



Role of vitamin D in asthma

Asthma is a prevalent disease that leads to high morbidity and healthcare costs. The search for prevention and better treatment strategies is ongoing. Vitamin D deficiency has been shown to occur commonly and is associated with poorer asthma control measures. As the understanding of the biological effects of vitamin D emerges, there appears to be strong evidence for an important role of vitamin D in the respiratory and immune systems. Discovering the complexities of the functions of vitamin D may extend the possibilities of vitamin D use to include prevention and/or treatment of asthma. This article explores what is known about vitamin D, and its known and potential role in asthma.

KEYWORDS: asthma ■ calcitriol ■ cholecalciferol ■ ergocalciferol ■ Tregs ■ vitamin D

The prevalence of asthma has been increasing in parallel with trends in vitamin D deficiency. Some researchers have suggested a causal link between vitamin D deficiency and the development of asthma [1], while others have suggested vitamin D supplementation, rather than deficiency, as the link [2,3]. Wjst *et al.* published two ground-breaking articles concerning the relationship between the increase in asthma and allergy prevalence and the start of vitamin D supplementation in foods. These articles suggested that supplementation of vitamin D has a potential causal role in increased asthma prevalence [2,3]. By contrast, Litonjua and Weiss were among the first to suggest vitamin D deficiency due to an affluent life spent mainly indoors as a causative factor for increased asthma and allergy prevalence [1].

Reasons for vitamin D deficiency occurring despite recommendations of supplementation include increased time spent indoors in industrialized countries, and the use of sunscreen and covering when outside to offset risks of skin cancer. Therefore, researchers have begun to examine the roles and functions of vitamin D in an attempt to clarify its possible association to asthma. The metabolism of vitamin D from sunlight, as well as dietary sources, will be explained. A review of studies examining vitamin D levels will be explored in an effort to show the relationship between lower vitamin D levels and less asthma control, even in individuals with apparent high sunlight exposure.

Asthma is a complex disease with multiple postulated pathogenic mechanisms. How these mechanisms could relate to vitamin D will be summarized briefly later, reviewing the genetics of the vitamin D receptor (VDR) and vitamin D

and the relationship with the immune system, particularly the Th1 and Th2 responses. In the allergic asthma phenotype, there is an increase in Th2 cytokines, such as IL-4, IL-13 and IL-5, which are important for IgE synthesis and eosinophilia in the airways. There is also a phenotype that involves neutrophilic infiltration of the airways, with Th17 cells producing IL-23 and IL-17.

Furthermore, there has been an established link between CD4⁺CD25⁺ regulatory T cells (Tregs) and asthma. An x-linked deficiency in these cells causing immunodysregulation, polyendocrinopathy and enteropathy (IPEX) leads to an increase in autoimmune and allergic diseases. This helped establish the role of Tregs in allergic asthma. When functioning normally, CD4⁺CD25⁺ Tregs will suppress Th2 responses, inhibiting cytokine release and the allergic asthma response. This role may be defective or overcome by allergen-driven pathways in patients with allergic disease. Therefore, the ability to restore CD4⁺CD25⁺ Treg function could be a potential therapeutic goal in allergic asthma patients [4]. The role of vitamin D in restoring CD4⁺CD25⁺ Tregs will be discussed later.

The interaction of vitamin D with bronchial smooth muscle, including its role in inflammation, will be discussed, with a separate discussion on the impact of vitamin D on respiratory infections. The role of vitamin D in patients with steroid-insensitive asthma is also discussed, as well as other aspects of the relationship of asthma and vitamin D, such as the association of vitamin D and asthma onset, and vitamin D and asthma control.

Elena Lewis¹
& Thomas Casale¹

¹Creighton University Medical Center,
601 N 30th Street, Suite 3M 100,
Omaha, NE 68131, USA
¹Author for correspondence:
Tel.: +1 402 280 4403
Fax: +1 402 280 4803
tbcasale@creighton.edu

future
medicine part of fsg

Vitamin D synthesis & metabolism

Vitamin D can be obtained from diet and sun exposure. Ultraviolet B rays from sunlight exposure convert 7-dehydrocholesterol present in the skin to previtamin D₃, which eventually becomes vitamin D₃. Owing to lifestyle changes causing individuals to spend the majority of their time inside and avoid the risk of sun-induced skin cancer, most people living in developed countries do not receive sufficient vitamin D from sunlight exposure alone. Even in areas of the world, such as Costa Rica, where lifestyle and climate allow for significant sun exposure, it has been discovered that inhabitants are still vitamin D deficient [5]. Therefore, dietary consumption of vitamin D is important, but difficult to acquire in sufficient quantities. Dietary vitamin D is found in fish, such as mackerel and salmon, but is also fortified in grains and dairy products [6]. Once vitamin D₃ is formed, it is converted to 25-hydroxyvitamin D (25(OH)D₃) in the liver. The kidney then transforms it to its active form, 1,25-dihydroxyvitamin D (1,25(OH)₂D₃). Catabolism of active 1,25(OH)₂D₃ and inactive 25(OH)D to calcitric acid occurs by 25-hydroxyvitamin D-24-hydroxylase (CYP24) (TABLE 1 & FIGURE 1) [7]. This process is controlled by the parathyroid hormone in order to keep a tight balance on calcium and vitamin D levels [6]. However, this tight endocrine control does not appear to play an important role in vitamin D regulation in nonendocrine processes, such as its role in immunity [8].

Vitamin D levels in the blood are best assessed via 25(OH)D₃ values. Controversy continues over what levels should be considered normal. Generally, deficiency is defined as

levels less than 10 ng/ml, insufficiency between 10 and 20 ng/ml with borderline levels considered between 20 and 30 ng/ml, and normal levels greater than 30 ng/ml. However, some researchers suggest levels above 40 ng/ml as a more appropriate normal cut-off. There is also likely to be a difference in levels needed for bone health and levels needed for immune health. Serum 25(OH)D₃ levels are dependent on multiple factors, including, but not limited to, diet, sunlight exposure, race and age. Therefore, the amount of vitamin D supplementation cannot be clearly defined.

