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AN INSIGHT OF THE ROLE OF VITAMIN D ON SKIN DISEASES

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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}$_2$D$_3$ 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}$_2$D, 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-γ; and enhances the functioning of the antigen-presenting cells. Besides that, an obvious role of 1,25{OH}$_2$D 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.[1] This vitamin affects the skin, brain, heart, and the immune system.[2] 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.[3] Ross et al.[4] 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".[4] 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.[5]

Vitamin D was identified as a vitamin in the early 20th century.[4] Now, it is known as a fat-soluble prohormone steroid.[2] Produced by the epidermal cells of the human body, particularly the keratinocytes,[6] under the effect of sunlight {Ultraviolet B}.[2] 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.[2] 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.[2]

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.

DISCUSION

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-dehydrocholestrol is

transformed to pre-vitamin D_3. This precise physiological mechanism occurs in the human body to ensure the maintenance of good health. When heat acts on pre-vitamin D_3, it metabolises into vitamin D_3 that circulates in the blood in this inactive form and is later transformed to $25\{OH\}_2D_3$. The serum concentration of $25\{OH\}_2D_3$ is measured by physicians to determine the level of vitamin D deficiency or insufficiency.[6, 23, 26]

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.[18] 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.[19] To tackle this issue, many governments have mandated that dietary items such as milk, yogurt, and fruit juices be fortified with extra vitamin D.[2] 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.[1, 2] 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 $1,25\{OH\}_2D$ and calcium as well.[1] 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.[29] 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.[1]

Many studies have focused on the association between $1,25\{OH\}_2D$ 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.[48, 50] 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-γ 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.[34, 52]

The studies reviewed above show that the risk of bacterial skin infections in AD patients could by 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}$_2$D is highly related to TLR function.[35] A lack of vitamin D would result in the dysfunction of the skin barrier and dysregulation of the immune defence system.[32] 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.[47, 52, 53] 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.[48, 53] Oren with colleague[112] 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.[112]

Some studies have shown that infant patients with allergic skin disease have mothers with adequate levels of vitamin D during pregnancy.[113] Likewise, Gale et al.[114] 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,[114] while Back et al. stated an age of six years.[115]

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

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.[68] 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.[116]

In some studies consider 1,25$\{OH\}_2$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.[68] Despite that, Huckins et al.[69] 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.[69]

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-γ. Meanwhile, other substances for example, IL-10 and T regulatory cells are more likely to be elevated due to vitamin D.[36, 37]

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.[57]

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

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.[119]

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}$_2$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.[120] 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 1a-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.[79]

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.[121]

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.[83] It has been postulated in Rasheed et al.[83] 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.[83] Regarding the treatment of alopecia with vitamin D, Kim et al.[84] 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.[84] 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 $1,25\{OH\}_2D$ in photo-protection aspect.[85, 86]

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.[89] Moreover, the hedgehog signalling pathway would be inhibited with restricted function for induce tumour.[89] 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 $25\{OH\}_2D_3$ 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 $25\{OH\}_2D_3$ and also increase risk for patients to develop skin cancer.[88]

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 $1,25\{OH\}_2D$ and VDR, both are able to work as stimulator and protective on the melanocytes.[95, 96] Therefore, a mutation of VDR or inadequate concentration of the serum $25\{OH\}_2D_3$ may contribute to melanoma severity.[97]

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.[99, 102]

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.

