Vitamin D in allergic disease: Shedding light on a complex problem

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Vitamin D is unique among nutritional factors because the intake of this special vitamin represents the sum of vitamin D obtained from diet, nutritional supplements, and endogenous production after exposure to sunlight. The current recommended nutritional intake requirements reflect needs based on its established role in calcium absorption and bone health. However, recent studies have revealed that vitamin D has important functions in the immune system and might influence the course of immune-mediated disorders, including atopic dermatitis and asthma. This review discusses the scientific rationale for a role for vitamin D in immune function, gives an update on allergic disease associations with lower vitamin D serum levels, and discusses recent observations relating to vitamin D in immune function. (J Allergy Clin Immunol 2013;131:324-9.)

Key words: *Vitamin D, allergy, immune function, atopic dermatitis, asthma*

Abbreviations used

AD:	Atopic dermatitis
CYP27B1:	25-OH-vitamin D3 1-α-hydroxylase
DC:	Dendritic cell
$1,25(OH)_2$-D3:	1,25-Dihydroxyvitamin D
25OH-D3:	25-Hydroxyvitamin D
OR:	Odds ratio
PTH:	Parathyroid hormone
TLR:	Toll-like receptor
Treg:	Regulatory T
VDR:	Vitamin D receptor

The terminology, recommended laboratory values, and statements of biological function for vitamin D are points of frequent confusion. Therefore to begin any discussion of vitamin D in human health, it is important to review the basics of the physiology of this unique molecule and highlight what is generally accepted and what remains a point of controversy. The most common nutritional source of vitamin D is in the form of vitamin D3. In the general population vitamin D status is best monitored by measurements of serum 25-hydroxyvitamin D (25OH-D3) levels. The most biologically active form of vitamin D is 1,25-dihydroxyvitamin D ($1,25[OH]_2$-D3). Vitamin D status is carefully regulated on a systemic basis, and together with parathyroid hormone (PTH), it carefully regulates the uptake and use of calcium. The capacity to compensate for lower vitamin D levels results in a nonlinear relationship between intake and biological effects. Adjusting for these complex interactions and based on the sum of the existing literature, recent Institute of Medicine recommendations for adequate vitamin D intake were based on obtaining a minimum 25OH-D3 serum value of 20 ng/mL (50 nmol/L). At the time these committee recommendations were adopted, higher serum 25OH-D3 values were not consistently observed to be associated with greater health benefits.[1] However, despite inadequate evidence from randomized clinical trials for additional health benefits at higher serum 25OH-D3 values, many clinical laboratories continue to routinely report a value of 20 ng/mL as inadequate, and the endocrine society has stated that 25OH-D3 values from 21 to 29 ng/mL are insufficient.[2]

Compounding the confusion, much misinformation has been popularized regarding what sources of vitamin D intake are adequate. In particular, great potential harm has been done by claims that brief solar exposure is a satisfactory source of vitamin D for the general population. The contradictory recommendations for how to obtain adequate vitamin D and the total amount necessary for health are the source of ongoing debate fueled by inadequate data. It is not the goal of this review to address these or enter into this controversy. Instead, this review will discuss recent progress from a wide variety of laboratory studies that have illuminated mechanisms by which vitamin D can influence immunity and present some promising recent clinical observational studies that suggest possible effects of vitamin D on the manifestations of allergic diseases. These data have demonstrated that vitamin D is active in laboratory models of immune function and shows the need for a better understanding of this vitamin in maintaining a healthy immune system.

MOLECULAR MECHANISMS FOR THE IMMUNOLOGIC EFFECTS OF VITAMIN D

Vitamin D target genes typically contain vitamin D response elements in their promoters, to which heterodimers of the vitamin D receptor (VDR) and retinoid X receptors can bind to transactivate expression of the target genes.[3] Coactivators of the VDR, such as SRC3 and DRIP205, further regulate transcription of vitamin D–dependent innate immune target genes.[4,5] Insight into how vitamin D can participate in rapid and local immune responses was gained by understanding that the final activation step for 25OH-D3 to $1,25(OH)_2$-D3 is quickly stimulated in monocytes and epithelial cells.[6,7] Toll-like receptor (TLR) 2 ligands and cytokines, such as TGF-β or IFN-γ, can further trigger

