

# Vitamin D and autoimmune dermatoses: A review

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## Abstract

Historically, vitamin D was associated with rickets and osteomalacia. Recent evidence demonstrates that vitamin D is crucial in influencing general health and the immune system. Vitamin D has been associated as a natural immunomodulator through its strong association between vitamin D signaling and immune response regulation, both cellular and humoral. The hypothesis of a disease-specific alteration of vitamin D metabolism, including various autoimmune diseases, further reinforces vitamin D's role in maintaining a balanced immune system. The pathogenesis of many skin diseases, specifically autoimmune dermatoses, is also associated with disturbance in immune system regulation. Administration of vitamin D or its analogues is the therapeutic choice for the treatment of several skin diseases. This review summarizes recent epidemiological and experimental studies on vitamin D involvement in autoimmune dermatoses, specifically psoriasis, autoimmune bullous disease (pemphigus vulgaris and bullous pemphigoid), and vitiligo.

## Key words

Vitamin D, vitamin D receptor, psoriasis, autoimmune bullous, vitiligo.

## Introduction

The mosaic of autoimmunity is a complex interaction among endogenous and exogenous elements consisting of genetic, hormonal, and environmental ones, of which vitamin D has been identified as both an exogenous and endogenous contributor.<sup>1</sup> Vitamin D, also referred to as the sunshine vitamin, is available in two distinct forms, ergocalciferol (vitamin D<sub>2</sub>) and cholecalciferol (vitamin D<sub>3</sub>). Previtamin D<sub>3</sub> is an intermediate in the production of Vitamin D<sub>3</sub>.<sup>2</sup> Vitamin D is fat-soluble vitamin obtained from exogenous and endogenous sources; exogenously, the primary dietary source of

vitamin D is primarily present in foods of animal origin, while endogenously, most vitamin D is obtained from ultraviolet radiation (UVR) exposure of the skin, and more, specifically UVB.<sup>2-4</sup>

Following the syntheses or consumption of vitamin D, it is converted *in vivo* into biologically active metabolites, namely 25(OH)D and 1, 25(OH)<sub>2</sub>D. The latter regulate numerous functions in various cell types through binding to vitamin D receptors (VDR), a nuclear hormone receptor superfamily member expressed universally in nucleated cells. Vitamin D functions as a hormone and regulates parathyroid hormone (PTH), calcium and phosphorus metabolism implicating its role in the integrity of the skeletal system and calcium homeostasis.<sup>5</sup> However, upon activation of VDRs, the mechanism is not only limited to calcium metabolism but also elicits a wide variety of biological responses influencing cellular growth, proliferation, apoptosis, and

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immunomodulatory responses.<sup>1,6</sup> For immunomodulatory response, via VDR (a key transcription factor in the differentiation process of myeloid progenitors into monocytes and granulocytes), vitamin D modulates the activity of the immune system, both innate and adaptive immune systems.<sup>7</sup>

The cutaneous synthesis of vitamin D and its role in certain skin disorders through its immunomodulatory properties has made it an engaging topic for dermatologists. Research pointing to vitamin D's role as an immunomodulator has paved the way for further research into its role and therapeutic effects in allergic and autoimmune disorders, such as systemic lupus erythematosus, Sjogren syndrome, rheumatoid arthritis, multiple sclerosis, type 1 diabetes mellitus, and antiphospholipid syndrome.<sup>8</sup> In particular, vitamin D has several effects on the skin, such as keratinocyte stimulation and apoptosis, skin immune system, and a barrier function.<sup>9,10</sup>

This review article aims to provide a concise understanding of the role of vitamin D in autoimmune dermatoses, such as psoriasis, autoimmune bullous disease (pemphigus vulgaris and bullous pemphigoid), and vitiligo.

