

Microorganism-induced exacerbations in atopic dermatitis: A possible preventive role for vitamin D?

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ABSTRACT

Atopic dermatitis (AD) is a common skin disease characterized by a complex pathogenesis not completely understood despite numerous studies to date. The clinical patterns result from interactions between genetic disorders determining abnormalities in the epidermis differentiation complex, modification of the cutaneous barrier, and dysfunction of immune responses. Several studies have shown that an alteration of the skin barrier combined with immune dysfunction is important for the onset, maintenance, and risk of exacerbations of the disease. In recent years, new aspects regarding the pathogenesis of the disease, such as the effects of vitamin D (VD) on immunity at the skin level and the role of certain microorganisms (particularly *Staphylococcus* and *Malassezia* species) on eczema exacerbations, have been evaluated. This article provides an overview of the evidences supporting the link between VD (deficiency) and microorganisms (skin colonization/sensitization) in AD pathogenesis, based on comprehensive review of the literature. By considering different aspects of disease, it might be possible to improve our understanding, particularly in those patients refractory to conventional treatments. An electronic research strategy was used to search in Medline Pub-Med Library using as research words AD, exacerbation, VD, *Staphylococcus aureus* (SA), and *Malassezia*. The results were downloaded and analyzed for systematic review. Few studies actually consider the relationship between VD deficiency (VDD), AD, and SA and *Malassezia*, but many suggest a correlation between these factors. VDs play a major role against microorganisms in the development of AD and should be considered when treating patients.

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Atopic dermatitis (AD) is a complex inflammatory epidermal condition with significant associated social and financial burden. AD affects adults and children with worldwide prevalence rates of 1–20%.¹ It is a chronic relapsing condition characterized by defective skin barrier and immune dysregulation that confers an increased risk for cutaneous infections to patients.²

Vitamin D (VD) has been linked to the prevalence of many allergic diseases in the last decades, particularly to AD. The role of this vitamin on AD is probably connected to the capability of VD to be involved in both the innate and the adaptive responses of the immune system.

Considering the innate immune mechanisms of the skin, VD induces the synthesis of some antimicrobial peptides (AMPs), such as cathelicidin. Cathelicidin provides a nonspecific, rapid response to foreign pathogens and has a crucial role as an antibiotic in the protection of epithelial surfaces, particularly the

skin.^{3,4} Its level is negligible in normal skin, but VD, by raising the level of cathelicidin in atopic skin, could significantly help in fighting infections.^{5,6} Moreover, any injury or damage to the skin can induce the synthesis of AMPs as well. Schaubert *et al.* demonstrated that injury and damage increased the production of active VD in the skin.⁷ As a consequence, the levels of cluster of differentiation 14, cathelicidin, and Toll-like receptor (TLR)2 mRNA rose, thus making the skin stronger against injuries and infections.⁷ It has been shown that the TLR activation triggers a VD-mediated human antimicrobial response, effective in the skin of AD patients. In fact, in vitro TLR stimulation of human macrophages induced production of the enzyme that catalyzes conversion of 25(OH)D3 to active 1,25(OH)2D3, the expression of the VD receptor (VDR), and relevant downstream targets of VDR, including cathelicidin.⁸

VD interacts with the innate immune defenses also by stimulating the synthesis of filaggrin (FLG), a protein with a major role in the skin barrier, expressed by keratinocytes.⁹ FLG aggregates the keratin cytoskeleton to facilitate the collapse and flattening of keratinocytes in the outermost skin layer, and its expression plays an important role in the onset and development of the AD disease.^{9,10} Various linkage studies have demonstrated that the gene encoding for FLG is one of the most strongly associated with AD. As an example, in 2006, Palmer *et al.* showed that in a European Cau-

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casian population, homozygous nonsense mutations in FLG (R501X and 2282del4), which stop protein translation, were strongly associated with AD.^{10,11} A meta-analysis later confirmed that these mutations were among the strongest genetic risk factors for the development of AD.¹² Given this strong link between FLG and AD, the influence of VD on the expression of FLG reported in early studies, moreover, evidences that calcitriol plays an essential role in maintaining the skin barrier in atopic individuals.¹³ Furthermore, VD is known to have an effect on the growth and differentiation of keratinocytes in the skin.¹⁴ Hosomi *et al.* firstly observed that the active form of VD, the 1,25(OH)₂D₃, induces keratinocyte differentiation.¹⁵ However, it was demonstrated that 1,25(OH)₂D₃ acts both to induce and to suppress, being able to modulate the growth of keratinocytes by suppressing them at concentrations higher than 10⁻⁸ and stimulating at concentrations lower than 10⁻⁹.^{14,15} VD has been shown to increase the expression of involucrine, transglutaminase, locricin, and FLG, thus increasing the formation of the cell cornified envelope.¹⁶ All these actions are most likely due to ability of VD to increase calcium levels in the cells, resulting in keratinocyte differentiation.¹⁷