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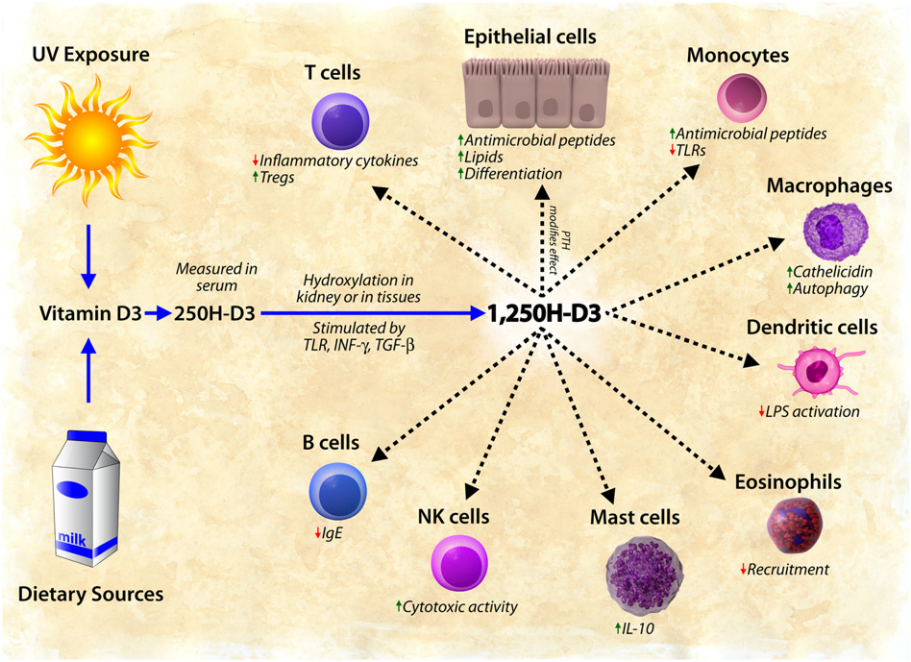

FIG 1. Overview of vitamin D and its interactions with cells of the immune system. Vitamin D3 intake is the combination of dietary consumption and UV exposure. After 25- hydroxylation of vitamin D3 in the liver, the serum 25OH-D3 value is a good indicator of the level of intake. The optimal value for serum 25OH-D3 remains a point of controversy. Hydroxylation of 25OH-D3 to 1,25OH-D3 occurs mainly in the kidney, but this step also occurs on peripheral cells, enabling rapid fine control of the activation of vitamin D in immune cells. Laboratory evidence suggests 1,25$(OH)_2$-D3 can affect the function of a wide range of immunocytes, generally enhancing innate defense mechanisms and inhibiting inflammatory events.

local conversion of stored inactive 25OH-D3 to the highly active 1,25$(OH)_2$-D3.[6,8] This enzymatic activation of vitamin D permits rapid triggering of gene expression and enables it to participate in a relevant way during defense against microbes. However, simple deficiency of 25OH-D3 does not necessarily result in loss of activity for genes activated by 1,25$(OH)_2$-D3. For example, the antimicrobial peptide cathelicidin is strongly induced by increased 1,25$(OH)_2$-D3 levels in cell culture.[9,10] However, *in vivo* low vitamin D levels are accompanied by increased PTH levels. PTH has been found to induce cathelicidin, thus counteracting the potential for decreases in levels of this antimicrobial peptide and maintaining appropriate immune defense against infection by group A *Streptococcus*.[11] Such observations of the existence of systems to compensate for low vitamin D values in immune function supports the important role of this molecule in immunity and sheds light on the difficulty in consistently detecting clinical phenotypes associated with specific serum vitamin D values. Of note, PTH was only able to compensate for low vitamin D values if 1,25$(OH)_2$-D3 was present because PTH had no effect in the 25-OH-vitamin D3 1-α-hydroxylase (CYP27B1) knock-out mouse model, which is lacking the enzyme 25-OH-vitamin D1-α-hydroxylase and therefore has no 1,25$(OH)_2$-D3.[11]

