Vitamin D and the skin: an immunologic and therapeutic update

Naglaa N. El Mongy, Rana F. Hilal

Department of Dermatology, Kasr Al Ainy Teaching Hospital, Cairo University, Cairo, Egypt

Correspondence to Rana F. Hilal, MD, Department of Dermatology, Kasr Al Ainy Teaching Hospital, Cairo University, Al-Saray Street, Kasr Al Ainy, El Manial, Cairo 11956, Egypt. Tel: +20 100 148 8869; Fax: +20 26 28 884; e-mail: rana.hilal@kasralainy.edu.eg

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Vitamin D plays a vital role in skin diseases, and vitamin D supplementation seems to warrant protection against occurrence and exacerbation of several dermatological conditions. This review covers the immunopathological and therapeutic role of vitamin D, with a comprehensive illustration in some diseases.

Keywords:
alopecia areata, atopic dermatitis, autoimmune connective tissue diseases, ichthyosis, psoriasis, skin fibrosis, skin tumors, vitamin D, vitiligo

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Introduction

Cholecalciferol (vitamin D) is normally synthesized in the skin when ultraviolet B radiation triggers the conversion of 7-dehydrocholesterol in the skin into vitamin D [1]. There are two forms of vitamin D: 25-hydroxyvitamin D [25(OH)D3], which is the primary circulating form, and 1,25-dihydroxyvitamin D [1,25 $(OH)_2D3$], which is the active form [2]. Vitamin D can also be obtained from the diet or through supplements. It can be ingested in the form of vitamin D3 or vitamin D2 (ergocalciferol, which is derived from irradiation of the fungal steroid ergosterol) [3]. Vitamin D is processed by 25-hydroxylases present in the liver and other tissues to produce 25(OH)D3 [4] and then converted to 1,25 $(OH)_2D3$ by the enzyme 25-hydroxyvitamin D-1-α-hydroxylase, CYP27B1 [5,6].

Vitamin D deficiency

Deficiency is often defined by circulating 25(OH)D3 levels below 20 ng/ml (50 nmol/l), whereas insufficiency refers to levels between 20 and 30 ng/ml (50–75 nmol/l) [5–9]. The longer biological half-life of 25(OH)D3 makes it detected in higher concentrations than its active metabolite, in normal conditions. Moreover, vitamin D deficiency increases levels of parathyroid hormone, which in turn stimulates renal hydroxylation of 25(OH)D3 via renal CYP27B1, resulting in elevated or normal 1,25$(OH)_2D3$ levels [8,10]. For all such reasons, screening for and monitoring of vitamin D status should not depend on levels of 1,25$(OH)_2D3$, the active form of vitamin D.

Vitamin D deficiency has been considered as a possible pandemic owing to its high incidence among healthy and diseased populations. Risk factors for vitamin D deficiency include obesity [11], smoking [12], a high skin phototype [13], old age, and inadequate sun exposure [14].

Beyond calcium and bone

Vitamin D has been traditionally known for its role in calcium homeostasis and bone mineralization, but it does exhibit more diverse functions. The most important of which are the immunological functions of active vitamin D, as evidenced by the expression of vitamin D receptors (VDRs) on T and B lymphocytes, macrophages, and dendritic cells (DCs) [15], demonstrating profound effects on human immunity.

CYP27B1, an enzyme that activates vitamin D, irrespective of calcium metabolism signaling [10,16,17], and keratinocyte injury, stimulates the systemic feedback mechanism [18].

Antiviral functions of vitamin D

The protective aspect of vitamin D against various skin infections, especially those of viral etiology has been addressed previously [19] Figure 1 demonstrates the antiviral actions of vitmin D.

Viral particles gain entry through the damaged epidermis reaching down to the basal layer, thus infecting dividing keratinocytes (KCs) (part of innate immune defense). The initial inflammatory response produced by tissue damage leads to infiltration of

innate immune cells, followed by Dendritic cells (DCs) and later lymphocytes (part of the adaptive immune system) [20].

Vitamin D influences the immunological cascade following viral infections on various levels. Direct damage of the virus is mediated by vitamin D through binding the VDR and inducing endogenous antimicrobial peptides (AMP), for example, cathelicidin LL-37; α-defensin; β defensin[2]; hCAP-18, the only human cathelicidin; and LL-37, its functional cleavage product, both of which promote disruption of the viral membrane [21]. Autophagy, which entails pathogen encapsulation and lysosomal fusion [22], represents an alternative action of vitamin D-mediated direct degradation of viruses [23].

On an innate immunity scope, vitamin D-mediated cathelicidins stimulate chemotaxis for immune cells, as a result boosting an antiviral innate response [21].

