

## AN INSIGHT OF THE ROLE OF VITAMIN D ON SKIN DISEASES

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Article Received on  
27 Nov. 2017,Revised on 18 Dec. 2017,  
Accepted on 08 Jan. 2018

DOI: 10.20959/wjpr20182-10725

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**ABSTRACT**

Vitamin D is one of the most essential hormones in the human body which is produced by epidermal keratinocytes under the effect of the sun's radiation {Ultraviolet B}. Further,  $25\{OH\}_2D_3$  is the inactive form of vitamin D that helps physicians investigate the serum level of vitamin D and determine whether an individual has an insufficient amount of this hormone or is deficient. The other form of vitamin D,  $1,25\{OH\}_2D$ , which is the active type, is more likely to have pleiotropic actions on different parts of the body: it regulates the growth of epidermal keratinocytes and cell proliferation and differentiation; also, vitamin D could functions as an immunomodulator especially in the cases of autoinflammatory

diseases, for instance, atopic dermatitis, psoriasis, and alopecia areata. Basically, the immune response of vitamin D to such skin conditions involves the promotion T regulatory cells and production of IL-10, which controls the response of T helper cell proliferation; inhibits the release of IL-2, IL-17, IL-8, and interferon- $\gamma$ ; and enhances the functioning of the antigen-presenting cells. Besides that, an obvious role of  $1,25\{OH\}_2D$  on some elements such as calcium and phosphate, both of them are tend to be absorbed through the intestine secondary to the action of vitamin D receptor with vitamin D itself. Evidences show that the serum concentration of vitamin D to some extent affects the severity of some skin diseases. Accordingly, distinct clinical and laboratory trials have been conducted in order to address the therapeutic impact of this hormone on the patients, either to underline the safety of the vitamin D as a medication.

**KEYWORDS:** Vitamin D,  $1,25[OH]_2D$ , Skin, Atopic dermatitis, Psoriasis, Alopecia Areata.

## INTRODUCTION

Vitamin D is considered one of the most important hormones for the human body for several reasons besides calcium regulation and bone mineral homeostasis.<sup>[1]</sup> This vitamin affects the skin, brain, heart, and the immune system.<sup>[2]</sup> Physiologically, the intestines absorb calcium with the help of vitamin D and even the kidneys during their inhibitory action on the calcium excretion the vitamin D appear to control this mechanism. Further, this hormone also aids in the resorption and metabolisation of calcium from the skeleton.<sup>[3]</sup> Ross et al.<sup>[4]</sup> argued that there are inadequate studies on the effect of vitamin D on the skin, which are “inconsistent, inconclusive, and insufficient to inform nutritional requirements”.<sup>[4]</sup> In spite of this statement, many studies have focused on vitamin D and its potential effects on human skin, especially enhancement of skin health and prevention of skin diseases.<sup>[5]</sup>

Vitamin D was identified as a vitamin in the early 20<sup>th</sup> century.<sup>[4]</sup> Now, it is known as a fat-soluble prohormone steroid.<sup>[2]</sup> Produced by the epidermal cells of the human body, particularly the keratinocytes,<sup>[6]</sup> under the effect of sunlight {Ultraviolet B}.<sup>[2]</sup> Vitamin D has an inclination to acts on three systems, one of them being the endocrine system, through which it regulates serum calcium and phosphate levels. Furthermore, this steroid hormone plays a major role in the inhibition of cell proliferation and promotes the differentiation of keratinocytes. This mechanism is regulated by the paracrine and autocrine systems.<sup>[2]</sup> Medically speaking, it has been believed that the skin synthesises vitamin D and metabolises it in order to produce the active form of this hormone.<sup>[2]</sup>

The main objective of this article is to determine the action of vitamin D on the human skin. In addition, this study also aims to understand the basic mechanism of this hormone with regard to production, synthesis, and metabolism. Finally, a review of the articles and studies on the impact of this hormone on different skin conditions, mainly atopic dermatitis, psoriasis and alopecia, will be presented. As other skin conditions cannot be ignored such as skin cancer, acne vulgaris, and vitiligo, these will be discussed briefly.

