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REVIEW ARTICLE

The role of vitamin D in the immunopathogenesis of allergic skin diseases

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Abstract

Vitamin D plays key roles in innate and adaptive immunity through the stimulation of Toll-like receptors, increasing pro-inflammatory cytokine production, and possibly enhancing T helper type 2 responses. These mechanisms may explain the growing body of evidence connecting vitamin D to allergic diseases, including asthma, food allergies, and allergic rhinitis. The data relating vitamin D to allergic skin diseases are equivocal with studies linking both high and low vitamin D levels to an increased risk of developing atopic dermatitis. In this paper, we describe the role of vitamin D in the immunopathogenesis of atopic dermatitis and other allergic skin diseases.

Introduction

A growing body of literature has linked decreased serum vitamin D levels with distinct diseases, both those related to skeletal health and others (1–3). Vitamin D deficiency is defined as serum 25(OH)D <10 ng/ml, and leads to the development of vitamin D-related bone disease (e.g. rickets). There is also an increasing concern for vitamin D insufficiency, which is characterized by 25(OH)D levels between 21 and 29 ng/ml (2, 3). Several studies have connected lower vitamin D levels with higher cardiovascular mortality rates, increased risk of diabetes mellitus, increased risk of cancer, and an increased risk of infections (2). Vitamin D deficiency has also been inconsistently associated with atopic diseases, although large-scale prospective and randomized studies are lacking. While many of the pathways of vitamin D metabolism in the body are well known, the precise mechanisms underlying vitamin D's effects on allergic diseases have not been elucidated.

Vitamin D metabolism (Fig. 1) begins both through absorption in the skin as vitamin D3 (cholecalciferol) and absorption through the gut as either vitamin D2 (ergocalciferol) or vitamin D3. Cholecalciferol and ergocalciferol are then metabolized in the liver to 25-hydroxyvitamin-D (25(OH)D), which is the vitamin D pro-hormone usually used to measure vitamin D levels clinically. 25(OH)D is beneficial clinically since it is stable, has a half life of 3 weeks in human serum, and most accurately represents total vitamin D stores in the body (1, 3). 25(OH)D is subsequently metabolized in the kidney to its active form, 1,25-dihydroxyvitamin D (1,25(OH)2D), or calcitriol. Calcitriol plays a key role in skeletal as well as extraskeletal functions including immunity and glucose metabolism (2).

In light of several conflicting hypotheses that are further described in the next section, vitamin D levels have been both positively and negatively correlated with allergic disease prevalence. For example, high asthma prevalence and increased

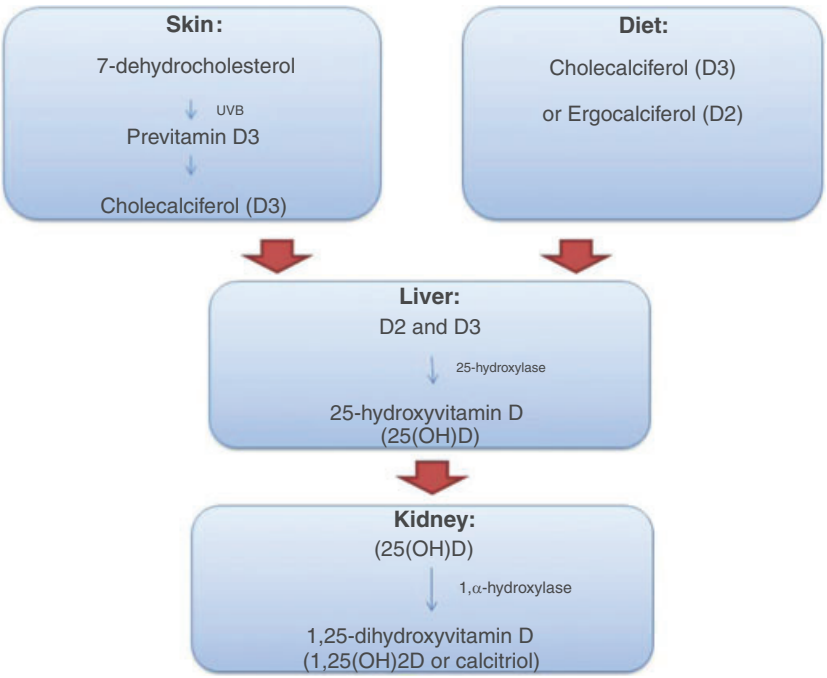

Figure 1 Metabolism of Vitamin D.

