (MAPK)-mediated fashion leading to loss of glucocorticoid receptors function by altering their binding affinity for glucocorticoid [72,73]. Glucocorticoids induce the expression of MAPK-1 phosphatase (MPK-1), an inactivator of MAPK thereby resulting in an anti-inflammatory cell response [74]. Recently, increased vitamin D serum concentrations were shown to have a positive correlation with glucocorticoid-induced MKP-1 expression *in vitro*. The relationship was stronger in patients who were not treated with corticosteroid, although still significant in all participants with asthma. This suggests that supplementation with vitamin D could heighten glucocorticoid response in asthma patients [70••]. An important aspect of this study to take note of was the use of inhaled corticosteroids not oral corticosteroids. As further research is done in this area, the exact role of oral corticosteroids in glucocorticoid-resistant asthma remains to be discovered.

Conclusion

Vitamin D deficiency is under-recognized in the general population, and increasing research is being done that has linked its role in many chronic diseases, including asthma. The immune system has clearly been associated with vitamin D and several mechanisms have been described in its relationship with asthma. Currently published studies have demonstrated associations between vitamin D and lung function, markers of inflammation, and modulation in response to steroids; however, more investigation needs to be completed to fully evaluate the causality between all these factors. Specifically, in-vivo studies should be undertaken to assess the clinical significance of vitamin D deficiency in the asthma patient population.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 50).

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