

EXPERT
REVIEWS

Role of vitamin D in the pathogenesis and treatment of atopic dermatitis

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Atopic dermatitis (AD) is a highly prevalent allergic skin disease that affects children worldwide. Epidemiological, clinical and basic immunological studies have suggested an association between vitamin D (VD) deficiency and the development of AD and other allergic diseases. Low levels of VD, a pleiotropic hormone that has widespread effects on the immune system and skin integrity, appear to be inversely correlated with AD severity, and VD deficiency at birth is associated with higher risk of developing AD. Recent randomized trials have reported inconsistent, but still promising, results on whether VD supplementation may improve AD severity. The apparent differences are likely due to small samples, different regimens and different patient populations. The mechanisms underlying this potential improvement in AD severity remain under investigation.

KEYWORDS: allergy • atopic dermatitis • cathelicidin • dendritic cells • epidermal barrier • filaggrin • latitude • *Staphylococcus aureus* • tolerance • vitamin D

Atopic dermatitis (AD) is a chronic and relapsing inflammatory condition of skin characterized by dry, itchy skin and immunological hyperresponsiveness to allergens [1]. It is an important public health concern affecting around 5–20% of children worldwide, with increasing prevalence, particularly in industrialized countries [2]. Moreover, severe AD greatly affects quality of life and is frequently a cause of significant morbidity due to associated skin infections. AD is commonly associated to other atopic diseases (such as food allergies, allergic rhinitis and asthma), and is commonly the first manifestation of an atopic diathesis [1]. Cellular immunity has been shown to be essential for the development of AD, as this disease is characterized by imbalances in T helper (Th) subsets, with predominance of Th2 immunity that generates allergic responses [3]. Patients with severe AD have larger areas of skin involvement, more extreme Th2 polarization, higher IgE levels and more frequent and severe viral and bacterial skin infections [4,5]. In addition, a breach of immunological tolerance in AD is evidenced by widespread hyperresponsiveness to foreign antigens, such as allergens and *Staphylococcus aureus* exotoxins, and in severe cases to self-antigens, such as proteins from epidermal components [6,7].

A growing body of epidemiological and clinical evidence suggests that vitamin D (VD) deficiency may be involved in the etiology and pathogenesis of AD and other allergic diseases [8]. VD is a liposoluble vitamin that acts as a pleiotropic hormone in most human tissues by regulating mineral homeostasis and a variety of other biological functions, including strong effects on immunity. Geographic areas with lower ultraviolet B (UVB) radiation exposure, a proxy of VD status, appear to have higher prevalence of AD in both northern and southern hemispheres [9,10]. Recent research has reported that low VD status at birth is associated with higher risk of AD during infancy [11]. In addition, low VD status has been associated with worse AD severity [12,13], although a recent study did not support these findings [14]. Overall, most of the literature suggests a pathogenic role of VD deficiency in AD.

Current treatments of AD are focused on decreasing skin inflammation and immune responses, as well as improving skin barrier function. However, potential side effects of effective treatments and poor adherence to topical treatments make the search for safe, low-cost, easy to use and effective treatments essential. Recent studies suggest that VD supplementation may be a safe and effective therapy in AD, although

results of interventional trials are still inconsistent and clinical equipoise remains on this subject. This review will discuss the state-of-the-art knowledge on AD pathogenesis and the impact of VD on the immune system and the skin. Further, we will examine the evidence of an association between VD deficiency and AD, and the potential role of this vitamin-hormone as a novel, adjunct treatment of AD.

Overview of AD pathogenesis

AD is characterized by dry and itchy skin and an exacerbated local immune and inflammatory response. Itch leads to scratching, which causes mechanical injury and contributed to subsequent inflammation. Histopathology of acute lesional skin in AD shows an influx of activated CD4⁺ T cells into the dermis. However, the immunopathology of the chronic phase shows that in addition to T cells, inflammatory dendritic epidermal cells and activated Langerhans cells infiltrate the epidermis, and macrophages and eosinophils dominate the dermal cellular infiltrate [15].