asthma symptoms have been observed in patients with low vitamin D levels and in children whose mothers had low intake of vitamin D during pregnancy (4–12). In addition, higher Epi-pen prescription rates and higher emergency room visit rates for acute allergic reactions have been observed in geographic areas in which people have less sun exposure and therefore lower vitamin D skin absorption (13–15). Recently, vitamin D deficiency has been shown to correlate with many food and environmental allergies in children (16). Conversely, other studies have shown an association between high vitamin D levels and the development of allergic rhinitis (17, 18). Since most vitamin D is absorbed via the skin, the impact of vitamin D levels on allergic skin diseases is of particular interest and may be unique. This paper reviews the immunologic mechanisms of vitamin D, specifically as they relate to atopy, and examines the data connecting vitamin D to the development of allergic skin diseases.

Vitamin D and immunologic mechanisms

Vitamin D plays a key role in the immune responses generated by lymphocytes and antigen-presenting cells. Its role on the regulation of cells of the immune system has been recognized recently with the discovery of Vitamin D receptors (VDRs) on distinct cell types. Specifically, VDRs have been identified on nearly all cells of the immune system including T cells, B cells, neutrophils, macrophages, and dendritic cells (DCs) (19). The continued elucidation of the mechanisms surrounding vitamin D's actions through VDRs helped clarify the link between vitamin D and immune functions.

Recent data have suggested that vitamin D affects both innate and adaptive immune mechanisms (Fig. 2). These mechanisms begin with the binding of 1,25(OH)2D to the VDR, a nuclear hormone receptor, which leads to VDR dimerization with the retinoid X receptor (RXR) (19–21) (Fig. 3). The 1,25(OH)2D-RXR-VDR complex then binds to Vitamin D response elements (VDRE) on DNA. Furthermore, the VDR shows enhanced expression in immature monocytes and contributes to increased nitric oxide production by macrophages in the setting of infection (22). Vitamin D also impacts the innate immune system by stimulating the production of cathelicidin, which is an anti-microbial peptide that is activated through toll-like receptors (TLRs), particularly TLR2 and TLR4 (19, 20, 23, 24). With regards to adaptive immunity, the VDR-RXR complex binds to target genes to moderate gene expression in DCs, macrophages, and other antigen presenting cells (25). Vitamin D may also have anti-inflammatory properties, as observed by the 1,25(OH)2D-mediated reduction of DC maturation (26). Furthermore, 1,25(OH)2D inhibits DC migration and IL-12 and IL-23 cytokine production (19).

Through its inhibition of adaptive immune responses, vitamin D may suppress the production of IL-12, thereby reducing the production of T helper type 1 (Th1) cells and potentially leading to increased proliferation of allergy-associated T helper type 2 (Th2) cells (27). Upon stimulation by vitamin D, naïve CD4+ T cells have also been shown to lead to a Th2 response and increase production of IL-4, IL-5, and IL-10 (28). In contrast to these findings, other studies have shown that vitamin D contributes to the conversion of CD4+ T cells to T regulatory cells, which have been shown to play a role in the suppression of pro-allergic mechanisms (29).

Two seemingly contradictory hypotheses have emerged regarding the role of vitamin D in the generation of allergic

