

## REVIEW ARTICLE

### VITAMIN D AND ITS ROLE IN DERMATOLOGY: A REVIEW OF LITERATURE

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**ABSTRACT:** Vitamin D is a fat-soluble steroid hormone that is crucial for human health. Since long the role of epidermal keratinocytes in the UVB-induced photochemical conversion of 7-dehydrocholesterol to vitamin D<sub>3</sub> is known, and also for the enzymatically controlled hydroxylation of the photolysis product. This whole process results in the formation of the biologically active final product 1, 25-(OH)<sub>2</sub> D<sub>3</sub> (Calcitriol). Moreover recently various research articles have shown benefits of calcitriol and various other vitamin D analogues having a therapeutic role in various dermatologic conditions like psoriasis, atopic dermatitis, acne, vitiligo owing to its anti-inflammatory, anti-proliferative action. The present review shows a summary of role of vitamin D in dermatologic perspective.

**KEYWORDS:** Vitamin D, calcitriol, anti-inflammatory, anti-proliferative.

**INTRODUCTION:** Vitamin D is a fat-soluble prohormone and was identified after the discovery of the anti-rachitic effect of cod liver oil somewhere in the early part of the 20<sup>th</sup> century. This vitamin which was found in cod liver oil was assigned as "vitamin D" following Vitamin A, B and C.<sup>1</sup> Vitamin D has two major biologically inert precursors, vitamin D<sub>3</sub> (Cholecalciferol) and vitamin D<sub>2</sub> (Ergocalciferol).<sup>2,3</sup> Out of these precursors, vitamin D<sub>3</sub> is formed from 7-dehydrocholesterol present in the skin, which following exposure to solar ultraviolet B (UVB, 290-320 nm), is converted to previtamin D<sub>3</sub>. Previtamin D<sub>3</sub> is immediately converted to vitamin D in a heat dependent process. Moreover excess of UVB rays also transform previtamin D<sub>3</sub> into biologically inactive metabolites, tachysterol and lumisterol. On the other hand, the other precursor vitamin D<sub>2</sub> is plant derived and its source is through diet.<sup>1</sup> Vitamin D has both endocrine and autocrine functions. The endocrine role of vitamin D is mainly in serum calcium homeostasis.

The autocrine effects of vitamin D depend mainly on genetic transcription specific to the various types of cells expressing nuclear vitamin D receptors. These functions lead to inhibition of cell proliferation, promotion of cell differentiation and apoptosis. Thus vitamin D has an important role in modulation of calcium homeostasis, cardiovascular dynamics, musculoskeletal health and genetic expression.<sup>4, 5, 6</sup> In Dermatology, topical vitamin D and its analogues are being used since time immemorial in various conditions like vitiligo, psoriasis in the form calcitriol, calcipotriol, etc. Recently vitamin D deficiency and its reduced levels in serum has been seen in various skin diseases.

**BIOCHEMISTRY AND PHYSIOLOGY OF VITAMIN D:** The primary form of vitamin D is cholecalciferol [25 (OH) D<sub>3</sub>], which is synthesized in the liver and is the form used to measure the levels of vitamin D in the blood whereas the active form of vitamin D [1, 25-(OH)<sub>2</sub> D<sub>3</sub>] is a secosteroid (Steroid with an opened B-ring) hormone and is synthesized in the kidney via the hydroxylation of 25(OH)D<sub>3</sub> by 1 $\alpha$ -hydroxylase.<sup>7, 8</sup> This active form of vitamin D is the one that is important in various functions like regulation of calcium and bone metabolism, cellular proliferation and differentiation and

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immunoregulation. It is because of this range of functions that vitamin D has been exploited clinically to treat various disorders like secondary hyperparathyroidism, osteoporosis, psoriasis, and vitiligo. Recent advances and novel insights in the understanding of 1, 25(OH)<sub>2</sub> D<sub>3</sub>, its functions and mechanisms of its immunomodulatory properties suggest a wider utility and role of this hormone in the treatment of various autoimmune diseases and inflammatory disorders.

**VITAMIN D PATHWAY IN SKIN:** The skin is the only tissue in the human body yet known which incorporates complete Ultraviolet-B induced pathway from 7-dehydrocholesterol to the hormonally active calcitriol under normal physiological conditions. The synthesis of calcitriol in the epidermis is fundamentally important because it regulates important cellular functions in keratinocytes and immunocompetent cells.<sup>4,9</sup> The UVB action spectrum that is responsible for the sunburn response and photocarcinogenesis is involved in vitamin D biosynthesis. The conversion of previtamin D<sub>3</sub> to the inactive photoproducts lumisterol and tachysterol is an important step as it balances the cutaneous biosynthesis of vitamin D<sub>3</sub> as a feedback mechanism. This mechanism keeps a check on “overdose” of vitamin D<sub>3</sub> by photoexposure alone.<sup>10,11</sup>