Vitamin D levels

Multiple studies have demonstrated a high prevalence of vitamin D deficiency, despite adequate sun exposure and supplementation and fortification of foods. Adults from Hawaii (USA) and inhabitants of Costa Rica (as mentioned previously) were found to have low serum 25(OH)D₃ levels, despite high levels of sun exposure [5,9]. Another study of Puerto Rican farmers with reported sun exposure of 32–70 h/week found two out of 18 individuals with 25(OH)D₃ level of less than 30 ng/ml [10]. Both of these studies relied on self-reported sun exposure, which could be inaccurate. However, they still reveal that sun exposure alone is likely inadequate to create normal vitamin D levels. Explanations for relatively low 25(OH)D₃ levels in individuals with apparently high levels of sun exposure include inadequate production in the skin, increased degradation or abnormalities in transport from the skin to the circulation. There is evidence of both decreasing conversion of 7-dehydrocholesterol to previtamin D₃ with advancing age, as well as abnormalities in the ability of the skin to regulate vitamin D production [9]. However, the exact mechanism that affects the process of 1,25(OH)₂D₃ production via the skin is still unclear. There are also known racial differences in skin production of vitamin D as well. Increased skin pigmentation inhibits the production of vitamin D₃ (cholecalciferol) [11]. In a study by Gutiérrez *et al.*, 50% of subjects were found to be vitamin D deficient. Broken down into race, 28% of white subjects were deficient compared with 58% of Mexican–American and 81% of black subjects. These authors considered vitamin D deficiency to occur at less than 20 ng/ml, whereas most experts place the cut-off at 30 ng/ml. If 30 ng/ml was used as a cut-off, 67% of white individuals are vitamin D deficient, compared with 89% of Mexican–Americans and 96% of

Table 1. Vitamin D catabolism and metabolism.

Vitamin D types	Definition and function
Ergocalciferol (vitamin D ₂)	Plant-derived form of vitamin D
Cholecalciferol (vitamin D ₃)	Produced in the skin of vertebrates after exposure to ultraviolet B light from the sun or artificial sources, and occurs naturally in a small range of foods. In some countries, staples, such as milk, flour and margarine, are artificially fortified with vitamin D, and it is also available as a supplement in pill form
Prohormone calcidiol (25(OH)D)	Formed in the liver from vitamin D ₃ in the blood
Calcitriol (1,25(OH) ₂ D ₃)	The biologically active form of vitamin D, converted in the kidneys or by monocyte macrophages in the immune system from circulating calcidiol
25-hydroxyvitamin D-24-hydroxylase (CYP24)	Enzyme that converts active 1,25(OH) ₂ D ₃ and inactive 25(OH)D to calcitric acid
25-hydroxyvitamin D-1 α-hydroxylase (CYP27B1)	Enzyme present in the kidney that converts 25(OH)D to 1,25(OH) ₂ D ₃

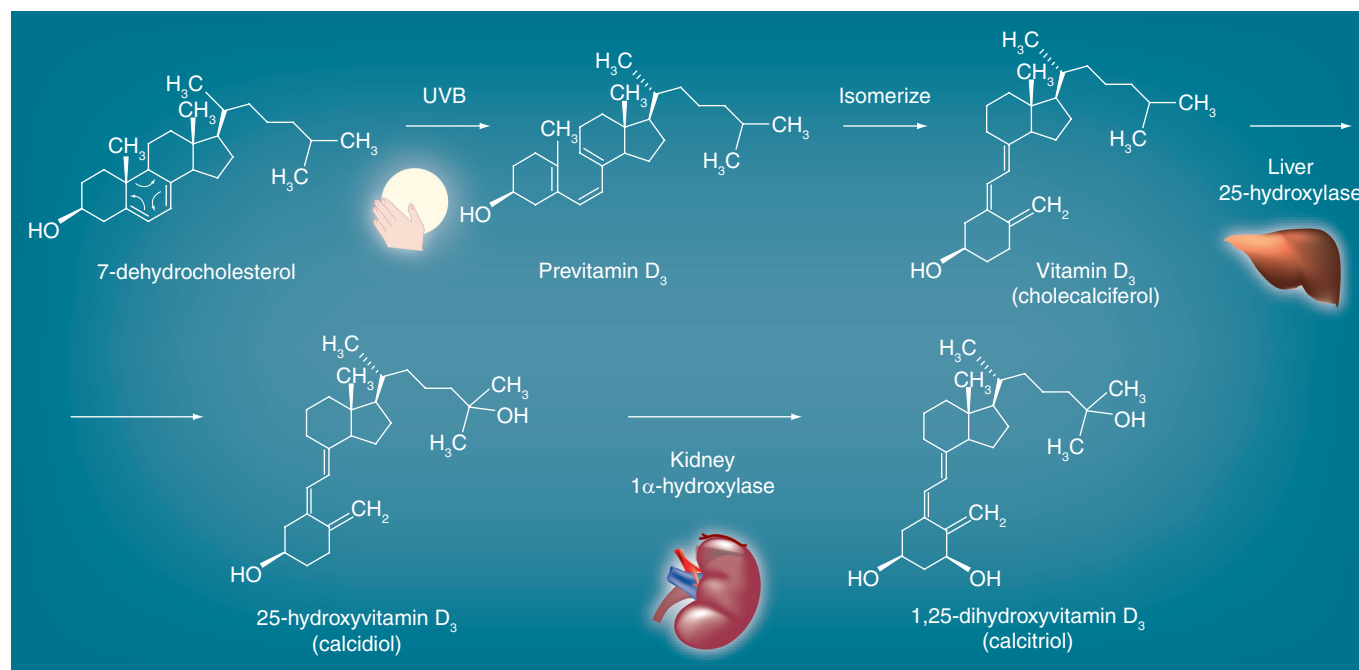


Figure 1. Metabolism of vitamin D. 7-dehydrocholesterol, found in the skin, is converted via UVB sunlight to previtamin D. This isomerizes to vitamin D₃ (cholecalciferol). In the liver, vitamin D₃ is converted via 25-hydroxylase to 25-hydroxyvitamin D₃ (calcidiol). Calcidiol is then converted via 1α-hydroxylase to 1,25-dihydroxyvitamin D₃ (calcitriol), which is the active form of vitamin D. UVB: Ultraviolet B.

black people [12]. Therefore, vitamin D deficiency and insufficiency are common, especially in darker-skinned individuals.

