

Vitamin D and Skin: An Review and Update

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Abstract

Vitamin D was recognized for its pivotal role in bone formation, but it is now recognized for its impact on the optimal functioning of various tissues throughout the body, including the brain, heart, muscles, immune system, and skin.¹ Vitamin D is a fat-soluble prohormone steroid with endocrine, paracrine, and autocrine functions. Vitamin D receptors and the enzymes that can convert 25-hydroxyvitamin D [25(OH)D] into the active form, 1,25-hydroxyvitamin D [1,25(OH)D], have been identified in numerous cells throughout the body, including the skin.² Vitamin D analogs are widely acknowledged for effective treatment of psoriasis vulgaris due to their anti-proliferative and pro-differentiating impact on keratinocytes.³ Beyond this, emerging roles for vitamin D in skin health include immunomodulatory and anti-apoptotic effects, suggesting potential applications in conditions like atopic dermatitis and infections including verucca vulgaris.³ Epidemiological studies have linked low vitamin D levels to autoimmune diseases like vitiligo, leading to the use of topical vitamin D in its treatment.³ Recent evidence also suggests that cutaneous vitamin D synthesis may contribute to preventing skin malignancies, and oral supplementation may reduce cancer mortality. Its role in the pathogenesis of various dermatological diseases has not been an exception and has been extensively studied in recent years. In this review, we will shed light on roles of vitamin D in various skin disorders.

Key words: Immunotherapy, Recalcitrant, Vitamin D, Warts

Introduction

Adequate exposure to sunlight and a diet abundant in oily fish and fortified milk act as primary sources of vitamin D for humans.³ Vitamin D plays an important role in regulating parathyroid hormone (PTH) as well as the metabolism of calcium and phosphorous, thereby significantly influencing the integrity of the skeletal system.⁴ The identification of vitamin D receptors (VDRs) in numerous body cells and the presence of enzymes synthesizing the active form of vitamin D, namely 1,25-dihydroxyvitamin D [1,25(OH) 2D], not only in the kidneys but also in non-renal sites like the skin, have sparked renewed interest in their functions. This interest is particularly focused on its role in diminishing the risk of various chronic and debilitating conditions, including carcinomas, autoimmune diseases, infectious

diseases, and cardiovascular diseases.⁵

The synthesis of vitamin D in the skin and its significance in treating prevalent skin conditions such as psoriasis have made it a subject of interest for dermatologists. Research indicating vitamin D's role as an immunomodulator has paved the way to explore its therapeutic potential in conditions like atopic dermatitis, psoriasis, verruca vulgaris and skin cancer.^{3,4}

Cutaneous biosynthesis of vitamin D3

In both epidermal basal and suprabasal keratinocytes, as well as dermal fibroblasts, the precursor 7-dehydrocholesterol is present in the plasma membranes and undergoes conversion to previtamin D.³ The synthesized vitamin D3 in the skin is then released from the plasma membrane and enters the

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systemic circulation, binding to vitamin D-binding protein (DBP).⁶ Following exposure to UV radiation, serum concentrations of vitamin D3 reach their peak within 24–48 hours. Subsequently, vitamin D3 levels experience an exponential decline, with a serum half-life ranging from 36 to 78 hours. Being a lipid-soluble molecule, vitamin D3 can be taken up by adipocytes, where it is stored in subcutaneous or omental fat for later use.^{1,6}

Vitamin D, once in the bloodstream, undergoes conversion by hepatic hydroxylase, leading to the formation of 25-hydroxyvitamin D (25(OH)D, or calcidiol). The circulating level of 25(OH)D serves as an indicator of an individual's vitamin D status, reflecting both ultraviolet exposure and dietary vitamin D intake, with a serum half-life of approximately 15 days, 25(OH)D remains biologically inactive except at exceptionally high, non-physiological levels. As necessary, 25(OH)D is transformed into its active hormonal form, 1,25-dihydroxyvitamin D (1,25(OH)2D or calcitriol), within the kidneys. This conversion process is typically tightly regulated by parathyroid hormone, whose levels begin to rise when 25(OH)D drops to cutoff levels of 75 nmol/L or lower.⁴ Despite this regulation, insufficient vitamin D supply can result in a decrease in circulating calcitriol levels. Circulating calcitriol is further influenced negatively by factors such as a reduced number of viable nephrons, high serum concentrations of fibroblast growth factor-23, and elevated levels of inflammatory cytokines, including interleukin-1, interleukin-6, and tumor necrosis factor- α (TNF- α).^{1,5}