### **The Cutaneous Biosynthesis Pathway of Vitamin D**

The skin is unique in that it may respond to the active metabolite of vitamin D, 1, 25(OH)<sub>2</sub>D, as well as being a source of vitamin D for the body. Both 1, 25(OH)<sub>2</sub>D and VDR play an essential role in the skin.<sup>11</sup> Keratinocyte, a primary functional cell of the skin, actively participated in vitamin D metabolism, ensuring the action of vitamin D through an autocrine/ paracrine manner. They synthesize vitamin D from 7-dehydrocholesterol (7-DHC) and express

CYP27A1 and CYP27B1 for activation of vitamin D to produce 1, 25(OH)<sub>2</sub>D.<sup>12</sup>

### *Effects of Vitamin D on the Immune System*

The immunomodulatory role of vitamin D on cells of the innate and adaptive immune system has been extensively investigated. From an innate immune system's perspective, e.g., neutrophils and macrophages (as the two critical cells in clearing pathogens through their phagocytic action) have shown a correlation with vitamin D.<sup>13</sup> Neutrophils express VDR mRNA to a similar extent to monocytes, and also induce expression of CD14 and CAMP in the presence of 1, 25(OH)<sub>2</sub>D.<sup>14</sup> 1, 25(OH)<sub>2</sub>D has also been observed to reduce bystander destruction of the pro-inflammatory response through the reduction of Trappin-2/elafin/skin-derived anti-leucoproteinase expression and neutrophil migration. Vitamin D has also been shown to reduce neutrophil extracellular traps (NETs) formation, subsequently reducing the response against invading pathogens and the risk of autoimmunity.<sup>15</sup>

Vitamin D was shown to be essential for physiological macrophage function, where insufficiency was linked to impairment in chemotaxis, phagocytosis, and an increase in monocyte toll-like receptors, which are known inflammatory inducers.<sup>16</sup> It is also believed that the local production of 1, 25(OH)<sub>2</sub>D exerts a protective effect during infection through the upregulation of cathelicidin and human  $\beta$ -defensin (HBD)2 in phagocytes (monocytes/macrophages) and various human cell lines (keratinocytes, myeloid cells, and neutrophils).<sup>13,17</sup>

In terms of adaptive immunity, VDR expression by B- and T cells are deficient in resting conditions but shifted to a high expression of VDR expression upon expression, allowing

regulation of 500 vitamin D responsive genes influencing the differentiation and proliferation of these cells.<sup>18</sup> In B cells, several noted effects of calcitriol are: 1) antiproliferative effects (such as the inhibition of differentiation, proliferation, initiation of apoptosis, and decreased immunoglobulin production), 2) inhibition of memory- and plasma cell generation, and 3) anti-inflammatory immune regulation.<sup>19</sup> Notably, this regulation on B cell activation and proliferation may be physiologically essential in autoimmune diseases as B-cells that produce autoreactive antibodies play a crucial part in the pathogenesis of autoimmunity.<sup>18</sup>

The other primary type of adaptive immune cells, T cells, has also been shown to be modulated by vitamin D. 1, 25(OH)<sub>2</sub>D acts as a regulator of mature T cells by altering the balance between T helper (Th)1 and Th2 cell differentiation through the suppression of immune responses mediated by Th1.<sup>16</sup> In specific, treatment of T cells with vitamin D showed repression of pro-inflammatory Th1 secretion (interleukin [IL]-2, interferon [IFN]- $\gamma$ , and tumor necrosis factor (TNF)- $\alpha$ ) and promoting the shift to an anti-inflammatory Th2 cytokines (IL-3, IL-4, IL-5, and IL-10).<sup>16, 18, 20</sup> Additionally, 1, 25(OH)<sub>2</sub>D increases lymphocyte-homing capacity in the skin through the increment of CC-chemokine receptor (CCR)10.<sup>12</sup>