Genetics

The *VDR* gene is located on the long arm of chromosome 12, a region commonly linked to asthma, and was discovered to be present in most body tissues [13]. This led to the assumption that vitamin D plays a role in many different organ systems in addition to its well-known skeletal effects. In its active form, 1,25(OH)₂D₃ acts as a gene transcription factor. It binds to the VDR and, subsequently, is dimerized with the retinoic x receptor and translocated to the nucleus. In the nucleus, it binds to the vitamin D response elements within the promoter region of the DNA and is involved in the transcription of more than 200 proteins [8,14]. Genetic analysis in multiple studies has found contradicting evidence on the importance of *VDR* polymorphisms in relation to asthma and allergies [13].

Local vitamin D production

The enzyme 25-hydroxyvitamin D-1 α-hydroxylase (CYP27B1) is present in the kidney, and converts 25(OH)D to 1,25(OH)₂D₃. Conversion of 25(OH)D to its biologically active form 1,25(OH)₂D₃ is not exclusively controlled via the parathyroid, calcium, calcitonin and phosphorus pathway present in the kidney. Respiratory

epithelium, similar to many tissues and cells, can express CYP27B1, creating an environment with high 1,25(OH)₂D₃. This occurs secondary to infections, such as respiratory syncytial virus, but not in response to Toll-like receptor (TLR) activation. Hansdottir *et al.* showed that in the presence of 1,25(OH)₂D₃, activation by mycobacterial ligand of TLR2/1 caused increased cathelicidin and increased macrophage killing of mycobacteria [14]. TLRs and IFN-γ can also increase expression of CYP27B1 activity on many cells, including epithelial cells, keratinocytes, activated macrophages and dendritic cells. They also increase *VDR* expression, leading to 24-hydroxylase activation, which converts vitamin D to an inactive form [7]. These processes help to maintain a steady-state system in tissues. However, TLRs and IFN-γ also act to inhibit 24-hydroxylase activity, both via indirect inhibition of *VDR* and direct inhibition via STAT1α [15].

Vitamin D & immunity

The VDR is found on antigen-presenting cells, either constitutively or as an inducible receptor. Activation of VDR on dendritic cells causes suppression of the dendritic cell with downregulation of costimulatory receptors. The overall effect of vitamin D on the immune system depends upon where it acts [8]. When monocytes/macrophages are exposed

to $1,25(\text{OH})_2\text{D}_3$, they have increased phagocytosis and chemotaxis necessary to fight infection [15].

Vitamin D results in suppression of T cells directly and indirectly through suppression of antigen-presenting cells. Studies have shown Th1 cell suppression by $1,25(\text{OH})_2\text{D}_3$ (FIGURE 2). Th1 cells secrete IFN- γ , IL-2 and TNF- α . The activation of Th1 cells is important in response to pathogens, including bacteria, viruses and tumors. $1,25(\text{OH})_2\text{D}_3$ decreases the production of IL-2 and IFN- γ , with a loss of suppression seen in *VDR*-knockout mice [16]. However, as discussed later, the putative role of vitamin D in infections is complex.

Studies on the effects of $1,25(\text{OH})_2\text{D}_3$ on Th2 cells are not completely congruent. The literature reveals both suppression and enhancement of the Th2 response (FIGURE 2) [6]. *VDR*-deficient mice were unable to develop allergic asthma after attempted ovalbumin (OVA) sensitization [17]. However, it has been suggested that this may be secondary to increases in IgE antibodies, seen in *VDR*-knockout mice, saturating the mast cell Fc ϵ RI, preventing binding of the OVA-specific

antibodies. The result is lack of mast cell activation owing to inability of sensitization not attributable to the effects of $1,25(\text{OH})_2\text{D}_3$ and the VDR [18]. Other studies have demonstrated that $1,25(\text{OH})_2\text{D}_3$ created a developmental stage-specific effect, halting final maturation of Fc ϵ RI expressing late mast cells and inducing apoptosis in early mast cell progenitor cells [18]. Matheu *et al.* reported a dual role, both stimulatory and inhibitory, of $1,25(\text{OH})_2\text{D}_3$ toward the Th2 response [19]. Another study using OVA-sensitized mice demonstrated that, after topical application of $1,25(\text{OH})_2\text{D}_3$, CD4⁺CD25⁺ cells had an increased ability to suppress Th2 cell-driven immune response. Naturally occurring CD4⁺CD25⁺ cells are known to have the ability to suppress Th2 responses via IL-10 and TGF- β . However, in this experiment there was no increase in IL-10 and TGF- β production. In addition, there was no increase in CD4⁺CD25⁺ proliferation. Further evidence of Th2 suppression by $1,25(\text{OH})_2\text{D}_3$ was seen in human cord blood that expressed decreased levels of Th2 cytokines IL-4 and IL-13 after $1,25(\text{OH})_2\text{D}_3$ exposure in cell culture [20].