## DISCUSSION

The existence of the sun is crucial to human life, as its light makes everything visible in the world and its heat enables living creatures to carry out various functions for their survival. Also, the sun is considered the cornerstone in the formation and regulation of vitamin D in the human body. The ultraviolet B rays generated from the sun are absorbed by the keratinocytes in the epidermis of the human skin. Thereafter, 7-dehydrocholesterol is

transformed to pre-vitamin D<sub>3</sub>. This precise physiological mechanism occurs in the human body to ensure the maintenance of good health. When heat acts on pre-vitamin D<sub>3</sub>, it metabolises into vitamin D<sub>3</sub> that circulates in the blood in this inactive form and is later transformed to 25{OH}<sub>2</sub>D<sub>3</sub>. The serum concentration of 25{OH}<sub>2</sub>D<sub>3</sub> is measured by physicians to determine the level of vitamin D deficiency or insufficiency.<sup>[6, 23, 26]</sup>

The sun's radiation may not be sufficient enough to increase the level of vitamin D in the human body, so a variety of food items that contain high levels of vitamin D, particularly sea food {salmon fish and tuna}, cheese, yolk egg and beef liver, are generally consumed.<sup>[18]</sup> Some developing countries are facing the issue of vitamin D deficiency among their citizens owing to the lack of access to dietary sources of vitamin D facing the poorer segments of society.<sup>[19]</sup> To tackle this issue, many governments have mandated that dietary items such as milk, yogurt, and fruit juices be fortified with extra vitamin D.<sup>[2]</sup> The question arising here is why should humans consider vitamin D as an essential nutrient.

Many evidences highlight the significant role of vitamin D in the body in different aspects, for example, the functioning of the autocrine or paracrine system and the well-being of other organs like bones, muscles, intestine, heart, and brain.<sup>[1, 2]</sup> However, this dissertation focuses on the function of vitamin D in skin health and explores the considerable action of this hormone in the treatment of different skin diseases.

The stratum corneum, which is the superficial layer in the skin, is formed by a physiological process after keratinocyte differentiation. When certain changes occur in the epidermal cells, e.g. increase in the number of stratified foci and reduction of the size of the basal cells, they transform to squamous cells. This mechanism is a consequence of the action of 1,25{OH}<sub>2</sub>D and calcium as well.<sup>[1]</sup> A high concentration of intracellular calcium in combination with other enzymes such as involucrin, transglutaminase, loricrin, and filaggrin has a major effect on epidermal keratinocytes because of the presence of vitamin D receptors in the epidermal cells, so the stratum corneum is created.<sup>[29]</sup> On the other way, a skin proliferation would take a contrary process through being inhibited secondary to the vitamin D action with vitamin D receptors.<sup>[1]</sup>

Many studies have focused on the association between 1,25{OH}<sub>2</sub>D and atopic dermatitis. The patients with AD are more likely to present with low vitamin D levels as compared with healthy individuals. Moreover, it has been proven that severe AD on the SCORAD index is

correlated to severe serum vitamin D deficiency.<sup>[48, 50]</sup> Owing to the main function of vitamin D which is an immunomodulator, as it been described in the AD mechanism where infiltrations of Th-1 and 2 cells accompanied with other interleukins {4, 13, 5 and 12} GM-CSF and IFN- $\gamma$  trigger the inflammation of the skin. Therefore, the action of calcitriol is that of balancing the immune reaction through control IgE by B cells, while induce expression of IL-10 from dendritic cells.<sup>[34, 52]</sup>

The studies reviewed above show that the risk of bacterial skin infections in AD patients could be controlled by high levels of vitamin D in a human body. This hormone acts on the skin by producing antimicrobial peptides such as cathelicidins and reduces the activity of the Langerhans cells as well. Thus, 1,25{OH}<sub>2</sub>D is highly related to TLR function.<sup>[35]</sup> A lack of vitamin D would result in the dysfunction of the skin barrier and dysregulation of the immune defence system.<sup>[32]</sup> The serum levels of vitamin D in AD patients have shown remarkable improvements after oral supplementation of vitamin D in different doses and for different periods.<sup>[47, 52, 53]</sup> In spite of this improvement, there is no consensus on the adequate concentration of vitamin D which is above 30 ng/mL. But even though the AD lesions in some patients appeared to improve significantly after oral vitamin D also with decrease in the condition severity.<sup>[48, 53]</sup> Oren with colleague<sup>[112]</sup> pinpointed a remarkable risk to get atopic dermatitis disease in the patients who suffer from vitamin D deficiency more than the patients with vitamin D insufficiency.<sup>[112]</sup>

Some studies have shown that infant patients with allergic skin disease have mothers with adequate levels of vitamin D during pregnancy.<sup>[113]</sup> Likewise, Gale et al.<sup>[114]</sup> stated that because of the high serum level of vitamin D in some pregnant ladies, their infants might suffer from AD at nine months of age,<sup>[114]</sup> while Back et al. stated an age of six years.<sup>[115]</sup>