Vitamin D seems to show contradicting actions on the adaptive immune system, possibly promoting a state of disease persistence, through stimulation of T regulatory cells (Tregs) and interleukin (IL) 10 [24], promoting a T helper (Th) 2 response, which have been found in persistent human papilloma viral infections [25]. Moreover, antigenic costimulation is inhibited due to immature antigen-presenting cells, upon vitamin D supplementation [26]. This raised a question as to whether the involvement of vitamin D in viral infections creates an antiviral state or allows for chronicity of infections. Studies on viral warts showed significantly low levels of vitamin D in human papilloma viral infections [27]. Higher expression of VDR has been demonstrated in warts, justifying the therapeutic role of intralesional injection of vitamin D [28], which was found effective in clearing warts [29]. However, the effect of a genetic factor should be taken into consideration, as VDR polymorphism can result in low serum 25(OH) levels [30], and should be investigated within the context of viral warts in future studies.

On the contrary, the role of vitamin D as an anti-inflammatory agent and an inhibitor of the Th-1 arm of the adaptive immunity is suggested to be beneficial in lowering the cytokine storm and surge of inflammatory markers such as interferon gamma and tumor necrosis factor, which stigmatize the coronavirus disease 2019 infection. Other actions of vitamin D include maintaining cell and gap junctions [31]. Although inconclusive evidence exists between circulating 25(OH)D levels and the morbidity and mortality during the global coronavirus disease 2019 pandemic, yet several reports suggested a prophylactic and protective role of vitamin D, especially for the at-risk population [32–34].

Therapeutic implications

Psoriasis

Psoriasis is a chronic skin disease of epidermal hyperproliferation [35] that could benefit from the pharmacological actions of vitamin D. In the epidermis, vitamin D, following nuclear VDR signaling [36], lowers expression of anti-apoptotic Bcl-xL, thereby stimulating apoptosis and preventing KC proliferation [35]. Vitamin D also lowers the elevated RANTES (regulated on activation, normal T expressed and secreted) and IL-8 expression, thereby preventing neutrophil recruitment and chemotaxis [37]. Moreover, at the level of the KC, vitamin D increases IL-10R gene transcripts, increasing the expression of the negative immunomodulatory cytokine IL-10, resulting in an anti-inflammatory and anti-psoriatic effect [38].

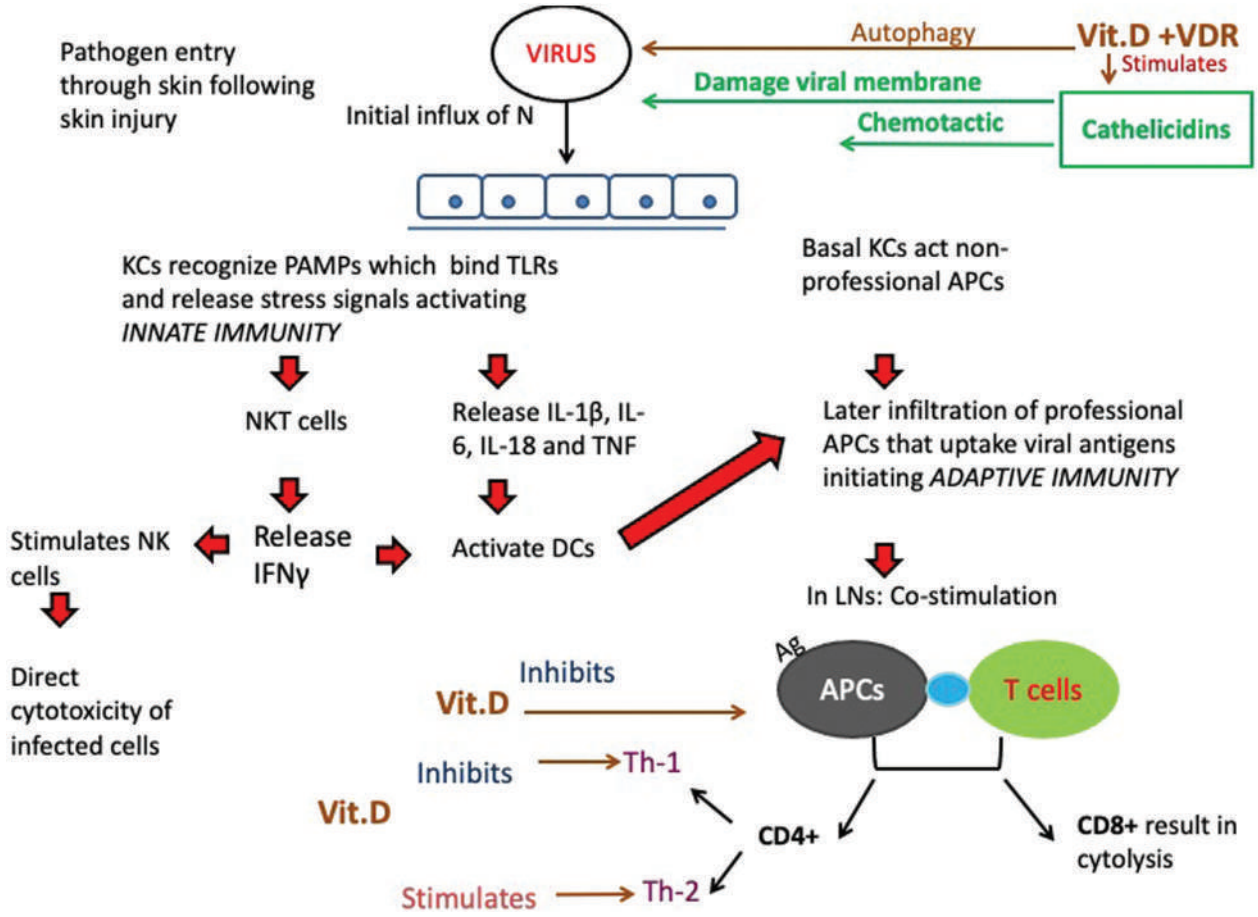
Psoriasis is a Th-1 disease [39], so within the dermis and in the presence of vitamin D, it undergoes resolution as vitamin D diverts the immune response toward the Th-2 pole, through promoting the release of IL-10 [38]. Vitamin D inhibits the release of IL-2, which inhibits monocyte differentiation into DCs, which in turn prevents T-cell proliferation [40]. Vitamin D also has anti-Th-17 actions [41].