AD has a multifactorial etiology with strong genetic and environmental components. The pathogenesis of AD intertwines defects in the epidermal barrier with an abnormal immune response (FIGURE 1). An altered epidermal barrier (due to mutations in the genes encoding epidermal proteins and other defects) has been consistently demonstrated in AD, and it permits transepidermal water loss that leads to dryness and the entry of allergens and microbes (or their components) into the skin [16]. These processes

lead to irritation, pruritus and scratching causing mechanical injury of the epidermis. The epidermal barrier function largely depends on the integrity of the stratum corneum and thus, on the appropriate differentiation of keratinocytes from granular cells to corneocytes. About 70 genes grouped together on chromosome 1q21, the epidermal differentiation complex, are involved in this process [16]. Different mutations in one of these genes called filaggrin have been found to be a predisposing factor for AD in a significant proportion of patients from different ethnic populations [17]. Filaggrin, which also is associated with ichthyosis vulgaris, is key in the skin barrier as it aggregates the keratin filament cytoskeleton, collapsing granular cells that are then added to the cornified layers. Mutations in other epidermal barrier proteins, as well as tight junction defects have also been described with AD [16,18]. Alterations in epidermal barrier-specific proteins have been associated with IgE levels, eosinophilia and with other atopic diseases such as asthma [19], suggesting that the immune defects in these patients may be secondary to the epidermal barrier function defects, which cause epicutaneous exposure to allergens and skewing of the immunological response.

Mechanical injury of the skin and activation of innate immunity in the epidermis drive keratinocytes, inflammatory cells and dendritic cells (DCs) to secrete chemoattractants and cytokines that recruit CD4⁺ T cells to the skin [20,21]. In addition, keratinocyte-derived thymic stromal lymphopoietin (TSLP) signals DCs to polarize naive T cells to a Th2 phenotype by driving secretion of IL-4 and IL-13 [22]. These lead to an imbalanced immunological response and to the stimulation of B cells to isotype class switch from IgM to IgE driving allergen hyperresponsiveness [23]. Th1 and Th17 effector subsets also appear to be involved in the development and persistence of AD [24,25]. Th17 cells infiltrate the dermis preferentially in acute lesions, while Th1-mediated immunity participates in the chronic phase of AD. CD8⁺ T cells also participate at this stage, contributing to the inflammatory milieu by secreting both Th1 (IFN- γ) and Th2 (IL-13) cytokines [26].

In addition to abnormalities in effector Th cell compartments, AD is affected by alterations in immune tolerance that are characterized by exaggerated immune responses to food and aeroallergens, skin micro-organisms and autoallergens in epidermal cells [6,7,27,28]. This breach in tolerance led investigators to study alterations in number and function of antigen-presenting cells and regulatory T cells in AD. DCs are critical for activating and polarizing

