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Review

Vitamin D for the treatment of respiratory diseases: Is it the end or just the beginning?

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ABSTRACT

A large number of human, animal and *in vitro* studies have suggested that vitamin D3 (VD3) plays a critical role in inflammatory airway diseases such as asthma, chronic rhinosinusitis, and allergic rhinitis. VD3 acts upon a broad range of immune cells involved in the pathogenesis of these diseases including T-cells, dendritic cells (DCs), macrophages, and B-cells. In addition, VD3 can also regulate the functions of a number of non-immune cells including epithelial cells, fibroblasts, and smooth muscle cells. Given that VD3 has known effects on the immune system, it seems logical that supplementation with VD3 would prove efficacious in the treatment of these three diseases. While many studies, most of which are observational, have suggested that VD3 deficiency is associated with more severe disease, VD3 supplementation trials in humans have resulted in varied outcomes in terms of efficacy. In this review article we will discuss the role of VD3 in these three commonly associated respiratory diseases. We will explore the literature describing associations of VD3 deficiency with patient outcomes, cells in the respiratory microenvironment susceptible to VD3 regulation, conflicting results of VD3 supplementation trials, and potential gaps in our knowledge that may be limiting the widespread use of VD3 for the treatment of respiratory diseases such as asthma, chronic rhinosinusitis and allergic rhinitis.

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Abbreviations: 1,25(OH)₂D, 1,25-dihydroxyvitamin D3; 25(OH)D, 25-hydroxyvitamin D3; AFRS, allergic fungal rhinosinusitis; APC, antigen presenting cell; AR, allergic rhinitis; ASM, airway smooth muscle; ATAQ, asthma therapy assessment questionnaire; CCL, chemokine (C–C motif) ligand; CRS, chronic rhinosinusitis; CRSNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; CTLA, cytotoxic T-lymphocyte-associated protein; DBP, vitamin D binding protein; DC, dendritic cell; ECM, extracellular matrix; EPOS, European position paper on rhinosinusitis and nasal polyps; ETS, environmental tobacco smoke; FEV₁, forced expiratory volume in one second; FENO, fractional exhaled nitric oxide; FVC, forced vital capacity; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSNEC, human sinonasal epithelial cells; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IP, interferon gamma-induced protein; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa B; PDGF, platelet-derived growth factor; PGE₂, prostaglandin E₂; PFT, pulmonary function test; RANTES, chemokine ligand 5; SNP, single nucleotide polymorphism; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinase; TLR, toll like receptor; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin; URTI, upper respiratory tract infection; VD, vitamin D; VD2, vitamin D2; VD3, vitamin D3; VDR, vitamin D receptor.

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1. Introduction

The relationship between inflammatory conditions of the upper and lower airways is well recognized and has resulted in the unified airway hypothesis. It appears that as inflammation of the respiratory tract develops, it typically begins in the upper airway and then progresses to the lower airway. Studies have demonstrated that 25–30% of chronic rhinosinusitis (CRS) patients have been diagnosed with asthma [1,2]. Conversely, 80–94% of asthmatics have rhinitis and/or chronic rhinosinusitis with nasal polyps (CRSwNP) [1–3]. This progression of disease from the upper airway to the lower airway was demonstrated by Williamson [2] who examined a cohort of patients with CRSwNP and found that while 39% had diagnosed asthma, an additional 30% had subclinical asthma. Although they had no clinical symptoms, these patients had signs of inflammation on fractional exhaled nitric oxide (FENO) or decreased lung function on pulmonary function tests (PFTs). Only 31% of CRS patients had no evidence of lower airway involvement. Asthma, CRSwNP, and allergic rhinitis (AR) are also all characterized by a disruption in Th1/Th2 cytokine balance with a shift towards Th2 [4–8]. The significance of these elevations in Th2 cytokines is that they drive the physical symptoms of airway disease including tissue rhinorrhea and excessive mucus production [9].

Corticosteroids are the most widely used treatment for asthma, CRS, and AR. However, many of these patients' symptoms persist even with a high or prolonged course of steroids. Additionally, corticosteroids may cause significant side effects and in some studies as many as 100% of patients experienced adverse effects [10]. Vitamin D3 (VD3), a naturally occurring steroid hormone, shares a number of anti-inflammatory functions with corticosteroids [11] and can regulate the function of a broad number of immune and non-immune cell types [12,13]. Therefore, it has been hypothesized that a deficiency in this steroid hormone could exacerbate upper and lower airway inflammation. Similar to the increasing incidence of allergies and asthma over the last 40 years, the incidence of VD3 deficiency (<20 ng/ml) has now climbed to over 40% of the US population. When examined by race, 69% of Hispanics and 82% of African Americans are VD3 deficient [14]. Individuals in Westernized countries are particularly susceptible to VD3 deficiencies due to a variety of factors. For example, obesity is a well-known cause of VD3 deficiency and is becoming increasingly prevalent particularly among Americans. While VD3 may be acquired through diet or vitamin supplements, greater than 90% of circulating VD3 is synthesized by the body following exposure to the sun [15]. Furthermore, many individuals have heeded the advice of health care providers and over 90% of people use sunscreen to protect themselves from the adverse effects of the sun [16]. However, sunscreen rated higher than SPF 8 blocks the synthesis of the VD3 precursor in the skin [17] and is suspected to be a contributing factor to VD3 deficiency. Individuals with respiratory diseases, especially those with known allergies, may also limit their time outdoors to avoid allergens, thus reducing their exposure to the sun and increasing their likelihood of being

VD3 deficient. Given the multifactorial nature of the causes, it likely that VD3 deficiency will continue to be a public health concern for many years to come.

In this review article we will explore the literature describing the association between VD3 deficiency and clinical outcomes in patients with asthma, CRS, and AR. We will then explore mechanisms by which VD3 regulates airway immune and non-immune cell functions. Next, we will examine the results of the limited number of VD3 supplementation trials, some of which have called into question the utility of VD3 in treating respiratory diseases. Lastly, we discuss potential hurdles that may be preventing the successful widespread use of VD3 for the treatment of these three linked respiratory diseases, as well as gaps in our understanding of VD3 supplementation, metabolism, and regulation of cellular functions in the airway.