Figures 1 and 2 illustrate how vitamin D provides clinical efficacy by exerting effects on both the psoriatic epidermis and dermis.

Several studies confirmed that significantly low serum levels of 25(OH) vitamin D were found in patients with psoriasis, compared with controls [42,43,44], which improved significantly following phototherapy [45]. Another study found no correlation between 25 (OH)D levels and severity of skin psoriasis and psoriatic arthritis [46]. Nevertheless, dietary or supplemental vitamin D was not found to prevent psoriasis [47], yet vitamin D supplementation, was found to lower mortality in patients with psoriasis [48] and ameliorate components of the metabolic syndrome [49]. Still large-scale studies are required to assess the efficacy, ideal dosage, and adverse effects of vitamin D administration in patients with psoriasis [50,51].

The use of oral calcitriol was feared owing to the risk of hypercalcemia and was suggested to be avoided by

Figure 1



Immunological cascade in viral infection and role of vitamin D at different check points. IFN, interferon; KC, keratinocytes; LN, lymph nodes; N, neutrophils; NK, natural killer cells; NK T cells, natural killer T cells; TH, T helper; Vit D, vitamin D; PAMPS, pathogen associated microbial products.

night-time dosing [42], and later vitamin D analogs like calcipotriol revolutionized the treatment strategy for psoriasis [52].

Atopic dermatitis

Various factors are involved in the pathogenesis of atopic dermatitis (AD), including the interaction of a defective skin barrier, immune system malfunction (both innate and adaptive), high IgE levels, and eosinophil infiltration. Moreover, AD skin is more susceptible to bacterial and viral infections that exacerbate pre-existing AD.

Aggravation of AD in winter has been documented, especially in higher latitude countries where serum 25 (OH)D tends to be particularly low in this season [53].

Immunologically, acute AD is characterized by a Th-2 profile with elevated levels of IL-4, IL-5, and IL-13. On the contrary, chronic AD shows a prevailing Th-1 inflammatory response with a surge of IFN-γ, Granulocyte Monocyte colony Stimulating factor (GM-CSF), and IL-12 in chronic lesions [54]. This accordingly makes such patients at risk for cutaneous infections [55].

Eczema herpeticum (EH) is a severe infection due to disseminated Herpes Simplex Virus (HSV), occurring in 10–20% of patients with AD [56], characterized by Th-2 dominant inflammation [57]. Lowered induction of AMPs, Human beta Defensins (HBD-2,3) HBD-2, HBD-3, and cathelicidin [58] has been encountered in atopic dermatitis eczema herpeticum (ADEH), proposed to be corrected by vitamin D.

