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Vitamin D and the Pathophysiology of Inflammatory Skin Diseases

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Abstract
Background: Vitamin D is a secosteroid, which was initially known for its skeletal role; however, in recent years, its functions in different organs have been increasingly recognized. In this review, we will provide an overview of vitamin D functions in the skin physiology with specific focus on its role in certain inflammatory skin conditions such as psoriasis and atopic dermatitis. ***Methods:*** A comprehensive literature search was carried out in PubMed and Google Scholar databases using keywords like "vitamin D," "skin," "atopic dermatitis," and "psoriasis." Only articles published in English and related to the study topic were included in this review. ***Results:*** Vitamin D is integrally connected to the skin for its synthesis, metabolism, and activity. It regulates many physiological processes in the skin ranging from cellular proliferation, differentiation, and apoptosis to barrier maintenance and immune functions. Vitamin D deficiency is associated with the risk of psoriasis and atopic dermatitis, and several clinical/observational studies have suggested the beneficial effect of vitamin D in the therapy of these 2 inflammatory skin disorders. ***Conclusions:*** Vitamin D exerts a pleiotropic effect in the skin and could be an important therapeutic option for psoriasis and atopic dermatitis.

Introduction

The human skin acts as site of synthesis of vitamin D and also as target organ for the biologically active form of this vitamin. Vitamin D affects multiple functions in the skin ranging from keratinocyte proliferation, differentiation, and apoptosis to barrier maintenance and immunoregulatory processes [1]. Also, vitamin D is being considered as a therapeutic option for many skin pathologies [2]. In this review, we will discuss the nonclassical function of vitamin D in the skin and will evaluate its role in certain inflammatory skin conditions using atopic dermatitis (AD) and psoriasis as examples.

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Main Structural and Functional Molecules in the Skin

The skin acts as first line of defense against infections. It consists of mainly 3 layers, the epidermis, dermis and hypodermis, and associated with it are several appendages like hair follicles, eccrine sweat glands, sebaceous glands, and apocrine glands. The epidermis consists of many cells like keratinocytes, melanocytes, Langerhans cells (a specialized subset of myeloid dendritic cells, DCs) and Merkel cells, among which keratinocytes account for 95% of the total epidermal cells. There are 4 distinct epidermal layers, each composed of keratinocytes at various differentiation stages [1]:

1. stratum basale: it consists of columnar, proliferating keratinocytes with an extensive network of keratins K5 and K14;
2. stratum spinosum: in this layer, keratinocytes initiate differentiation through synthesis of K1 and K10 keratins, involucrin, and enzyme transglutaminase;
3. granular layer: it is characterized by keratinocytes rich in electron-dense keratohyalin granules containing late differentiation markers like profilaggrin (precursor of filaggrin), and loricrin; it also consists of lipid-filled lamellar bodies that empty their contents into the intercellular spaces between the stratum granulare and stratum corneum and contribute to the permeability barrier;
4. stratum corneum (SC): the uppermost layer, consists of terminally differentiated dead cells known as corneocytes. The plasma membrane of corneocytes is replaced by an insoluble protein layer called "cornified envelope," made of structural proteins like involucrin, loricrin, filaggrin, and small proline-rich protein cross-linked by transglutaminase.

Filaggrin is a particularly important molecule in the SC, as it facilitates the aggregation of keratin filaments of the cytoskeleton into bundles, consequently collapsing corneocytes into flattened disks. Also, it contributes to the hydration of the SC by proteolysing into pyrrolidine carboxylic acid and transurocanic acid in conditions of low water content [3]. The constant thickness of the epidermis is maintained by the fine balance between basal cell proliferation and corneocyte desquamation. The desquamation process starts with the degradation of corneodesmosomes (modified desmosomes present in the SC) and is controlled by a number of proteases and their inhibitors. The human kallikrein (KLK)-related peptidases including the KLK5, KLK7, and KLK14 are the prominent proteases involved in desquamation. The lymphoepithelial Kazal-type 5 serine protease inhibitor is an important protease inhibitor encoded by the *SPINK5* gene which has confirmed activity against the members of the KLK family [4].