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REFRENCESS

1. Bikle DD, Pillai S. VITAMIN- D, CALCIUM, AND EPIDERMAL DIFFERENTIATION. Endocr Rev1993. p. 3-19.
2. Mostafa WZ, Hegazy RA. Vitamin D and the skin: Focus on a complex relationship: A reviewVitamin D and skin: A complex relationship. Journal of Advanced Research. 2014.
3. Vanchinathan V, Lim HW. A Dermatologist's Perspective on Vitamin D. Mayo Clinic Proceedings. 2012; 87[4]: 372-80.
4. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know. The Journal of Clinical Endocrinology and Metabolism. 2011; 96[1]: 53-8.
5. Shahriari M, Kerr PE, Slade K, Grant-Kels JE. Vitamin D and the skin. Clinics in Dermatology. 2010; 28[6]: 663-8.
6. Bikle DD. Vitamin D metabolism and function in the skin. Molecular and Cellular Endocrinology. 2011; 347[1]: 80-9.
7. Du Vivier A. Atlas of clinical dermatology. 4th ed. ed. Salisbury JR, editor: Oxford : Elsevier Saunders; 2013.

8. Graham-Brown RAC. Lecture notes. Dermatology. 9th ed. ed. Burns T, Graham-Brown RAC, editors: Malden, Mass. : Blackwell Pub.; 2007.
9. Snell RS. Clinical anatomy by regions. 9th ed. ed: Philadelphia ; London : Wolters Kluwer/Lippincott Williams & Wilkins; 2012.
10. The role of keratin subfamilies and keratin pairs in the formation of human epidermal intermediate filaments. The Journal of Cell Biology. 1986; 102[5]: 1767-77.
11. Mehrel T, Hohl D, Rothnagel JA, Longley MA, Bundman D, Cheng C, et al. Identification of a major keratinocyte cell envelope protein, loricrin. Cell. 1990; 61[6]: 1103-12.
12. Hennings H, Holbrook KA. Calcium regulation of cell-cell contact and differentiation of epidermal cells in culture. An ultrastructural study. Exp Cell Res. 1983; 143[1]: 127-42.
13. McLafferty E, Hendry C, Alistair F. The integumentary system: anatomy, physiology and function of skin. Nursing standard [Royal College of Nursing [Great Britain] : 1987]. 2012; 27[3]: 35-42.
14. Sinnatamby CS, Last RJ. Last's anatomy : regional and applied. 12th ed. / [edited by] Chummy S. Sinnatamby. ed: Oxford : Churchill Livingstone/Elsevier; 2011.
15. Shapiro J. Hair loss : principles of diagnosis and management of alopecia: London : Martin Dunitz; 2002.
16. Alonso L, Fuchs E. The hair cycle. Journal of Cell Science. 2006; 119[3]: 391-3.
17. Gilhar A, Etzioni A, Paus R. Alopecia areata. New England Journal of Medicine. 2012; 366[16]: 1515-25.
18. Tang J, Fu T, Lau C, Oh D, Bikle DD, Asgari MM. Vitamin D in cutaneous carcinogenesis Part I. Journal Of The American Academy Of Dermatology. 2012; 67[5].
19. Holick M. Vitamin D deficiency. N Engl J Med2007. p. 266-81.
20. Houghton LA, Vieth R. The case against ergocalciferol [vitamin D 2] as a vitamin supplement. American Journal of Clinical Nutrition. 2006; 84[4]: 694-7.
21. Hall LM, Stephensen CB, Aronov PA, Hammock BD, Woodhouse LR, Kimlin MG, et al. Vitamin D intake needed to maintain target serum 25- hydroxyvitamin D concentrations in participants with low sun exposure and dark skin pigmentation is substantially higher than current recommendations. Journal of Nutrition. 2010; 140[3]: 542-50.
22. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D 3 : Exposure to winter sunlight in Boston and Edmonton will not promote vitamin D 3 synthesis in human skin. Journal of Clinical Endocrinology and Metabolism. 1988; 67[2]: 373-8.