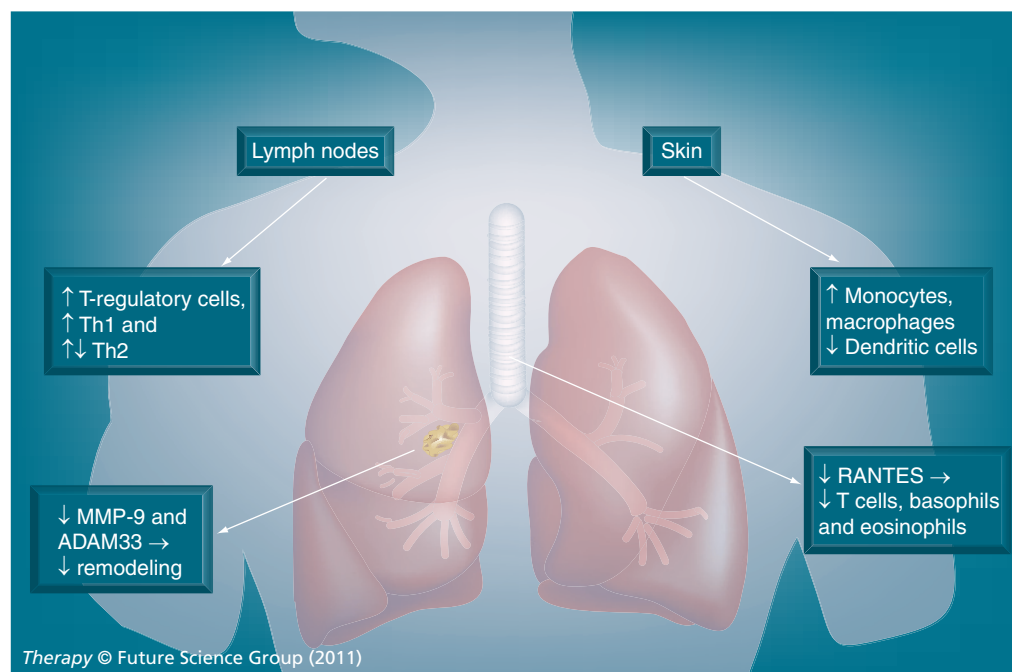


Figure 2. Known mechanisms of vitamin D on the pulmonary and the immune system.

Vitamin D causes an increase in monocyte and macrophage activation, and a decrease in activation of dendritic cells, as well as expression of costimulatory molecules, such as CD80/86 and CD40. In smooth muscle, there is decreased production of MMP-9 and ADAM33, which decrease remodeling. In the airway, vitamin D causes decrease in RANTES, which decreases recruitment of T cells, basophils and eosinophils to the airway. Vitamin D also causes an increase in Tregs with a decrease in Th1 cells. There is conflicting research concerning the role of vitamin D on Th2 cells, with both suppression and enhancement reported.

ADAM33: Disintegrin and metalloprotease domain-containing protein 33; MMP: Matrix metalloproteinase.

It appears that $1,25(\text{OH})_2\text{D}_3$ has both the ability to modulate cells to regulate the adaptive immune response, as well as enhancing the innate response via cathelicidin production, important to fight infection [21]. In *VDR*-knockout mice, there is lymphadenopathy with an increased proportion of dendritic cells found. This suggests an inhibitory and regulatory effect of $1,25(\text{OH})_2\text{D}_3$ on dendritic cell maturation (FIGURE 2) [22]. However, the relevancy of mice data to humans has been questioned, since mice are nocturnal mammals, which may have evolved nonvitamin D-dependent pathways that function to regulate immunity.

Studies have shown that $1,25(\text{OH})_2\text{D}_3$ causes increases in IL-10 and decreases in IL-12 production with downregulation of costimulatory molecules, such as CD40 and CD80/86 all resulting in decreased T-cell activation [23–26]. IL-10 can be released by Tregs, and acts to suppress both Th1 and Th2 responses [27]. This is accomplished through inhibition of antigen-presenting cell function and cytokine production. There are two main types of Tregs. The first are naturally occurring $\text{CD4}^+\text{CD25}^+$, and the second are inducible IL-10- and TGF- β -producing Tregs [28]. While studying the effects of $1,25(\text{OH})_2\text{D}_3$ in Tregs, it was discovered that $1,25(\text{OH})_2\text{D}_3$ was involved in upregulation of IL-10 and TLR9. When a TLR9 agonist, CpG oligonucleotide, was added to cells incubated with $1,25(\text{OH})_2\text{D}_3$, there was a decrease in IL-10 production. This is thought to be the mechanism by which $1,25(\text{OH})_2\text{D}_3$ allows for both response to infection and regulation of inflammation. When $1,25(\text{OH})_2\text{D}_3$ is present, it both allows for an initial innate immune response to infection via TLR9 with initial downregulation of IL-10, and increases IL-10 via Tregs to control the inflammatory response to protect the host from collateral damage. $1,25(\text{OH})_2\text{D}_3$ has also been shown to interact with TLR1 and TLR2 to enhance innate immunity [27].

Testing on peripheral blood mononuclear cells pretreated with $1,25(\text{OH})_2\text{D}_3$ revealed enhancement of MKP-1 and IL-10 providing more evidence for an anti-inflammatory role of $1,25(\text{OH})_2\text{D}_3$.

Vitamin D & bronchial smooth muscle

Bronchial smooth muscle undergoes hypertrophy and hyperplasia, contributing to airway narrowing [29]. Bronchial smooth muscle also plays a role in airway inflammation via secretion of chemokines and cytokines, as well as expression of cell-adhesion molecules and TLRs [30]. Owing to the large impact that bronchial smooth

muscle plays in asthma, the role of vitamin D in regulating bronchial smooth muscle function has been examined.

The effect of $1,25(\text{OH})_2\text{D}_3$ on passively sensitized human bronchial smooth muscle cell proliferation and matrix metalloproteinase (MMP)-9 and disintegrin and metalloproteinase domain-containing protein 33 (ADAM33) expression were examined by Song *et al.* [31]. MMP-9 is an extracellular matrix protein that is involved in airway remodeling via the enzymatic degradation of the extracellular matrix. MMP-9 increases eosinophil migration and affects smooth muscle cell migration and proliferation. ADAM33 also plays an important role in airway remodeling. Song *et al.* revealed that $1,25(\text{OH})_2\text{D}_3$ had antiproliferative activity, causing arrest of the cell cycle in the G1 phase. Also, there was downregulation of MMP-9 and ADAM33 by $1,25(\text{OH})_2\text{D}_3$ (FIGURE 2) [31,32].

Bosse *et al.* used microarray technology and real-time PCR to demonstrate gene expression of prostaglandin F synthase in bronchial smooth muscle in response to vitamin D [29,32]. Prostaglandin F synthase is involved in production of PGD_2 and PGF_2 , which are responsible for early recruitment of T cells to the lung after allergen exposure and also inactivates cortisol, an anti-inflammatory molecule. In contrast to other studies, these data suggest a beneficial effect of lower vitamin D levels with regard to asthma [29,32].