Vitamin D: Synthesis and Functions

Vitamin D is a fat-soluble vitamin that occurs in 2 main forms: ergocalciferol (vitamin D_2) produced by plants and cholecalciferol (vitamin D_3) derived from animal-based foods. The major source of vitamin D in humans is the cutaneous synthesis in the presence of sunlight. The exposure of 7-dehydrocholesterol (7-DHC) to ultraviolet radiation B (UVB) of wavelength 290–315 nm results in the formation of previtamin D in the skin, which is thermally isomerized to the stabler vitamin D (cholecalciferol). The vitamin D, whether synthesized in the skin or obtained from diet, undergoes 2 hydroxylation reactions: first in the liver by vitamin D 25-hydroxylase (CYP2R1) enzyme to form 25-hydroxyvitamin D, 25(OH)D, also known as calcidiol and then in the kidney by 1α-hydroxylase (CYP27B1) to form an active metabolite, 1,25-dihydroxyvitamin D, $1,25(OH)_2D$, also known as calcitriol. Both 25(OH)D and $1,25(OH)_2D$ may be metabolically inactivated through hydroxylation by 24-hydroxylase (CYP24A1) [5]. The levels of vitamin D in serum are tightly regulated by a feedback mechanism of calcium, phosphorus, parathyroid hormone, fibroblast growth factor and vitamin D itself [6, 7]. The vitamin D status is evaluated by measuring the serum 25(OH)D level, which is its major circulating form. According to the US Endocrine Society guidelines, vitamin D deficiency is defined as a serum level of 25(OH)D below 20 ng/mL (50 nmol/L) and vitamin D insufficiency as a serum 25(OH)D level between 21 and 29 ng/mL (52.5–72.5 nmol/L) [8].

The function of vitamin D was for a long time considered to be the maintenance of a normal skeletal architecture through calcium and phosphorus homeostasis, but in the last few decades, the extraskeletal effects of vitamin D became apparent, and its roles in the regulation of cell proliferation, differentiation, apoptosis, and in the immune modulation are increasingly recognized [9, 10]. These actions of vitamin D are mediated by the vitamin D receptor (VDR), which after activation interacts with retinoid X receptor (RXR) to form a heterodimeric complex. The VDR-RXR complex is recruited to the vitamin D response elements (VDREs) in the promoter of target genes to regulate their expression. This process is described as the genomic action of vitamin D, in contrast to the nongenomic action which is the direct effect that vitamin D has on several signaling pathways.