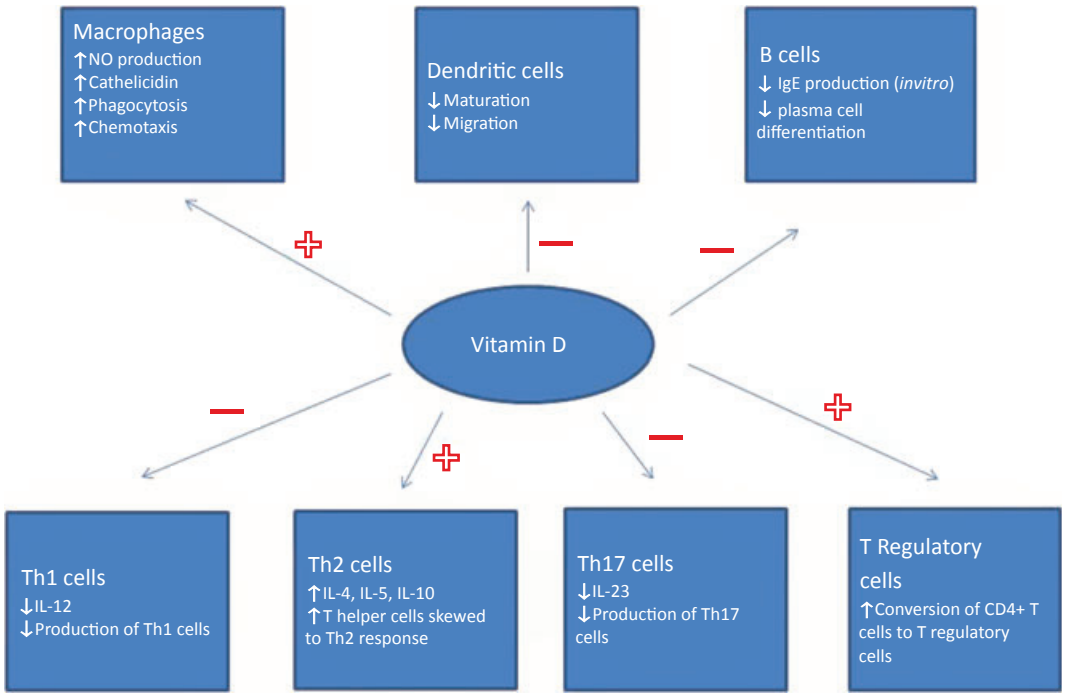

Figure 2 The impact of vitamin D on the immune system.

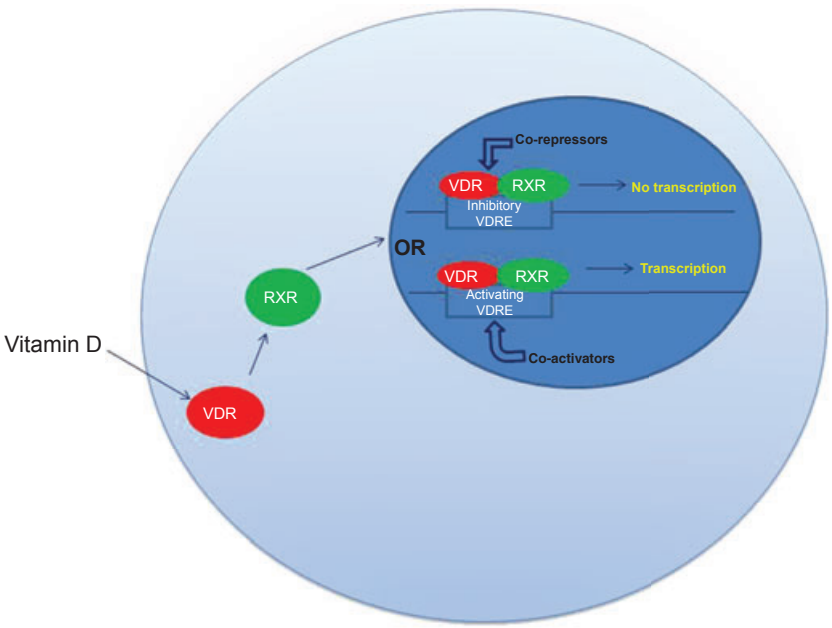

Figure 3 Vitamin D and gene expression.

diseases. The first hypothesis suggests that high vitamin D levels are responsible for the rise in prevalence of allergies and asthma (30). This theory was initially based on the observed increase in allergies coinciding with an increase in vitamin D supplementation for pregnant women and newborns in order to prevent infantile rickets (30). A competing hypothesis developed several years later postulated that low vitamin D levels may contribute to the increase in allergy prevalence (5). This theory was supported by an observed association between vitamin D deficiency/insufficiency and an

increased prevalence of allergic diseases, such as asthma (4, 6–12).

