

# Vitamin D in dermatology

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## Abstract

### Introduction

Vitamin D is classically known for its role in calcium homeostasis and bone mineralization. However, recent studies have shown that vitamin D is important in numerous physiological processes, including the modulation of cell proliferation, differentiation, and apoptosis, and in neuromuscular, hormonal, and immune functions. On the other hand, vitamin D may also play a role in multiple chronic diseases such as cancer, autoimmune diseases, and infections. In this review, we focus on vitamin D and skin disease.

### Conclusion

Long-term and interdisciplinary clinical studies are needed, and the potential for side effects should be considered in order to determine whether vitamin D is safe for extended use.

## Introduction

Vitamin D is a fat-soluble compound that humans obtain endogenously when the skin is exposed to ultraviolet (UV) light and exogenously through dietary intake. Although naturally present in very few foods, two forms of dietary vitamin D are available: vitamin D<sub>2</sub> (ergocalciferol) and vitamin D<sub>3</sub> (cholecalciferol)<sup>1</sup>. Humans synthesize vitamin D<sub>3</sub> when 7-dehydrocholesterol, present in epidermal keratinocytes, interacts with UV light. 7-Dehydrocholesterol absorbs light at wavelengths in the range of 270 to 300 nm, although optimal vitamin D<sub>3</sub> synthesis occurs at wavelengths of 295 to 300 nm<sup>2</sup>. The highest concentrations of 7-dehydrocholesterol are found in keratinocytes in the basal and spinous cell layers<sup>3</sup>. Because cutaneous melanin naturally prevents UV light from affecting the deeper portions of the epidermis, individuals with a higher melanin content in their skin require more UV light exposure to produce the same level of vitamin D<sub>3</sub> as individuals with less melanin<sup>4</sup>.

Vitamin D is needed to maintain calcium and phosphate homeostasis<sup>5</sup>. Most tissues can convert vitamin D<sub>3</sub> to its active form (1,25[OH]<sub>2</sub>D<sub>3</sub>) via vitamin D receptors (VDRs). The role of vitamin D in the development of rickets and other bone disorders has long been known<sup>6</sup>; however, interest in the relationship between vitamin D and other systemic diseases has increased<sup>1</sup>. Today, we know that vitamin D exerts important effects on various types of cells, including immunomodulatory effects and

pro-differentiating and antiproliferative effects on normal and cancer cells<sup>7</sup>. The potentially important relationship between vitamin D and cancer has received significant attention<sup>1</sup>. The strongest case for a meaningful link between vitamin D and the incidence of specific cancers has been made for colon cancer. Recent work demonstrated a dose-response curve in which increasing serum 25-hydroxyvitamin D levels were associated with a progressively decreasing risk of colorectal cancer<sup>8</sup>. Still, observational studies suggest a role for vitamin D in the incidence of cancer of the breast, prostate, ovary, kidney, endometrium, and other organs<sup>1</sup>.

In accordance with its effects on immune homeostasis, recent data suggest that there is a relationship between vitamin D levels and autoimmune or inflammatory diseases<sup>9,10</sup>. Studies indicate that vitamin D may modulate inflammatory responses. Indeed, vitamin D can regulate the expression of genes that generate pro-inflammatory mediators, including cyclooxygenase and 5-lipoxygenase<sup>9</sup>. On the other hand, vitamin D can modulate nuclear factor- $\kappa$ B activation and signaling<sup>11</sup>. In addition to this effect, vitamin D inhibits the p38 MAP kinase pathway, which mediates inflammatory responses by suppressing pro-inflammatory cytokines such as tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)-6<sup>12</sup>.

On the other hand, the demonstration of a role for vitamin D in various diseases, including dermatological diseases, osteoporosis, cancer, and autoimmune diseases, suggests clinical applications for vitamin D and its analogs<sup>13</sup>. As mentioned above, several studies have shown that vitamin D has dose-dependent antiproliferative effects<sup>14</sup>. Moreover, vitamin D can reduce the risk of skin infections<sup>14</sup>. Further, vitamin D deficiency is related to dermatological diseases such as psoriasis, atopic dermatitis (AD), vitiligo, acne, rosacea, and skin cancer. Therefore, the aim of this review was to summarize the role of vitamin D in dermatological diseases.