It has been implied that restoring the balance between Th-1 and Th-2 cytokines in patients with AD could be achieved by vitamin D supplementation [59]. On a general immunological basis, $1,25(OH)_2D$ suppresses Th-1 cell proliferation, with lowered production of IFN-γ and IL-2 [60–62], which results in less antigen presentation by DCs, in addition to less T lymphocyte recruitment and proliferation [62]. On the contrary, expression of Th-2 associated cytokines, including IL-

Figure 2

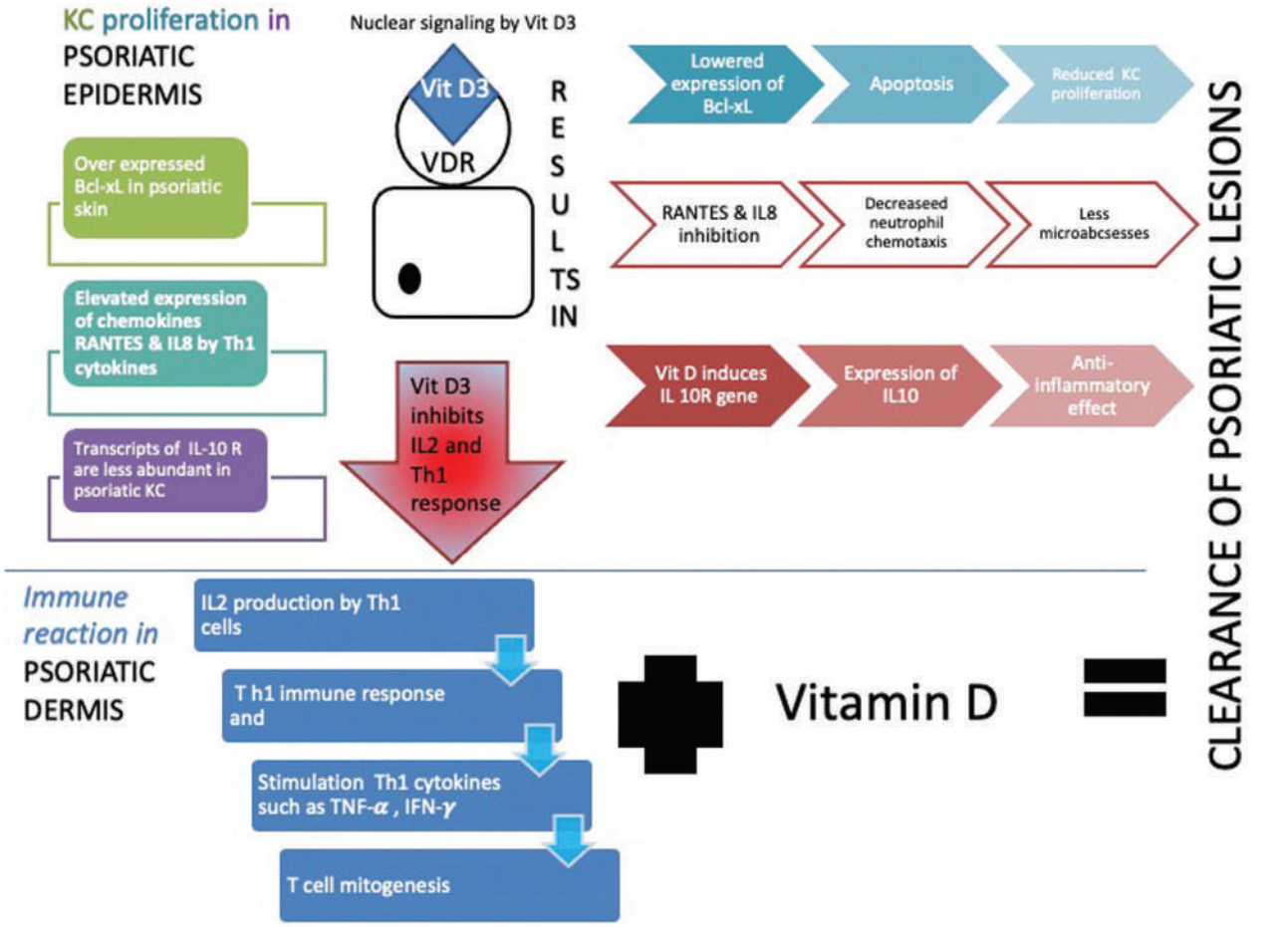


Illustration of the mechanisms by which vitamin D causes resolution of psoriasis. KC, IL, interleukin; keratinocyte; Th, T helper; TNF=tumor necrosis factor; VDR, vitamin D receptor.