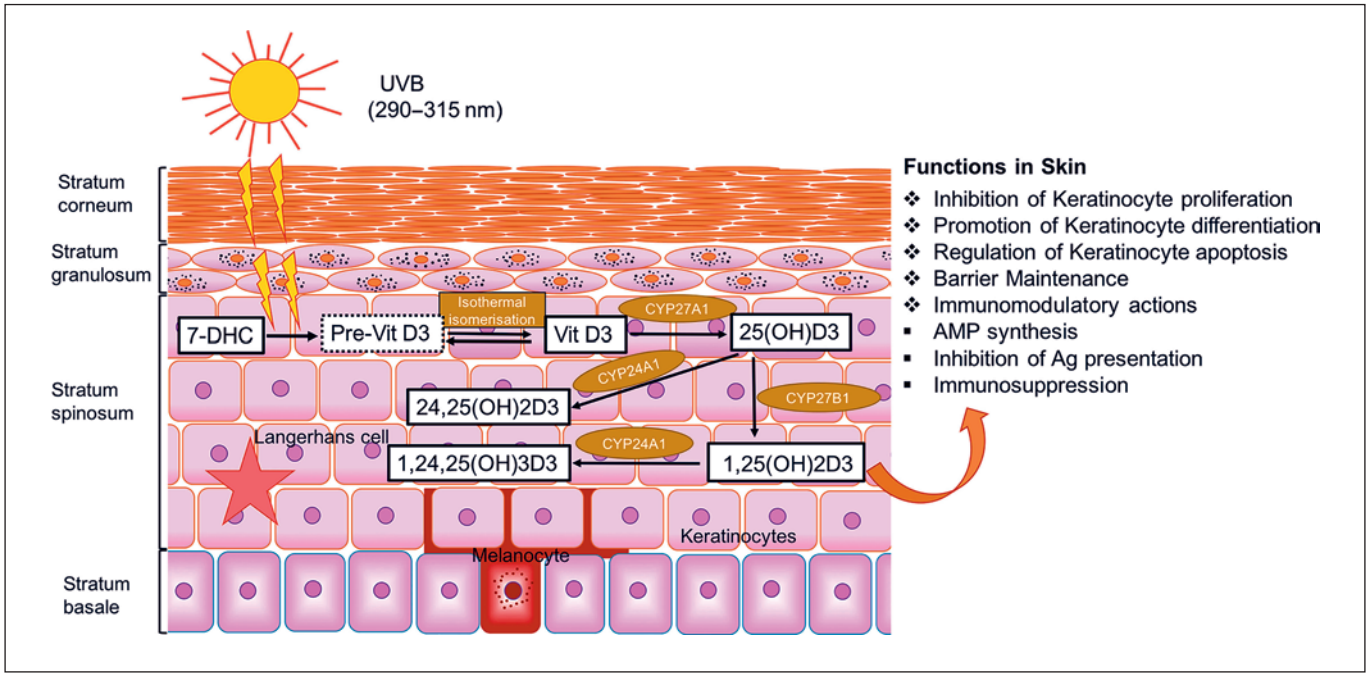

Fig. 1. Summary of vitamin D_3 pathway and functions in the human skin. Vitamin D_3 (Vit D_3) is synthesized in the skin from its precursor 7-DHC under the influence of UVB and metabolized to its active form, $1,25(OH)_2D_3$ through 2 subsequent hydroxylation reactions by CYP27A1 and CYP27B1 enzymes. It is rendered inactive through the catabolic enzyme CYP24A1. 7-DHC, 7-dehydrocholesterol; $25(OH)D_3$, 25-hydroxyvitamin D_3; $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; $24,25(OH)_2D_3$, 24,25-dihydroxycholecalciferol; $1,24,25(OH)_3D_3$, 1,24,25-trihydroxycholecalciferol; CYP27A1, 25-hydroxylase; CYP27B1, 1α-hydroxylase; CYP24A1, 24-hydroxylase; AMP, antimicrobial peptide; Ag, antigen; UVB, ultraviolet radiation B.

Role of Vitamin D in Skin Physiology

Vitamin D plays a vital role in the skin: the keratinocytes are not only a source of vitamin D, but also a responder to its active form [1]. They are the only cells in the body that can synthesize vitamin D from its precursor 7-DHC, and which are equipped with the entire enzymatic machinery (CYP27A1 and CYP27B1) necessary to metabolize vitamin D into its active metabolite $1,25(OH)_2D$. Keratinocytes also express VDR, thus they respond in an autocrine and paracrine manner to the active form of vitamin D. The entire pathway of vitamin D_3 in human skin is shown in Figure 1.

Vitamin D and Epidermal Differentiation and Proliferation

Vitamin D affects the proliferation and differentiation of the skin either directly or through its interaction with calcium. Many in vitro studies have shown a dose-dependent effect of vitamin D on keratinocyte proliferation and differentiation. At low concentration (10^{-9} M or less), $1,25(OH)_2D_3$ was found to enhance keratinocyte proliferation, while at high concentration (greater than 10^{-8} M), it inhibited the proliferation and promoted the differentiation [11, 12]. Several other factors like density of cells, calcium concentrations and presence or absence of serum influence the effect of vitamin D on in vitro keratinocyte proliferation [13]. The antiproliferative action of vitamin D on keratinocytes is mediated by the decreased expression of c-myc and cyclin D and by the increased expression of the cell cycle inhibitors $p21^{cip}$ and $p27^{kip}$ [1, 14]. $1,25(OH)_2D$ promotes keratinocyte differentiation through an increased synthesis of structural components (involucrin, transglutaminase, loricrin, and filaggrin) of the cornified envelope [14, 15]. The effect of vitamin D in the differentiation is also in part mediated by the (1) elevation of intracellular calcium levels caused by calcium receptor stimulation, (2) increased phospholipase C-γ_1 expression, and (3) enhanced formation of ceramides [15–17]. Vitamin D may also directly regulate the keratinocyte differentiation through interaction with VDR. This is evidenced by the fact that VDR knockout mice show reduced epidermal differentiation and exhibit low levels of involucrin, profilaggrin, and loricrin [18]. The

process of vitamin D-mediated epidermal differentiation through VDR is sequential and requires selective binding of VDR to 2 major coactivators: vitamin D receptor-interacting protein (DRIP) and steroid receptor coactivator (SRC). It was observed that DRIP205 is predominantly expressed in proliferating keratinocytes and, as the cells differentiate, the expression of DRIP205 goes down, while the expression of SRC3 increases [19]. It was demonstrated that calcium also regulates the expression of these 2 coactivators and interacts with VDR for the differentiation of keratinocytes [20].

Vitamin D and Barrier Function

Another aspect of keratinocyte proliferation and differentiation is the maintenance of a proper epidermal barrier. Previous studies have shown that topical application of calcitriol ($1,25[OH]_2D$) restores the permeability barrier which was disrupted by application of corticosteroid or sodium lauryl sulfate [21, 22]. Vitamin D mediates its effect on the epidermal barrier by enhanced synthesis of structural proteins of the cornified envelope. Additionally, $1,25(OH)_2D$ regulates the processing of the long-chain glycosylceramides essential for lipid barrier formation. Oda et al. [23] have shown that VDR knockout mice display a defective permeability barrier due to the reduced production of glucosylceramide and its decreased transport into the lamellar bodies, resulting in a lower lipid content in these bodies.