Effects of calcitriol on cutaneous biology

Both calcium and 1,25(OH)2D play crucial and interconnected roles in regulating the skin differentiation process. 1,25(OH)2D enhances the expression of key proteins like involucrin, transglutaminase, loricrin, and filaggrin, promoting the formation of keratinocyte cornified envelopes while inhibiting proliferation.⁷ These effects are, in part, attributed to the ability of 1,25(OH)2D to elevate intracellular calcium levels through the induction of the calcium receptor and phospholipase C.⁸ These molecular events are essential for calcium's stimulatory impact on keratinocyte differentiation. Mice lacking the vitamin D receptor (VDR) exhibit defective epidermal differentiation, characterized by reduced levels of involucrin and loricrin, along with the loss of keratohyaline granules.⁹

Vitamin D and Cutaneous Adaptive Immunity

Vitamin D interacts with our immune system by using special receptors called vitamin D receptors (VDR) found in T and B cells.¹ These receptors are most active when the cells are actively growing, suggesting that vitamin D may slow down their growth. One important type of immune cell, called T helper (Th) cells, is a main focus.¹⁰ Vitamin D can reduce their

growth and influence the production of different signals, affecting Th cells that support either cell-mediated immunity (Th1) or humoral immunity (Th2). 1,25(OH)2D suppresses Th1 cytokines and encourages the production of Th2 cytokines.¹⁰ Another subset of Th cells affected by vitamin D is the group of T cells that secrete interleukin-17 (IL-17), known as Th17 cells.¹¹

Vitamin D and Innate Immunity

The innate immune system of the skin includes protective structures such as the stratum corneum (SC), immune cells (including neutrophils, monocytes, macrophages, dendritic cells, natural killer cells, etc.), and antimicrobial peptides (AMPs).¹²

Cathelicidin and β -defensin are directly controlled by vitamin D, where cathelicidin is activated by the binding of the 1,25(OH)2D-VDR complex to the VDRE in the gene's promoter region. In contrast, β -defensin necessitates the presence of nuclear factor κ B in addition to the 1,25(OH)2D-VDR complex for its transcription [14]. Beyond direct transcriptional activation, vitamin D is known to regulate the synthesis of AMP through mechanisms other than transcription.^{12,13}

Additionally, they stimulate toll-like receptor 2 (TLR2) and its coreceptor CD14, initiating the innate immune response in the skin.¹⁴ Activation of these receptors induces the expression of CYP27B1, leading to the production of cathelicidin and enhancing the skin's ability to eliminate invasive organisms.^{12,14} Likewise, numerous studies have demonstrated elevated levels of hCAP18/LL-37 and defensin following treatment with 1,25(OH)2D3 in both keratinocytes and sebocytes.¹²

The sebaceous gland

Researchers have found that the internal production or alteration of vitamin D substances in sebaceous glands could play a significant role in regulating growth and various cellular functions. Sebaceous glands represent promising targets for therapy with vitamin D analogs or for pharmacological modulation of calcitriol synthesis and metabolism.¹⁵