23. Göring H, Koshuchowa S. Vitamin D — the sun hormone. Life in environmental mismatch. Biochemistry Moscow. 2015; 80[1]: 8-20.
24. Holick M, Maclaughlin J, Clark M, Holick S, Potts J, Anderson R, et al. Photosynthesis of previtamin D3 in human skin and the physiologic consequences. Science. 1980; 210[4466]: 203-5.
25. Rasmussen H, Wong M, Bikle D, Goodman DB. Hormonal control of the renal conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol. J Clin Invest. 1972; 51[9]: 2502-4.
26. DeLuca HF. Overview of general physiologic features and functions of vitamin D. The American Journal Of Clinical Nutrition. 2004; 80[6 Suppl]: 1689S-96S.
27. Bikle DD, Nemanic MK, Gee E, Elias P. 1,25-Dihydroxyvitamin D3 production by human keratinocytes. Kinetics and regulation. J Clin Invest. 1986; 78[2]: 557-66.
28. Bikle DD, Pillai S, Gee E, Hincenbergs M. REGULATION OF 1,25-DIHYDROXYVITAMIN- D PRODUCTION IN HUMAN KERATINOCYTES BY INTERFERON- GAMMA. Endocrinology. 1989; 124[2]: 655-60.
29. Hosomi J, Hosoi J, Abe E, Suda T, Kuroki T. Regulation of terminal differentiation of cultured mouse epidermal cells by 1α, 25- dihydroxyvitamin D 3. Endocrinology. 1983; 113[6]: 1950-7.
30. Matsumoto K, Hashimoto K, Nishida Y, Hashiro M, Yoshikawa K. Growth-inhibitory effects of 1,25-dihydroxyvitamin D3 on normal human keratinocytes cultured in serum-free medium. Biochem Biophys Res Commun. 1990; 166[2]: 916-23.
31. Oda Y, Ishikawa MH, Hawker NP, Yun Q-C, Bikle DD. Differential role of two VDR coactivators, DRIP205 and SRC- 3, in keratinocyte proliferation and differentiation. Journal of Steroid Biochemistry and Molecular Biology. 2007; 103[3-5]: 776-80.
32. Pillai S, Bikle DB, Eessalu TE, Aggarwal BB, Elias PM. Binding and biological effects of tumor necrosis factor alpha on cultured human neonatal foreskin keratinocytes. Journal of Clinical Investigation. 1989; 83[3]: 816-21.
33. Oda Y, Uchida Y, Moradian S, Crumrine D, Elias PM, Bikle DD. Vitamin D Receptor and Coactivators SRC2 and 3 Regulate Epidermis- Specific Sphingolipid Production and Permeability Barrier Formation. Journal of Investigative Dermatology. 2009; 129[6]: 1367-78.
34. Edfeldt K, Liu PT, Chun R, Fabri M, Schenk M, Wheelwright M, et al. T-cell cytokines differentially control human monocyte antimicrobial responses by regulating vitamin D metabolism. Proceedings of the National Academy of Sciences. 2010; 107[52]: 22593-8.