The role of vitamin D in treating allergic conditions among the infants is still controversial.<sup>[115]</sup>

After the understanding of the normal action of vitamin D on the human epidermal keratinocytes, an influence of this vitamin with the psoriasis pathomechanism in case of vitamin D receptor mutation. Basically, a hyperproliferation of the epidermal cells would be visible in psoriasis. The immature cells and immature involucrin with membrane-bound transglutaminase could be presented in the stratum corneum as a result of abnormal anti-filaggrin antibodies. In addition, the rapid turnover of the keratinocytes production from 311

hours to 36 hours that could lead to incomplete terminal differentiation.<sup>[68]</sup> It has been stated that, present of sufficient amount of vitamin D in the body, would control the action of VDR then to help the epidermal keratinocytes to be in a normal proliferation process.<sup>[116]</sup>

In some studies consider 1,25{OH}<sub>2</sub>D as a therapy for psoriasis has been argued that it is safe and effective option for patients with psoriasis and psoriatic arthritis who suffer from vitamin D deficiency. However, lack of trials which demonstrate the usage of high-dose of vitamin D as a treatment rather than calcitriol or alfacalcidol. It has been suggested that an extra studies on the high dose of vitamin D would be needed.<sup>[68]</sup> Despite that, Huckins et al.<sup>[69]</sup> asserted that a potential effect of oral vitamin D was been observed in the widespread psoriasis vulgaris, or patients who complain of erythrodermic psoriasis and scales. On top of that, the patients who are on oral calcitriol have mentioned a great improvement of their nail psoriasis.<sup>[69]</sup>

Furthermore, vitamin D would act as immunomodulator. Through modulate and change the function of the antigen-presenting cells. Similarly, this vitamin would decrease the proliferative action of the T-cells and T helper 1, diminish of IL-2, IL-17, IL-18 and interferon- $\gamma$ . Meanwhile, other substances for example, IL-10 and T regulatory cells are more likely to be elevated due to vitamin D.<sup>[36, 37]</sup>

It has been proved in the previous studies that level of vitamin D in the body have a potential effect on the activity of T1 helper cells and it's cytokines for the autoimmune diseases activity. Clearly, any mutation in isoenzymes which contribute to form vitamin D could lead to decline of this hormone. Also, a mutation in VDR in psoriatic patients may play a role in that problem. Above all, Vitamin D as it been known would induce the terminal differentiation of the murine epidermal cells and control the proliferation.<sup>[57]</sup>

Regarding the vitamin D receptors, it has been claim that in different studies, a mutation of VDR would contribute to the psoriasis mechanism.<sup>[117, 118]</sup> Thus, a clear statement from Dayangac-Erden et al.,<sup>[117]</sup> “ We suggested that the alleles of the polymorphic regions of the VDR gene may be related to responsiveness or no responsiveness to calcipotriol treatment.”<sup>[117]</sup>

Turning on to the hair follicle and alopecia conditions, a review of the literature shows a link between the vitamin D receptor and hair cycle. Mainly, the vitamin D receptor locates in the

outer root sheath and the dermal papilla of the hair follicle and a clear ligand-dependent function with Wnt/b-catenin signalling would promote the hair follicle differentiation and proliferation. Also, they could regulate the gene expression of hair follicle cycling and the hedgehog signalling pathway, while an un-liganded action more likely for the stem cells in the HF. It has been declare the expression of the VDR during the murine hair cycle was remarkable stronger in anagen IV-VI and catagen more than other phases.<sup>[119]</sup>

By contrast, dysfunction in the Wnt/b-catenin signalling or VDR would demonstrate hair loss condition as a consequence of interruption for the hair cycle and the anagen phase. According to this concept, different studies were done clinically and laboratory to emphasizes the role of 1,25(OH)<sub>2</sub>D with the HF. One of the animal trial revealed that the affected mice with alopecia was more likely to be under influence of the vitamin D level more than the mineral homeostasis such as calcium and phosphate.<sup>[120]</sup> Thus, significant impact of vitamin D deficiency with hair loss either alopecia areata or androgenic hair loss. Regarding the AA, because of the autoimmunity mechanism of this disease, a VDR and the vitamin D-activating enzyme 1 $\alpha$ -hydroxylase tend to contribute in AA process through various cells such as macrophages, dendritic cells and T lymphocytes. Yet, still further precise trials are required in this aspect.<sup>[79]</sup>