### Dermatological disease and vitamin D

Vitamin D is of particular interest to dermatologists for two important reasons: it is synthesized in the skin upon exposure to UV light, and it is an important treatment option for psoriasis and other skin diseases<sup>1</sup>.

Studies have shown that vitamin D has dose-dependent effects in the skin, including the modulation of growth factor and cytokine synthesis and signaling<sup>13</sup>. It also reduces the synthesis of IL-1 $\alpha$  and IL-6, resulting in decreased inflammation<sup>13</sup>. On the other hand, vitamin D induces the expression of thymic stromal lymphopoietin and cathelicidin in psoriatic skin<sup>13</sup>. It also increases the synthesis of platelet-derived growth factor (PDGF) in keratinocytes cells to promote wound healing and TNF- $\alpha$  to

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promote keratinocyte differentiation<sup>13</sup>. Furthermore, vitamin D analogs have comedolytic activity<sup>13</sup>. Given these effects, vitamin D may be used in the treatment of some skin disorders.

### Psoriasis

Psoriasis is a chronic immune-mediated inflammatory disorder involving epidermal hyperplasia. The pathogenesis of psoriasis is not fully understood. The treatment of psoriasis is difficult because the appearance of the disease can vary widely. The use of oral vitamin D supplements for the treatment of psoriasis was first reported about 60 years ago based on the beneficial effects of sunlight on the disease<sup>1</sup>. However, the therapeutic benefit of oral vitamin D for psoriasis is limited due to the risk of adverse side effects such as hypercalcemia, hypercalciuria, nephrocalcinosis, nephrolithiasis, and a reduction in bone mineral density secondary to its calcemic effects<sup>1,15</sup>. Today, topical calcipotriol, a vitamin D analog, is used safely and effectively in the treatment of psoriasis without the systemic effects described above. Studies indicate that vitamin D inhibits the production of IL-2, IL-6, and interferon (INF)- $\gamma$ , which are potent mediators of inflammation<sup>1,13</sup>. Studies have also verified the existence of interplay between T helper (Th17) cells and vitamin D in psoriatic patients<sup>16</sup>. Moreover, vitamin D promotes suppressor T-cell activity and inhibits cytotoxic and natural killer cell formation. It has been proposed that a combination of the mechanisms of reduced cellular proliferation, increased cellular differentiation, and immunomodulation may explain the therapeutic effects of topical vitamin D and its analogs on psoriatic lesions<sup>1</sup>. However, vitamin D treatment is not effective for all patients with psoriasis. Because of this, the exact mechanism of action of vitamin D in psoriasis and the etiology of the disease should be clarified.

### Atopic dermatitis (AD)

AD, a chronic inflammatory disease, is clinically characterized by pruritus, eczematous plaques, and a defective epidermal barrier<sup>17</sup>. Its pathogenesis can be explained by immunological and inflammatory dysfunction, in addition to environmental factors. The relationship between innate and adaptive immune responses in patients with AD remains to be clarified<sup>18</sup>. Recent studies suggest that a relationship between AD and vitamin D exists; however, this finding is controversial. For example, Bäck et al.<sup>19</sup> showed that the increased intake of vitamin D during childhood correlates with an increased risk of AD. Conversely, Peroni et al.<sup>18</sup> evaluated the relationship between vitamin D and AD severity in 37 children. They suggested that a deficiency in vitamin D is related to the severity of AD. Other data indicate that patients with AD, especially those with a low vitamin D level, may benefit from UVB maintenance treatment not only to suppress the function of Langerhans cells or inflammatory cells infiltrating the skin but also to diminish the risk of bacterial infections, which may result in part

from UVB-induced vitamin D synthesis<sup>20</sup>. This should be considered, especially during the winter season, in patients living at northern geographic latitudes.

### Vitiligo

Vitiligo is an autoimmune pigmentary disorder characterized by well-demarcated depigmented patches or macules of different shapes and sizes<sup>21</sup>. Several hypotheses have been proposed to explain the relationship between vitamin D and vitiligo:

1. It has been reported that the increased expression of pro-inflammatory and proapoptotic cytokines such as IL-6, IL-8, IL-10, IL-12, INF- $\alpha$ , and TNF- $\alpha$  plays a role in the pathogenesis of vitiligo. Vitamin D might exert immunomodulatory effects by inhibiting the expression of IL-6, IL-8, TNF- $\alpha$ , and TNF- $\gamma$ <sup>1,21</sup>.
2. Another study investigated the association between VDR polymorphisms and vitiligo<sup>22</sup>. It revealed that the Apa-I polymorphism of the VDR gene is associated with vitiligo. Thus, vitamin D or its receptor might play a role in the etiopathogenesis of skin pigmentation.
3. In recent studies, vitamin D levels were found to be insufficient or very low in most patients with vitiligo vulgaris<sup>23,24</sup>. Therefore, supplementation with vitamin D could be used to treat autoimmune diseases such as vitiligo.