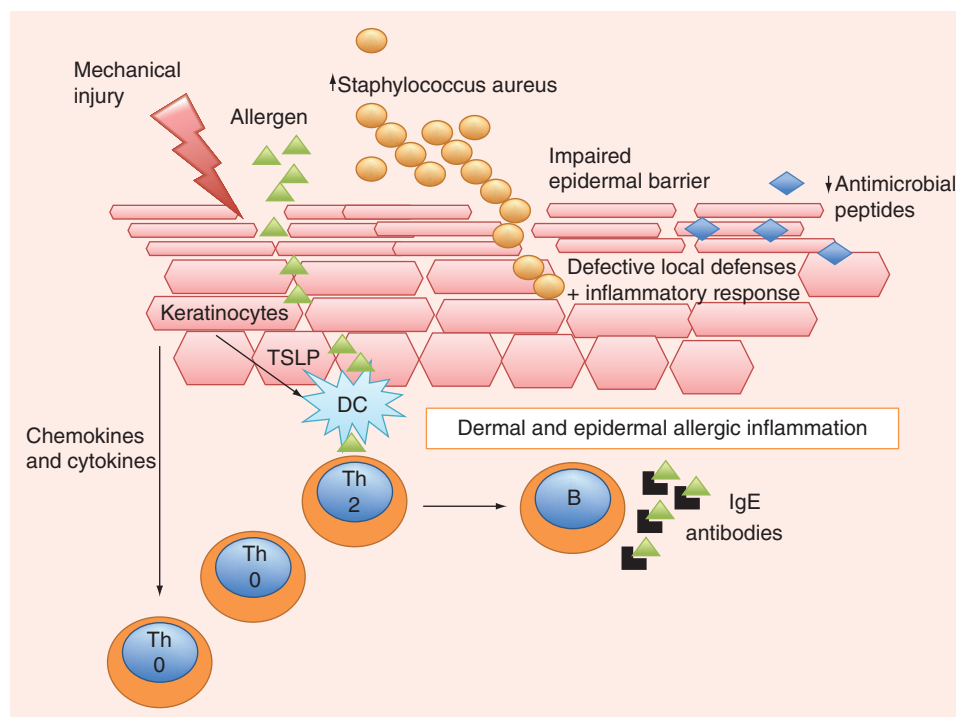


Figure 1. Overview of the pathogenesis of acute lesions of atopic dermatitis. Acute skin lesions that characterize AD are driven by a combination of a defective epidermal barrier, and a dermal and epidermal allergic inflammatory response. In the initial stages of AD, allergen presentation to CD4⁺ T cells plays a prominent role by skewing immunity to a Th2 phenotype leading to allergen sensitization.

AD: Atopic dermatitis; Th2: T helper 2; VD: Vitamin D.

effector Th cells or to prime T cells with regulatory properties that attenuate immune responses. Increased numbers of Langerhans cells and inflammatory dendritic epidermal cells expressing the high-affinity receptor for IgE (FcεRI) are present in lesional AD skin [29]. Furthermore, plasmacytoid DCs (pDCs), which are strong producers of type I interferon and essential in fighting viral infections, are reduced in the epidermis of AD patients [30]. This may explain in part the Th2 skewing of T-cell infiltrate in the skin and the susceptibility to skin infections by viruses like herpes simplex. To date, few studies have evaluated circulating DCs in AD patients. Sary *et al.* showed that both myeloid DCs (mDCs) and pDCs from whole blood of AD patients are phenotypically different than those from healthy controls, by having increased expression of FcεRI and cell-bound IgE. However, no significant differences were observed in number of mDCs and pDCs or in expression of other activation markers such as CD40 or CD80 [29]. In contrast, a different study showed higher expression of CD80 and MHC1 in blood pDCs from AD patients compared to controls, but lower skin-homing molecules such as cutaneous lymphocyte-associated antigen and CD62L [31]. In addition, they showed that these pDCs produced less type I interferons upon stimulation, and enhanced Th2 immune responses. Thus, circulating DCs from AD patients have characteristic immunopathogenic alterations that differentiate them from DCs from non-atopic controls. In addition, FOXP3⁺ regulatory T cells (Tregs) are absent in lesional skin from AD patients, suggesting a decreased control of inflammation [32]. Surprisingly, Treg numbers are increased in whole blood of AD patients and are fully functional in their suppressive activity [33]. Of note, Treg numbers in these studies correlated with AD severity and peripheral eosinophil count suggesting that their increased levels may occur in response to allergic inflammation [32,33].

Skin affected by AD has difficulty controlling bacterial and viral infections and is colonized by *S. aureus* in up to 93% of patients [34,35]. Microorganisms invading the skin of patients with AD play a role in disease pathogenesis. The cause of skin infection in AD patients probably is related to downregulation in antimicrobial peptides (AMPs), alterations in Toll-like receptor 2 (TLR2) induced inflammation, and in defects of Th1-mediated antiviral immunity [34,36,37]. Of note, AMPs produced by keratinocytes, such as cathelicidin (hCAP18/LL-37) and β-defensins, have an antistaphylococcal effect and antiviral activity against herpes simplex virus [38,39]. Downregulation of AMPs is aggravated by Th2 cytokines IL-4, IL-13, and the regulatory IL-10 [40], allowing bacterial overgrowth that drive additional inflammation in a vicious feedback loop. Thus, the infectious burden of the skin augments and perpetuates inflammation, progressively becoming chronic. Patients with moderate to severe AD frequently have specific IgEs against staphylococcal superantigens, evidencing Th2 immunity against this bacteria [6]. In a similar fashion, in severe AD, Th2 immunity is driven against epidermal proteins leading to specific IgE production against proteins from keratinocytes

and endothelial cells such as manganese superoxide dismutase and calcium-binding proteins [41]. These autoallergic reactions in AD may even begin in infancy and contribute to chronic disease [42].