2. VD3 and clinical associations with asthma, chronic sinusitis and allergic rhinitis

2.1. VD3 and asthma

In 2009, the prevalence of asthma in the U.S. was estimated to be 24.6 million people, or 8.2% of the population, with loss of productivity costing an estimated \$56 billion [18]. Asthma prevalence has been increasing since the 1960s and a number of hypotheses have attempted to explain the increase, focusing on changes in the immune system that occur with asthma [19,20]. VD3 deficiency has also been proposed as a contributor to the asthma epidemic, as it has been noted that asthma prevalence is highest in countries furthest from the equator [19].

A number of studies have investigated the association between VD3 status and asthma, and noted that with VD3 insufficiency, a serum 25-hydroxyVD3 (25(OH)D) level below 30 ng/ml (alternately, 32 ng/ml), or VD3 deficiency, a serum 25(OH)D below 20 ng/ml, lung function is decreased and exacerbations are both more common and more difficult to treat [21–26]. One study of nonsmoking adult asthmatics found that those with VD3 insufficiency had decreased lung function, increased airway hyperresponsiveness, and reduced response to glucocorticoid therapy [21]. In this study, lung function was assessed as a measure of FEV₁ (forced expiratory volume in 1 s) and patients were determined to have airway hyperresponsiveness if there was a 20% fall in FEV₁ in response to a methacholine challenge [21]. A similar investigation involving pediatric asthmatics noted that lower VD3 status was associated with increased steroid use and decreased lung function, which was assessed by measuring FEV₁ and the ratio of FEV₁ to FVC (forced vital capacity) [22].

These studies are consistent with other reports on asthma and VD3 insufficiency [23–25]. In preschool children with severe intermittent wheezing, a 25(OH)D level below 20 ng/ml was associated with a higher rate of exacerbations requiring oral corticosteroids [23]. In children with mild to moderate persistent asthma, 35% were 25(OH)D insufficient with insufficiency being associated with higher odds of hospitalization or emergency

department visit [24]. In children with persistent asthma treated with inhaled corticosteroids, VD3 deficiency was associated with poorer lung function, determined by mean change in prebronchodilator FEV₁ before and after 12 months of inhaled corticosteroid use, compared to children with VD3 insufficiency or sufficiency [25]. Additionally, serum VD3 levels have been found to correlate inversely with steroid requirement in pediatric patients, but not adults [26]. Children with severe asthma are less likely to be physically active, and spend less time outdoors, than healthy children. Therefore, it is not possible to rule out VD3 deficiency as a product of their more severe condition, rather than the cause.

VD3 has also been shown to contribute to lung growth and development as well as surfactant synthesis by type II alveolar cells, with deficiency possibly contributing to the risk of asthma even before birth [27,28]. Maternal VD3 status during pregnancy has been assessed through the use of food questionnaires and low VD3 status has been found to be associated with increased risk of recurrent wheeze in preschool aged children [29,30]. Additionally, a French study measured 25(OH)D in cord blood to assess maternal VD3 status, followed the children until five years of age, and determined that low 25(OH)D levels in cord blood were associated with the risk of early transient wheezing [31]. In contrast, a study involving a Finnish birth cohort found that VD3 supplementation

through the administration of cod liver oil during infancy was associated with increased incidence of asthma in adulthood, though maternal VD3 status was not assessed [32].

In families with asthma, 25(OH)D status has also been shown to have a heritable component [33]. Wjst et al. examined a number of single nucleotide polymorphisms (SNP) in genes involved with VD3 metabolism and signaling pathways and looked for associations between these genes and asthma, IgE level, 25(OH)D level, and 1,25-dihydroxyVD3 (1,25(OH)₂D; the active metabolite of VD3) level. At least one SNP was seen in 6 genes (IL-10, GC, IL-12B, CYP2R1, IL4R, and CYP24A1) and a haplotype association was found for CYP24A1, the main 25(OH)D degrading enzyme [33].

2.2. VD3 and chronic rhinosinusitis

CRS affects up to 16% of the US population with direct costs of nearly \$8 billion per year in the United States [34–36]. CRS also has a negative impact on quality of life that exceeds other chronic conditions, such as heart failure, angina, chronic obstructive pulmonary disease or back pain [34–36]. CRS involves inflammation within the nasal cavity and paranasal sinuses lasting longer than 12 weeks and has two distinct pathologies within CRS: CRS

Table 1
Summary of VD3 supplementation trials examining selected diseases of the respiratory tract.