Hong *et al.*¹⁸ investigated VD functions in the formation of the lipid barrier in the skin and the role it has in the immune defense of the skin. They found that the inhibition of CYP27B1, a key enzyme in the activation of the vitamin, by ketoconazole, can block epidermal lipid synthesis, AMP expression, and permeability barrier homeostasis. This demonstrates, again, that VD system is fundamental in the physiology of the immune system at the skin level.^{18,19}

Regarding the adaptative immune response, studies showed the presence of VDR and VD-activating enzymes on both T and B cells. In resting conditions, the expression of VDR is very low, but it can be significantly enhanced by stimulation. Other studies showed that VD is able to induce allergen-specific interleukin (IL)-10-secreting regulatory T cells, which seem to have a regulatory role in vitro and might help in contrasting allergy in vivo by suppressing the activity of Th2 cells, previously activated by antigens.²⁰ VD has different effects on B and T cells, acting as a regulator of B-cell proliferation and activation by inhibiting memory and plasma cell generation and promoting apoptosis of immunoglobulin-producing B cells. Its role on T cells is even more complex, leading to a shift from a proinflammatory to a more tolerogenic immune status. For example, VD can inhibit the secretion of proinflammatory Th1, Th9, and Th22 cytokines and promote the production of more antiinflammatory Th2 cytokines,²¹ amplifying the inflammatory response of AD. AD per se is characterized by infiltrating lymphocytes in skin lesions, which are capable of secreting a variety of ILs that may promote IgE synthesis.²² These adaptive re-

sponses are particularly useful in case of superinfections of the AD lesions determined by microorganisms.

THE ROLE OF VD IN AD: THE CLINICAL EVIDENCES

Several studies have investigated the relationship between VD and AD with conflicting results. Epidemiologic studies have shown that children born in autumn/winter present a higher risk of developing AD than children born in spring/summer,²³ when the vitamin levels induced by light exposure are naturally higher than in the winter season. Significant inverse associations have been observed between cord serum VD levels and the risk in the offspring to develop later AD.^{24,25} Moreover, VD deficiency (VDD) could be considered as a risk factor for other allergic disorders and immune system dysregulation, being positively correlated with prevalence of rashes, sneezing, and sinus infections.²⁶ VD sufficiency at birth might be an important protective factor for food allergy in the first year of life, as shown by studies by Allen *et al.*²⁷ and by Mo-hiuddin *et al.*²⁸ The role of VDD has been also considered in asthma, not only evaluating the incidence of the disease but also the effects on the control of symptoms and the related use of drugs.^{29,30} Coming back to AD, the role of VDD has been demonstrated in children, where it was possible to show an inverse correlation between VD serum levels and the severity of the disease.³¹ This was confirmed in a study on obese patients, where VDD patients presented more frequently with AD.³² However, results of the literature are again conflicting: some trials have shown that severe AD is often linked to a lower serum level of VD in comparison with controls,^{31,33-35} whereas other studies have not confirmed this trend.³⁶⁻³⁸

Interestingly, few studies, recently reviewed by Demjrian and Ong,³⁹ have dealt with the effects of VD supplementation as a management tool in AD. This point is crucial to demonstrate the role of the vitamin in the disease. After supplementation, Hata *et al.*⁶ have demonstrated an increased expression of cathelicidin in AD lesioned skin, possibly correcting the deficiency in cathelicidins seen in the skin of atopic subjects. Sidbury *et al.* in a pilot study found significant improvement of the symptom global score.⁴⁰ Two double-blind placebo studies from Iran showed, respectively, significant improvement in Scoring Atopic Dermatitis evaluation after VD (1600 IU daily)⁴¹ and after VD plus vitamin E but in the latter not after VD alone.⁴² Therefore, in the review, the authors concluded that VD supplementation may be a beneficial tool in the management of AD, even though it is difficult to definitely conclude whether VD supplementation can be recommended in the daily practice, because studies are limited in number and have small sample sizes, variability in dosage, and design.³⁹

However, all these findings suggest that VD could play a central role in the immune system regulation and in particular in the maintenance of a regular skin barrier and in the repair of the AD skin that has been damaged by inflammation and/or scratching. VD helps to drive the immunologic defense at the skin level, and its deficiency creates a great risk of a more severe disease complicated also by microorganism colonization/infection.