CELLULAR EFFECTS OF VITAMIN D ON INNATE AND ADAPTIVE IMMUNITY

Laboratory models of the effects of vitamin D on immune function have shown a wide range of effects. Part of the difficulty in attributing a clear physiologic role for vitamin D in immune disorders stems from the many diverse and at times contradictory observations (Fig 1). In the innate immune system vitamin D appears to improve antimicrobial defenses in general. As mentioned earlier, vitamin D induces endogenous expression of the antimicrobial peptide cathelicidin. This can be seen in the skin, in monocytes, and in the lung.[12,13] Because cathelicidin has been found in multiple experimental systems to be essential for defense against a variety of microbial infections,[14,15] it has been proposed that vitamin D can enhance resistance to infection. Recently, Hong et al[16] reported in mice that low-dose UVB treatment to enhance cutaneous vitamin D production also enhanced other elements of the skin innate immune system, such as the antimicrobial peptides β-defensin 2 and β-defensin 3, and this occurred in parallel with increased values of the epidermal lipid synthesis enzymes fatty acid synthase, serine C-palmitoyltransferase, and 3-hydroxy-3-methylglutaryl–coenzyme A and differentiation markers, such as involucrin and filaggrin. This effect was dependent on active vitamin D (1,25$[OH]_2$-D3) because inhibition of the 25-OH-vitamin D1-α-hydroxylase (CYP27B1) with ketoconazole blocked epidermal lipid synthesis, antimicrobial peptide expression, and permeability barrier homeostasis.[16]

In addition to enhancing antimicrobial peptide expression and skin barrier function, vitamin D also induces autophagy in human macrophages. Autophagy is the ingestion of sequestered material inside phagosomes, which is important in the defense against infections, such as in patients with tuberculosis.[17] Yuk et al[18] used physiologic vitamin D levels to show that vitamin D induces human cathelicidin in the peptide form of LL-37, which is localized to autophagosomes to induce autophagy. Thus LL-37 enables

both access to and killing of *Mycobacterium tuberculosis* in a vitamin D–mediated manner. Notably, a large amount of literature has been published suggesting that patients with *M tuberculosis* infection have abnormal vitamin D intake or function.[19]

Natural killer cells play a critical role in the innate immune system and are able to kill infected cells or tumor cells in an MHC-independent manner. Vitamin D induces cathelicidin, and cathelicidin was required for cytotoxic activity of natural killer cells against tumor cells in a transplantable mouse melanoma model.[20]

Complementing the protective actions of vitamin D in stimulating antimicrobial functions, vitamin D also has been observed to initiate events that support the dampening of excessive inflammation. In monocytes vitamin D decreased expression of TLRs and suppressed TLR-mediated inflammation.[21] Vitamin D was also observed to lead to enhanced cathelicidin and IL-10 production by mast cells, thus providing another potential mechanism by which vitamin D can decrease inflammation while increasing antimicrobial action. A similar effect was seen in eosinophils in a murine asthma model in which vitamin D reduced eosinophil infiltrates in the respiratory system.[22]

In combination with the observations described above in innate immune systems, vitamin D has also inspired much interest for its potential to benefit inflammatory disorders by modifying the function of cells classically associated with adaptive immunity. Vitamin D decreased immune receptor expression on monocyte-derived dendritic cells (DCs), inhibited DC activation by LPS, and reduced the function of these cells.[12,13,23] Vitamin D decreased proinflammatory cytokine release from PBMCs in general and from T cells in particular.[24,25] Vitamin D inhibited T-cell proliferation through decreased T_H1 cytokine secretion.[26,27] However, the direct effects on T_H2 cells are less clear. One study found that vitamin D induced IL-4, IL-5, and IL-13 *in vitro*, whereas another study found no effect.[28-30] Vitamin D supplementation was not found to induce T_H2 responses *in vivo*.[31] In contrast, proinflammatory T_H17 responses were observed to be blocked by administration of vitamin D in mice and human subjects.[32] Similar to observations described earlier in mast cells, vitamin D increased IL-10 and decreased IL-2 production from regulatory T (Treg) cells, thereby inducing a state of hyporesponsiveness.[24,33,34] Mouse models have also demonstrated the induction of Treg cells in response to either the topical vitamin D analog calcipotriol or UV radiation to enhance endogenous production of vitamin D.[35,36] Vitamin D has been found to lead to inhibition of effector T cells, suggesting vitamin D deficiency can promote autoimmunity by favoring the excessive production of T_H17 and T_H9 cells at the expense of IL-10–producing Treg cells.[37] Finally, vitamin D has also been shown to inhibit B-lymphocyte function and modulate the humoral immune response, resulting in a diminished secretion of IgE.[38]