Disease	Trial Name	Dosing	Primary Outcome	Results	Ref.
Asthma	Vitamin D add-on therapy enhances corticosteroid responsiveness in asthma (VIDA)	Oral VD3 (100,000 IU once, then 4000 IU/day for 28 weeks; n = 201) or placebo (n = 207)	Time to first treatment failure	No change in VD3 treatment group	[148]
	Vitamin D supplementation in children to prevent asthma exacerbations	Budesonide (800 µg/day) with oral VD3 (500 IU/day n = 24) or placebo (n = 24)	Number of exacerbations, ATAQ score, and lung function (measured by FEV ₁)	VD3 treatment group had significantly less exacerbations	[149]
	Vitamin D supplementation on airway functions in mild to moderate persistent asthma	Asthma controllers (budesonide or budesonide plus formoterol) according to stage and vitamin D (100,000 U once intramuscularly followed by 50,000 U/week orally n = 64) or no vitamin D (n = 66) for 24 weeks	Airway function (measured by FEV ₁ and FEV ₁ /FVC)	Significant improvement in FEV ₁ in vitamin D treatment group after 16 and 24 weeks	[150]
	VD3 treatment in glucocorticoid-resistant asthma	VD3 (25 µg twice daily n = 13) or placebo (n = 11) for 4 weeks, with course of oral prednisone during the final 2 weeks	Improvement in absolute and percent predicted FEV ₁	Significant improvement in absolute and percent predicted FEV ₁ in the VD3 treatment group	[151]
CRS	Nutritional supplements as adjunctive therapy for children with chronic or recurrent sinusitis	Initial dosing of vitamin A (3750 IU/day) and vitamin D (700 IU/day), escalated as necessary over 2–3 weeks to maximal doses of vitamin A (7500 IU/day), vitamin D (1400 IU/day) and fish oil (3 g/day), duration of 8 weeks, n = 4	Effective treatment of chronic/recurrent sinusitis	Decreased sinus symptoms, fewer episodes of acute sinusitis, and fewer doctors' visits for acute illnesses	[153]
AR	Infant vitamin D supplementation and allergic conditions in adulthood	Oral vitamin D in various products (<50 µg, 50 µg, or >50 µg) during the first year of life, given regularly, irregularly, or not all, n = 7,648	AR and asthma at 31 years of age, reported by questionnaire	Increased incidence of both asthma and AR in vitamin D supplementation group	[32]
URTI	VD3 supplementation to reduce number of upper respiratory tract infections in healthy adults (VIDARIS)	Oral VD3 (200,000 IU initial dose, 200,000 IU dose 1 month later, and 100,000 IU/month n = 161) or placebo (n = 161) for 18 months	Number of URTI	No change in VD3 treatment group	[154]
	VD3 supplementation for the prevention of symptomatic upper respiratory tract infections	Oral VD3 (2000 IU/day n = 84) or placebo (n = 78) for 12 weeks	Incidence, duration, and severity of URTI	No change in VD3 treatment group	[155]
	VD3 supplementation and upper respiratory tract infections	Oral VD3 (1000 IU/day n = 1130) or placebo (n = 1129) for 3–5 years	Frequency and duration of URTI	No change in VD3 treatment group	[156]
	VD3 supplementation for the prevention of acute respiratory tract infection	Oral VD3 (400 IU/day n = 80) or placebo (n = 84) for 6 months	Number of days absent from work due to URTI	No change in VD3 treatment group	[175]
Prevention	Prenatal vitamin D supplementation and child respiratory health	Oral VD2 (800 IU/day n = 60) or single oral bolus VD3 (200,000 IU n = 60) or no treatment (n = 60) at 27 weeks of pregnancy	History of any wheezing in offspring at 3 years	No change in VD3 treatment group	[152]

CRS: chronic rhinosinusitis, AR: allergic rhinitis, URTI: upper respiratory tract infection, VD3: vitamin D3, VD2: vitamin D2, FEV₁: forced expiratory volume in 1 s, FVC: forced vital capacity, ATAQ: asthma therapy assessment questionnaire.

without nasal polyps (CRSsNP) and CRSwNP. CRSsNP is a less severe form of disease that typically involves a blockage in sinus drainage and is primarily a mechanical or bacterial problem. The most difficult form of the disease to treat is CRSwNP, which often fails despite aggressive therapy including antibiotics, oral and topical steroids, immunotherapy, and repeated surgeries [37].

VD3 deficiency is more prevalent in CRSwNP patients compared to CRSsNP, and especially in African American populations [38]. It has also been associated with more severe disease on sinus CT scans [38] and greater nasal polyp size [39]. Additionally, VD3 status correlates inversely with systemic dendritic cell (DC) numbers and bone erosion in patients with CRSwNP and allergic fungal rhinosinusitis (AFRS), a subset of CRSwNP [40]. VD3 deficiency is also prevalent in pediatric CRSwNP patients. An estimated 18% of children in the general population are VD3 deficient, while 90% of pediatric CRSwNP and AFRS patients were found to be VD3 deficient [41].

2.3. VD3 and allergic rhinitis

AR is a disorder of the nasal mucosa characterized by IgE mediated hypersensitivity in response to allergens. Like asthma and CRSwNP, it is associated with Th2 skewing [8]. AR and CRS have some similarities in immune function and they are also functionally related. AR is one source of sinonasal inflammation, which can block sinus drainage and lead to CRS [42]. Pathology related to AR is limited to the nasal passages, while CRS affects both the nasal cavity and the sinuses.

With epidemiologic and pathophysiologic relationships to asthma and CRS [43], it would seem likely that the role of VD3 in AR would be similar, though this is not entirely supported by current research on VD3 and AR. Associations between AR and VD3 are less consistent, with some studies reporting an

association between low levels of VD3 and AR and others reporting a converse finding.

When measuring VD3 serum levels in 18,224 adults in the Third National Health and Nutrition Examination, episodes of AR, as assessed by questionnaire, were found to increase as VD3 levels increased across all age groups [44]. A Norwegian study found similar results in women, but opposite results in men. The study followed patients with no history of AR for an average of 11 years and compared baseline VD3 levels to AR incidence [45]. One Korean study found a potential association between low VD3 levels and AR, while another Korean study reported no association [46,47]. With the inhibitory effect of VD3 seen in the pathology of other airway diseases it would seem likely that it would serve the same function in AR, but the role of VD3 in AR appears to be more complex.

3. VD3 regulation of immune function

VD3 has an undoubtedly complex role in the immune response, having a broad spectrum of functional effects (summarized in Fig. 1). As a nuclear hormone receptor, vitamin D receptor (VDR) binds to 1,25(OH)₂D in the cell nucleus, leading to the VDR-retinoic acid receptor complex. This alters the transcriptional activity of the cell, ultimately leading to an increased or decreased expression of specific chemokines, enzymes, and cell surface receptors. One of the common themes for both innate and adaptive immunity is the suppression of nuclear factor kappa b (NF-κB), a fast-acting nuclear transcription factor that rapidly upregulates the immune response. The proteins ultimately expressed or repressed are highly variable depending on the cell lineage involved. This may be due in part to differential expression of VDR isoforms, as well as differences in DNA methylation and acetylation in each cell line, immune or otherwise.