THE ROLE OF STAPHYLOCOCCUS IN AD

It is well known that the skin of AD patients has a high susceptibility to *Staphylococcus aureus* (SA) colonization, with approximately 90% of patients colonized compared with 5%–30% of normal individuals.^{43,44} More than 15% of those colonized are then positive to methicillin-resistant SA,⁴⁵ and a recent communication showed a correlation between serum levels of VD and methicillin-resistant SA skin infections in AD patients. Even though this did not reach a statistical significant difference, the patients with methicillin-resistant SA skin infections presented lower serum levels of 25(OH)D.⁴⁶

SA colonization produces several proinflammatory factors at the cutaneous immune level, creating stimulation for chronic inflammation. This is particularly effective in the skin of AD patients, where lesions and inflammation are chronically present. There are many theories as to why atopic skin is more likely to be colonized than the skin of normal individuals. Atopic skin has reduced activity of acid ceramidases and a consequential lower concentration of ceramides and sphingosines in the stratum corneum. This facilitates the colonization of atopic skin by SA, because, in normal circumstances, sphingosine exerts a protective role against SA.⁴⁴ Furthermore, it is thought that SA can cause the hydrolyzation of ceramides by means of a bacterial ceramidase.⁴⁴ Another factor that explains the colonization is that SA has many adhesions for dermal and epidermal laminin and fibronectin. In damaged skin, such as that of AD patients, these proteins are exposed, and this might increase the chances to bind to the skin of atopic individuals.⁴³ Moreover, atopic skin has a higher production of IL-4, which is released by lymphocytes T and which stimulates the synthesis of fibronectin, further increasing the chances of SA to bind to atopic skin.⁴⁴

It has also been demonstrated that atopic skin produces a lesser amount of AMPs, such as cathelicidins and defensins, in particular of LL-37 and human β -defensin 2, when compared with other types of inflamed skin.^{47,48} Given that these two proteins have a synergistic antimicrobial activity effective in killing SA, a lack of these, as in VDD AD patients, can probably result in a higher susceptibility to colonization/infec-

tions.^{45,48} It has also been reported that in AD lesions, the expression of cathelicidin is down-regulated after acute wounding. Again, this could affect antimicrobial protection and tissue repair in AD.⁴⁹ This in turn may be amplified in the case of VDD, which directly down-loads a series of immune responses.

Recent studies have shown that microorganisms colonizing the epidermidis are able to produce molecules similar to human AMPs, called bacteriocins, which help the host skin against pathogens.^{47,50} *Staphylococcus epidermidis*, a major component of the normal skin micro flora, produces many different bacteriocins, called phenol-soluble modulins (PSMs). SA also produces PSMs, but its antimicrobial activity⁵¹ is rather weak. It has been discovered that PSMs produced by SA can attract neutrophils and then lyse them. This process might contribute to the pathogenicity of SA. PSMs produced by *S. epidermidis* do not lyse neutrophils but enhance their capacity to kill bacteria.⁵² These findings can explain why the skin of atopic patients, which is often colonized primarily by SA, is much more likely to be damaged and infected than the skin of nonatopic individuals, which is mainly colonized by *S. epidermidis*.

Once an AD patient has been colonized by SA, the course of the disease can be modified by the microorganisms themselves. SA can produce three different kinds of esotoxins: pore-forming toxins, exfoliative toxins, and the enterotoxins or superantigens (SAGs).⁵³ SAGs are the toxins mainly responsible for SA damage in AD patients. The International Nomenclature Committee for Staphylococcal Superantigens of 2004 introduced a new nomenclature for SA SAGs: staphylococcal enterotoxins (SE), SE-like toxins, and toxic shock syndrome toxin-1.⁵⁴ Approximately 80% of SA can produce five to six different Sags.⁵³ A recent research study has shown how SA colonizing AD patients are more likely to produce enterotoxins than those colonizing the skin of normal individuals.⁵⁵ The influence of enterotoxins produced by SA on AD depends on the concentration of the toxin. In the nanogram range and above, toxic shock syndrome toxin-1 can increase the concentration of peripheral-blood mononuclear cells and IFN- γ secretion, with sequential inhibition of IgE production. At lower concentrations (picograms and femptograms), they can decrease IFN- γ production and stimulate the B cells with an increase in the synthesis of IgE.⁵⁶ A very interesting study showed that in humanized severe combined immunodeficiency mice, which were given human-peripheral mononuclear blood cells intraperitoneally, the epidermal application of both SEB and mite allergens together caused an important dermal inflammation, whereas the application of mite allergens alone did not cause any reaction, despite the fact that the donor was sensitized to mites.⁵⁷ Indeed, the epicutaneous application of house