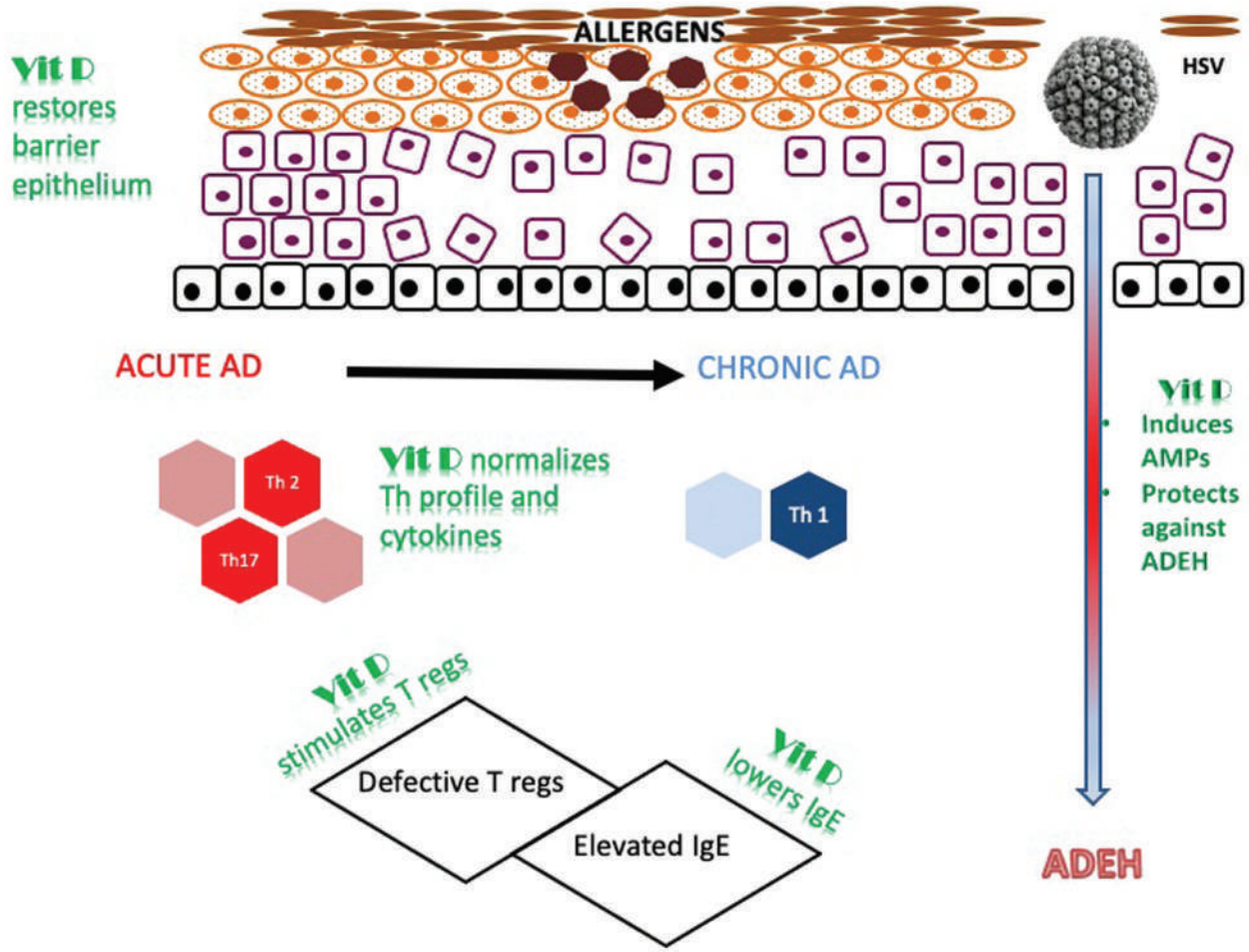
4, is induced by $1,25(OH)_2$ [63]. Overall, vitamin D polarizes the adaptive immune system away from Th-1 and toward Th-2 responses; thus, it would rather potentiate ADEH [21]. However, the induced expression of the AMP LL-37 by vitamin D improved ADEH [64]. In the clinical setting of AD, showing both a Th-1 and Th-2 immune profile, vitamin D is proposed to have more of a therapeutic role in acute and chronic AD, through normalizing the disturbed levels of Th-1 and Th-2 cytokines, that is, IL-2, IL-4, IL-6, and IFN-γ [59].

The toll-like receptors on immune cells and keratinocytes play an important role in innate immunity [65,66] and are induced by $1,25(OH)_2D$ [18,67]. Activated toll-like receptors through recognition of Pathogen associated microbial products (PAMPs) release AMPs and reactive oxygen species. The role of IL-17-secreting Th-17 cells in AD has been investigated in several studies [68]. IL-17 was shown to be preferentially elevated in acute versus chronic AD lesions [69]. Vitamin D inhibits Th-17 and IL-17 [70] and enhances Treg cells [71] and IL-10 (promoting the anti-inflammatory wing and inhibiting the proinflammatory wing).

Tregs did show a high blood level with normal immunosuppressive activity in patients with AD, which positively correlated with the disease severity [72–75], but on stimulation with *Staphylococcus enterotoxin* B, they lost their immunosuppressive activity [72,73]. On the contrary, few reports revealed either low frequency or absence of Treg cells in the peripheral blood and in skin lesions of patients with AD [76,77]. Figure 3 illustrates the role of vitamin D in AD.