Vitamin D and Hair Follicle Cycle

Studies have shown that the vitamin D receptor (VDR) might be crucial for keeping hair follicles healthy after birth.¹ Cells in the mesodermal papilla and the outer root sheath (ORS) of the epidermis show varying levels of VDR expression, and this varies depending on the stage of the hair growth cycle.¹⁶ When the hair is in the late anagen and catagen stages, there's an increase in VDR, which is linked with decreased proliferation and increased differentiation of the keratinocytes, which is believed to support the natural progression of the hair growth cycle.¹⁷ Limited human studies have delved into vitamin D's role in the hair cycle, with a potential application identified in preventing chemotherapy-induced alopecia. Topical calcitriol has shown protective effects against alopecia induced by

paclitaxel and cyclophosphamide. However, it proved ineffective against alopecia caused by combinations of 5-fluorouracil, doxorubicin, and cyclophosphamide, as well as cyclophosphamide, methotrexate, and 5-fluorouracil.¹⁷

Cutaneous Antimicrobial Effect on Vitamin D

The active form of vitamin D, 1,25(OH)₂D, along with its receptor, plays a crucial role in regulating the processing of long-chain glycosylceramides, essential for the formation of the skin barrier, which is vital for skin defense.¹⁸ Additionally, they stimulate toll-like receptor 2 (TLR2) and its coreceptor CD14, initiating the innate immune response in the skin. Activation of these receptors induces the expression of CYP27B1, leading to the production of cathelicidin and enhancing the skin's ability to eliminate invasive organisms. Mice lacking the vitamin D receptor (VDR) or the enzyme CYP27B1 exhibit decreased lipid content in lamellar bodies, resulting in a compromised permeability barrier and an impaired response of the innate immune system to invading infections.¹⁹

Role of vitamin D in Inflammatory Skin Disease

1. Vitamin D and Atopic Dermatitis:

Atopic dermatitis (AD) is a common chronic inflammatory type of eczema.¹ The pathogenesis of AD involves a complex interplay of epidermal barrier dysfunction and dysregulated immune response.²⁰ As vitamin D is involved in both processes, it could be associated with the risk or severity of atopic dermatitis.²¹

In a study by Oren et al. (2008), involving 290 obese patients, those with a deficiency in vitamin D were found to be five times more likely to have AD compared to the group with sufficient vitamin D.²²

Another study by Peroni et al. (2011) involved 37 children with AD and found that the levels of 25(OH)D in the blood were higher in patients with mild AD than in those with moderate or severe cases suggesting that vitamin D deficiency may be related to the severity of AD.²³

While some studies suggest a positive link between low vitamin D levels and a higher prevalence or severity of atopic dermatitis, it's essential to acknowledge controversies in the findings. Back et al. (2009) found an unexpected inverse association, which indicated that increased vitamin D intake during childhood correlated with an increased risk of AD at the age of 6. They collected data on vitamin D₃ intake in the first year of life and investigated the cumulative incidence of AD, allergic rhinitis, or asthma at 6 years in 123 children through a postal questionnaire. Interestingly, AD was more prevalent in the group with the highest vitamin D₃ intake, irrespective of family history of atopy.²⁴

Various theories have been proposed that show the role of vitamin D supplementation in atopic dermatitis (AD). These include the restoration of normal levels of

IL-2, IL-4, IL-6, and IFN- γ , the suppression of allergic responses by reducing IgE production, the correction of the barrier defect, and the enhanced production of antimicrobial peptides like LL-37.²⁵

In a study involving 14 patients with moderate to severe atopic dermatitis who were given a daily dose of 4,000 IU of vitamin D₃ for 21 days, the examined skin biopsies from affected areas revealed a notable rise in the expression of cathelicidin.²⁶

In a double-blind randomized controlled trial involving children with atopic dermatitis, mainly of mild severity, a regimen of 1,000 IU/day of vitamin D was administered for one month during the winter. Among the participants, five received vitamin D supplementation, while six received a placebo. It revealed a significant improvement in the baseline score for the vitamin D treatment group compared to the placebo group.²⁷

The result of these studies indicates the therapeutic role of vitamin D with a good safety profile. However, further studies, including larger sample sizes and longer durations may be required to fully assess the therapeutic effect of vitamin D in atopic dermatitis.¹