Effects of VD on the immune system & skin integrity

VD has traditionally been linked to calcium metabolism and bone health. Over the past two decades, however, a myriad of effects on various target organs have been shown and therapeutic possibilities have arisen in diverse fields [43]. Comprehension of VD metabolism is important to understand the mechanisms through which VD exerts its effects. VD is acquired in two forms: VD2 (ergocalciferol) and VD3 (cholecalciferol). VD3 is mainly synthesized from cholesterol precursors in the skin in response to UVB radiation, but also is available in some types of fish; while VD2 comes from plant sources used to produce VD2 supplements. VD2 and VD3 are converted in the liver to 25-hydroxy vitamin D/calcifediol (25(OH)D), the circulating prohormone that is commonly measured to determine VD sufficiency status. Then, 25(OH)D is converted in the kidney to 1,25(OH)₂D3 (calcitriol), the active form of VD, which binds the vitamin D receptor (VDR) in different tissues. Multiple VDR-mediated effects in innate and adaptive immunity have been described [44], which could potentially modulate AD development and pathogenesis (FIGURE 2). In addition, VD is relevant for epidermal differentiation and skin barrier permeability [45]. Thus, several possible explanations exist for the putative beneficial effects of VD in AD. Importantly, *in vivo* studies of the immunologic effects of VD in AD patients are limited, and most *in vitro* studies have used supraphysiological doses of calcitriol or calcitriol analogues to evaluate the effects of 'VD' on immunity [46].

Although the immunologic effects of VD require further study, VD is known to modulate DC phenotype and function inducing tolerogenic properties [47–49]. Monocyte-derived DCs treated with 1,25(OH)₂D3 during LPS-induced maturation fail to up-regulate the expression of the costimulatory molecules CD40 and CD86 [48,49]. In addition, VD decreases expression of proinflammatory cytokines like IL-12 and increases expression of the regulatory cytokine IL-10, leading to reduced T cell activation [48,49]. VD also induces the expression of the inhibitory receptor

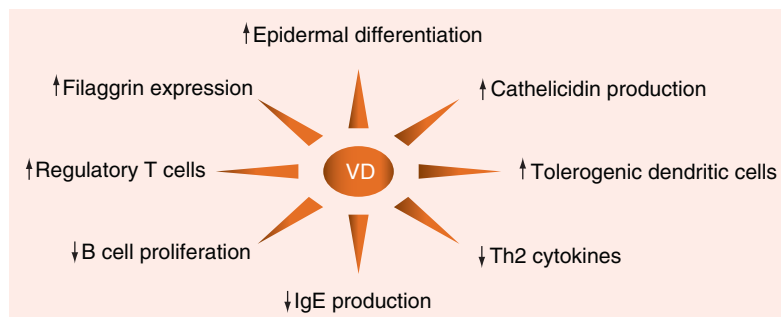


Figure 2. Possible mechanisms through which vitamin D may modulate the development and pathogenesis of atopic dermatitis.

VD may exert effects that contribute to AD etiology and pathogenesis by improvement of the epidermal barrier, strengthening of innate immunity to skin bacteria, promotion of tolerance and reduction of Th2 immunity. AD: Atopic dermatitis; Th2: T helper 2; VD: Vitamin D.

ILT3 in DCs [50]. Of note, the pro-tolerogenic effect of VD selectively modulates myeloid DC function, but appears to have no discernible effect on plasmacytoid DC function [47]. The immature and tolerogenic VD-treated DCs produce cytokines with suppressor activity including IL-10 and TGF- β and effectively induce Tregs [51]. This effect has not only been shown *in vitro*, but also *in vivo* in murine models [52] and healthy humans [53]. Indirect evidence from AD patients treated with narrowband UVB phototherapy, a known inducer of VD₃ production, showed an increase in circulating Tregs [54]; but Treg changes after oral VD supplementation have not yet been evaluated in AD patients.

VD also affects B and T lymphocyte differentiation and function *in vitro* [55]. Expression of VDR is induced upon activation in B and T cells [56]. VD decreases B cell proliferation, plasma cell differentiation and immunoglobulin production [57]. Of particular relevance to AD pathogenesis, VD inhibits the production of IgE by B cells stimulated by anti-CD40 and IL-4 *in vitro* [58]. Engagement of the VDR by 1,25(OH)₂D₃ regulates T cell activation and cytokine production in Th1 and Th2 cells, and as described above, induces Tregs. It also down-regulates expression of cutaneous lymphocyte-associated antigen, a cell-surface glycoprotein that is critical in skin T-cell infiltration [59]. *In vitro*, several studies show that VD exerts a direct inhibitory effect on transcription of the Th1 hallmark cytokines IFN- γ and IL-2, but augments Th2 cytokines such as IL-4 and IL-5 [60–62]. In contrast, another study showed 1,25(OH)₂D₃ inhibits IL-4 production during *in vitro* polarization of primary murine CD4⁺ T cells [63]. Similar results were obtained in human cord blood T cells, where 1,25(OH)₂D₃ suppressed IL-4 and IL-13 expression [64]. *In vivo*, VD's effects on T cells are even more complex, as evidenced by studies in VDR knock-out mice that have reduced Th1 cells and high IL-4 production by stimulated T cells [65]. In a murine asthma model, 1,25(OH)₂D₃ inhibited early Th2 responses and reduced IL-4 in bronchoalveolar lavage [66], and in patients with allergic bronchopulmonary aspergillosis, VD₃ attenuated Th2 responses to *Aspergillus* [67], supporting a possible antiallergic role of VD.