Due to the conflicting observations regarding vitamin D's impact on allergy, *in vitro* human and *in vivo* murine studies have been performed to assess whether vitamin D directly affects serum levels of immunoglobulin E (IgE). In one study, previously stimulated B cells showed markedly decreased production of IgE following the administration of vitamin D (31). In a second study, calcitriol and VDR agonists led to suppressed IgE production by cultured human B cells (32). Furthermore, calcitriol and VDR agonists also reduced IgE production in an allergy mouse model (32).

Effects of vitamin D on atopic dermatitis and urticaria

As with many of the atopic diseases, there are conflicting data surrounding the effect that vitamin D has on the development of allergic skin diseases (Table 1). Most of the studies to assess the impact of vitamin D on allergic skin diseases focus on atopic dermatitis (AD). The first study that investigated the possible connection between vitamin D and AD was a prospective study primarily conducted to assess the risk of recurrent wheeze in children based on maternal vitamin D intake (5). While the authors found a decreased risk of recurrent wheeze in children of mothers with higher intake of vitamin D during pregnancy, there was no decreased risk of AD in these same individuals (5). Another study prospectively demonstrated that increased maternal serum levels of 25(OH)D predisposed infants to AD at 9 months of age (33). Along these lines, Back et al. (34) observed that increased vitamin D intake during infancy correlated with a heightened risk of AD at 6 years of age. These studies collectively support the theory that increased vitamin D may be tied to allergic diseases, including AD.

However, there are several studies that suggest that vitamin D deficiency contributes to the development of AD. Oren et al. (36) compared vitamin D deficient patients with vitamin D sufficient patients, and assessed the prevalence of atopic disorders. In these patients, there was an increased risk of AD among those who were vitamin D deficient, although there was no significant difference in the risk of asthma or allergic rhinitis (36).

As compared to AD, there are significantly fewer studies that have evaluated the potential link between vitamin D and urticaria. One study showed that vitamin D levels were significantly reduced in subjects with chronic urticaria as compared to controls (40). Goetz et al. (41) conducted a chart review to investigate the possible therapeutic benefit of vitamin D for idiopathic itch, rash, and urticaria symptoms. Baseline 25(OH)D levels were significantly lower in those patients who were later responsive to vitamin D as compared to the patients who were unresponsive to vitamin D (41). Furthermore, 70% of patients with cutaneous symptoms and concurrent vitamin D deficiency showed resolution of symptoms following vitamin D replacement (41).

Effects of vitamin D on severity of atopic dermatitis

There are several studies that have linked vitamin D supplementation with either the decreased risk or clinical improvement of AD. Javanbahkt et al. (37) assessed the potential treatment benefit of vitamin D supplementation in improving

Table 1 Studies assessing a link between allergic skin diseases and vitamin D

Study	Conclusion
Atopic dermatitis	
Camargo, C.A., et al. (2007) (5)	Maternal intake of vitamin D not correlated with early childhood eczema
Sidbury, R., et al. (2008) (38)	Beneficial, but no statistically significant different change in the mean AD clinical severity score of those treated with vitamin D and placebo
Oren, E., et al. (2008) (36)	Increased likelihood of AD in obese patients with vitamin D deficiency as compared to normal vitamin D levels
Gale, C.R., et al., (2008) (33)	Increased maternal serum levels of vitamin D predisposed to infant AD at nine months old
Back, O., et al. (2009) (34)	Increased vitamin D intake during infancy correlated with a heightened risk of AD at six years of age
Miyake, Y., et al. (2010) (39)	Decreased risk of childhood AD above a threshold level of maternal vitamin D intake during pregnancy
Peroni, D.G., et al. (2011) (35)	In series of 37 Italian children, there was an inverse correlation between serum concentrations of vitamin D and severity of AD
Javanbakht, M.H., et al. (2011) (37)	Vitamin D alone or vitamin D with vitamin E showed a significant improvement in SCORAD index as compared to placebo
Urticaria	
Thorp, W.A., et al. (2010) (40)	Vitamin D levels were significantly reduced in subjects with chronic urticaria compared to subjects with allergic rhinitis
Goetz, D.W. (2011) (41)	70% vitamin D treatment success rate for patients with idiopathic itch, rash, and urticaria/angioedema
Contact dermatitis	
Malley, R.C., et al. (2009) (42)	Vitamin D deficient male mice had an increased contact hypersensitivity response as compared to those with normal vitamin D