Vitamin D and Keratinocyte Apoptosis

The effect of vitamin D on the keratinocyte apoptosis is dose dependent, similar to its effect on cellular proliferation. At physiological concentrations, vitamin D prevents apoptosis triggered by various proapoptotic stimuli like ceramide, UV radiation, TNF-α, etc., while at high concentrations it induces apoptosis in keratinocytes [24]. The antiapoptotic or cytoprotective effect of vitamin D is shown to be mediated by sphinosine-1-phosphate. Other mechanisms are also reported to be responsible for the antiapoptotic effect of vitamin D like the activation of MEK/ERK and PI3K/Akt signaling pathways, and the increased ratio of antiapoptotic protein (Bcl-2) to proapoptotic protein (Bad and Bax) [25].

Vitamin D and Skin Immune Functions

The skin innate immune system comprises physical barrier structures like SC, immune cells (like neutrophils, monocytes, macrophages, DCs, natural killer [NK] cells, etc.) and antimicrobial peptides (AMPs). The cutaneous synthesis of AMPs is the primary protection mechanism of the skin against environmental insults or microbial invasion. Many resident cells of the skin (like keratinocytes, sebocytes, eccrine gland cells, and mast cells) and circulating cells recruited to the skin (like neutrophils and NK cells) contribute to the synthesis of AMPs in the skin [26, 27]. More than 20 proteins with antimicrobial function are recognized in the skin; however, β-defensin and cathelicidins are the 2 main groups of skin AMPs [26]. Defensins are classified in 3 subfamilies based on cysteine-disulfide pairing between β-sheet structure – α, β, and θ – of which only β-defensin is appreciably expressed in the skin. Humans have a single cathelicidin gene which encodes the inactive peptide hCAP18, which after cleavage generates the mature peptide LL-37. Cathelicidin and β-defensin mediate antimicrobial activity either directly by disrupting the bacterial cell membrane and viral envelope or indirectly by affecting various signaling pathways in the cells to initiate a host response. These 2 AMPs are also reported to promote keratinocyte proliferation and migration through EGFR signaling and STAT activation (necessary for skin wound healing), to stimulate cytokine or chemokine release through stimulation of G protein-coupled receptors and to induce IL-8 secretion through the ERK p38/MAPK pathway in mast cells and keratinocytes [28].

The level of AMPs is low in intact skin, and it increases following barrier disruption or infection. One of the possible ways it is done is through enhanced CYP27B1 expression, subsequent to skin insult, which increases the local synthesis of active vitamin D. Schauber et al. [29] have shown that following skin injury, TLR-2 is increased which in turn increases the level of cathelicidin through a vitamin D-dependent mechanism. Similarly, many studies have shown an increased expression of hCAP18/LL-37 and defensin after $1,25(OH)_2D_3$ treatment in keratinocytes and sebocytes [30–33]. Cathelicidin and β-defensin are direct transcriptional targets of vitamin D, with cathelicidin being induced by binding of the $1,25(OH)_2D$-VDR complex to the VDRE in the promoter region of the gene; however, β-defensin requires nuclear factor κB along with the $1,25(OH)_2D$-VDR complex for its transcription [34]. Vitamin D is also reported to regulate the AMP synthesis by mechanisms other than the direct transcriptional activation. The activity of cathelicidin and other AMPs in human skin is controlled through an enzymatic processing by serine proteases KLK5 and KLK7 [35]. Morizane et al. [36] showed that $1,25(OH)_2D_3$ could affect the production of AMPs in the skin by regulating synthesis and protease activity of KLK5 and KLK7. In another study, Dai et al. [33] showed that the induc-

tion of cathelicidin and β-defensin HBD-3 expression by $1,25(OH)_2D_3$ is regulated by peroxisome proliferator-activated receptor-γ through AP-1 and p38 activity.

Besides regulating AMP synthesis in the skin, $1,25(OH)_2D_3$ and calcipotriol (an analog of vitamin D) mediate an immunosuppressive action in the skin through decreased antigen presentation either directly by affecting Langerhans cells or indirectly by modulating cytokine production by keratinocytes [37, 38]. Recently, many studies suggested that calcipotriol mediates tolerance or immunosuppression in the skin through induction of CD4+CD25+ T regulatory (T_{reg}) cells which prevents subsequent antigen-specific CD8+ T-cell proliferation and IFN-γ production [39, 40]. Skin-homing cutaneous lymphocyte-associated antigen (CLA+) memory T cells preferentially home to cutaneous sites for host defense against pathogens. CCR10 is a chemokine receptor that is preferentially expressed by skin-homing CLA+ T cells which facilitate their entry into cutaneous sites by interacting with skin-associated CLC27 antigen. Studies investigating the effect of vitamin D on homing of memory T cells to the skin are contradictory. While some studies suggested that $1,25(OH)_2D_3$ and its analogs prevent skin T-cell infiltration by downregulating the expression of CLA [41, 42], other studies showed that $1,25(OH)_2D_3$ induces CCR10 receptor expression on T cells promoting their homing to cutaneous sites [43–45]. Recently, a study has shown that seasonal variation in vitamin D level affects the skin-homing receptor expression with increased levels of CLA during the summer [46].