35. Krutzik SR, Hewison M, Liu PT, Robles JA, Stenger S, Adams JS, et al. IL-15 Links TLR2/1-Induced Macrophage Differentiation to the Vitamin D-Dependent Antimicrobial Pathway. The Journal of Immunology. 2008; 181[10]: 7115-20.
36. Penna G, Adorini L. 1α,25-Dihydroxyvitamin D3 Inhibits Differentiation, Maturation, Activation, and Survival of Dendritic Cells Leading to Impaired Alloreactive T Cell Activation. The Journal of Immunology. 2000; 164[5]: 2405-11.
37. Lemire JM, Archer DC, Beck L, Spiegelberg HL. Immunosuppressive actions of 1,25-dihydroxyvitamin D 3 : Preferential inhibition of Th 1 functions. 1995. p. 1704S.
38. Tang J, Zhou R, Luger D, Zhu W, Silver PB, Grajewski RS, et al. Calcitriol suppresses antiretinal autoimmunity through inhibitory effects on the Th17 effector response. Journal of Immunology. 2009; 182[8]: 4624-32.
39. Joshi S, Pantalena LC, Liu XK, Gaffen SL, Liu H, Rohowsky-Kochan C, et al. 1,25-Dihydroxyvitamin D 3 ameliorates Th17 autoimmunity via transcriptional modulation of interleukin- 17A. Molecular and Cellular Biology. 2011; 31[17]: 3653-69.
40. Rudensky A. Regulatory T cells and Foxp3. Immunol Rev2011. p. 260-8.
41. Ardalan MR, Maljaei H, Shoja MM, Piri AR, Khosroshahi HT, Noshad H, et al. Calcitriol Started in the Donor, Expands the Population of CD4 + CD25 + T Cells in Renal Transplant Recipients. Transplantation Proceedings. 2007; 39[4]: 951-3.
42. Royal W, Mia Y, Li H, Naunton K. Peripheral blood regulatory T cell measurements correlate with serum vitamin D levels in patients with multiple sclerosis. Journal of Neuroimmunology. 2009; 213[1]: 135-41.
43. Heine G, Niesner U, Chang Hd, Steinmeyer A, Zügel U, Zuberbier T, et al. 1,25-dihydroxyvitamin D 3 promotes IL- 10 production in human B cells. European Journal of Immunology. 2008; 38[8]: 2210-8.
44. Benson AA, Toh JA, Vernon N, Jariwala SP. The role of vitamin D in the immunopathogenesis of allergic skin diseases. 2012. p. 296-301.
45. Wolff K, Johnson RA, Fitzpatrick TB. Fitzpatrick's color atlas and synopsis of clinical dermatology. 6th ed. ed: New York : McGraw-Hill Medical ; London : McGraw-Hill distributor; 2009.
46. Boguniewicz M, Leung D. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. Immunol Rev2011. p. 233-46.
47. Hata TR, Audish D, Kotol P, Coda A, Kabigting F, Miller J, et al. A randomized controlled double- blind investigation of the effects of vitamin D dietary supplementation

in subjects with atopic dermatitis. Journal of the European Academy of Dermatology and Venereology. 2013.

48. Samochocki Z, Bogaczewicz J, Jeziorkowska R, Sysa-Jędrzejowska A, Glińska O, Karczmarewicz E, et al. Vitamin D effects in atopic dermatitis. Journal of the American Academy of Dermatology. 2013; 69[2]: 238-44.
49. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology. 1993; 186[1]: 23-31.
50. Wang SS, Hon KL, Kong APS, Pong HNH, Wong GWK, Leung TF. Vitamin D deficiency is associated with diagnosis and severity of childhood atopic dermatitis. Pediatric Allergy and Immunology. 2014; 25[1]: 30-5.
51. Tollefson MM, Bruckner AL, Cohen BA, Antaya R, Bruckner A, Horii K, et al. Atopic Dermatitis: Skin-Directed Management. Pediatrics. 2014; 134[6]: e1735-e44.
52. Di Filippo P, Scaparrotta A, Rapino D, Cingolani A, Attanasi M, Petrosino MI, et al. Vitamin D Supplementation Modulates the Immune System and Improves Atopic Dermatitis in Children. International Archives of Allergy and Immunology. 2015; 166[2]: 91-6.
53. Javanbakht MH, Keshavarz SA, Djalali M, Siassi F, Eshraghian MR, Firooz A, et al. Randomized controlled trial using vitamins E and D supplementation in atopic dermatitis. Journal of Dermatological Treatment, 2011; 22[3]: 144-150.
54. Pathogenesis of Psoriasis: Oxford, UK: Blackwell Publishing Ltd; 2007. 45-60 p.
55. Lowes MA, Bowcock A, Krueger J. Pathogenesis and therapy of psoriasis. Nature2007. p. 866-73.
56. Gisondi P, Rossini M, Di Cesare A, Idolazzi L, Farina S, Beltrami G, et al. Vitamin D status in patients with chronic plaque psoriasis. British Journal of Dermatology. 2012; 166[3]: 505-10.
57. Orgaz-Molina J, Buendía-Eisman A, Arrabal-Polo MA, Ruiz JC, Arias-Santiago S. Deficiency of serum concentration of 25- hydroxyvitamin D in psoriatic patients: A case-control study. Journal of the American Academy of Dermatology. 2012; 67[5]: 931-8.
58. Berth-jones J, Hutchinson PE. Vitamin D analogues and psoriasis. British Journal of Dermatology. 1992; 127[2]: 71-8.
59. Barna M, Bos JD, Kapsenberg ML, Snijdewint FGM. Effect of calcitriol on the production of T-cell-derived cytokines in psoriasis. British Journal of Dermatology. 1997; 136[4]: 536-41.