The VDR was discovered to be present both at the mRNA transcript and protein level in airway smooth muscle [29]. Upon stimulation of the VDR with $1,25(\text{OH})_2\text{D}_3$, there is increased expression of 24-hydroxylase on bronchial smooth muscle [33].

Banerjee *et al.* examined bronchial smooth muscle treated with TNF- α and/or IFN- γ for 24 h in the presence of $1,25(\text{OH})_2\text{D}_3$ and/or the glucocorticoid fluticasone. RANTES, a chemokine known to recruit monocytes, eosinophils and T cells, was decreased dose dependently by $1,25(\text{OH})_2\text{D}_3$, suggesting an anti-inflammatory role of $1,25(\text{OH})_2\text{D}_3$ (FIGURE 2) [30].

Vitamin D & infections

In infants requiring hospitalization for viral bronchiolitis, there is a significantly increased risk of asthma by the age of 13 years of 43%, compared with 8–10% in the normal population. Infections are also a major exacerbating factor for asthma [34]. Therefore, the role of vitamin D in the prevention of infection could be important with regard to both possible asthma

development and exacerbations. In a large population-based study, Pingsheng and colleagues reported an increase in asthma prevalence in infants born in winter virus-peak months, a time also known to be associated with lower vitamin D levels. Infants who were approximately 4 months of age during this virus peak time had an increased incidence of bronchiolitis and development of childhood asthma [34]. Another study found a decrease in viral upper respiratory tract infections and influenza in black women given vitamin D supplementation [35]. The same authors conducted a follow-up to this study between December 2006 and March 2007 enrolling 162 patients in a randomized, double-blind, placebo-controlled trial of vitamin D supplementation using a higher dose of vitamin D at 2000 international units (IU) versus the previous study, which used only 400 IU. Supplementation up to 2000 IU has been stated to be safe according to the Food and Nutritional Board of the Institute of Medicine. The results were not significant, possibly owing to the fact that patients were started on supplementation during the winter cold virus season, and there was an insufficient time for vitamin D levels to increase, which usually takes 3 months after supplementation. The authors also report that their study may have been underpowered [36].

More promising results were demonstrated in two other randomized, double-blind controlled studies. The first was conducted in Japan, randomizing children age 6–15 years to 1200 IU or placebo, starting in December 2008 and ending in March 2009. In total, 334 children were followed to the end of the study, with similar dropout rates in each group, and compliance via diary logs at 96%. The results found a significant decrease in influenza A diagnosis in children on vitamin D supplementation, but not influenza B [37]. The second study was in a Finnish population of 164 adult males randomized to 400 IU of vitamin D or placebo in October 2005. The results reported no difference in workdays missed for respiratory illness, but there was a decreased hazard ratio for workdays missed owing to a respiratory tract infection in the men taking vitamin D [38].

It has been proposed that vitamin D increases the production of antimicrobial peptides, such as defensin, which blocks membrane fusion of influenza and other viruses to the respiratory epithelium, thus blocking infection. Overall, vitamin D enhances the

innate immune response, therefore possibly accounting for the decreases in the incidence of infection [37].

Vitamin D & steroid insensitivity

Although most asthmatics respond well to inhaled corticosteroids, there are approximately 15% of asthmatics that are considered steroid insensitive. Fractalkine is a steroid-resistant chemokine that recruits mast cells to airway smooth muscle. Its expression on tracheal smooth muscle cells is inhibited by $1,25(\text{OH})_2\text{D}_3$ in steroid-resistant asthmatics [30]. Glucocorticoids have also been found to increase the production of IL-10 from CD4^+ and CD8^+ T cells. The administration of dexamethasone and $1,25(\text{OH})_2\text{D}_3$ resulted in an increase of IL-10-producing T cells that made negligible Th1 and Th2 cytokines. In steroid-resistant patients, there is no increase in IL-10 synthesis after glucocorticoid administration. However, if IL-10 and $1,25(\text{OH})_2\text{D}_3$ were added to cell cultures from steroid-resistant patients, the CD4^+ cells were able to produce IL-10 in amounts comparable to steroid-sensitive patients when stimulated with glucocorticoids [39]. Similarly, oral ingestion of $1,25(\text{OH})_2\text{D}_3$ by steroid-resistant patients enhanced their response of IL-10 production to dexamethasone administration, which is clinically relevant [39]. A recent study in children found that a lower serum vitamin D level inversely correlated with need for inhaled steroid use, oral steroid use and total steroid dose [40]. A possible explanation for this observation is that low vitamin D levels contribute to the severity of asthma, requiring the increase in steroid administration. A second theory is that vitamin D is involved in the glucocorticoid pathway, where vitamin D deficiency leads to increased steroid requirement. Another explanation could be that children with asthma are less likely to go outside owing to asthma triggers, such as allergens, exercise or climate; therefore, they have decreased sunlight exposure, resulting in decreased vitamin D levels. However, studies discussed previously have shown that even high levels of sunlight exposure do not ensure adequate vitamin D levels. Therefore, the time spent indoors does not necessarily correlate with serum vitamin D levels.

Vitamin D & asthma onset

Many studies have been – and are being – conducted in order to determine the potential role of vitamin D in asthma development. Initial studies examined prenatal and early vitamin D

supplementation. Three retrospective analyses of children looked at maternal consumption of vitamin D and wheezing. In each study, the highest maternally reported vitamin D consumption was protective. Reports discussed an up to 62% reduction in recurrent wheeze at 3 years of age, a 67% reduction in persistent wheeze at 5 years of age but no association with spirometry or exhaled nitric oxide levels, and an inverse correlation between vitamin D dietary intake, but not supplementation, on asthma (defined as physician diagnosis of asthma with either symptoms of asthma, such as wheezing or being on asthma medication, in the last 12 months) [41–43]. A recent study by Camargo *et al.* examined the association of cord blood vitamin D levels and wheezing, risk of respiratory infections and asthma at 5 years of age. This analysis revealed increased incidence of respiratory tract infections and wheezing in children with low vitamin D cord levels, without any association found between vitamin D levels and incident asthma at 5 years of age. This supports a role for vitamin D in decreasing wheezing episodes that may be secondary to respiratory infections, but does not support a role for vitamin D in asthma development. However, vitamin D levels were only analyzed at birth, so there may be a discrepancy in the initial vitamin D levels reflecting maternal levels and the serum vitamin D levels of the children during the first 5 years of life [44].