Furthermore, Th17 cells, secreting IL-17, exert anti- and pro-inflammatory effects by binding to IL-17 receptor, and IL-17 suppresses CD4+ T cell development into Th1 cells and plays a role in the control of immunological activity.<sup>21</sup> Similar to Th1, the long-term presence of Th17 cells in a tissue can lead to tissue destruction due to its pro-inflammatory effects and the recruitment of neutrophils to the tissue site. Recent evidence has suggested that Th17 cells may play an essential role in autoimmune

disorders and inflammation.<sup>22</sup> Addition of 1, 25(OH)<sub>2</sub>D *in vitro* inhibits IL-17 production and reduces the production of IL-17.<sup>23</sup> This is achieved through blockade of NFAT and Runx1 binding to the IL-17 promoter and induction of Foxp3 as well as through the inhibition of the transcription factor ROR $\gamma$ t, which is required for the differentiation of Th17 cells.<sup>20,24</sup>

#### *Vitamin D and Autoimmunity*

Autoimmune diseases are characterized by self-tissue destruction via the adaptive immune responses evading the immune regulation. As described above, vitamin D has been defined as a natural immunomodulator. Vitamin D regulates the balance of Th1/Th2, limiting the development of self-reactive T cells.<sup>25</sup>

#### *Vitamin D and Psoriasis*

Psoriasis is a chronic immune-mediated skin disease characterized by an erythematous pruritic plaque with thick silvery scales due to the high proliferation rate of keratinocytes.<sup>26</sup> Plaque psoriasis is the most common variant, contributing to more than 80% of the psoriasis cases with other morphologic variants of psoriasis, including guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis. The pathogenesis of psoriasis involves primarily an inflammatory focus mediated by the Th17 cells pathway.<sup>27</sup> For mild cases of psoriasis, the first-line therapy is topical corticosteroids and/or topical vitamin D<sub>3</sub> and analogues.<sup>26,27</sup>

The therapeutic effect of topical vitamin D is achieved through VDR mediated genomic mechanism inhibiting keratinocyte hyperproliferation.<sup>28</sup> 1, 25(OH)<sub>2</sub>D also regulates cell proliferation in the basal layers and increases the synthesis of keratins (K1 and K10), involucrin, transglutaminase, loricrin and filaggrin in the spinous layer of the epidermis. It

was also reported that the deficiency of calcipotriol and defect in its receptor function leads to disruption of epidermal differentiation, reduction of involucrin and loricrin, and subsequently hyperproliferation of the basal layer cell.<sup>29,30</sup>

Vitamin D also inhibits the production of several pro-inflammatory cytokines by psoriatic T-cell clones, including IL-2 and IFN- $\gamma$ , IL-6, and IL-8.<sup>26</sup> Additionally, topical vitamin D suppresses HBD2, HBD3, IL-17A, and IL-17F, which are detected in high numbers in psoriatic lesions.<sup>31</sup> Thus, the biological activity of vitamin D analogues leads to suppression of T cell-mediated immune response and blocking the cathelicidin pathway, lowering inflammation and restoring some of the changes that occur in psoriatic lesions.<sup>28</sup> This is noteworthy since vitamin D analogues may serve as a “steroid-sparing” topical agents as long-term use of topical steroids may lead to potential complications (e.g., cutaneous atrophy, striae, persistent erythema, telangiectasia, suppression of the hypothalamic-pituitary-adrenal axis, etc.) and tachyphylaxis.<sup>31,32</sup> In terms of therapeutic effects of oral vitamin D, no statistically significant effects of vitamin D supplementation and serum vitamin D level on psoriasis and its severity were reported.<sup>33-35</sup>

On a molecular level, a relationship has recently been discovered between VDR polymorphism and psoriasis susceptibility. According to a study conducted by Richetta *et al.*<sup>36</sup> the A-1012G promoter polymorphism of the VDR gene is significant to the probability of psoriasis development through the inhibition of VDRmRNA expression, resulting in skin barrier disruption and the development of psoriatic lesions (p-value=0.0028). A recent study by Lesiak *et al.*<sup>37</sup> found that the *Taal/Cdx-2* GG genotype frequency was significantly higher in psoriasis patients than in controls, where this

polymorphism contributes to the transcription of the VDR gene. These findings were further supported by a meta-analysis from 16 studies about VDR polymorphism and psoriasis, constituting 2086 patients and 2182 control, where VDR TaqI polymorphism was associated with susceptibility to psoriasis in Caucasian populations.<sup>38</sup> Hence, targeting vitamin D as one of the therapeutic approaches in psoriasis may provide a beneficial effect on psoriasis.