S. aureus is the most frequent pathogen that induces and perpetuates skin inflammation in AD. Colonization by *S. aureus* correlates with AD severity, which may in part be due to decreased local skin immunity associated to lower levels and function of AMPs [34]. VD levels correlate with *S. aureus* colonization in healthy population [68]. In a recent study, severe AD patients had lower 25(OH)D levels and higher allergic sensitization rates to staphylococcal superantigens, suggesting an association between VD and *S. aureus* colonization [13]. Kanda *et al.* showed that serum cathelicidin (LL-37) levels positively correlated with 25(OH)D levels in AD patients [69]. Furthermore, VD supplementation of patients with AD induces cathelicidin production in lesional AD skin [70]. However, the effect of VD on *S. aureus* carriage of AD skin has not been studied. *S. aureus* also affects adaptive immune responses of AD patients and appears to play a central role in skewing T cell responses, particularly through staphylococcal superantigens that condition DCs to induce Th2 responses [71].

Lastly, VD appears to be essential for normal epidermal differentiation and skin barrier permeability [45], crucial factors in the pathogenesis AD. VD drives keratinocyte differentiation in the lower epidermal layers. The epidermis of mice deficient in 1- α -hydroxylase, the enzyme required to synthesize the active form of VD, have decreased expression of epidermal barrier proteins and fail to recover the epidermal barrier after injury [72]. In addition, research shows that VDR-deficient mice have altered skin morphology [73]. Treatment of a murine model of AD with VDR agonists demonstrated a marked increase in expression of skin barrier genes including flaggrin [74], suggesting that VD might be helpful in restoring the epidermal barrier of AD patients.

Association of VD deficiency with AD pathogenesis

The reasons behind an increasing prevalence of AD and other allergic diseases are unclear. Recent epidemiologic studies have linked the rise in classic allergic diseases, such as food allergy/anaphylaxis, with latitude, sunlight and VD deficiency [10,75–79]. Hypovitaminosis D is currently a growing epidemic of the modern indoor lifestyle associated with reduced sun exposure, and may in part explain the rising incidence of AD and other allergic diseases [8,80]. Data from several countries that are geographically distant from the equator, have shown that the prevalence of allergic diseases, including AD, food allergy and anaphylaxis, increase at higher latitude, which is used as a proxy of sun exposure and therefore VD status [10,75,77]. VD status, as measured by circulating levels of 25(OH)D, has been inversely correlated with levels of IgE sensitization in children and adults [78]. An epidemiologic study from Australia showed that AD prevalence was inversely correlated with latitude, with a twofold odds of having AD in children from southernmost regions compared to northern regions [10]. A more recent study, evaluated the effect of UV exposure on prevalence of self-reported AD in a sample of 91,462 United States children from the 2007 National Survey of Children's Health. High UV exposure was significantly correlated with a lower prevalence of AD [9]. Further support for an association between VD levels and AD severity comes from the fact that AD exacerbations frequently occur in winter, the season of lowest sun exposure and VD status [81]. However, other factors may also be involved in this association, such as the fact that winter at high latitudes in the Northern hemisphere is characterized by low humidity, that may contribute to skin dryness, increased allergen permeation and worsening of AD [9].