60. Smith EL, Pincus SH, Donovan L, Holick MF. A novel approach for the evaluation and treatment of psoriasis: Oral or topical use of 1,25-dihydroxyvitamin D can be a safe and effective therapy for psoriasis. Journal of the American Academy of Dermatology. 1988; 19[3]: 516-28.
61. Sips AJAM, Netelenbos JC, Barto R, Verburgh CA, Nieboer C, van Der Vijgh WJF. Topically applied low-dose calcitriol has no calciotropic effect in patients with stable plaque psoriasis. Journal of the American Academy of Dermatology. 1994; 30[6]: 966-9.
62. Long CC, Marks R. Calcipotriol and betamethasone valerate for psoriasis. 1991. p. 921-2.
63. Ala-Houhala MJ, Reunala T, Karppinen T, Snellman E, Vähävihu K, Kautiainen H, et al. Narrow- band ultraviolet B treatment boosts serum 25- hydroxyvitamin D in patients with psoriasis on oral vitamin D supplementation. Acta Dermato-Venereologica. 2014; 94[2]: 146-51.
64. Osmancevic A, Landin-wilhelmsen K, Larkö O, Wennberg Am, Krogstad AL. Vitamin D production in psoriasis patients increases less with narrowband than with broadband ultraviolet B phototherapy. Photodermatology, Photoimmunology & Photomedicine. 2009; 25[3]: 119-23.
65. Perez A, Raab R, Chen TC, Turner A, Holick M. Safety and efficacy of oral calcitriol [1,25- dihydroxyvitamin D-3] for the treatment of psoriasis. British Journal Of Dermatology. 1996; 134[6]: 1070-8.
66. Gaál J, Kiss J, Horváth I, Lakos G, Szodoray P, Horkay E, et al. Immunological and clinical effects of alphacalcidol in patients with psoriatic arthropathy: Results of an open, follow- up pilot study. Acta Dermato-Venereologica. 2009; 89[2]: 140-4.
67. Petho Z, Kulcsar-Jakab E, Kalina E, Balogh A, Pusztai A, Gulyas K, et al. Vitamin D status in men with psoriatic arthritis: a case- control study. With other metabolic bone diseases. 2015; 26[7]: 1965-70.
68. Werner de Castro G, Neves F, Pereira I, Fialho S, Ribeiro G, Zimmermann A. Resolution of adalimumab- induced psoriasis after vitamin D deficiency treatment. Clinical and Experimental Investigations. 2012; 32[5]: 1313-6.
69. Huckins D, Felson DT, Holick M. Treatment of psoriatic arthritis with oral 1,25-dihydroxyvitamin D 3 : a pilot study. Arthritis & Rheumatism. 1990; 33[11]: 1723-7.
70. Kragballe K, Hoffmann V, Ortonne JP, Tan J, Nordin P, Segaert S. Efficacy and safety of calcipotriol plus betamethasone dipropionate scalp formulation compared with calcipotriol scalp solution in the treatment of scalp psoriasis: a randomized controlled trial. Br J Dermatol. 2009; 161[1]: 159-66.