#### *Vitamin D and Autoimmune Bullous Disease*

Autoimmune bullous disease (AIBD), such as pemphigus and bullous pemphigoid (BP), is an autoimmune dermatosis mediated by essentially IgG autoantibodies against structural proteins of the desmosomes at cell-cell junctions and hemidesmosomes at epidermal-dermal junctions, respectively. It has been postulated that the imbalance of the relationship between autoreactive Th and T regulatory cells as well as Th17 cell activation serves as a critical point to the outbreak of autoimmune disorders.<sup>39</sup> These diseases are characterized by blisters and erosions in the skin and/or mucous membranes. Environmental factors, such as drugs, viral infection, nutrients, radiotherapy, and pregnancy, are recognized as crucial triggers for the pathogenesis of AIBD.<sup>26,40</sup> Growing evidence has shown that inadequate vitamin D levels are associated with AIBD.

A recent meta-analysis conducted by Yang *et al.*<sup>41</sup> reported that pemphigus and BP patients showed decreased serum 25(OH)D levels than that in control subjects (70.2% vs. 54.6% and 80.0% vs. 65.9%, respectively) with four out of ten studies included showing statistically significant than that in control subjects. The analysis also showed that vitamin D insufficiency was not significantly related to the disease status of pemphigus (odds ratio [OR]: 3.04, 95% confidence interval [CI]: 0.74-12.48)

and BP (OR: 2.44, 95% CI: 0.75-7.93), yet the serum 25(OH)D level is inversely associated with the risk of pemphigus and BP.

It is also noteworthy to remember that vitamin D is synthesized in the skin in the presence of sunlight. However, UV radiation has been recognized as a triggering factor of AIBD. Exposure to UVB may induce acantholysis of uninvolved skin in pemphigus patients.<sup>42</sup> This condition may lead to hypovitaminosis D among AIBD populations. Vitamin D inhibits the autoantigen expression in pemphigus vulgaris and BP through keratinocyte regulatory mechanisms at the post-transcriptional level.<sup>41</sup> Additionally, *in vitro*, calcitriol decreased the BP-IgG induced IL-6 and IL-8 release from human keratinocytes and contributed to the anti-inflammatory role in BP. Additionally, calcitriol blunted BP IgG-mediated STAT3 phosphorylation and NFκB activity.<sup>43,44</sup> Epidermal expression of 1, 25(OH)<sub>2</sub>D bridging the environment to the immune system via expansion of CD4+ CD25+ regulatory T cells and down-regulating cutaneous immune responses, where CD4+ CD25+ regulatory T cells have been shown to play an essential role in the inhibition of self-reactivity and are essential for the control of immune responses in inflammatory, autoimmune, or cancer diseases.<sup>45,46</sup> These findings propose protective effects exerted by vitamin D and serve as a critical therapeutic approach in AIBD.

#### *Vitamin D and Vitiligo*

Vitiligo is a common pigmentary disorder characterized by well-demarcated depigmented macules or patches of varying size orchestrated through T-cell mediated destruction of melanocytes.<sup>26</sup> However, its exact pathogenesis is complex and not yet fully understood, but growing data supports the idea of an immune dysregulation triggered by oxidative stress

among patients with a genetic predisposition.<sup>47</sup> Previous studies have linked several dietary components to vitiligo, including selenium, copper, and zinc. Lately, vitamin D insufficiency has been identified as a possible risk factor for vitiligo.<sup>48</sup>