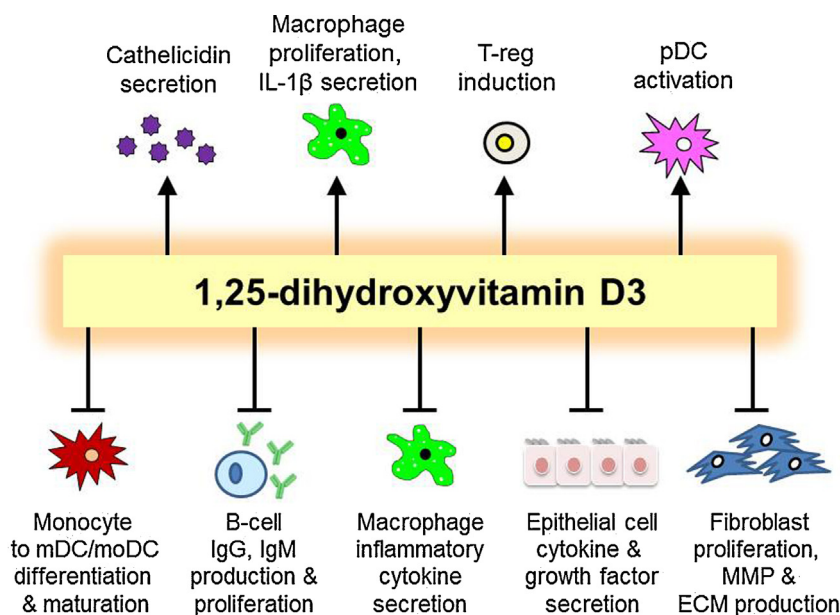


Fig. 1. Summary of the effects of 1,25-dihydroxyvitamin D3 on mediators of inflammatory upper and lower respiratory tract diseases. 1,25-dihydroxyvitamin D3 (1,25(OH)₂D) has a broad array of effects on the respiratory microenvironment with both activating (top row) and inhibitory functions (bottom row). In the presence of 1,25(OH)₂D, secretion of the antimicrobial peptide cathelicidin is increased by epithelial cells and macrophages. 1,25(OH)₂D also induces macrophages to proliferate and increase secretion of IL-1β, while down regulating production of factors such as TNFα and IL-6. Naive T-cells are directed towards anti-inflammatory T-regulatory cells by 1,25(OH)₂D. 1,25(OH)₂D has varying effects on dendritic cells (DCs) depending on subset. Plasmacytoid DCs are induced to block T-cell activation and proliferation. 1,25(OH)₂D also blocks monocyte to DC differentiation and reduces expression of co-stimulatory molecules such as CD80 and CD86 on monocyte-derived DCs (moDC) and myeloid DCs (mDC). Another type of antigen presenting cell, B-cells, are also susceptible to 1,25(OH)₂D regulation resulting in reduced proliferation and diminished antibody production. Other cells in the airway microenvironment, particularly epithelial cells and fibroblasts, are also susceptible to 1,25(OH)₂D regulation. 1,25(OH)₂D can reduce inflammatory cytokine and growth factor production by both of these cell types. Furthermore, 1,25(OH)₂D can down regulate production of matrix metalloproteinases and extracellular matrix products, such as collagen and fibronectin.

3.1. Innate immunity

Two innate immune cell types that are involved in inflammatory airway diseases and susceptible to regulation by $1,25(\text{OH})_2\text{D}$ include macrophages and DCs. These are the first line of defense against invading pathogens, capable of phagocytosing invading organisms and releasing antimicrobial peptides such as cathelicidin and defensin [48–50]. Upon recognition of foreign epitopes through toll-like receptors (TLRs), macrophages induce local $1,25(\text{OH})_2\text{D}$ production through up-regulation of 1α -hydroxylase, encoded by CYP27B1 [51]. Chemokines involved in the macrophage response, interferon- γ (IFN- γ) and IL-4, also increase activity of 1α -hydroxylase [52]. At the same time, the response is further enhanced by increased expression of VDR. This causes a surge in cathelicidin production. Mostly likely because of the ability of macrophages to activate VD3, both $25(\text{OH})\text{D}$ and $1,25(\text{OH})_2\text{D}$ are able to suppress macrophage IL-6 and tumor necrosis factor- α (TNF- α) production in response to lipopolysaccharide (LPS) [53]. Conversely, VD3 also induces macrophages to increase expression of IL-1 β [54].

Aside from direct antimicrobial activity, macrophages and DCs also function as antigen-presenting cells (APCs) for the adaptive arm of immunity. When presenting antigens to T- and B-cells, they can create either a tolerogenic or immunogenic response to a given epitope through differential expression of co-stimulatory molecules [55–57]. For APCs, DCs are particularly susceptible to VD3 regulation. $1,25(\text{OH})_2\text{D}$ changes the morphology of DCs to a more immature form, characterized by decreased expression of MHC-II, the co-stimulators CD40, CD80, and CD86, and IL-12 [58–62]. At the same time, IL-10 secretion is increased, with the end result being a tolerogenic state. This has been supported by recent studies in VDR/ 1α -hydroxylase knockout mice that showed a large increase in mature DCs [63–65]. Human studies in CRSwNP patients have corroborated this trend, demonstrating an inversely correlated relationship between systemic VD3 and DC proliferation in inflamed sinonasal tissue [41,66].

3.2. Adaptive immunity

The adaptive immune system allows for recognition and memory of specific epitopes that are either foreign or mistakenly interpreted as such. As mentioned above, VD3 plays a critical role in determining whether a selected epitope elicits a tolerogenic response from APC and T-/B-cell interactions. While dormant, B- and T-cells have limited expression of VDR and 1α -hydroxylase [67], but in proliferation this significantly increases [68–70]. Thus if a given APC is under the influence of VD3, the paracrine action of $1,25(\text{OH})_2\text{D}$ cascades through clonal expansion.