In early life the gastrointestinal tract is an important site of codevelopment between the microbiota and the host immune system. Interactions between the gut microbiota and host immune cells in the intestine might affect the risk for having allergic diseases, such as asthma, later in life (reviewed by Litonjua and Gold[39]). Given the role of vitamin D in Treg cells and DCs, it is possible that the host's vitamin D status could modify the effect of gut microbiota on the immune system. Interestingly, mice lacking the VDR have chronic, low-grade gastrointestinal inflammation. Furthermore, T-cell homing into the gastrointestinal tract was decreased, resulting in further enhanced inflammation in response to normally nonpathogenic microbes.[40] Another study showed that intact VDR function was able to directly attenuate microbe-induced nuclear factor κB activation in the intestine.[41] In summary, these results indicate an important role for vitamin D in the development of the immune system and in protection from excessive inflammation in the gut and other organs (reviewed by Ly et al[42]).

ASSOCIATIONS OF VITAMIN D WITH ALLERGIC DISEASES

Several groups have investigated whether 25OH-D3 serum values correlate with the risk of allergic disease. Dependent on the threshold value used to define vitamin D insufficiency, it is very common to identify large segments of the population that have inadequate vitamin D intake. A Danish study that measured the distribution of serum 25OH-D3 in 182 participants in January showed that 67% were vitamin D insufficient, as defined by 25OH-D3 values of less than 50 nmol/L, and 18% were vitamin D deficient (25OH-D3 value, <25 nmol/L).[43] With the high prevalence of low serum 25OH-D3 levels based on these threshold values, it has been attractive to seek associations between low vitamin D values and common immunologic disorders. For example, a recent study measured serum 25OH-D3 values in patients with atopic dermatitis (AD), patients with psoriasis, and healthy control subjects in Finland in the winter and found that atopic patients had significantly lower values than healthy control subjects.[44] Interestingly, both low and very high 25OH-D3 values were associated with increased IgE values. Hypponen et al[45] showed that IgE concentrations were higher in study subjects with low 25OH-D3 values (<25 nmol/L) and with very high 25OH-D3 serum values (>135 nmol/L). In children and adolescents allergic sensitization to 11 of 17 investigated allergens was more common in those with vitamin D deficiency. In particular, 25OH-D3 values of less than 15 ng/mL were associated with peanut (odds ratio [OR], 2.39), ragweed (OR, 1.83), and oak (OR, 4.75) allergy.[46]

Concerning childhood asthma, Brehm et al[47] observed that children with asthma had low serum 25OH-D3 values, even in Costa Rica. Of 616 children with asthma, 21 (3.4%) had 25OH-D3 serum values of less than 20 ng/mL (considered deficient), and an additional 152 (24.6%) had values of between 20 and 30 ng/nL.[47] In a recent large prospective cohort study in 103 asthmatic children, Goleva et al[48] found an inverse correlation between serum 25OH-D3 and IgE values ($P = .006$) and an inverse relationship between daily inhaled corticosteroid doses and serum 25OH-D3 values ($P = .05$) or expression of the vitamin D–regulated *CYP24A1* gene in PBMCs ($P = .03$), indicating a steroid-sparing effect of vitamin D3. Other studies did not confirm these results, and Hughes et al[49] found no association between any of the UVR- or vitamin D–related measures and childhood asthma. In contrast, greater time in the sun in winter between the ages of 6 and 15 years increased the odds of having hay fever, and oral supplementation with cod liver oil in childhood even increased the odds of a history of having both asthma and hay fever.[49]