dust mite (HDM) extract resulted in the induction of thymic stromal lymphopoietin (TSLP) and in chemokine ligand 17/thymus and activation-regulated chemokine gene expression in nonlesional skin of AD patients sensitized to HDM with a positive atopy patch tests.⁵⁸ The expression of TSLP protein by keratinocytes in atopy patch test biopsies was comparable with that in lesional AD skin with respect to location and pattern, leading to consider that TSLP plays a role in the induction of eczema by HDM in patients with AD.⁵⁸

These findings suggest that SAGs produced by SA have a significant impact on the generation of lesions in atopic patients. A study conducted by Leung *et al.* showed how enterotoxins can up-regulate the expression of the cutaneous leukocyte-associated antigen receptor by peripheral-blood mononuclear cell, thus increasing the amount of cells that can migrate to the site of inflammation.⁵⁹ Due to their ability to bind major histocompatibility complex II molecules, SE can also activate antigen-presenting cells with an increase in the amount of cytokines they produce.^{43,60} Very recently, it has been shown that in AD moderately severe children, there was an association between egg and Sags IgE sensitization, leading to consider that food IgE levels may identify AD patients with more severe disease who are at risk for IgE sensitization to staphylococcal SAGs.⁶¹

The proinflammatory effects of SA colonization are further underlined by other findings. Travers *et al.* reported that the expression of human leukocyte antigen-DR in the keratinocytes of atopic patients can exacerbate the response to SAGs. This means that a smaller amount of SAGs is required to trigger inflammation in AD patients.⁶² Other studies show that atopic keratinocytes produce a higher amount of various cytokines, such as tumor necrosis factor- α , IL-1 α , and IL-1 β , in response to Sags.⁶³ A recent research study by Reginald *et al.*⁶⁴ discovered a novel IgE-reactive molecule in SA, known as a fibronectin-binding protein. This molecule is different from SAGs, because it requires antigen presentation to induce T-cell responses. Once in the organism, it can activate T cells and trigger the secretions of more proinflammatory cytokines from peripheral mononuclear blood cells.⁶⁴ A study by Lee *et al.*⁶⁵ demonstrated that SEA can stimulate a variety of cells such as keratinocytes and epithelial cells. This study showed that the expression of E-selectin, intercellular adhesion molecule-1, monocyte chemotactic protein-1, IL-6, and IL-8 is significantly up-regulated in both human immortalized keratinocyte cells and human umbilical vein endothelial cells after treatment with SEA. These results show that SEA can act as a potent inducer of several proinflammatory cytokines and adhesion molecules.⁶⁵

THE ROLE OF *Malassezia* IN AD

Malassezia furfur (MF) is a lipophilic yeast that belongs to the normal cutaneous flora. This microorganism colonizes sebum-rich areas such as the head, face, and neck rather than the limbs or trunk, because MF requires lipids for growth.⁶⁶ The colonization starts immediately after birth and sensitization can take place as early as during infancy⁶⁷ in individuals with an impaired skin barrier, such as those with AD.⁶⁸ *Malassezia* species, in particular *Malassezia restricta*, *Malassezia globosa*, and *Malassezia sympodialis*, colonize approximately 90% of patients with AD and 34% of normal individuals.⁴⁴

Malassezia can easily colonize the skin of patients with AD because of impairment in the production of β -defensin 2 by keratinocytes. In normal skin, the production of β -defensin 2 is increased after interaction with *Malassezia*, but this does not happen in atopic individuals; and we have previously described how these mechanisms are defective in cases of VDD. It has been shown that *M. globosa* can produce lipases able to downgrade the constituents of the compromised lipidic barrier in atopic patients,⁶⁹ thus compromising the skin barrier of colonized individuals with a consequential uncontrolled penetration of the yeast into human keratinocytes.⁴⁴