Some patients with alopecia seem to complain of HVDRR as it has been mentioned before, this disorder characterise by mutation in the vitamin D receptor that would affect negatively on the calcium absorption from the intestine. So, the hair loss would be the result of the defect in the RXR heterodimerization, or in the DNA binding.<sup>[121]</sup>

The androgenic alopecia is quite differ from AA, by the combination action between vitamin D and iron, a probable consequence would be hair loss in case of overexpression of c-Myc which affect on the balancing for iron and ferritin.<sup>[83]</sup> It has been postulated in Rasheed et al.<sup>[83]</sup> study that female patients with hair loss {TE and FPHL} could be secondary to low concentration of serum vitamin D and low ferritin as well.<sup>[83]</sup> Regarding the treatment of alopecia with vitamin D, Kim et al.<sup>[84]</sup> declared that, an effective treatment with topical calcipotriol for the child patient who presented with AA due to vitamin D regulatory function by differentiate B cells, T cells, and dendritic cells, also controlling Toll-like receptor in order to prevent the inflammation.<sup>[84]</sup> Although an extra considerable studies are worthy to implied especially on adult patients and other sort of alopecia.

The role of vitamin D with the photoprotection and skin cancer has been a matter of interest for many years. Doubtful ideas about the vitamin D as a protective from DNA damage and prevent the keratinocytes to be died after a long time of UVB exposure, it has been postulated two substances would interfere with the vitamin D impact, one of them is a protein metallothionein and the second one is an inhibition of mutagenic cyclobutane dimer. Based on this in vivo and in vitro studies were done to explore the role of  $1,25\{\text{OH}\}_2\text{D}$  in photoprotection aspect.<sup>[85, 86]</sup>

However, the risk of skin cancer in some studies showed limited probability for patients with adequate level of vitamin D, the circumstances behind this idea could be due to the action of vitamin D on controlling the cellular division and DNA.<sup>[89]</sup> Moreover, the hedgehog signalling pathway would be inhibited with restricted function for induce tumour.<sup>[89]</sup> Controversy, some evidences tend to disagree with this concept about the protection of vitamin D, as it been mentioned in some evidences that the epidermal keratinocytes turn to abnormal structure and become carcinogenic after a remarkable influence from the UVB, so a high concentration of serum  $25\{\text{OH}\}_2\text{D}_3$  would be clear in those patients. The results of that studies might make sense because of chronic exposure to the sun lead to increase level on serum  $25\{\text{OH}\}_2\text{D}_3$  and also increase risk for patients to develop skin cancer.<sup>[88]</sup>

The melanocytes also tend to possess vitamin D receptor in order to prevent itself from the negative impact of UVB. A potential action of tyrosinase activity, in addition to regulate cell division and tumour cells invasion. All these actions would be under a control of  $1,25\{\text{OH}\}_2\text{D}$  and VDR, both are able to work as stimulator and protective on the melanocytes.<sup>[95, 96]</sup> Therefore, a mutation of VDR or inadequate concentration of the serum  $25\{\text{OH}\}_2\text{D}_3$  may contribute to melanoma severity.<sup>[97]</sup>

A concordance point regarding the vitiligo, the vitamin D because of the immunomodulatory function to some extent would prevent the onset of the depigmentation to take place on the skin, so the preventable action could be through initiate a melanogenesis process and therefore repigmented the affected areas in the body.<sup>[99, 102]</sup>

## CONCLUSION

To sum up, considerable benefits from vitamin D on distinct skin conditions have been pointed throughout this dissertation, one of the positive points is that it regulates the keratinocytes proliferation and differentiation mechanism in psoriasis, improving the severity



of the diseases in some patients. Moreover, the hormone could play an antibacterial function particularly on the atopic dermatitis reducing the risk of bacterial skin infection in patients. Both psoriasis and atopic dermatitis are inflammatory condition, thus the immunomodulatory role of vitamin D also has a tendency to control and regulate the immune response toward the diseases. On top of that, an adequate amount of vitamin D should be taken to enhance the health status for people suffering with skin condition, but others too. It is believed that vitamin D may protect the skin from apoptosis and aging. The easiest way and commonest source of vitamin D is the sun radiation, though caution must be taken from developing skin cancer especially for people with high risk. Further trials and studies are needed frequently with updated outcomes and valid evidences.

#### **ACKNOWLEDGMENT**

A special thanks to Dr. Faraz Ali, my supervisor, for all his help, professional guidance, and assistance throughout this course.

Also, I would like to thank all the staff in the Department of Dermatology at the University Hospital of Wales.

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