2. Vitamin D and Psoriasis Vulgaris :

Psoriasis is a chronic autoimmune inflammatory skin disease characterized by abnormal proliferation and differentiation of keratinocytes and erythematous skin plaques covered by a silvery scale with a prevalence of 2-3%.¹

The precise mechanism of psoriasis is not entirely clear. It is established that psoriatic skin lesions arise from an immune system imbalance leading to the release of pro-inflammatory mediators, which in turn trigger an inflammatory response through the release of cytokines, resulting in the uncontrolled growth of keratinocytes. Along with this researchers have proposed the likely role of both genetic and non-genetic factors, including factors like obesity, alcohol consumption, smoking and hypovitamin D in the pathogenesis of psoriasis.²⁸

Multiple pathways have been identified, including the loss of the anti-proliferative function of vitamin D. Since 1 α ,25-dihydroxyvitamin D₃ is recognized for suppressing the proliferation of Th1 and Th17 cells and inducing Tregs, another suggested pathway linking vitamin D deficiency to the psoriatic condition involves the uncontrolled increase in Th1 and Th17 cells, paired with uncontrolled inhibition of Tregs.¹⁰

Similarly, the use of calcipotriol in topical treatment has been demonstrated to notably reduce the levels of human beta defensins (HBD) 2 and HBD3, along with IL-17A, IL-17F, and IL-8, all of which play crucial roles in psoriasis. This provides additional evidence linking vitamin D deficiency to the development of psoriasis.¹ Marino et al. referred to a study that examined the effects of 60,000 IU oral vitamin D in 45 patients compared to a placebo over a period of six months.

The findings revealed an elevation in serum vitamin D levels and reductions in the Psoriasis Area and Severity Index (PASI).²⁹

In another study, Barrea et al. proposed that daily intakes of oral vitamin D up to 10,000 IU were not linked to adverse effects, aligning with the maximum cutaneous vitamin D production. and no study had reported vitamin D intoxication solely from skin synthesis. While specific details about the doses and durations of vitamin D administration were not provided, the study showed clinical improvement in the Psoriasis Area and Severity Index (PASI) score for 88% of patients, and the other reported moderate or better improvements in 25–50% of patients with psoriasis.³⁰

McCullough et al. demonstrated significant clinical benefits in psoriasis, with doses ranging from 25,000 IU/day to 60,000 IU/day, without the emergence of toxicity or hypercalcemia. However, another study showed that the oral administration of 10,000 IU/day to 25,000 IU/day of vitamin D is considered safe for the general population.³¹

The positive effects of sunlight-induced vitamin D exposure in treating psoriasis have been recognized for many years. The efficacy of vitamin D and its derivatives (such as calcitriol, calcipotriol, tacalcitol, hexafluoro-1,25(OH)₂D, and maxacalcitol) for psoriasis treatment has been established since 1985 and has been reaffirmed through numerous trials.³²

Vitamin D therapy, particularly the use of topical medications, is commonly prescribed as one of the first-line treatments for psoriasis. It is often recommended, either alone or in conjunction with topical corticosteroids. Numerous studies have provided evidence supporting the effectiveness and safety of employing topical calcipotriol in the treatment of localized plaque psoriasis.³⁰

The US Food and Drug Administration (FDA) has approved topical calcitriol for the treatment of psoriasis due to its minimal impact on serum calcium levels. Numerous studies have documented the effectiveness and safety of various vitamin D analogs, including calcitriol, calcipotriol, tacalcitol, hexafluoro-1,25-dihydroxyvitamin D₃, and maxacalcitol, in the topical treatment of psoriasis.¹

In a prospective clinical trial involving patients with chronic plaque psoriasis (N = 257) treated for a duration of three months and up to a maximum of 18 months, the average Psoriasis Area Severity Index (PASI) score exhibited a significant reduction. Specifically, during the initial three months of active treatment with calcitriol ointment applied twice daily, the mean PASI score decreased by 53%, dropping from 9.71 at the baseline to 4.24. No statistically significant differences or clinically meaningful changes were noted in any laboratory values, including calcium and phosphorus, when comparing baseline to post-treatment measurements.³³