AD symptoms, and found that administration of oral vitamin D alone or vitamin D in combination with vitamin E showed a significant improvement in SCORAD ('SCORing AD') index as compared to placebo. Sidbury et al. (38) evaluated the effect of vitamin D supplementation on AD improvement, and randomly assigned vitamin D or placebo to eleven children with AD. Although there was a beneficial effect in the treatment group, there was no statistically significant change in the mean of either group's AD clinical severity score (38). A Japanese cohort of mothers and children demonstrated the decreased risk of childhood AD above a certain threshold level of maternal vitamin D intake during pregnancy (39).

Peroni et al. (35) demonstrated an inverse association between vitamin D levels and severity of AD. The study determined serum 25(OH)D levels and SCORAD index levels in 37 Italian children. There was an inverse correlation between serum concentrations of 25(OH)D and clinical severity of AD (35). Mean serum levels of 25(OH)D were significantly higher in patients with mild disease (36.9 ± 17.7 ng/ml) compared with those with moderate (27.5 ± 8.3 ng/ml) or severe AD (20.5 ± 5.9 ng/ml) (35)

Although there are no clinical studies to evaluate a potential connection between vitamin D and contact dermatitis in humans, there is one murine study that assessed this potential link. Malley et al. (42) compared the contact hypersensitivity responses of mice with normal levels of vitamin D and mice with deficient vitamin D levels. Within the group of mice with normal levels of vitamin D, female mice displayed a higher response as compared to males. However, vitamin D deficient males showed a significantly increased contact hypersensitivity response as compared to males with normal vitamin D levels. Interestingly, there were no significant differences in contact hypersensitivity responses for the female mice between the vitamin D deficient and sufficient groups (42).

Conclusion

While there is increasing evidence to show that vitamin D plays a significant role in the immune system, and specifically in allergic diseases, the extent of the impact has not been fully elucidated. Although many studies have sought to determine the effect that vitamin D has on allergic diseases, and specifically allergic skin diseases, there have been no large-scale prospective studies. Furthermore, there are conflicting results among the studies and many of the studies have significant limitations. The larger studies to assess the link between vitamin D and allergic skin diseases have focused on the effects of maternal vitamin D intake during pregnancy on AD in children. Studies attempting to evaluate the treatment effect of vitamin D on allergic skin diseases have measured small sample sizes. Finally, a second limitation of most studies, especially the case-control and cross-sectional protocols, is that they did not ascertain a causal relationship between vitamin D deficiency and AD. In each study, it is difficult to determine if the low serum vitamin D levels contributed to the development of AD, whether damage of skin from AD led to low vitamin D absorption from the sun, or if the two are unrelated.

One potential reason for the inconsistent connection between vitamin D and allergic skin diseases is that there may be a bimodal and/or gender-specific association. Hyponnen et al. (43) demonstrated a statistically significant non-linear association between serum 25(OH)D and serum IgE. In this study, patients with both low and high levels of serum 25(OH)D exhibited increased levels of serum IgE (43). Regarding the gender-specific differences in contact hypersensitivity responses in mice with regards to vitamin D status, one must wonder if these findings would similarly manifest in humans. As is evident by the many studies reviewed in this paper, it is difficult to completely assess the role that vitamin D plays in the development of atopic diseases. In order to further delineate a possible correlation between vitamin D and allergic skin diseases, large and prospective studies need to be conducted. Randomized controlled trials regarding treatment with vitamin D in the context of allergic diseases may also assist in determining a definitive link.

Conflict of interest

Ariel A. Benson, MD, Jennifer A. Toh, MD, Natalia Vernon, MD, and Sunit P. Jariwala, MD have no conflicts of interest.

Author contributions

Ariel A. Benson, MD, Jennifer A. Toh, MD, Natalia Vernon, MD, and Sunit P. Jariwala, MD have (i) made substantial contributions to conception and design of, or acquisition of data or analysis and interpretation of data; (ii) drafted the article and revised it critically for important intellectual content; and (iii) gave final approval of the version to be published.

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