Approximately 80% of AD cases display high serum IgE levels with specific IgEs to food allergens or aeroallergens [78]. Treatment with vitamin D suppresses the IgE production by human B cells and diminished IgE-mediated mast cell activation [79].

Figure 3



Display of the therapeutic implications of vitamin D in atopic dermatitis. AD, atopic dermatitis; HSV, herpes simplex; IgE, immunoglobulin E; Tregs, T regulatory cells; Vit D, vitamin D.

Vitamin D has been found to induce expression of skin barrier structural proteins (involucrin, filaggrin, and loricin), thus restoring the defective skin barrier, a pathogenetic hallmark in AD [54].

Clinical studies also showed some controversy. Compared with healthy controls, patients with AD had lower levels of vitamin D, especially the pediatric population [80]. Oral vitamin D supplements improved the severity of eczema lesions in pediatric patients and is considered to be a possible adjuvant treatment in patients with a deficiency (levels below 20 ng/ml). Colonization with *Staphylococcus aureus*, a microorganism that plays a role in outbreaks of AD, was reported to decrease in children after vitamin D supplementation [81–83].

Van der Schaft *et al.* [84] reported in a series of 210 adult patients with AD that vitamin D supplementation in patients with deficient levels did not lead to any significant improvement in eczematous lesions. Nevertheless, published reports proved vitamin D deficiency and insufficiency in adulthood AD [80], yet controversy exists regarding the therapeutic role of vitamin D supplements in this clinical scenario [52]. This debate may be related to the dynamic and complexed role of vitamin D in immunity, which needs further studies. The varied Th response between acute and chronic phases of AD, and in cases of ADEH, as well as the contradiction in Treg role raise different questions toward the clinical implications of vitamin D in AD, again requiring more research.

Overall, the AD population, especially the pediatric subset, may be at high risk for lower serum 25(OH)D. Supplementation with around 1600 IU/daily results in a clinically meaningful AD severity reduction [85].

Alopecia areata

Several studies reported lower levels of serum 25 OH vitamin 3 in patients with alopecia areata (AA) [86,87], as well as decreased expression of VDRs in hair follicle keratinocytes [88] than healthy controls . Expression of

VDRs in keratinocytes is necessary for the maintenance of the normal hair cycle [89]. The lack of which inhibits epidermal differentiation and hair follicle growth [90].

Findings suggested that vitamin D deficiency could be an environmental trigger for the induction of autoimmunity [91], and as AA is a tissue-restricted autoimmune disease mediated by T lymphocytes with a Th-1 cytokine profile [92], vitamin D deficiency does contribute to it pathogenesis [93]. Through this context, active vitamin D prevents autoimmunity by inhibiting IL-12 secretion, a cytokine potentiating Th-1 immune profile, followed by the secretion of Th-2 cytokines (IL-4, IL-5, and IL-10) shifting the immune response toward a Th-2 phenotype, therefore inhibiting Th-1 mediated autoimmune diseases [94,95]. Moreover, 1,25 OH vitamin D3 inhibits secretion of IL-6 and 17, thus inhibiting Th-17 cells, which are more potent in inducing autoimmunity [94,96]. Vitamin D also causes inhibition of autoimmune diseases through potentiating the production and function of Tregs [97], which maintain peripheral self-tolerance [98].

Further studies are required to determine a possible role for oral vitamin D3 in the treatment of AA.

Vitiligo

Strong evidence was found regarding vitiligo being significantly associated with low serum vitamin D concentration, based on the findings from a systematic review and meta-analysis [99].

The therapeutic effect of vitamin D in vitiligo, a disease of autoimmune etiology [100], is through an immunological action mediated by vitamin D against autoimmunity, as mentioned earlier. Additionally, vitamin D promotes a protective pathway for melanocytes from necrosis or apoptosis by protecting DNA from oxidative damage, in turn preserving pigmentation of the skin [101]. Vitamin D also may stimulate melanogenesis by activating specific receptors [102].

Chronic urticaria

Research has demonstrated that 30–50% of patients with chronic spontaneous urticaria produce an immunoglobulin IgG type autoantibody against either the high affinity receptor FcεRIα or IgE [103]. The autologous serum skin test has been used to test for chronic autoimmune urticaria by detecting auto-antibodies against FcεRIα [104].

Urticaria shows mainly a Th-1/Th-2 imbalance and defects in Treg function as well as numerous immune cells and cytokines that contribute to its pathogenesis [105].

Several studies showed low serum levels of vitamin D in patients with chronic spontaneous urticaria compared with healthy controls, and vitamin D supplementation in such patients can be used as adjuvant therapy [106–109]. Furthermore, Woo *et al.* [104] hypothesized that severe vitamin D deficiency could trigger the progression of acute urticaria to chronic urticaria and that autologous serum skin test-positive patients had even lower serum vitamin D levels.