71. Lim YY, Kim SY, Kim HM, Li KS, Kim MN, Park KC, et al. Potential relationship between the canonical Wnt signalling pathway and expression of the vitamin D receptor in alopecia. Clinical and Experimental Dermatology. 2014; 39[3]: 368-75.
72. Komiya Y, Habas R. Wnt signal transduction pathways. Organogenesis. 2008; 4[2]: 68-75.
73. Wang J, Lu Z, Au J. Protection Against Chemotherapy-Induced Alopecia. Pharm Res. 2006; 23[11]: 2505-14.
74. Alkhalifah A, Alsantali A, Wang E, McElwee KJ, Shapiro J. Alopecia areata update: Part I. Clinical picture, histopathology, and pathogenesis. Journal of the American Academy of Dermatology. 2010; 62[2]: 177-88.
75. Ito T. Recent Advances in the Pathogenesis of Autoimmune Hair Loss Disease Alopecia Areata. 2013; 2013.
76. Mady LJ, Ajibade DV, Hsaio C, Teichert A, Fong C, Wang Y, et al. The Transient Role for Calcium and Vitamin D during the Developmental Hair Follicle Cycle. Journal of Investigative Dermatology. 2016.
77. Demay MB. The hair cycle and Vitamin D receptor. Archives of Biochemistry and Biophysics. 2012; 523[1]: 19-21.
78. Mahamid M, Samamra M, Abu-Elhija O, Nseir W, Mahamid A. Association between vitamin D levels and alopecia areata. Israel Medical Association Journal. 2014; 16[6]: 367-70.
79. Aksu Cerman A, Sarikaya Solak S, Kivanc Altunay I. Vitamin D deficiency in alopecia areata. British Journal of Dermatology. 2014; 170[6]: 1299-304.
80. Fawzi MMT, Mahmoud SB, Ahmed SF, Shaker OG. Assessment of vitamin D receptors in alopecia areata and androgenetic alopecia. Journal of Cosmetic Dermatology. 2016:<xocs:firstpage xmlns:xocs=""/>.
81. Sakai Y, Demay MB. Evaluation of keratinocyte proliferation and differentiation in vitamin D receptor knockout mice. Endocrinology. 2000; 141[6]: 2043-9.
82. Bolland MJ, Ames RW, Grey AB, Horne AM, Mason BH, Gamble GD, et al. Does degree of baldness influence vitamin D status? Med J Aust. 2008; 189[11-12]: 674-5.
83. Rasheed H, Mahgoub D, Hegazy R, El-Komy M, Abdel Hay R, Hamid MA, et al. Serum Ferritin and Vitamin D in Female Hair Loss: Do They Play a Role? Skin Pharmacology and Physiology. 2013; 26[2]: 101-7.
84. Kim D, Lee JW, Kim I, Choi S, Lim Y, Kim HM, et al. Successful Treatment of Alopecia Areata with Topical Calcipotriol. Ann Dermatol. 2012; 24[3]: 341-4.