An increased risk of asthma and atopy with supplementation of vitamin D in the first year of life and in children born to mothers with higher serum vitamin D levels during pregnancy was found in two other studies. However, of note, the analysis in these two studies was univariate, and did not attempt to account for any potential confounding variables, and one study had a high rate of subjects lost to follow-up (61.8%) [5,45]. Another explanation for the apparently contrasting results of vitamin D effects on asthma and atopy development could be owing to a dual concentration-dependent role of vitamin D. A cohort study revealed a bimodal response of IgE to serum 25(OH)D₃ levels with increased IgE seen at very low (<25 nmol/l or <10 ng/ml) and very high (>135 nmol/l or 54 ng/ml) serum 25(OH)D₃ levels [46]. A study conducted in Costa Rica found an inverse correlation between serum 25(OH)D₃ level and IgE and blood eosinophils. Subjects in this study had serum 25(OH)D₃ levels, ranging from 12.5 to 98.1 ng/ml. After adjustment for anti-inflammatory medication use, only IgE levels remained significantly associated with serum 25(OH)D₃ levels [5].

Vitamin D & asthma control

A key question is whether serum vitamin D levels correlate with asthma control and lung function. Black and Scragg, using the Third National Health and Nutrition Examination Survey (NHANES III) data, showed a dose-dependent positive association between serum 25(OH)D₃ and forced expiratory volume in 1 s (FEV₁). These results retained significance when adjusted for multiple potential confounding factors, including physical activity. Since these data are based on a cross-sectional survey, causality cannot be determined [47]. Another study found serum 25(OH)D₃ levels inversely correlated with increased airway responsiveness. Higher vitamin D levels were also associated with a decreased incidence of asthma-related hospitalization in the previous year [46]. In the Childhood Asthma Program (CAMP) study, there was an increase in severe asthma exacerbations measured by hospital and emergency room visits in subjects with vitamin D deficiency. They also demonstrated lower FEV₁ values in subjects with lower vitamin D levels. In this study, sufficient levels of vitamin D were considered those greater than 30 ng/ml [48]. A retrospective study, conducted at National Jewish Health (CO, USA), examined the comparison of serum vitamin D levels to lung function and atopy in children. They reported an inverse correlation with FEV₁ percentage predicted and forced expiratory volume in 1 s/forced vital capacity (FEV₁:FVC) ratio and vitamin D level. Subjects were also found to have an increased risk of positive skin-prick testing to indoor allergens if they had lower serum vitamin D levels [40]. Several other studies have reported the same correlation with improved lung function in both adults and children with sufficient vitamin D levels (>30 ng/ml) [49–51].

Conclusion & future perspective

Future studies need to prospectively study vitamin D supplementation prenatally, in infancy and beyond, to determine any effects on development of asthma. Also, studies need to examine vitamin D supplementation, in a randomized, controlled fashion, and the effects on asthma control, focusing both on impairment and risk domains, to allow for a better understanding of the role of vitamin D in asthma. Indeed, there are many gaps in our true understanding of the complex role of vitamin D in asthma and other diseases. Even deciding on dosing for supplementation is an issue. It is likely

that levels of vitamin D needed to contribute to bone health are different to the levels needed to regulate immune processes [36]. Future studies will be necessary to clearly identify how and if vitamin D might fit into asthma care strategies. Once these studies are completed, physicians will be better able to determine appropriate vitamin D supplementation recommendations for lung health.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

Executive summary

Vitamin D receptor

- The vitamin D receptor is found in most body tissues.
- It is involved in the transcription of more than 200 proteins.

Vitamin D action on immune cells

- Increase in monocyte and macrophage activity to fight infection.
- Decrease in dendritic cell proliferation and expression of costimulatory molecules, such as CD40, CD80 and CD86.
- Decrease in Th1 cells and Th1 cytokines, such as IFN- γ , IL-2 and TNF- α .
- Either increase or decrease in Th2 cells and Th2 cytokines IL-4, IL-5 and IL-13.
- Increased activity of Tregs and IL-10 production.

Vitamin D & bronchial smooth muscle

- Decreased RANTES, an important chemoattractant for T cells, basophils and eosinophils.
- Decreased matrix metalloproteinases and metalloprotease 33, causing decreased airway remodeling.
- Increase in prostaglandin F synthase (AKR1C3) causing increase in PGD₂ and PGF₂, which are proinflammatory.

Vitamin D & asthma onset

- A total of three studies found a positive association between maternal vitamin D intake and decreased childhood asthma and wheeze.
- Opposite trends were demonstrated in two other studies.

Vitamin D & asthma control

- The Third National Health and Nutrition Examination Survey data showed a dose-dependent positive association between serum 25-hydroxyvitamin D and forced expiratory volume in 1s (FEV₁).
- Serum 25-hydroxyvitamin D levels inversely correlate with increased airway responsiveness.
- Higher vitamin D levels associated with a decrease in asthma-related hospitalization in the previous year.
- Increase in severe asthma exacerbations measured by hospital and emergency room visits in subjects with vitamin D deficiency, as well as lower FEV₁ values in subjects with lower vitamin D levels.
- Inverse correlation with FEV₁ percentage predicted and forced expiratory volume in 1 s/forced vital capacity (FEV₁:FVC) ratio and vitamin D level.

Conclusion

- Vitamin D is likely to have a role in asthma, but the exact role and mechanism are still unclear.
- There is a need for prospective studies on vitamin D both prenatally and in infancy. As well as in the management of asthma.