T-cells undergo a wide variety of changes upon exposure to $1,25(\text{OH})_2\text{D}$. T-regulatory cells have both a systemic response as well as an intracellular conversion by 1α -hydroxylase [71,72]. They are essential in both preventing excessive responses to appropriate antigens and inducing self-tolerance. While encouraging T-regulatory cell proliferation and expression of transforming growth factor- β (TGF- β) and Foxp3/cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), $1,25(\text{OH})_2\text{D}$ also suppresses secretion of pro-inflammatory cytokines by CD4+ T-cells [73]. Specifically, helper T-cells produce fewer Th1,9,17, and 22-associated inflammatory cytokines (TNF- α , IFN- γ , IL-2, IL-9, and IL-22) [74–78]. Instead, $1,25(\text{OH})_2\text{D}$ is associated with the development of Th2 cells, and in appropriate physiologic levels does not skew the immune profile to a significant degree. This presents a complex picture, as both VD3 deficiency and a Th2-skewed response have been implicated in CRSwNP and asthma [79–81]. With CRSwNP, Ozkara et al. showed levels of $1,25(\text{OH})_2\text{D}$ were strongly correlated with Th2 skewing compared to controls only in patients that also had

AR. Conversely, patients with non-allergic polyposis showed no statistically significant difference in Th2 cytokines compared to control patients. This suggests a role for VD3 deficiency in the pathogenesis of allergic disease in the upper airway.

Although VD3 tends to promote Th2 cytokine production, it has other complex effects on the inflammatory process. In a mouse model of asthma, Topilski et al. found that treatment with $1,25(\text{OH})_2\text{D}$ inhibited chemotaxis of T-cells from lymph nodes to the lung, in part from a significantly reduced rate of actin polymerization [82]. So, on one hand, VD3 serves as the brakes of the immune system, tempering the immune response to appropriate targets. On the other, some groups have postulated that too much VD3 in utero and early life is actually a risk factor for atopy and asthma [29,30,83–85]. This is best described with a U-shaped curve of VD3 versus incidence of allergic disease. In a single center study by Rothers et al., neonates with cord blood levels either deficient or excessive in VD3 had an odds ratio of developing allergic disease of 2.4 or 4, respectively [86]. This is not surprising, since VD3 also promotes development of T-regulatory cells. A lack of control in VD3 deficiency likely contributes to the development of allergic disease through indirect mechanisms on both APCs and effector cells, although it is not necessarily the central component of immune dysfunction in allergy and asthma.

In the above studies with cord blood, allergic disease was established by detection of antigen-specific IgE levels to common aeroallergens. This brings another culprit in the pathogenesis of allergy to the forefront: the immunoglobulin (Ig)-secreting B-cell. Initial research into VD3 regulation of B-cells seemed to indicate that VD3 exerted its effects indirectly through T-cells [68], however this has been shown not to be the case. VD3 has instead been found to inhibit antibody production in peripheral blood mononuclear leukocytes challenged with *Candida albicans* [68]. $1,25(\text{OH})_2\text{D}$ directly promotes apoptosis of mature B-cells as well as inhibition of memory B-cell selection [58,59,69]. Recent studies also indicate that $1,25(\text{OH})_2\text{D}$ -primed B-cells cannot activate T-cells as effectively as cells cultured without $1,25(\text{OH})_2\text{D}$, suggesting a second mechanism of negative feedback [87]. VD3 also has anti-proliferative effects on plasma cells, antigen-specific B-cells capable of large amounts of Ig secretion, by directly decreasing their absolute number in *in vitro* studies [69]. Furthermore, multiple studies have confirmed that, *in vitro*, culturing B-cells with $1,25(\text{OH})_2\text{D}$ decreases production of all Ig classes [88–91]. However, *in vivo* human studies haven't been as promising. Supplementation with $1,25(\text{OH})_2\text{D}$ did not affect the levels of any Ig subclasses in patients with advanced multiple sclerosis, which suggests that pre-existing plasma cells *in vivo* are not as susceptible to the effects of VD3 regulation [92]. Evidently, the extent of VD3's regulatory capacity *in vivo* is not clear, although *in vitro* studies suggest it plays a role along the pathogenesis of different kinds of immune dysfunction.

4. VD3 as a regulator of non-immune cell functions in the airways

4.1. Epithelial cells

In addition to its role in the regulation of the immune system, VD3 also has the potential to regulate a number of non-immune cell types in the airway. One cell population identified as a therapeutic target for a number of respiratory diseases is respiratory epithelial cells. Environmental insults such as allergens, environmental toxins, and fungi, and topically delivered therapies, interact initially with epithelial cells in the respiratory tract. While not traditionally thought of as an immune regulatory cell, we now know that epithelial cells modulate the functions of a large number of cell types [93–102] through their secretion of a

broad range of factors including IL-6, IL-25, IL-33, granulocyte-macrophage colony-stimulating factor (GM-CSF), prostaglandin E2 (PGE2), thymic stromal lymphopoietin (TSLP), chemokine (C–C motif) ligand 2 (CCL2), and CCL20 [103–105]. Furthermore, airway epithelial cells from asthmatics and patients with CRSwNP have been identified as having a number of alterations in their function, including intrinsically altered production of pro/anti-inflammatory mediators [106–108] as well as hyperreactive responses to a number of commonly inhaled environmental irritants [109,110]. While the hyperresponsive nature of these cells is well established, a means by which to reduce epithelial cell-driven inflammation is less clear, though several studies suggest that VD3 may have that capability.

Epithelial cells in both the lung and sinonasal tract have also been identified as having the potential to convert 25(OH)D to its biologically active form, 1,25(OH)₂D [111,112]. While not described in the lower airway, 80% of the cells in the sinonasal mucosa containing 1 α -hydroxylase were found to be epithelial cells [112]. In addition to serving as a local source of 1,25(OH)₂D, epithelial cells also respond to it. For example, 1,25(OH)₂D has been shown to reduce small airway epithelial cell secretion of TNF α , IL-6, and IL-8 in response to an influenza A (H1N1) infection [113]. Bronchial epithelial cell expression of cathelicidin and other anti-microbial defenses were increased in the presence of 1,25(OH)₂D compared to controls [114]. 1,25(OH)₂D was also able to reduce human sinonasal epithelial cell (HSNEC) inflammatory cytokine production induced by cigarette smoke extract [112]. 1,25(OH)₂D can also directly promote transcription of TSLP [115], which acts on both myeloid and plasmacytoid dendritic cells resulting in T-regulatory maturation [116,117]. Collectively, these results suggest that VD3 may be efficacious in reducing epithelial cell-derived inflammation to a broad range of insults experienced in the upper and lower airway.