The exact mode of action of vitamin D in urticaria is unclear, as both immune and nonimmune mechanisms give rise to the activation of mast cells in urticaria [110]. Proposed immunological roles include suppression of IL-1, IL-6, IL-12, IFN-γ, and normal T cell expression and secretion by vitamin D. It also stimulates tolerogenic cytokines like IL-10 and TGF-β by Tregs, DCs, and mast cells [111]. In vitro studies also revealed that vitamin D prevents IgE mediated mast cell activation via direct interaction on mast cell-CYP27B1 and VDR [112], decreases IgE production by B cells [113], and counteracts spontaneous eosinophil activation [114].

Congenital ichthyoses

The association between vitamin D deficiency and congenital ichthyoses has been reported. This could be secondary to a number of extrinsic factors such as limited sun exposure for cosmetic reasons and inadequate dietary supplementation. Intrinsic factors include defective epidermis, which results in decreased synthesis of vitamin D, and dark hyperkeratotic skin color, which causes poor penetration of sunlight. Excessive water loss leading to dehydration and constipation in children can also interfere with dietary intake of vitamin D [115]. The use of vitamin A derivatives such as retinoids for treatment of ichthyoses was reported to hinder the action of vitamin D owing to antagonism between vitamins A and D at the receptor level and an interaction with calcium-regulating hormones, such as parathyroid hormone [116], and possible skeletal adverse effects.

Owing to all aforementioned reasons, vitamin D supplementation was recommended in combination with oral retinoids in patients with ichthyotic disorders [115]. Another good reason for adding vitamin D supplements in the treatment regimen of ichthyotic diseases is its antiproliferative and

pro-differentiating actions that normalize keratinization and decrease scaling [89,117]. These actions are achieved by 1,25(OH_2)D3 via regulation of vitamin D responsive genes such as involucrin, transglutaminase 1 (both for cornified envelope formation), and kallikrein (for shedding of old corneocytes) [118]. Clinical trials concluded therapeutic efficacy of oral vitamin D [119] and topical calcipotriol [120] in congenital ichthyosis.

Acne

Acne severity was found to negatively correlate with vitamin D levels, and vitamin D supplementation could improve inflammatory acne lesions [121].

Therapeutic implications of vitamin D in autoimmune connective tissue diseases

Systemic lupus erythematosus

Various factors contribute to vitamin D deficiency and insufficiency in systemic lupus erythematosus (SLE), including inadequate sun exposure owing to photosensitivity, photo-protection, and the alteration of renal vitamin D metabolism [122].

VDR polymorphism was detected in association with SLE [123,124]. Low serum 25(OH_2)D3 levels in patients with SLE were found in several studies, which correlated inversely with disease activity [125,126], yet vitamin D supplementation failed to improve disease activity in such patients [127]. Nevertheless, systematic reviews recommend prescribing vitamin D in patients with SLE [128,129].

On an immunological basis, SLE shows an inflammatory milieu which drives T cells through proinflammatory pathways and autoantibody production by autoreactive B cells and shows defective Tregs, which allows for loss of self-tolerance [130]. All of these immunological outcomes are reversed by calcitriol, which downregulates Th-1 proinflammatory cytokines (IL-1, IL-2, tumor necrosis factor –α, and IFN-χ), upregulates Th-2 anti-inflammatory cytokines (IL-4, IL-5, and IL-10), and Tregs, which effectively leads to dampening of the inflammatory process [131]. Vitamin D was also shown to inhibit B-cell autoreactivity [60].

Therefore, an issue that could be considered is how vitamin D deficiency could be both a cause and result of SLE [129].

Systemic sclerosis

Vitamin D seems to exhibit similar beneficial immunological effects in systemic sclerosis (SSc) as in SLE, as both diseases have an autoimmune genesis, with an additional effect on directly decreasing fibrosis through a decreased expression of transforming growth factor (TGF) β1, collagen I, and collagen III and increased expression of some anti-fibrotic factors [132]. Vitamin D deficiency may be secondary to several factors, such as limited sun exposure due to disability and skin fibrosis and inadequate dietary intake because of gut involvement and malabsorption [133].

Previous studies have revealed vitamin D deficiency in patients with SSc compared with healthy controls [133,134]. Interestingly, seasonal fluctuation of 25 (OH)D levels has been reported, with lowest values detected during rainy and winter months [135]. Low 25(OH)D levels correlated with decreased carbon monoxide-diffusing capacity in patients with SSc, highlighting an association between vitamin D and lung fibrosis [136].

Dedicated clinical trials did not conclude therapeutic efficacy of calcitriol in SSc [137], whereas other studies suggested high supra-physiological doses of vitamin D are needed to correct the deficiency [138,139]. There still remains a need to conduct future studies to establish the ideal dosing of vitamin D supplements, required to reach the best clinical outcome in SSc [140].