Clinical data show that 25(OH)D levels correlate with development of AD and its severity, suggesting that VD may play a role in both the etiology and pathogenesis of this disease. In 2008 a study on 290 obese patients from Boston, aged 10 years or older found that VD-deficient patients were more likely to report AD than VD-sufficient patients [76]. A recent prospective cohort study has shown that VD deficiency during pregnancy increases the risk of AD at one year of age [11]. Regarding disease severity, Peroni *et al.* showed an inverse association between 25(OH)D levels and AD severity evaluated by the Scoring Atopic Dermatitis (SCORAD) index [13]. In a different study, Akan *et al.* found that 25(OH)D level correlated with AD severity in children with

allergic sensitization [12]. However, a recent study challenged this association: Chiu *et al.* found no association between VD status and disease severity in US children with AD [14]. A prospective population-based birth cohort from England found an inverse correlation between 25(OH)D₂ and risk of flexural dermatitis, but in contrast, this same study found that higher 25(OH)D₃ concentrations were associated with increased risk of flexural dermatitis, suggesting a possible differential association for the two isoforms of VD [82].

Although most of this observational evidence supports a pathogenic role of VD deficiency on AD, the non-longitudinal studies have an alternative explanation: more severe AD could lead to less sun exposure and consequently lower levels of 25(OH)D [80]. This would not be the case for the few longitudinal studies to date [11,82], but is important to keep in mind when interpreting the epidemiologic data. Moreover, some authors even postulate that VD supplementation is related to the development of allergies, an association that is supported by a few population-based epidemiologic studies [83]. Interestingly, a prospective cohort study demonstrated that both low and high levels of cord-blood 25(OH)D were associated with increased aeroallergen sensitization in children [84]. Taken together, we believe that current data strongly favor a role of VD deficiency in the development and pathogenesis of allergic diseases including AD [8], but we acknowledge the possibility that excess supplementation may have increased allergic risk. The epidemiologic data suggest that VD supplementation might be an effective intervention for both prevention and treatment of AD, particularly in populations with low baseline levels of 25(OH)D.

Another consideration for the design and interpretation of results from studies that use VD to prevent and treat AD relates to genetics. The effect of VD on target tissues is regulated by single nucleotide polymorphisms (SNPs) in the VDR. This is a nuclear receptor that directs cellular transcription in hundreds of genes that have VD response elements, including multiple immune-related genes [85]. Several VDR SNPs modulate the pathogenesis of different immune-mediated diseases such as type I diabetes [44]. In addition, VDR haplotypes have been associated to risk of atopy and asthma, a related allergic condition [86], although other studies did not replicate these associations [87]. A single study that examined VDR SNPs in adults with AD recently described that in patients with severe AD the VDR SNPs Bsm1, Apa1 and Taq1 were overrepresented when compared to healthy controls [88]. This provides further evidence of the likely relevance of the VD pathway in AD severity.

Treatment of AD with vitamin D

Current treatments of AD are focused on decreasing skin inflammation and improving skin barrier function. Thus, patients are usually treated with emollient creams and topical corticosteroids. Topical therapy is time consuming to apply and is frequently disliked by patients due to its greasy visible nature. Chronic use of topical corticosteroids may induce skin alterations, such as atrophy, striae and pigmentation changes [89]. In addition, frequent and abundant treatment with high-potency corticosteroids can

produce adrenal suppression [90]. On the other hand, non-steroidal topical calcineurin inhibitors have a 'black box' warning in the United States about potential cancer risk [91]. In severe cases, other treatments can be prescribed such as systemic immunosuppressive drugs. Systemic immunosuppression, however, can potentially cause severe adverse effects including life-threatening infections and malignancy [92].

Of particular relevance to the VD-AD hypothesis is the role of ultraviolet light phototherapy, which is known to be effective for at least some cases of AD [93]. Phototherapy is too cumbersome, however, for widespread use, particularly in low-resource settings. Given the strong association between UV light and 25(OH)D levels, it's possible, of course, that the beneficial effects of phototherapy are, at least partly, mediated by VD [54]. If effective, oral VD supplementation would be a simple, low-cost and safe treatment that is likely to be widely accepted by a wide variety of patients, parents and providers.

Currently, there is only preliminary evidence to suggest AD improvement after VD supplementation, and VD is not part of the standard AD treatment. With regard to the evidence, a recent study of a murine model of AD treated with VDR agonists demonstrated improved allergen-triggered eczema, increased skin Tregs and induction of skin barrier and antimicrobial genes [74]. Over the last 5 years, several human trials have evaluated the effect of VD supplementation on the severity of AD in children and adults (TABLE 1). In the recently published Cochrane Systematic Review that evaluated VD supplementation in AD patients [94], two randomized controlled trials (RCTs) were included for analysis [95,96]. Neither trial found a significant difference in AD severity scales after VD supplementation compared to placebo. Nonetheless, the 2008 trial by Sidbury *et al.* did report a significant improvement in the Investigator Global Assessment (IGA) among children with winter-related AD, and the investigators did show an important but not statistically significant difference in change of mean scores after treatment. These promising findings, which were based on only 11 Boston children, suggested the importance of undertaking a larger RCT.