Few studies have investigated how MF can trigger an immune response and influence the disease activity once it has colonized atopic skin. Dendritic cells, particularly Langerhans cells, seem to be important in an initial phase, because antigens from MF can penetrate either by pinocytosis or by binding to mannose receptors. Inflammatory cytokines are then released, and these create an inflammatory environment, which attracts and then stimulates a Th2 response.⁴⁴ IgE binding allergens have been identified in *M. sympodialis*, MF, and, lately, in *M. globosa*.⁶⁹ One study reported that children with oozing lesions were more likely to develop *Malassezia* sensitization, suggesting that the higher pH of these lesions could lead to a higher release of allergens, thus increasing the risk of sensitization.⁷⁰

A recent study has shown that a protein produced by *Malassezia*, called MGL 1304, is found in the sweat of atopic individuals. The mechanism used by this protein to enter the skin is unknown, but it is thought to penetrate the skin either through sweat glands or through defects in the skin barrier. Once inside the skin, this protein is capable of inducing the degranulation of mast cells and the production of cytokines by basophils,⁷¹ thus increasing the inflammation of the skin of the patient colonized with *Malassezia*. Other studies have shown that the effect of MF yeasts on the production of cytokines from keratinocytes *in vitro* depends on the culture phase of the yeast, the *Malassezia*

species used, and the manipulations that the yeast cell lipid layer has undergone. However, it has been shown that *M. globosa* and *M. restricta* can equally stimulate keratinocytes and increase production of TSLP.⁶⁹ TSLP can affect the activity of the dermatitis by inducing a Th2 inflammatory response through activation of dendritic cells.⁶⁹ Furthermore, *Malassezia* is capable of binding C-type lectins, proteins that recognize carbohydrate structures, thus activating an immune response against them.⁷²

Exposure to *M. sympodialis* can up-regulate macrophage-inducible C-type lectin receptor mRNA expression in mast cells, thus influencing the immune response of the organism.⁷³ An interesting study by Ribbing *et al.* showed how mast cells of atopic individuals can differ from those of healthy controls when exposed to *M. sympodialis*.⁷³ They observed that the amount of preformed granule mediators was greater in mast cells derived from atopic individuals. Moreover, they showed that IL-6 secretion in response to *M. sympodialis* exposure only happens in mast cells from atopic patients. Finally, the fungal recognition receptor Dectin-1 on the mast cell surface is not up-regulated to the same extent in subjects with AD as it is in healthy individuals.⁷³

A study on mice further analyzed the interaction between cells in the skin and *Malassezia*. In particular, the researchers investigated the activation of macrophage-inducible C-type lectin in murine macrophages through interaction with *Malassezia*. Results showed that *Malassezia* can lead to an increase in the production of tumor necrosis factor- α , macrophage inflammatory protein 2, keratinocyte chemo-attractant, and IL-10.⁷⁴

CONCLUSIONS

A body of evidences shows that VD plays an important role in the physiology of the immune defenses of the skin, because it is able to modulate both innate and adaptive immune responses.⁷⁵ In AD patients, VD has a central role in the maintenance of a regular skin barrier and in the response to colonization/infection by microorganisms. This is crucial in the AD pathogenesis and maintenance, because eczematous skin is highly susceptible to microorganism colonization, particularly by SA and MF. Schaubert *et al.* demonstrated how VD stimulates the production of AMPs in epidermis and, in turn, reduces skin colonization by SA.⁷

Because AD is often an atopic disease, when considering the effects of microorganisms, clinicians should not only focus on the colonization issue^{45,55,76,77} but also investigate the sensitization aspect.^{31,78} In fact, there have been few studies in the past decade that observed a relationship between VD and sensitization to SA and MF. Indeed, in a preliminary study, we

found that patients with lower VD serum levels have a higher chance of having positive IgE against MF and SEA, SEB, and SEC.³¹

If the relationship between a low blood level of VD and a higher sensitization to these microbes could be confirmed, we could understand how and why these microbes colonize particularly the skin of some patients with AD by finding a possible explanation in the lack of the vitamin.

In conclusion, the main pathogenic factors in AD are impaired skin barrier and alterations in the immune system. However, there are possibly more aspects that are only partially known at present, which are likely to play an important role in the progression of the disease. More research studies are needed to provide more data and information about the two aspects we have discussed. However, from our review, it would appear that both VD and microorganisms have a major role in the development of AD and should be considered carefully when treating patients, particularly when they are recalcitrant to the effects of the usual therapy. Despite the relatively few studies, the robustness of the effect and the multiple lines of evidence suggest that systemic VD supplementation might be of benefit, particularly in those who have a documented low level or low vitamin intake or appear to worse in winter.⁷⁹

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