### VITAMIN D USES IN DERMATOLOGICAL CONDITIONS:

- **PSORIASIS:** Psoriasis is a common Th1 mediated chronic inflammatory skin disease. Various studies have shown a prevalence of 2-3% for psoriasis in the world population.<sup>12</sup> Recent studies carried out among psoriasis patients have shown deficiency of serum concentration of 25(OH) vitamin D<sub>3</sub> in these patients and further evidence is growing. Psoriasis involves altered secretion of cAMP by the epidermal keratinocytes. Dysfunction of these and other peptides has been involved in the pathogenesis of psoriasis and many other inflammatory skin diseases.<sup>13</sup> Also LL-37, the only cathelicidin present in humans has been found to be over expressed in the inflamed skin of patients of psoriasis.<sup>14</sup> Vitamin D<sub>3</sub> is directly involved in the regulation of the expression of cathelicidins.<sup>15</sup> Topical forms of vitamin D have been used in psoriasis. These bind to vitamin D receptors (VDRs) over keratinocytes and leads to transcription of genes and influencing the growth and differentiation of keratinocytes in psoriatic skin.<sup>16</sup>
- **VITILIGO:** Vitiligo is a common skin condition with well-defined depigmented patches and macules over skin and is characterized by destruction of melanocytes. According to the convergence theory various factors like autoimmunity, accumulation of melanocyte toxic chemicals, genetic predisposition and defective free radical clearance lead to the development of vitiliginous skin.<sup>17</sup> The serum vitamin D levels are lower in vitiligo patients as compared to non vitiligo patients. In vitro studies have shown that murine B-16 melanoma cells when treated with vitamin D<sub>3</sub> exhibit an increase in tyrosinase activity and melanogenesis. The presence of melanosomes at more advanced stages when seen through electron microscopy on treatment with 1, 25(OH)<sub>2</sub> D<sub>3</sub> further substantiates the role of vitamin D in vitiligo.<sup>18</sup> Topical Vitamin D<sub>3</sub> analogues like calcipotriol either alone or in combination with PUVA, NB-UVB are new therapeutic modalities and these act through the vitamin D receptors.
- **ATOPIC DERMATITIS:** Atopic dermatitis is a common skin condition characterized by impaired and dysfunctional skin barrier system and a dominant Th<sub>2</sub> response. Genetic factors like filaggrin mutation and environmental factors both contribute to atopic dermatitis.<sup>19</sup> 1, 25 (OH)<sub>2</sub> vitamin D<sub>3</sub> exerts its effects through VDRs present in human epidermis. VDRs are present in a

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variable distribution in human epidermis with more concentration in the basal epidermis. VDRs are also located on the macrophages and dendritic cells. 1, 25, (OH)<sub>2</sub> vitamin D<sub>3</sub> acts on these VDRs and results in increased IL-10 production, regularizes cathelicidin production, suppresses the inflammatory response and helps in restoring the integrity of the impaired permeability barrier.<sup>20</sup>

- **ACNE VULGARIS:** It is a disorder of the pilosebaceous follicles involving mainly the face, chest, back and shoulders. It involves four main processes which include hyperkeratinization of the pilosebaceous follicles, increased sebum production, increased propionobacterium colonization and inflammation.<sup>21</sup> Also it has been known that inflammatory cytokines play a major role in the pathophysiology of acne. These inflammatory cytokines are produced from the sebocytes as well as keratinocytes. Recently it has been shown in various studies that vitamin D does influence the expression of these cytokines thus proving beneficial in acne.<sup>22</sup>
- **HAIR DISORDERS:** Various animal studies have shown the role of Vitamin D in hair cycle and has also found beneficial effects of vitamin D analogues in various hair disorders. These studies suggest an important role of VDRs independent of vitamin D<sub>3</sub> in hair follicle cycle, specifically “Anagen” initiation. But studies on humans using vitamin D analogues are limited. However few studies have found a protective role of calcitriol against chemotherapy induced alopecia caused by paclitaxel and cyclophosphamide.<sup>23</sup>
- **AUTOIMMUNE DISORDERS:** The role of vitamin D on the immune system has been studied a lot. VDRs are present in significant concentrations on immature thymus cells, macrophages and CD8 lymphocytes. Vitamin D has been known to stimulate the transforming growth factor beta-1 and interleukin-4 thus resulting in suppression of inflammatory T cells. All these actions have led to the role of vitamin D in autoimmune disorders.<sup>24</sup> Various studies have shown that vitamin D supplementation has been found useful in various autoimmune diseases like rheumatoid arthritis and systemic lupus erythematosus. One study even found that supplementation with Vitamin D in SLE patients resulted in improvement in disease activity score and proteinuria.<sup>25</sup>

**VITAMIN D<sub>3</sub> ANALOGUES:** Over the past few years, vitamin D analogues have found a significant place in Dermatology as a therapeutic entity. Various vitamin D analogues discovered are calcipotriol, maxacalcitol, tacalcitol and calcitriol. These agents have been shown to be minimally absorbed systemically and have been even involved with phototherapy and other systemic agents in conditions like vitiligo and psoriasis.

**CONCLUSION:** Vitamin D has always been known to be an important nutrient for human body. Recently its role in the pathophysiology of various biological functions has been studied and its role in various dermatological and non-dermatological diseases has gained much impetus. But more studies are required to establish its role in management of various disorders.

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