Role of Vitamin D in Certain Inflammatory Skin Diseases

Psoriasis

Psoriasis is a chronic multifactorial inflammatory disease where the immune dysregulation plays a major role by involving a crosstalk between the innate and adaptive immune system. There is an increased infiltration of innate immune system effectors like plasmacytoid dendritic cells (pDCs), myeloid dendritic cells (CD11c+ mDCs), neutrophils and NK cells, and abnormally high levels of AMPs (like β-defensins, S100 proteins or LL-37) in psoriatic lesions. It is suggested that a complex of host DNA and LL-37 acts as potent trigger for IFN-α production by pDCs and provides a mechanism of initiation of intolerance to self-DNA [47]. IFN-α derived from pDCs is supposed to drive the early inflammatory cascade in psoriasis by activating "quiescent" autoimmune T cells into pathogenic effectors through promoting activation or maturation of mDCs [48]. On activation, a subset of CD11c+ mDCs, known as TIP-DCs, expresses an increased level of TNF-α and inducible nitric oxide synthase enzyme (generates nitric oxide to induce vasodilation and inflammation) [49]. Additionally, another subset of mDCs produces IL-20 to enhance keratinocyte activation and proliferation, and IL-23 and IL-12 to activate a specific subset of T cells [50]. Neutrophils and NK cells recruited in psoriatic lesions further add to the inflammatory milieu of psoriasis through secretion of AMPs and proinflammatory cytokines [51, 52].

Psoriatic lesions are also characterized by an increased infiltration and activation of T cells particularly CD4+ T helper 1 (Th1) and CD8+ cytotoxic T cells, which predominantly secrete type 1 cytokines like TNF-α and IFN-γ. These lesions are also enriched in other types of T cells like IL-17-producing T cells and NK T cells. It was observed that IL-23 secreted by mDCs and other leukocytes induces the differentiation of naïve T cells into type 17 helper T cells (Th17) and type 17 cytotoxic T cells, both secrete IL-17, IL-17F, and IL-22 cytokines [53]. After activation, NK T cells also secrete Th1, Th2, and Th17 cytokines [54]. These type 17 cytokines together with IFN-γ and TNF-α result in activation and proliferation of keratinocytes. Thus, in response to cytokines secreted from DCs and T cells, keratinocytes become activated and produce AMPs, proinflammatory cytokines (IL-1, IL-6 and TNF-α), chemokines (CXCL8 through CXCL11 and CXCL20) and S100 proteins (S100A7–9) [55]. These soluble mediators act as chemoattractants for neutrophils and other immune cells. Therefore, a feedback loop exists between keratinocytes and infiltrating immune cells, which maintains a constant deregulated inflammatory process, characteristics of psoriatic disease. Unrestrained function of T cells in psoriasis may also be due to the dysfunction of T_{reg} cells. In fact, some studies have shown that T_{reg} cells isolated from psoriatic patients have a decreased suppressive function [56, 57], others demonstrated that they produce IFN-γ, TNF-α, and IL-17, suggesting a switch of their function from suppressive to proliferative [58].

Role of Vitamin D in Psoriasis

Vitamin D plays a critical role in psoriasis, and this is evidenced in many studies which reported either a deficiency or insufficiency of serum vitamin D in psoriatic patients [59–61]. Several case-control studies have shown significant lower levels of serum 25(OH)D in psoriatic patients compared to controls and reported an inverse

correlation between serum 25(OH)D and the severity of the disease [62–66]. However, in a population-based screening, Wilson [67] showed that vitamin D deficiency is not common in psoriatic patients and that there is no significant difference in serum 25(OH)D levels in subjects with or without psoriasis. The 25(OH)D level varies with several factors, including race, dietary intake, and UV light exposure, therefore results of studies on vitamin D need cautious interpretation.

Vitamin D treatment may be effective in resolving psoriasis symptoms, and this is confirmed by many clinical studies. Finamor et al. [68] showed that psoriasis patients, who were receiving 35,000 IU of vitamin D_3 once daily for 6 months, had significant improvement in psoriasis area severity index score (PASI) with a marked increase in their serum 25(OH)D level. Several clinical trials have also demonstrated an excellent efficacy and safety profile of vitamin D analogs like calcipotriol, tacalcitol, and maxacalcitol in the treatment of psoriasis [69–71].