In another clinical trial, the cutaneous safety and efficacy of calcitriol (3µg/g) ointment and calcipotriene (50µg/g) ointment were compared in 75 patients with mild-to-moderate chronic plaque psoriasis affecting sensitive skin areas like the face, hairline, retroauricular folds, and flexural areas. Calcitriol demonstrated a significantly greater improvement compared to calcipotriene and Tolerability ratings were excellent for 80% of patients (24 out of 30) with flexural lesions treated with calcitriol, compared to 57% (17 out of 30) for those treated with calcipotriene.³⁴

A different study compared calcitriol (3µg/g) ointment with a high-potency topical corticosteroid, betamethasone dipropionate (0.05%) ointment, for six weeks. In the calcitriol group, the mean Psoriasis Area Severity Index (PASI) score decreased from 15.7 at baseline to 5.4 after six weeks, while in the betamethasone dipropionate group, it decreased from 15.02 to 3.67 over the same period. The calcitriol group exhibited a remission rate nearly twice as high as the betamethasone dipropionate group upon discontinuation of treatment.³⁵

In another study involving patients with moderate-to-severe chronic plaque psoriasis, the efficacy and safety of UVB phototherapy in combination with calcitriol ointment were compared to UVB phototherapy alone. Participants applied either calcitriol (3µg/g) ointment or a vehicle ointment twice daily for up to eight weeks, and all subjects underwent a maximum of 24 UVB sessions. The improvement or clearance of chronic plaque psoriasis (CPP) was reported in 45% of subjects who received UVB and calcitriol, compared to 20% of subjects who received UVB alone. Both treatments were well tolerated; however, the calcitriol group experienced 34% less UVB radiation exposure compared to subjects in the vehicle group, thus reducing the carcinogenic risks associated with UV irradiation.³⁶

Vitamin D analogs are now acknowledged as both effective and safe for treating challenging and slow-responding skin areas. They demonstrate a lack of tachyphylaxis, allowing for the indefinite continuation of topical treatment.¹ Additionally, they have proven effective in treating psoriatic skin lesions in children and HIV patients. The absence of skin atrophy or adrenal suppression further supports their inclusion in the therapeutic options for psoriasis.³⁷

3. Vitamin D and verruca

Cutaneous warts, which are benign epidermal proliferations, result from a human papillomavirus (HPV) infection. They can be classified into various types, including common warts (verruca vulgaris), plantar warts (verruca plantaris), and flat warts (verruca plana).³⁸ Using Vitamin D to treat warts is a new and innovative method that avoids the side effects associated with other common treatments. The simplicity, safety, and effectiveness of this approach

make it a promising option for dealing with a common skin condition.³⁹ Intralesional vitamin have proven to be both safe and effective, while only a limited number of studies have indicated the effectiveness of applying vitamin D derivatives topically.⁴⁰

Imagawa and Suzuki initially achieved success in treating refractory warts in 17 patients using topical vitamin D3 (maxacalcitol). For all of the patients, the warts disappeared.³⁸

In a randomized controlled trial, the calcipotriol group received calcipotriol 0.05% ointment twice daily, while the control group received a placebo for two months, extendable for an additional two months if resolution did not occur. Initially, the mean number and size of lesions were similar between groups, but by the 1st, 2nd, and 4th months, both parameters were significantly lower in the calcipotriol group. Moreover, the calcipotriol group exhibited a significantly higher rate of complete response to treatment.⁴⁰

Another study with 42 patients experiencing multiple cutaneous warts demonstrated a complete response in 78.8 percent of patients treated with intralesional vitamin D3.⁴¹

In a study involving 64 patients with recurrent warts, injections of 0.2–0.5 mL at a concentration of 15 mg/mL were administered at 3-week intervals. Ninety percent of the patients reported a complete resolution after 15 weeks.⁴²