In the study by Javanbakht *et al.* although no significant difference in SCORAD was found at the end of the treatment between VD and placebo, there was a significant difference in SCORAD reduction within the VD group (*i.e.*, comparing pre- and post-treatment scores) [96]. A new and larger RCT also showed a significant reduction in SCORAD after VD supplementation during 60 days (again comparing pre- and post-treatment scores in the vitamin D group only), but no difference from patients given placebo [97]. Unfortunately, because the latter trials [96,97] are unclear about allocation concealment, this precludes a solid conclusion about their results. Moreover, they only included patients aged 13–14 years and older, restricting applicability to younger patients, where AD is of greatest frequency and public health importance.

A recently published multicenter RCT of VD vs placebo included only 30 subjects with AD, and failed to show an improvement in eczema area and severity index (EASI) or in skin antimicrobial peptides cathelicidin and human beta-defensin 3 after 21 days of VD supplementation [98]. The short

Table 1. Interventional studies that have evaluated the effect of vitamin D supplementation on severity of atopic dermatitis.

Study (year)	Trial design	Patients (n)	Intervention	Main results	Ref.
Sidbury <i>et al.</i> (2008)	RCT	children (11)	Daily 1000 IU VD2 vs. placebo for 1 month	Significant improvement in IGA, but not EASI, in VD group versus placebo	[94]
Javanbakht <i>et al.</i> (2011)	RCT	ages 13+ (52) mostly adults	Daily 1600 IU VD3 ± vitamin E vs. placebo for 60 days	Significant improvement in SCORAD of VD groups (versus baseline), but not better in VD groups versus placebo	[95]
Amestajani <i>et al.</i> (2012)	RCT	ages 14+ (60) mostly adults	Daily 1600 IU VD3 vs. placebo for 60 days	Significant improvement in SCORAD of VD group (versus baseline), but not better in VD group versus placebo	[96]
Hata <i>et al.</i> (2013)	RCT	adults (30)	Daily 4000 IU VD3 vs. placebo for 21 days	No significant improvement of EASI in VD group versus placebo	[97]
Samochocki <i>et al.</i> (2013)	open-label, single arm	adults (20)	Daily 2000 IU VD3 for 3 months	Significant improvement in SCORAD of VD group (versus baseline); no placebo group	[98]

EASI: Eczema Area and Severity Index; IGA: Investigators Global Assessment; RCT: randomized controlled trial; SCORAD: Scoring Atopic Dermatitis Index; VD2: ergocalciferol; VD3: cholecalciferol.

follow-up period and a relatively high mean baseline 25(OH)D level (28 ng/ml) may have influenced these negative results. By contrast a recent open-label intervention reported significant improvement of SCORAD after 3 months of daily VD supplementation in 20 adults with moderate to severe AD, history of winter exacerbations and skin infections, and very low 25(OH)D levels [99]. Of note, these patients also were found to have significantly reduced total IgE levels after receiving VD treatment. However, co-interventions in this study, including antihistamines and topical corticosteroids, were not controlled for and are a potential source of bias. Preliminary results of a RCT done in Mongolia, showed significant improvement of AD severity in 107 children with winter-related AD after one month of VD supplementation (Camargo CA, personal communication). Although these unpublished data suggest that VD supplementation may be a helpful adjunct treatment, at least for winter-related AD, the totality of the evidence is inconsistent and there are important methodological issues to address before a strong clinical recommendation is possible.

Expert commentary

AD is a highly prevalent skin disease in children that greatly reduces quality of life and leads to important morbidity. Based on currently available data from both basic research and preliminary clinical experiences, VD, a potent immunomodulator, appears to be involved in the etiology and pathogenesis of AD and other allergic diseases. Although the growing body of VD-related literature on allergic diseases leaves little doubt of an association, the causality of the association remains unclear. For example, it is possible that VD deficiency during pregnancy may affect the development of AD among infants, as suggested by the recent cohort study by Jones *et al.* [11], but the impact of VD deficiency on AD later in childhood, or adult life, is less clear. These timing issues are important because it has been hypothesized that VD deficiency during a critical period may influence the acquisition of gastrointestinal flora, altering the normal

intestinal barrier permeability, predisposing to food allergies [8]. Similar mechanisms might be involved in the predisposition to AD, by affecting the epidermal barrier and increasing susceptibility to colonization by pathogenic skin bacteria such as *S. aureus*.