Therapeutic implications of vitamin D in skin fibrosis

Morphea

Vitamin D shows similar actions in morphea to those described with SSc. Calcitriol demonstrated clinical improvement of stiffness and mobility in cases of localized and generalized morphea [137,141], and topical calcipotriol proved effective in localized scleroderma [142,143].

Lichen sclerosus et atrophicus

Low 25(OH)D levels have been detected in patients with lichen sclerosus et atrophicus (LSEA); however, further research is recommended to study this association [144,145].

Vitamin D regulates cellular differentiation and proliferation and restores the immune balance. Daily supplements of oral calcitriol at a dose of 0.5 μg showed clinical improvement in a case of LSEA, but hypercalciuria occurred [146].

Topical vitamin D analogs were found effective in extragenital LSEA [145,147]. Although the exact mechanism is yet to be elucidated [148], calcipotriol

probably acts by interaction with VDR, diminishing the stimulatory effects of TGF-β1 on fibroblasts, thereby inhibiting fibroblast proliferation, collagen production, and myofibroblast differentiation [149].

Keloids

Vitamin D deficiency has been implicated in patients with keloids [150], as such patients are usually dark skinned [151]. Concomitantly, vitamin D3 has been shown to have positive therapeutic roles in keloids through a number of mechanisms such as antiproliferative effect on keloid fibroblasts [152], downregulation of TGF-β1 with resultant decreased collagen production, and preventing myofibroblast differentiation [149]. Vitamin D also inhibits the anti-apoptotic BCL2 with increased proapoptotic caspase [152], causing apoptosis of keloid fibroblasts, which are more resistant to apoptosis than normal fibroblasts [153]. Renin-angiotensin system plays a pivotal role in keloid pathogenesis by stimulating a cascade of events that ultimately lead to skin fibrosis. Based on these implications, vitamin D supplementation could be a potential therapy for keloids [154].

Therapeutic implications of vitamin D in cutaneous tumors

Melanoma

Sunlight is a major risk factor for skin cancer, and treatment guidelines recommend sun protection following skin cancer diagnosis. Yet recently, the protective role of vitamin D became of concern in cancer pathogenesis [155].

In vitro studies revealed the anticancer actions of vitamin D, including promotion of cell differentiation and apoptosis with inhibition of cellular proliferation and angiogenesis of the tumor [156]. Several studies reported that high vitamin status is associated with a better prognosis in patients with melanoma [155,157]. A study demonstrated certain haplotypes of single nucleotide polymorphisms of the VDR gene related to increased survival in patients with melanomas in sun-exposed sites [158].

Inconclusive results have been shown in previous reports regarding the association between melanoma risk and serum vitamin D level, yet experimental and clinical trials do suggest that disturbances in vitamin D signaling may be related to melanoma course and disease-free and overall survival of patients. Additionally, altered local vitamin D level might result from disturbed vitamin D metabolism in melanoma cells [159]. Reduced risk of melanoma has been observed in postmenopausal women with history of nonmelanoma skin cancer (NMSC), on calcium and vitamin D supplementation [160].

Nonmelanoma skin cancer

The role of vitamin D in NMSC seems debatable. Some studies revealed that high serum vitamin D levels were associated with increased risk of NMSC [161], namely, basal cell carcinoma [162]. Other studies concluded that vitamin D supplementation was not associated with squamous cell carcinoma or basal cell carcinoma risk [160,163,164]. On the contrary, significantly decreased levels of both vitamin D and vitamin D-binding protein as well a significantly low expression of VDR were found in patients with basal cell carcinoma compared with healthy controls [165]. In fact, some studies suggested a potential protective role of calcium supplements with or without vitamin D (in a dose of 1000 IU) [166]. Yet a recent systematic review and metanalysis concluded that NMSC risk is not related to vitamin D intake, status, or VDR polymorphism [167].

Vitamin D was also reported to suppress the Hedgehog signaling pathway with an anti-tumor effect in basal cell carcinoma [168]. Another research has showed that Bsml single nucleotide polymorphism of the VDR was associated with a higher incidence of NMSC [169].

Mycosis fungoides

Vitamin D deficiency has been reported in mycosis fungoides (MF) [170]. Aberrant clones of T cells did express the VDR [171]. Low serum vitamin D leads to decreased AMPs, thus a higher rate of colonization by *S. aureus* and sepsis are commonly encountered in patients with cutaneous T-cell lymphomas [171,172]. A study concluded that VDR polymorphism and decreased serum vitamin D correlated significantly with MF and that vitamin D deficiency possibly triggers MF but is not incriminated in the duration and extent of the disease [173].

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Conflicts of interest

There are no conflicts of interest.

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