4.2. Fibroblast and myofibroblast

The predominant stromal cell in the respiratory tract, as in many organs, is the fibroblast. Airway remodeling due to chronic inflammation and fibroblast proliferation is an area of continued investigation in diseases of the upper and lower respiratory tract [118–120]. While routinely studied as an effector cell that produces extracellular matrix (ECM), fibroblasts are also immunologically active. A less simplistic role of the fibroblast is now being elucidated that involves a complex cytokinetic immune regulatory function resulting in fibroblast proliferation, matrix metalloproteinase (MMP) imbalance, and ECM production with subsequent airway remodeling [121,122].

In response to an insult, fibroblasts transform into myofibroblasts, a process regulated by TGF- β [123,124]. Myofibroblasts are responsible for the bulk of collagen and ECM production. The synthesis and degradation of ECM is a dynamic process regulated by MMPs and tissue inhibitors of metalloproteinases (TIMPs) [125]. A disturbance in the balance between MMPs and TIMPs results in histopathologic remodeling characterized by sub-epithelial fibrosis, increased vascularity, angiogenesis, goblet cell hyperplasia, basement membrane thickening, and increased smooth muscle mass; all of which has been well documented in the lower airways of asthmatics [126–130].

The effect of VD3 on this balance is unknown, however there is evidence associating VD3 deficiency with a disrupted MMP/TIMP balance. A TIMP-1 polymorphism has been associated with asthma and aVDR TaqI polymorphism is associated with the decreased production of TIMP-1 [131,132]. In addition, patients with end stage renal disease and resultant VD3 dysregulation have decreased plasma MMP-9 [133]. Finally, MMP matrix vesicles have been shown to be regulated by VD3 metabolites in vitro [134].

VDR has been found on numerous cell types including fibroblasts, providing plausibility for an immune-modulatory effect [135], but exactly how VD3 modulates fibroblast function remains largely unknown. VD3 has also been shown to inhibit nasal polyp fibroblast growth as well as down-regulate the fibroblast production of chemokine ligand 5 (RANTES –a powerful eosinophil chemoattractant) [136]. In the lung, VD3 has been shown to down regulate fibroblast production of the pro-Th2 and pro-fibrotic factor PGE₂ [137] and in the upper airway there is significant growth inhibition of fibroblast cultures with VD3 [138]. VD3 has also clearly been shown to reduce fibroblast collagen production [138].

4.3. Smooth muscle cells

Airway remodeling in chronic inflammatory respiratory disease is a complex process and is associated with excess airway smooth muscle (ASM) [139]. Lower VD3 levels are associated with greater ASM by endobronchial biopsy from asthmatic children [140]. VD3 has been shown to decrease ASM mass in an in vivo murine model of chronic asthma [141,142], as well as human ASM *in vitro* [143]. The VDR has been shown to be expressed on ASM [144]. A number of possibilities have been investigated to elucidate the mechanism of VD3 action on reducing ASM.

NF- κ B p65 is inhibited by VD3, suggesting that inhibition of the NF- κ B pathway may be the mechanism by which VD3 attenuates airway remodeling [130]. Also, ASM expression of ADAM33 is associated with increased disease severity. When treated with VD3, ASM shows reduced mRNA and protein expression of MMP-9 and ADAM33 genes [80]. VD3 has been shown to inhibit platelet derived growth factor (PDGF)-induced ASM DNA synthesis, and it has been suggested that VD3 may inhibit ASM cycle progression from G0/G1 to S phase by growth factor-induced phosphorylation of the retinoblastoma protein and checkpoint kinase 1 [145]. VD3 also inhibits cultured ASM secretion of inflammatory cytokines [RANTES and interferon gamma-induced protein-10 (IP-10)] when stimulated with TNF- α [146].

5. VD3 supplementation as a treatment for respiratory diseases

Clinical trials have evaluated whether the supplementation of VD3 is effective in ameliorating disease processes known to be associated with VD3 deficiency. Randomized controlled trials have involved asthma patients, and a number have also looked at upper respiratory tract infections (URTI). URTI are of interest as they are an important cause of exacerbations in asthmatics [147]. A small number of studies involving supplementation of VD3 have also been implemented for CRS and AR. Trials were included following a Pubmed search using the terms “Vitamin D,” “Vitamin D supplementation,” and “randomized controlled trial” or “RCT” in conjunction with the terms “allergic rhinitis,” “chronic rhinosinusitis,” “asthma,” and “upper respiratory tract infection.” VD3 supplementation trials are included in Table 1. Chronic obstructive pulmonary disease is another disease of the respiratory tract where vitamin D may play an important role, but is not included in this paper.

Recently, results from the VIDA (VD3 add-on therapy enhances corticosteroid responsiveness in asthma) randomized controlled trial were published [148]. The trial took place between April 2011 and January 2014 across nine academic medical centers in the U.S. It enrolled 408 adult patients with symptomatic asthma and 25(OH)D levels less than 30 ng/ml. Patients enrolled in the trial were given either oral cholecalciferol (25(OH)D) (100,000 IU once and 4000 IU/day for 28 weeks) or a placebo in addition to inhaled ciclesonide (320 μ g/day). If asthma was controlled, the dose of ciclesonide was slowly tapered to one quarter of the original dose [148]. The primary outcome was time to first treatment failure,

which was not altered in the VD3 treatment group. The trial had a number of secondary outcomes, one of which was total inhaled corticosteroid dose, which was significantly lower in the VD3 treatment group. No other differences were seen between the groups in terms of asthma symptoms, though the serum 25(OH)D level did significantly increase in the treatment group. The VD3 supplementation group had mean serum 25(OH)D levels above 40 ng/ml for all time points of the trial, while the control group maintained a mean serum 25(OH)D levels below 20 ng/ml. The conclusion reached from the trial was that oral VD3 supplementation was not an effective therapeutic strategy for patients with symptomatic asthma [148].