Bibliography

Papers of special note have been highlighted as:

- of interest
- of considerable interest

<p>1 Litonjua AA, Weiss ST: Is vitamin D deficiency to blame for asthma epidemic? <i>J. Allergy Clin. Immunol.</i> 120(5), 1031–1035 (2007).</p> <p>2 Wjst M, Dold S: Genes, Factor X, and allergens: what causes allergic diseases? <i>Allergy</i> 54(7), 757–759 (1999).</p> <p>3 Wjst M: The vitamin D slant on allergy. <i>Pediatr. Allergy Immunol.</i> 17(7), 477–483 (2006).</p> <p>4 Robinson DS: Regulatory T cells and asthma. <i>Clin. Exp. Allergy</i> 39, 1314–1323 (2009).</p>	<p>5 Brehm JM, Celedon JC, Soto-Quiros ME <i>et al.</i>: Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. <i>Am. J. Resp. Crit. Care Med.</i> 179, 765–771 (2009).</p> <p>6 Lange NE, Litonjua A, Hawrylowicz CM, Weiss S: Vitamin D, the immune system and asthma. <i>Expert Rev. Clin. Immunol.</i> 5(6), 693–702 (2009).</p> <p>7 Searing DA, Leung DYM: Vitamin D in atopic dermatitis, asthma and allergic disease. <i>Immunol. Allergy Clin. N. Am.</i> 30, 397–409 (2010).</p> <p>8 Chesney RW: Vitamin D and the magic mountain: the anti-infectious role of vitamin D. <i>J. Pediatrics</i> 156(5), 698–703 (2010).</p>	<p>9 Binkley N, Novotny R, Krueger D <i>et al.</i>: Low vitamin D status despite adequate sun exposure. <i>J. Clin. Endocrinol. Metab.</i> 92(6), 2130–2135 (2007).</p> <p>10 Haddock L, Corcino J, Vazques MD: 25(OH)D serum levels in the normal Puerto Rican population and in subjects with tropical sprue and parathyroid disease. <i>P. R. Health Sci. J.</i> 1, 85–91 (1982).</p> <p>11 Clemens TL, Adams JS, Henderson SL, Holick MF: Increased skin pigment reduces the capacity of skin to synthesize vitamin D₃. <i>Lancet</i> 1, 74–76 (1982).</p> <p>12 Gutiérrez OM, Farwell WR, Kermah D, Taylor EN: Racial differences in the relationship between vitamin D, bone mineral density, and</p>
--	---	--