NB-UVB (narrow-band ultraviolet B light) and UVA/UVB phototherapy, widely used in the treatment of psoriasis, are thought to mediate its beneficial effect in part by elevating the serum 25(OH)D level [72–74]. A clinical trial compared the efficacy and safety of various treatment regimens for psoriasis (calcipotriol monotherapy, NB-UVB phototherapy alone and combination of calcipotriol and NB-UVB) and demonstrated that the combination of calcipotriol and NB-UVB twice a week was superior to other treatment regimens in rapidly reducing the PASI score of patients [75]. The combination of vitamin D or its analogs and corticosteroid is also reported to be more effective than either of their monotherapy because of their complementary actions. In combination treatment, vitamin D may counteract the steroid-induced skin atrophy by restoring the epidermal barrier, while corticosteroid may reduce the perilesional skin irritation caused by vitamin D analogs [76–78].

Vitamin D exhibits an inhibitory effect in psoriasis through a multitude of ways. pDCs, which are supposed to initiate the inflammatory cascade in psoriasis, express transcriptionally active VDR and the vitamin D-metabolizing enzymes CYP27B1 and CYP24A1. It was shown that vitamin D treatment impairs the capacity of pDCs to induce T-cell proliferation and IFN-γ secretion [79]. Vitamin D is also supposed to affect the Th17 pathway: it was observed that application of vitamin D and its analogs on psoriatic lesions significantly decreased the infiltration of Th17 cells in the skin and inhibited their ex vivo expansion [80, 81]. In other studies, vitamin D was reported to suppress inflammatory cytokines like IL-12/23 p40, IL-1α, IL-1β, and TNF-α, which were present in abnormally high levels in psoriatic skin [82, 83]. Psoraisin (S100A7) and koebnerisin (S100A15), induced by Th17 cytokines, synergistically act as chemoattractants and "alarmins" to amplify inflammation in psoriasis. Calcipotriol was found to suppress Th17-induced psoriasin and koebnerisin in psoriatic skin [84]. In an epidermal reconstructed model of psoriasis, Datta Mitra et al. [85] showed that 1α,25-dihydroxyvitamin D_3–3-bromoacetate, a vitamin D analog, has a more potent antiproliferative action compared to $1,25(OH)_2D_3$. He showed that bromoacetate reverses the psoriasiform changes induced by IL-22 in the reconstructed epidermal model by inhibiting the expression of AKT1, MTOR, chemokines (IL-8 and RANTES) and psoriasin (S100A7).

Vitamin D not only modulates or suppresses inflammation in psoriasis; it also rectifies the abnormal epidermal function related to this condition. It was demonstrated that deletion in late cornified envelope genes, LCE3B and LCE3C, located within PSORS4 is a genetic risk factor of psoriasis. A study by Hoss et al. [86] has shown that $1,25(OH)_2D$ upregulated the LCE proteins (LC3A–E) in keratinocytes and provided a mechanism of ameliorating psoriasis in patients with LCE defects. The expression of tight junction proteins like claudin, ZO-1, and occludin, which are reduced in psoriatic skin, is correlated with VDR status, pointing out the role of vitamin D in the regulation of tight junction proteins in psoriasis [87]. Furthermore, vitamin D topical use normalized the expression and topography pattern of integrins and other activation markers like ICAM-1, CD26 and HLA-DR, which were altered on psoriatic skin [88].

The role of VDR polymorphisms in the risk of psoriasis was studied in several populations, with contradictory results. Richetta et al. [89] showed that among 5 common VDR polymorphisms (A-1012G, FokI, BsmI, ApaI, and TaqI), the A-1021G polymorphism is associated with the risk of psoriasis in an Italian population. In another study, ApaI and a specific haplotype of 5 VDR polymorphisms were associated with the risk of psoriasis in a Chinese population [90]. In contrast, studies in Croatian and Egyptian populations did not find any role of VDR polymorphisms in psoriasis [91–93]. The meta-analysis of studies investigating the role of VDR polymorphisms in psoriasis also suggests their ethnic specific association [94, 95]. The VDR polymorphisms, besides conferring a risk of psoriasis, are also reported to modulate the response of psoriasis patients to different treatment regimens. Ryan et al. [96] showed that psoriatic patients with the VDR TaqI polymorphism had a shorter remission pe-

riod when treated with NB-UVB. Similarly, other studies suggested a positive association of wild-type alleles of A-1012G, FokI and TaqI VDR polymorphisms with topical calcipotriol response [97, 98].

Atopic Dermatitis

AD is a chronic or relapsing skin disorder caused by complex interactions between genetic, immunological, and environmental factors; it is characterized by chronic inflammation, disruption of the epithelial barrier, immunological abnormalities and increased serum IgE.

Skin Barrier Defect in AD. The epidermis of AD patients displays a significant barrier disruption and transepidermal water loss, which sensitizes AD skin to allergen penetration, bacterial, fungal, and virus invasion or colonization and inflammation. Various mechanisms are responsible for the barrier defect in AD: (1) deficiency or defects in structural proteins (like filaggrin, involucrin, loricrin, keratin K5 and K16, etc.), epidermal proteases, and protease inhibitors, (2) alteration in SC pH, and (3) decrease in skin ceramides, which supports lipid barrier and water retention [99, 100]. So far, loss of function mutation in the filaggrin gene represents the most significant genetic factor in the predisposition to AD, although only a fraction of patients (between a few and 50% depending on the populations studied) carry filaggrin mutations [101, 102].