The current literature generally supports VD as a low-cost, safe and potentially effective adjunct therapy for AD, but the inconsistent interventional studies suggest caution. Additional studies are needed to solve the clinical equipoise that exists on the question of whether VD is an effective therapy in AD. Moreover, the few trials of VD supplementation in AD have provided little insight into immunologic changes, which are essential to understand how VD affects the immune system *in vivo* in AD patients. Moreover, several clinical factors may influence the response to VD in AD patients. In this regard, allergic sensitization and age are probably crucial. A growing body of evidence points to a potential effect of VD deficiency on IgE mediated-allergies (e.g., food allergy/anaphylaxis). However, not all AD patients have evidence of allergic sensitization, particularly at young ages. Although the switch from non-IgE-associated to IgE-associated AD occurs early in childhood [100], this is variable among patients. It is possible that VD supplementation may influence this switch and may differentially affect AD severity in these subgroups of AD, although these issues have not been studied. Regarding age of AD patients, most published VD supplementation studies in AD are focused on adults. Epidemiological evidence strongly suggests that the association between allergic sensitization (i.e., specific IgE levels) with VD is stronger in children than in adults [78]. This may be similar for AD, where children have more frequently a Th2-skewed immunity and might have a stronger association with VD. Lastly, we note that there are many different AD phenotypes and it is entirely possible that VD only affects specific ones, such as winter-related AD, as suggested by the original work of Sidbury and colleagues [95]. Additional studies are underway to answer these many important questions on the effects of VD supplementation on disease severity. At the present time, and until additional studies have been

reported, we cannot make any definite recommendations on the efficacy of VD as an adjunct treatment of AD.

Five-year view

Over the next 5 years, additional scientific information will provide important insights in the mechanistic role of VD on the development of AD and other related allergic diseases, such as food allergy/anaphylaxis. The range of normality of 25(OH)D concentrations in humans are still a matter of debate. Although current consensus states that <20 ng/ml is deficient and between 20 and 29.9 ng/ml is insufficient, it is not clear what level is needed for healthy immune function at different ages. Population-based research has suggested that both low and high levels of VD may be detrimental for allergic diseases [84]. Like any hormone, the 'normal' range is crucial to define the treatment needs in any population. If an individual already has normal/healthy VD status, it is unlikely that he/she will derive benefit from taking supplemental doses of VD.

Several ongoing clinical trials will help answer if VD supplementation helps prevent AD and/or treat AD severity. Hopefully, these studies also will better define the window of opportunity when VD supplementation provides the most benefit (and least harm) in the prevention and/or treatment of AD. Much of the information that is currently available regarding the effects of VD

on the immune system are based on *in vitro* or animal models of disease. As scientists very well know, these findings do not necessarily reproduce in the same way in human subjects and clinical 'real-world' experience is much more variable than the research laboratory. In addition, new trials will likely provide further insight on genetic interactions of the VD pathway with AD pathogenesis and how specific genetic alterations might influence treatment decisions. Over the next 5 years, we expect that very relevant information on how VD affects the different branches of the innate and adaptive immune system of AD patients will be reported. We hope, for the sake of our patients, that all of this new immunologic information will provide a mechanistic understanding of trial results that validate VD as a safe, low-cost, easy to use and effective treatment for AD.

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Key issues

- Atopic dermatitis (AD) is a prevalent skin disease characterized by increased epidermal permeability and immunological hyperresponsiveness to allergens.
- Vitamin D (VD) is a pleiotropic hormone with widespread effects on innate and adaptive immunity, as well as the epidermal barrier.
- Basic and translational studies show that VD increases antimicrobial peptides, increases dendritic cell-mediated tolerance, modulates T- and B-cell immunity, and improves the epidermal barrier, key factors in the pathogenesis of AD.
- VD deficiency is associated with the development of AD and low VD status is correlated with increased AD severity.
- Interventional studies of VD supplementation in AD patients have shown inconsistent, but still promising, results.

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• of interest

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