Nevertheless, additional studies are needed to differentiate between the effects of low vitamin D levels on the pathogenesis of vitiligo vulgaris and lower vitamin D levels as a result of the disease.

### Alopecia areata (AA)

AA is recurrent, nonscarring hair loss affecting any hair-bearing area. It is an organ-specific autoimmune disease characterized by T-cell infiltrates and cytokine production around anagen-stage hair follicles<sup>25</sup>.

It is well known that VDR expression in keratinocytes is necessary for maintenance of the normal hair cycle, and a lack of VDRs reduces epidermal differentiation and hair follicle growth<sup>26</sup>. In light of this information, Kim et al.<sup>27</sup> described a 7-year-old male with AA and reduced VDR expression in which recovery was observed following the topical application of calcipotriol, a potent vitamin D analog. In addition, Aksu Cerman et al.<sup>25</sup> found decreased serum vitamin D levels in patients with AA. These levels were inversely correlated with disease severity, which may indicate a causal role for vitamin D deficiency in the pathogenesis of the disease. They suggested that vitamin D supplementation could be a reasonable and specific treatment strategy for AA.

### Acne

Acne is a multifactorial disease involving alterations in the pattern of keratinization within pilosebaceous follicles,

resulting in comedo formation, increased sebum production, the proliferation of *Propionibacterium acnes*, and peri-follicular inflammation<sup>28,29</sup>. *Propionibacterium acnes* has been shown to stimulate the production of inflammatory cytokines such as IL-8, TNF- $\alpha$ , and IL-1 $\beta$  in acne patients<sup>30</sup>.

Recently, sebocytes were identified as bioactive vitamin D-responsive target cells, indicating that vitamin D analogs may be effective in the treatment of acne<sup>31</sup>. Lee et al.<sup>32</sup> examined the effect of vitamin D on the expression of inflammatory biomarkers from sebocytes (IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$ ) and the role of Th17 cells in acne. They found that *P. acnes* is a potent inducer of IL-17 (IL-17 expression is the hallmark of human Th17 cells) and IL-22 in acne lesions. Vitamin D treatment decreased the expression of IL-6, IL-8, IL-17, and matrix metalloprotein-9 in cultured sebocytes. They proposed that vitamin D could be a therapeutic alternative for the treatment of acne and other Th17-mediated skin diseases.

### Rosacea

Rosacea is a common chronic inflammatory disease affecting the facial skin characterized by transient or persistent erythema, telangiectasia, papules, and pustules. Many factors have been suggested for the pathogenesis of rosacea, but the definite etiology is unknown.

Vitamin D causes the induction of thymic stromal lymphopoietin and cathelicidin. Cathelicidin dysfunction is associated with the pathogenesis of several cutaneous diseases, including AD, psoriasis, and rosacea<sup>33</sup>. Cathelicidins were among the first families of antimicrobial peptides (AMPs) discovered on the skin<sup>34</sup>. AMPs are molecules with antimicrobial activity that function like chemokines, enzymes, enzyme inhibitors, and neuropeptides. Vitamin D also plays an important role in the innate immune system in the course of AMP production<sup>6</sup>. Based on this hypothesis, Ekiz et al.<sup>35</sup> found high levels of vitamin D in rosacea patients and they suggested that increased vitamin D levels can lead to the development of rosacea. However, the relationship between vitamin D and rosacea remains unresolved because there is currently only one study on this issue.

### Conclusions

Additional studies on the etiopathogenesis of dermatological diseases and the role of vitamin D in these processes are needed. However, current data indicate that vitamin D and its analogs have therapeutic potential in dermatological disease. Vitamin D is a fat-soluble steroid hormone; thus, care must be taken when using vitamin D for the treatment of chronic diseases. Long-term and interdisciplinary clinical studies are needed, and the potential for side effects should be considered in order to determine whether vitamin D is safe for extended use.

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