- parathyroid hormone in the National Health and Nutrition Examination Survey. *Osteoporos. Int.* DOI: 10.1007/s00198-010-1383-2 (2010) (Epub ahead of print).
- 13 Raby BA, Lazarus R, Silverman EK *et al.*: Association of vitamin D receptor gene polymorphisms with childhood and adult asthma. *Am. J. Resp. Crit. Care Med.* 170, 1057–1065 (2004).
 - 14 Hansdottir S, Monick MM, Hinde SL, Lovan N, Look DC, Hunninghake GW: Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. *J. Immunol.* 181, 7090–7099 (2008).
 - 15 Bouillon R, Carmeliet G, Verlinden L *et al.*: Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr. Rev.* 29, 726–776 (2008).
 - 16 Cantorna MT, Zhu Y, Froicu M, Wittke A: Vitamin D status, 1,25-dihydroxyvitamin D₃, and the immune system. *Am. J. Clin. Nutr.* 80, 1717S–1720S (2004).
 - 17 Wittke A, Weaver V, Mahon BD, August A, Cantorna MT: Vitamin D receptor-deficient mice fail to develop experimental allergic asthma. *J. Immunol.* 173, 3432–3436 (2004).
 - 18 Baroni E, Biffi M, Benigni F *et al.*: VDR-dependent regulation of mast cell maturation mediated by 1,25-dihydroxyvitamin D₃. *J. Leuk. Biol.* 81, 250–262 (2007).
 - 19 Matheu V, Back O, Mondoc E, Issazadeh-Navikas S: Dual effects of vitamin D induced alteration of Th1/Th2 cytokine expression: enhancing IgE production and decreasing airway eosinophilia in murine allergic airway disease. *J. Allergy Clin. Immunol.* 112, 585–592 (2003).
 - 20 Pichler J, Gerstmayr M, Szepefalusi Z *et al.*: 1 α ,25(OH)₂D₃ inhibits not only Th1 but also Th2 differentiation in human cord blood T cells. *Pediatr. Res.* 52, 12–18 (2002).
 - 21 Gorman S, Judge MA, Burchell JT, Turner DJ, Hart PH: 1,25-dihydroxyvitamin D₃ enhances the ability of transferred CD4⁺CD25⁺ cells to modulate T helper type 2-driven asthmatic responses. *Immunology* 130, 181–192 (2010).
 - 22 Griffin MD, Lutz W, Phan VA, Bachman LA, McKean DJ, Kumar R: Dendritic cell modulation by 1 α ,25 dihydroxyvitamin D₃ and its analogs: a vitamin D receptor-dependent pathway that promotes a persistent state of immaturity *in vitro* and *in vivo*. *Proc. Natl Acad. Sci. USA* 98(12), 6800–6805 (2001).
 - 23 Penna G, Adorini L: 1 α ,25-dihydroxyvitamin D₃ inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *J. Immunol.* 164, 2405–2411 (2000).
 - 24 Piemonti L, Monti P, Sironi M *et al.*: Vitamin D₃ affects differentiation, maturation, and function of human monocyte-derived dendritic cells. *J. Immunol.* 164, 4443–4451 (2000).
 - 25 Griffin MD, Lutz WH, Phan VA, Bachman LA, McKean DJ, Kumar R: Potent inhibition of dendritic cell differentiation and maturation by vitamin D analogs. *Biochem. Biophys. Res. Commun.* 270, 701–708 (2000).
 - 26 van Halteren AG, van Etten E, de Jong EC, Bouillon R, Roep BO, Mathieu C: Redirection of human autoreactive T-cells upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D₃. *Diabetes* 51, 2119–2125 (2002).
 - 27 Gauzzi MC, Purificato C, Donato K *et al.*: Suppressive effect of 1 α ,25-dihydroxyvitamin D₃ on type I IFN-mediated monocyte differentiation into dendritic cells: impairment of functional activities and chemotaxis. *J. Immunol.* 174, 270–276 (2005).
 - 28 Urry Z, Xystrakis E, Richards DF *et al.*: Ligation of TLR9 induced on human IL-10-secreting Tregs by 1 α ,25-dihydroxyvitamin D₃ abrogates regulatory function. *J. Clin. Invest.* 119, 387–339 (2009).
 - 29 Bosse Y, Maghni K, Hudson TJ: 1 α ,25-dihydroxy-vitamin D₃ stimulation of bronchial smooth muscle cells induces autocrine, contractility, and remodeling processes. *Physiol. Genom.* 29, 161–168 (2007).
 - 30 Banerjee A, Damera G, Bhandare R *et al.*: Vitamin D and glucocorticoids differentially modulate chemokine expression in human airway smooth muscle cells. *Br. J. Pharmacol.* 155, 84–92 (2008).
 - 31 Song Y, Qi H, Wu C: Effect of 1,25-(OH)₂D₃ (a vitamin D analogue) on passively sensitized human airway smooth muscle cells. *Respirology* 12, 486–494 (2007).
 - 32 Sandhu MS, Casale TB: The role of vitamin D in asthma. *Ann. Allergy Asthma Immunol.* 105(3), 191–199 (2010).
 - A recent review on vitamin D in asthma that highlights many of the same aspects as this current paper.
 - 33 Damera G, Fogle H, Goncharova EA, Zhao H, Krymskaya VP, Panettieri RA: Vitamin D attenuates growth factor-induced human airway smooth muscle cell proliferation. Presented at: *ATS 2009 International Conference*. San Diego, CA, USA 15–20 May 2009 (Abstract 2723).
 - 34 Wu P, Dupont WD, Griffin MR *et al.*: Evidence of a causal role of winter virus infection during infancy in early childhood asthma. *Am. J. Resp. Crit. Care Med.* 178, 1123–1129 (2008).
 - 35 Aloia JF, Li-Ng M: Re: epidemic influenza and vitamin D. *Epidemiol. Infect.* 135, 1095–1096; author reply 1097–1098 (2007).
 - 36 Li-Ng M, Aloia JF, Pollack S *et al.*: A randomized controlled trial on vitamin D₃ supplementation for the prevention of symptomatic upper respiratory tract infections. *Epidemiol. Infect.* 137(10), 1396–1404 (2009).
 - 37 Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H: Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am. J. Clin. Nutr.* 91(5), 1255–1260 (2010).
 - 38 Laaksi I, Ruohola JP, Mattila V, Auvinen A, Ylikomi T, Pihlajamäki H: Vitamin D supplementation for the prevention of acute respiratory tract infections: a randomized, double-blinded trial among young Finnish men. *J. Infect. Dis.* 202(5), 809–814 (2010).
 - 39 Xystrakis E, Kusumakar S, Boswell S *et al.*: Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. *J. Clin. Invest.* 116, 146–155 (2006).
 - 40 Searing DA, Zhang Y, Murphy JR, Hauk PJ, Goleva E, Leung DYM: Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. *J. Allergy Clin. Immunol.* 125, 995–1000 (2010).
 - One of the publications that highlights the effects of vitamin D in asthmatic children.
 - 41 Camargo CA, Rifas-Shiman SL, Litonjua AA *et al.*: Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at age 3 years. *Am. J. Clin. Nutr.* 85, 788–795 (2007).
 - One of three studies on vitamin D levels in pregnancy affecting development of asthma in unborn child. Important due to need for studies relating asthma and vitamin D levels in subjects to determine the significance of vitamin D in asthma.
 - 42 Devereux G, Litonjua AA, Turner S *et al.*: Maternal vitamin D intake during pregnancy and early childhood wheezing. *Am. J. Clin. Nutr.* 85, 853–859 (2007).
 - One of three studies on vitamin D levels in pregnancy affecting development of asthma in the unborn child. Important due to the need for studies relating asthma and vitamin D levels in subjects to determine the significance of vitamin D in asthma.
 - 43 Erkkola M, Kaila M, Nwaru B *et al.*: Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year old children. *Clin. Exp. Allergy* 39(6), 875–882 (2009).

- One of three studies on vitamin D levels in pregnancy affecting development of asthma in the unborn child. Important due to the need for studies relating asthma and vitamin D levels in subjects to determine the significance of vitamin D in asthma.
- 44 Camargo CA Jr, Ingham T, Wickens K *et al.*: Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics* 127(1), E180–E187 (2011).
- 45 Hyppönen E, Sovio U, Wjst M *et al.*: Infant vitamin D supplementation and allergic conditions in adulthood: Northern Finland birth cohort 1966. *Ann. NY Acad. Sci.* 1037, 84–95 (2004).
- 46 Hyppönen E, Berry DJ, Wjst M, Power C: Serum 25-hydroxyvitamin D and IgE – a significant but nonlinear relationship. *Allergy* 64, 613–620 (2009).
- 47 Black PN, Scragg R: Relationship between serum 25-hydroxyvitamin D and pulmonary function in the third national health and nutrition examination survey. *Chest* 128(6), 3792–3798 (2005).
- 48 Brehm NM, Schuemann B, Fuhlbrigge AL *et al.*: Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. *J. Allergy Clin. Immunol.* 126, 52–58 (2010).
- 49 Chinellato I, Piazza M, Sandri M *et al.*: Vitamin D serum levels and exercise-induced bronchoconstriction in children with asthma. *Eur. Resp. J.* 1–18 (2010).
- 50 Li F, Peng M, Jiang L *et al.*: Vitamin D deficiency is associated with decreased lung function in chinese adults with asthma. *Respiration* DOI: 10.1159/000322008 (Epub ahead of print) (2010).
- 51 Chinellato I, Piazza M, Sandri M, Peroni D, Piacentini G, Boner AL: Vitamin D serum levels and markers of asthma control in Italian children. *J. Pediatrics* 158(3), 437–441 (2010).