Another randomized controlled trial involving pediatric asthmatics examined the effects of budesonide with and without VD3 on asthma symptoms [149]. Forty-eight children aged 5–18 years old with newly diagnosed asthma were enrolled in the study, which took place between September 2007 and February 2008. Patients received budesonide 800 µg/day with either cholecalciferol 500 IU/day or placebo. The number of asthma exacerbations, symptom score (assessed with the asthma therapy assessment questionnaire (ATAQ)), and lung function (assessed with FEV₁) were used to assess the effects of VD3 supplementation. Children in the cholecalciferol group experienced significantly less exacerbations than those in the steroid only treatment group. There was not a significant difference between the groups in regards to change in serum 25(OH)D level from baseline, but the steroid only treatment group did have a significantly higher number of children with a decrease in 25(OH)D level. A correlation was also noted between baseline ATAQ score and baseline serum 25(OH)D level, which is consistent with observational studies discussed previously [22–25]. Conclusions reached from the study were that VD3 supplementation could be used to facilitate the control of asthma symptoms in newly diagnosed patients [149]. Of note, both treatment groups had sufficient vitamin D levels at baseline.

Additional studies in asthmatics have observed an improvement in lung function (improved FEV₁) when patients were treated with VD3 in addition to steroids [150,151]. In one study, 100 patients received regular asthma control medications and either VD3 (100,000 IU once intramuscularly followed by 50,000 U/week orally) or no VD3 for 24 weeks [147]. The other study dosed calcitriol (1,25(OH)₂D) at 25 µg/day, or placebo, for 4 weeks, with oral prednisone in the final two weeks [151]. Notably, both the placebo and calcitriol treatment groups had sufficient vitamin D levels at the beginning of the study. Both studies noted an improvement in lung function in the VD3 treatment groups [150,151].

Another trial involving supplementation of VD3 during pregnancy did not find decreased incidence of wheezing in offspring, though the statistical power of the study was limited as it was small and the rate of wheezing in control patients was low [152]. One hundred eighty pregnant women were randomized at 27 weeks to receive 800 IU ergocalciferol (vitamin D₂) daily, a single oral bolus of 200,000 IU cholecalciferol (25(OH)D) or no VD3. The primary outcome of interest was history of ever wheezing, with additional outcomes including recurrent wheeze, atopy, and respiratory infection. Prenatal VD3 supplementation was not associated with decreased wheezing in offspring at three years, though an increase in cord blood VD3 was observed in the VD3 supplementation group [152].

VD3 supplementation studies have also been implemented for CRS and AR [32,153]. Cod liver oil and VD3 obtained from a multi-vitamin were used as an adjunctive therapy for four pediatric patients with chronic or recurrent sinusitis, with initial dosing of 3750 IU/day vitamin A and 700 IU/day vitamin D. Doses were escalated over two to three weeks as necessary to maximal

doses of 7500 IU/day vitamin A, 1400 IU/day VD3, and 3 g/day fish oil. Patients had decreased sinus symptoms, fewer episodes of acute sinusitis, and fewer doctors' visits for acute illnesses [153]. In another study involving VD3 supplementation during infancy, cholecalciferol supplementation was said to be associated with an increased risk of asthma and AR. This study was conducted as a part of the Northern Finland 1966 Birth Cohort and assessed VD3, given as a 25(OH)D supplement or in cod liver form to 7,648 infants, by categorizing the 25(OH)D levels in the supplement products as <50 µg, 50 µg, or >50 µg and the frequency of dosing as regular, irregular, or not at all. For the majority of study participants these doses would be similar to 2000 IU/day. However, in this study there were no serum measures of 25(OH)D status, so it is not possible to accurately state what the child's VD3 status was [32].

Similarly to asthma, CRS, and AR, VD3 deficiency has also been associated with an increased frequency of URTI [147]. One randomized controlled trial occurring between February 2010 and November 2011 in Christchurch, New Zealand administered monthly doses of either cholecalciferol (initial 200,000 IU dose, another 200,000 IU dose one month later, followed by 100,000 IU monthly doses) or placebo to healthy adults and monitored for number of URTI. Duration and severity of URTI and number of days of work missed were also assessed and no differences were found between the groups [154].

Similar findings were reported in two other randomized controlled trials looking at frequency of URTI with daily cholecalciferol supplementation [155,156]. One enrolled 162 adults 18–80 years old in Long Island, New York between December 2006 and March 2007, with patients receiving 2000 IU VD3 daily for 12 weeks [155]. The other included 2259 participants aged 45–75 with patients recruited from 11 clinical centers between May 2004 and November 2008 and receiving 1000 IU cholecalciferol daily for 3 to 5 years [156]. Notably, VD3 treatment groups did have significantly increased 25(OH)D serum levels despite lack of clinical improvement [148,154–156]. The ability of VD3 supplementation to result in clinical improvement may vary with dosing regimen or have different effects in different populations. The role of absorption and local metabolism may also be an important factor to consider for future clinical trials involving VD3 supplementation.

6. Why VD3 may not be an effective treatment for respiratory diseases

Much attention has been given to the associations found between VD3 deficiency and airway diseases. Given that a number of recent VD3 supplementation clinical trials have yielded mixed results, it is important to review factors that could be impairing VD3 effectiveness.

An estimated 90% of required VD3 is produced directly in the skin from a cholesterol precursor upon exposure to UV-B light [157]. VD3 synthesis begins in the skin where pro-VD3 is converted to pre-VD3. Following binding to VD3 binding protein (DBP), it is transported to the liver and converted to 25(OH)D. Originally it was thought that conversion of 25(OH)D to the active metabolite, 1,25(OH)₂D, by 1α-hydroxylase occurred solely in the kidneys [158]. However, 1α-hydroxylase expression has been shown in other tissues including the colon, lymph nodes, brain, skin, lungs and sinonasal tissue [112,159,160]. However, patients with CRSwNP have been shown to have downregulated sinonasal 1α-hydroxylase compared to controls as well as an impaired ability by their sinonasal epithelial cells to activate VD3. Similar impairments in VD3 activation were observed in active smokers or individuals exposed to environmental tobacco smoke (ETS) [112]. Cigarette smoke has also been shown to inhibit bronchial epithelial VDR

translocation [161]. These results suggest that even if a person is 25 (OH)D replete, that impaired tissue activation by disease or exposure to environmental factors may limit its effectiveness.