Immune Dysregulation in AD. The immune dysregulation in AD is biphasic, with an initial Th2 phase in acute lesions, and Th0 and Th1 dominant inflammation in chronic lesions. Thus, there is an increased level of IL-4, IL-5, and IL-13 (Th2 cytokines) in the acute phase lesions, while Th1 cytokines like IFN-γ, GM-CSF, and IL-12 are predominant in the chronic disease. Th0 cells are transitory and can differentiate into Th1 or Th2 cells [99]. Beside alteration in Th cytokines, the majority of AD cases (approx. 80%) displays high serum IgE levels with specific IgEs to food allergens or aeroallergens [103]. The outcome of Th cells in AD lesions is regulated by several factors. Thymic stromal lymphopoietin secreted by keratinocytes in atopic skin primes DCs, which drives naïve Th cells towards Th2 polarization and induces production of the proallergic cytokines IL-4, IL-5, IL-13, and TNF-α [104]. The DCs observed in atopic lesions are mainly of myeloid origin and comprise 2 populations: Langerhans cells and inflammatory DCs. It was observed that Langerhans cells are involved in Th2 polarization, while inflammatory DCs promote Th1 polarization in chronic lesions [105, 106]. T_{reg} cells play an important role in AD. Many studies have shown a high T_{reg} (CD4+CD25+Foxp3+) population with normal immunosuppressive activity in the peripheral blood of AD patients, which is also found to be positively correlated with the severity of the disease [107–110]. However, when stimulated with *Staphylococcus* enterotoxin B, T_{reg} cells lost their immunosuppressive activity suggesting a mechanism of T-cell activation by *Staphylococcus aureus* in AD lesions [107, 108]. There are few contradictory reports which suggested either low frequency or absence of T_{reg} cells in the peripheral blood and in skin lesions of AD patients [111, 112].

In addition to a defective adaptive immune system, AD patients have dysfunction in various components of the innate immune system like skin barrier disruption, diminished recruitment of innate immune cells (NK cells, pDCs, neutrophils) to the skin, TLR2 defects and reduced secretion of AMPs [113, 114].

Role of Vitamin D in AD

The effect of vitamin D levels on the prevalence and severity of AD was the subject of a large number of studies which yielded heterogeneous results. Epidemiological studies have shown an increased AD prevalence in populations living in higher geographic latitudes, with lower sun exposure and consequently less vitamin D production [115, 116]. Also, in large population-based studies, it was observed that there is an increased likelihood of developing AD in individuals with either deficient or insufficient vitamin D levels [117, 118]. Many observational studies including a meta-analysis have shown that the serum vitamin D level is lower in children and adults with AD compared to controls, and reported an association between vitamin D deficiency and risk of atopic eczema [119–121]. Also, the severity of AD was found to be negatively correlated with the vitamin D level, with moderate and severe AD groups having lower vitamin D levels compared to the mild AD group; this finding was supported by the use of objective tools, such as the SCORAD (Scoring Atopic Dermatitis) index, which was found to be inversely correlated with vitamin D levels in AD patients [120–123]. However, there are some contradictory reports, which suggest either no role of vitamin D or a positive association of vitamin D levels with the risk of developing AD [124, 125]. The maternal vitamin D level seems also to impact the risk of developing AD in infants: while 2 studies suggested that a higher maternal intake of vitamin D could increase the risk of infantile eczema [126, 127], others observed that a lower vitamin D level during pregnancy induced a risk of AD in infants during early years of their life [128]. Studies on the association of cord

serum 25(OH)D levels with infant AD are also contradictory [129–131]. The common polymorphisms in VDR and vitamin D-metabolizing genes have been investigated for their role in AD susceptibility. The VDR BsmI polymorphism increased the risk of AD in a Turkish population, and a specific haplotype of VDR BsmI, ApaI, and TaqI polymorphisms was overrepresented in severe AD patients in a German population [132, 133]. In another report, among 6 common polymorphisms in CYP24A1 and CYP27B1, CYP24A1rs2248359C allele and a specific haplotype were associated with an increased risk of severe AD [134].