In a separate study, 20 patients received injections of 7.5 mg/mL of vitamin D with 0.1 mL of 20 mg/mL prilocaine. After eight weeks, 80 percent of the patients showed a complete response with no signs of recurrence or adverse side effects.⁴³

4. Vitamin D and Alopecia

Vitamin D plays a crucial role in the signaling pathways that regulate the growth and differentiation of hair follicles. The majority of studies indicate a negative correlation between serum vitamin D levels and non-scarring forms of hair loss, including telogen effluvium, androgenetic alopecia, alopecia areata, and trichotillomania.⁴⁴

A hospital-based cross-sectional study revealed that individuals with alopecia areata (AA) had lower levels of 25(OH)D compared to healthy controls. Furthermore, an inverse correlation was observed between serum vitamin D levels and the severity of AA, suggesting a potential role of vitamin D in the onset of AA. This proposes the potential use of vitamin D supplementation as a treatment strategy for this condition.窗体底端

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D supplementation as a treatment strategy for this condition.⁴⁵

In another study involving 187 participants, the first group comprised 58 patients diagnosed with androgenic alopecia, the second group had 71 patients with telogen effluvium, and the control group included 58 healthy volunteers. When comparing the vitamin D levels of the androgenic alopecia group (AA) with both the telogen effluvium group (TE) and the control group, a statistically significant difference was observed. However, there was no statistically significant difference between the vitamin D levels of the telogen effluvium group (TE) and those of the healthy control group. This study concluded that there were higher levels of 25'(OH) vitamin D in the androgenic alopecia group than in the telogen effluvium and control groups. Understanding the relationship between Vitamin D levels and hair loss may open up new treatment options, especially for refractory patients.⁴⁶

There is still a lack of conclusive studies demonstrating the effectiveness of vitamin D in treating hair loss, and more research is needed before it can be consistently recommended as a treatment for these conditions.⁴⁵

5. Vitamin D and Vitiligo:

Vitiligo is a prevalent pigmentary disorder resulting from the destruction of functional melanocytes. Vitamin D, a crucial hormone synthesized in the skin, plays a role in skin pigmentation.⁴⁷

Vitiligo patients, as well as those with other autoimmune diseases, display reduced vitamin D levels. Hence, further investigation is necessary to thoroughly explore the connection between vitamin D and vitiligo.⁴⁷

Tomita et al. demonstrated that vitamin D3 elevated the tyrosinase content in cultured human melanocytes (in vitro).⁴⁸

Another study revealed that the combination of vitamin D and UVB irradiation promoted the proliferation of melanocytes, suggesting potential effectiveness in the treatment of vitiligo.⁴⁹

Parsad et al. were the first to report the use of vitamin D analogues in combination with PUVAol and topical calcipotriol for the treatment of vitiligo.⁵⁰

6. Vitamin D and Rosacea:

Rosacea is a persistent inflammatory skin condition identified by various features, including transient erythema (flushing), persistent erythema, papules, pustules, and telangiectasia on the face.¹

In a case-control study, 50 patients with rosacea were compared to 50 age- and gender-matched healthy controls, and measurements of serum vitamin D levels in both the rosacea group and the control group were done. The results were statistically compared, which indicated that serum vitamin D levels in patients with rosacea were significantly higher than those in the

control group.⁵¹

A similar study with 44 rosacea patients and 32 healthy controls, showed that the average serum vitamin D levels were significantly higher in the rosacea group compared to the control group. The study suggests that increased vitamin D levels could potentially be a risk factor for developing rosacea.⁵²

Studies have shown increased basal levels of cathelicidin, an antimicrobial peptide (AMP), and

kallikrein 5 (KLK 5), a serine protease that converts cathelicidin into its active form (LL-37), in individuals with rosacea.⁵³

Keratinocytes respond strongly to vitamin D, inducing the expression of cathelicidin, and UV light, a known trigger for rosacea. Novel therapeutic approaches might target the inhibition of cathelicidin expression through modulation of the vitamin D pathway.⁵¹

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