There are two basic forms of vitamin D in food and supplements, ergocalciferol or VD₂, and cholecalciferol, VD₃. Although a fat-soluble steroid derivative, it has not been determined with confidence that vitamin D must be taken with fat. However, some small studies have demonstrated faster correction to normal 25 (OH)D levels when taken with the largest meal of the day [162]. Although both forms of Vitamin D are approved for supplementation in VD₃ deficiency, there is some significant data for consideration when selecting appropriate patient therapy [163]. While they seem to be bioequivalent in raising serum 25(OH)D in some studies, others have shown that DBP has a weaker affinity for VD₂, accounting for the faster clearance of VD₂ from blood. VD₂ is also a poorer substrate for renal 1- α -hydroxylase, leading to less hormonally active 25(OH)₂D [164]. Some trials also reported a large age-related difference in metabolism, with younger patients responding equally well to VD₂ and VD₃ and elderly patients showing inadequate response to VD₂ [165]. This is similar to results by Govea et al., that demonstrated a greater responsiveness to VD₃ in children compared to adults with asthma [166].

Regardless of the type of supplement or the age of the patient, there is also likely a racial difference indicated by DBP polymorphisms [167]. A study recently published in the *New England Journal* investigated the genetic differences in Caucasians and African Americans and found an overwhelming majority (77%) of African American participants would be considered VD₃ deficient (25(OH)D <20 ng/ml). Genetic analysis revealed a high frequency of DBP polymorphism in the African American population that led to a significantly decreased level of DBP. The lack of “protection” in serum binding proteins leads to a shorter half-life of 25(OH)D, yet African Americans have consistently higher bone mineral density and serum calcium than Caucasians. The threshold values for sufficient 25(OH)D were determined by the initiation of the parathyroid response to calcium changes, but this does not seem to be clinically relevant to all African American participants in the study. Individuals with lower DBP, although susceptible to decreased production and intake in the short term, may allow for more immediate bioavailability (and therefore more active 1,25 (OH)₂D). The question that must be answered by future research is can we reliably correlate VD₃ deficiency as measured by 25(OH)D assays, and does a low value actually imply a clinically significant issue worth addressing? For some patients, it seems that raising 25 (OH)D levels may simply be a numbers game. Furthermore, there are currently no studies that demonstrate that raising 25(OH)D increases local production of 1,25(OH)₂D in the APCs or effector cells of the immune system.

Recent work is shining light on some of the mechanisms by which VD₃ is involved in respiratory disease. Classic histopathologic features of obstructive airway disease include hypertrophy of both the smooth muscle responsible for airway constriction and the mucinous goblet cells lining the airway. Recent studies in murine models of asthma have demonstrated that not only does VD₃ deficiency correlate with airway remodeling, but also that the effect is either mitigated or reversed by supplementation with dietary VD₃ [168] or intraperitoneal injections of 1,25(OH)₂D [141]. How if at all, does this model relate to chronic disease in humans and could this be significant enough to impact clinical decisions?

Another potentially limiting factor to the successful use of VD₃ therapeutically is the lack of clear guidelines with a strong evidence base on the duration or dose of 25(OH)D needed to correct a VD₃ deficiency. For example, a 400 IU/day dose, the estimated average requirement suggested in the Institute of Medicine's 2011 report [169], will have little to no impact on raising circulating VD₃ levels [170]. The IOM's recommendations

are based solely on maintaining skeletal function, which caused a degree of controversy due to the exclusion of non-skeletal studies. The Endocrine Society, after review the data, found benefit of VD₃ supplementation with respect to cancer and cardiovascular disease risk. Although admitting that it is unknown what dose of supplementation is necessary to achieve non-skeletal benefits of VD₃, their subsequent recommendations are 600 IU for all adults aged 50–70 and 800 IU for adults aged >70 [171]. Daily doses ranging from 2000–6000 IU have been shown to maintain 25(OH)D in the replete range for a large proportion of individuals. A large number of doses, ranges, and time courses have been tested clinically ranging from daily supplementation to large boluses given on an annual basis [170]. However, to date there are no standardized supplementation guidelines by which to achieve VD₃ sufficiency. Furthermore, there is still a great deal of controversy surrounding what the ideal circulating 25(OH)D level is. We know that >10 ng/ml 25(OH)D is needed to prevent the development of rickets and >20 ng/ml 25(OH)D is recommended to maintain skeletal health [172]. What remains unclear is what the optimal 25(OH)D levels are for other diseases such as asthma, CRS, or AR.

7. Conclusions

A growing body of literature supports that VD₃ is involved in the pathogenesis of asthma, sinusitis, and AR, most likely due to its ability to regulate a broad range of immune and non-immune cell functions. Some studies have suggested that VD₃ may not improve airway disease or allergies, and may in fact make it worse [32,173,174]. However, many of these studies were retrospective or based on questionnaires to estimate VD₃ intake. Given the limited number of VD₃ supplementation studies for the treatment of airway diseases and the mixed results in terms of patient outcomes, it would be premature to make any final claims about VD₃'s treatment efficacy in these diseases. Just as there are patients who are refractory to corticosteroid treatments, it is possible this phenomenon could exist with VD₃. Before we can make any final conclusions about the ability of VD₃ to treat the aforementioned respiratory diseases, we first need a greater understanding of how VD₃ functions at a tissue level as well as more supplementation trials to more appropriately identify the patients for whom VD₃ therapy may be best suited.

Conflict of interest

None of the authors have any conflicts of interest in this work.

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