A recent meta-analysis conducted by Varikasuvu *et al.*<sup>49</sup> of the ViViD Study reported that vitiligo patients had considerably low vitamin D levels than controls (standardized mean difference=-1.03; p-value=0.0001). In the sub-group analysis, vitiligo patients who worked indoors/urban work had significantly lower vitamin D levels than outdoor/ rural counterparts (standardized mean differences=-0.45; p-value=0.03). Several VDR gene polymorphisms were studied in vitiligo, such as ApaI (VDR 7975232 C > T), BsmI (VDR 1544410 A > G), FokI (VDR 2228570 C > T), and TaqI (VDR 731236 T > C). These polymorphic forms of VDR may be associated with decreased VDR activity, reduced vitamin D actions, and vitamin D deficiency, subsequently increasing the susceptibility to vitiligo development.<sup>50</sup>

There are studies suggesting that vitamin D may increase the melanogenesis and tyrosinase content of human melanocytes through its anti-apoptotic effect through the formation of sphingosine-1-phosphate, thus preventing the loss of skin pigment.<sup>51-53</sup> Watabe *et al.*<sup>54</sup> discovered that L-3, 4-dihydroxyphenylalanine-positive (DOPA-positive) cells are increased following 1, 25(OH)<sub>2</sub>D treatment in primary neural crest cell cultures, indicating a crucial insight to the understanding the role of vitamin D<sub>3</sub> in melanocyte formation and melanogenesis. The data suggested that 1, 25(OH)<sub>2</sub>D may stimulate the differentiation of immature melanocyte precursors. In comparison to untreated cells, electron microscopy revealed the presence of melanosomes at more advanced stages in 1, 25(OH)<sub>2</sub>D-treated cells. In addition,

vitamin D stimulates the differentiation and expression of endothelin B receptors in immature melanocytes in the bulge region of hair follicles, causing them to produce melanin.<sup>55</sup>

As with psoriasis, topical vitamin D analogues have been listed in the armamentarium of therapeutic modalities for vitiligo. Calcipotriol stimulates melanin formation by activating melanocytes and keratinocytes, and it is effective on immunomodulatory systems, inflammatory mediators, and melanocytes.<sup>56,57</sup> Additionally, after UV-irradiation of the skin, *in vivo* findings suggested that melanocytes in the epidermis enlarge with lengthened dendrites. Microphthalmia transcription factor (MITF) increases tyrosinase activity in these melanocytes, resulting in the deposition of the enzyme product, melanin, in the epidermis a few days after irradiation.<sup>51,57</sup> This finding suggested the use of topical vitamin D analogues as adjuvants to phototherapy as it has synergistic effects for vitiligo without apparent side effects.<sup>49,58</sup> Furthermore, a recent meta-analysis investigating the addition of calcipotriol to phototherapy for the enhancement of treatment in vitiligo found that the phototherapy reported that calcipotriol + 308nm excimer laser showed the most optimal effect when compared with calcipotriol+narrow band-UVB (NBUVB) and calcipotriol+psoralen plus UVA (PUVA) (>25% repigmentation [efficiency] of 97.30%, 84.68%, and 68.95%, respectively; >50% repigmentation [apparent efficiency] of 86.49%, 56.57%, and 65.71%, respectively).<sup>59</sup> Vitamin D may provide as an advantageous approach in the management of vitiligo.

## Conclusion

Vitamin D, one of the fat-soluble vitamins, has been an emerging topic for autoimmune disorders due to its immunomodulatory property

regulating innate and adaptive immunity. Vitamin D deficiency has been proposed as a risk factor in autoimmune dermatoses, specifically AIBD and vitiligo, and vitamin D supplementation and/or its analogue has been shown to play a role in the pathogenesis and disease management. Utilization of vitamin D as oral supplementation or topical therapy, either as monotherapy or adjuvant, should be individualized according to the type and extent of the disease, the presence of vitamin D deficiency, and the risk-benefit stratification for the disease.

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