Because the predisposition to allergies might already be acquired *in utero* or during the development of the immune system, several studies have also investigated whether maternal vitamin D status influences the allergy risk in children. Camargo et al[50] reported that high 25OH-D3 values during pregnancy

decreased childhood wheezing by nearly 50% compared with low maternal 25OH-D3 values. They suggested that cord blood 25OH-D3 values are inversely associated with the risk of respiratory tract infection and childhood wheezing but not with incident asthma.[50,51] However, Gale et al[52] reported that high vitamin D values during pregnancy might also be harmful with respect to allergic disease development: children whose mothers had a 25OH-D3 concentration during pregnancy of greater than 75 nmol/L had an increased risk of atopic eczema on examination at 9 months (OR, 3.26) and asthma at the age of 9 years (OR, 5.40) compared with children whose mothers had a concentration of less than 30 nmol/L. Vitamin D intake during pregnancy decreased the risk of wheeze symptoms in early childhood.[53] Even though Erkkola et al[54] showed that maternal vitamin D intake from foods during pregnancy was negatively associated with the risk of asthma and allergic rhinitis in childhood, the intake of vitamin D supplements was not associated with a decreased risk for allergic disease. The same was demonstrated by Nwaru et al[55] in a prospective study in which maternal vitamin D intake from foods during pregnancy was negatively associated with the risk of food allergies at the age of 5 years. These observations were confirmed in a meta-analysis of 11 databases performed by Nurmatov et al,[56] who concluded that high maternal dietary vitamin D and E intakes during pregnancy were protective against the development of childhood wheezing. In another study those results were reproduced, and reduced maternal intake of vitamin E, vitamin D, and zinc during pregnancy was associated with increased wheezing outcomes in children.[57] Notably, corrections for geographic region and month of examination did not change this association in those studies.

AD is characterized by an impaired skin barrier, enhanced skin inflammation, decreased induction of cathelicidin, and increased susceptibility to microbial colonization and infection. Each of these elements have been described earlier in this review to be influenced by vitamin D, and thus it has been of interest to extend these observations for clinical relevance. In children with AD, mean serum 25OH-D3 values were significantly higher in patients with mild disease compared with those seen in patients with moderate or severe AD.[58] In some studies correcting serum concentrations of 25OH-D3 to normal values promised benefit. For example, one study reported significantly reduced IgE values in atopic patients after supplementation.[52] However, Back et al[59] showed that children who were supplemented with vitamin D (>13 μg/d) showed an increased risk of either AD, allergic rhinitis, or allergic asthma.[59] In particular, vitamin D intake led to an increased risk of AD at the age of 6 years when a positive family history for AD was already reported. Similarly, Hypponen et al[60] showed that dietary intake of vitamin D during infancy promoted allergic disease at age 31 years. Further supporting a deleterious role for vitamin D supplementation, Milner et al[61] found that early vitamin supplementation in children was associated with increased risk for asthma and food allergies. These results have prompted the question of whether the mode of application of vitamin D might also be important for promoting allergic diseases. Kull et al[62] could show that vitamin D in water-soluble form seemed to increase the risk of allergic disease up to the age of 4 years compared with supplementation of vitamin D administered in peanut oil. Furthermore, Urashima et al[63] showed in a randomized controlled trial that vitamin D supplementation in children during the winter months reduced the rate of influenza A infections and the frequency of asthma attacks. Also, a recent pilot randomized controlled trial demonstrated a favorable effect of vitamin D supplementation on AD symptoms in children during the winter months.[64] A prospective study has recently suggested that vitamin D supplementation in asthmatic children reduces the risk for recurrent respiratory tract infections and thus the risk for disease exacerbation.[65] These effects could have been mediated by the induction of endogenous antimicrobial peptides in the skin in patients with AD by means of oral vitamin D supplementation.[66] Supporting this hypothesis, Hata et al[66] administered an oral dose of 4000 IU of vitamin D3 daily to 14 patients with AD and 14 healthy control subjects. The patients with AD experienced a 6-fold increase in cathelicidin levels. Thus when enough substrate is added to the enzyme, as in the study by Hata et al,[66] then keratinocytes might be able to produce adequate $1,25(OH)_2$-D3 values to activate cathelicidins.

CONCLUDING REMARKS

Taken together, it is not yet possible to definitively assign an absolute strategy for using vitamin D in the therapy of immunologic disorders. Many confounding and unidentified variables appear to be present in exiting studies that lead to inconclusive or inconsistent results. There is overwhelming experimental evidence that vitamin D acts on immune cell functions, but the complexity of this system as it applies to the general population has not yet made clear how to translate this information into nutritional guidelines. Hopefully, better understanding of the molecular mechanisms by which vitamin D influences specific aspects of immune function will enable design of the appropriate human trials to establish clinical efficacy.

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