As the majority of the literature suggests vitamin D deficiency as prominent risk factor of AD, studies have been carried out to examine the effect of vitamin D supplementation on phenotypes of AD. Many clinical trials including their meta-analysis have shown that vitamin D supplementation results in significant improvement in AD severity (measured by SCORAD and Eczema Area and Severity Index) [121, 135–138]. Di Filippo et al. [138] suggested that vitamin D supplementation exerts its positive effect on AD by normalizing the altered Th1 and Th2 cytokines like IL-2, IL-4, IL-6, and IFN-γ in AD patients. In another study, Drozdenko et al. [139] showed that the oral intake of vitamin D increases the frequencies of CD38+ B cells to enhance the B-cell receptor-mediated response and decreases the IFN-γ and IL-17 T-cell cytokine response in vitamin D-deficient individuals. Additionally UVA and UVB phototherapy is widely used in AD treatment because of its effects in the T cell-mediated immune response, and it is suggested that the beneficial effect of UVA/UVB phototherapy is also mediated by the correction of the vitamin D deficiency or insufficiency in AD patients [72]. An increased IgE response to common environmental and food allergens is a common feature in AD. It was found that vitamin D has an inhibitory effect on the allergic response: treatment of vitamin D suppressed the IgE production by human B cells and dampened IgE-mediated mast cell activation in both in vitro and in vivo settings [140]. Other than the effect on the adaptive immune system, vitamin D supplementation ameliorates the AD lesions by restoring the epidermal barrier defects and correcting the deregulated innate immune response. In fact, Kanda et al. [141] observed that a low serum vitamin D_3 level correlated with low serum LL-37 in AD patients. Also, the topical application and oral supplementation of vitamin D upregulated the expression of LL-37 in lesional and nonlesional skin in AD patients [114, 142]. More recently, a clinical improvement, assessed by a lower AD severity score, was noted in AD patients, concomitantly to the increase in the LL-37 level, after vitamin D supplementation [143]. Büchau et al. [144] suggested that the positive effect of vitamin D on AMPs could be mediated by the inhibition of the expression of Bcl-3, which is upregulated in AD lesions causing a reduced expression of cathelicidin. AD patients are susceptible to the skin colonization and infection by *S. aureus*, which through the production of exotoxins with supra-antigenic properties aggravates the disease. Gilaberte et al. [145] have observed a significant association between low serum vitamin D levels and certain virulence genes of *S. aureus* in isolates of AD children suggesting some role of vitamin D deficiency in *S. aureus* colonization. Thus, vitamin D supplementation could be promising in reducing the cutaneous *S. aureus* burden in AD patients. In fact, a recent clinical trial showed a reduction in the skin colonization by *S. aureus* and an improvement in clinical symptoms of AD patients, who received an oral supplementation of 2,000 IUs of vitamin D daily for 4 weeks [146].

AD patients are also prone to skin infections caused by herpes virus; this complication, known as eczema herpeticum, is particularly common in AD children and could be life threatening. It has been demonstrated that LL-37 is by far less expressed in skin of AD complicated by eczema herpeticum compared to skin of patients with uncomplicated AD [147]. Treatment by vitamin D has a beneficial effect in children with eczema herpeticum, and this effect seems to be mediated by an increase in the LL-37 level in the skin [143].

Studies addressing the relationship between vitamin D and AD could be hampered by the geographic, seasonal and diet-related vitamin D variations in AD patients and healthy controls, and despite the myriad of studies advocating the important role of vitamin D in AD, the relationship could not be stated with certainty. Animal studies evaluating the effect of vitamin D in AD are not consistent either and yielded conflictual findings: some studies showed an induction of thymic stromal lymphopoietin with topical application of calcitriol or its low calcemic analog MC903, which resulted in AD- like syndrome in mice [148, 149]. However, in an allergen-induced animal model of AD, systemic administration of a low calcemic vitamin D agonist significantly improved the symptoms of atopic eczema by restoring the epidermal barrier and modulating the immune system [150]. It was also observed that administration of a VDR agonist to allergen-induced AD mice selectively increased the frequency of Foxp3+ T_{reg} cells, reduced the expression of IL-4 in a lesional skin model, and induced a significant

improvement in barrier function through robust induction of several skin barrier genes (like loricrin, involucrin, filaggrin, and transglutaminase) and AMP β-defensin.

Conclusion

Beyond the classical phosphocalcic effect of vitamin D, its role in the proper functioning of several tissues/organs including the skin has been receiving a growing interest. Vitamin D exhibits a pleiotropic effect in the skin with its role as antiproliferative, prodifferentiative, antiapoptotic and immunomodulator. It is also intricately involved in many skin pathologies, and it positively influences the outcome of certain inflammatory dermopathologies. So far, therapeutic interventions (topical and systemic) based on vitamin D have been proved beneficial in psoriasis and AD. Future studies are needed to mechanistically and intensely explore the specific pathways affected by vitamin D using the latest advanced technologies and to assess the safety and efficacy of vitamin D-based treatment regimens in various inflammatory skin diseases.

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Disclosure Statement

The authors declare that there is no conflict of interest.

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