85. Lee J-H, Youn JI. The photoprotective effect of 1,25- dihydroxyvitamin D 3 on ultraviolet light B- induced damage in keratinocyte and its mechanism of action. Journal of Dermatological Science. 1998; 18[1]: 11-8.
86. Wong G, Gupta R, Dixon KM, Deo SS, Choong SM, Halliday GM, et al. 1,25-Dihydroxyvitamin D and three low- calcemic analogs decrease UV- induced DNA damage via the rapid response pathway. Journal of Steroid Biochemistry and Molecular Biology. 2004; 89: 567-70.
87. Matsuoka LY, Ide L, Wortsman J, Maclaughlin JA, Holick MF. Sunscreens Suppress Cutaneous Vitamin D3 Synthesis. Journal of Clinical Endocrinology & Metabolism. 1987; 64[6]: 1165-8.
88. Tang JY, Fu T, Lau C, Oh DH, Bikle DD, Asgari MM. Vitamin D in cutaneous carcinogenesis:Part II: Part II. Journal of the American Academy of Dermatology. 2012; 67[5]: 817.e1-.e11.
89. Picotto G, Liaudat AC, Bohl L, Talamoni NTD. Molecular Aspects of Vitamin D Anticancer Activity. Cancer Investigation, 2012; 30[8]: 604-14.
90. Tang J, Parimi N, Wu A, John Boscardin W, Shikany J, Chren M-M, et al. Inverse association between serum 25[OH] vitamin D levels and non- melanoma skin cancer in elderly men. An International Journal of Studies of Cancer in Human Populations. 2010; 21[3]: 387-91.
91. Tang JY, Xiao TZ, Oda Y, Chang KS, Shpall E, Wu A, et al. Vitamin D3 inhibits hedgehog signaling and proliferation in murine Basal cell carcinomas. Cancer Prev Res [Phila]. 2011; 4[5]: 744-51.
92. Ferguson-Yates BE, Li H, Dong TK, Hsiao JL, Oh DH. Impaired repair of cyclobutane pyrimidine dimers in human keratinocytes deficient in p53 and p63. Carcinogenesis. 2007; 29[1]: 70-5.
93. Maryam MA, Jean T, Margaret EW, Mary-Margaret C, Charles PQ, Dan B, et al. Association of Prediagnostic Serum Vitamin D Levels with the Development of Basal Cell Carcinoma. Journal of Investigative Dermatology. 2009; 130[5]: 1438.
94. Eide MJ, Johnson DA, Jacobsen GR, Krajenta RJ, Rao DS, Lim HW, et al. Vitamin D and nonmelanoma skin cancer in a health maintenance organization cohort. Archives of Dermatology. 2011; 147[12]: 1379-84.
95. Randerson-Moor JA, Taylor JC, Elliott F, Chang Y-M, Beswick S, Kukalizch K, et al. Vitamin D receptor gene polymorphisms, serum 25- hydroxyvitamin D levels, and

melanoma: UK case– control comparisons and a meta- analysis of published VDR data. European Journal of Cancer. 2009; 45[18]: 3271-81.

96. Eisman JA, Tutton PJM. Suppression of in Vivo Growth of Human Cancer Solid Tumor Xenografts by 1, 25- Dihydroxyvitamin D3. Cancer Research. 1986; 47[1]: 21-5.
97. Gambichler T, Bindsteiner M, Höxtermann S, Kreuter A. Serum 25- hydroxyvitamin D serum levels in a large German cohort of patients with melanoma. British Journal of Dermatology. 2013; 168[3]: 625-8.
98. Alghamdi K, Kumar A. Depigmentation therapies for normal skin in vitiligo universalis. J Eur Acad Dermatol Venereol2011. p. 749-57.
99. Ayd, amp, x, ng, x00F, z İE, et al. Analysis of Vitamin D Receptor Gene Polymorphisms in Vitiligo. Dermatology. 2012; 224[4]: 361-8.
100. Silverberg JI, Silverberg AI, Malka E, Silverberg NB. A pilot study assessing the role of 25 hydroxy vitamin D levels in patients with vitiligo vulgaris. Journal of the American Academy of Dermatology. 2010;62[6]:937-41.
101. Felsten LM, Alikhan A, Petronic-Rosic V. Vitiligo: A comprehensive overview: Part II: Treatment options and approach to treatment. Journal of the American Academy of Dermatology. 2011; 65[3]: 493-514.
102. Parsad D, Saini R, Nagpal R. Calcipotriol in Vitiligo: A Preliminary Study. Pediatric Dermatology. 1999; 16[4]: 317-20.
103. Parsad D, Saini R, Verma N. Combination of PUVAsol and Topical Calcipotriol in Vitiligo. Dermatology. 1998; 197[2]: 167-70.
104. George WA, Min Q, Jennifer N, Myung-Hwa K, Stephan RK, Grogan RT, et al. Propionibacterium acnes Induces an IL- 17 Response in Acne Vulgaris that Is Regulated by Vitamin A and Vitamin D. Journal of Investigative Dermatology. 2013; 134[2]: 366.
105. Buchanan P, Courtenay M. Prescribing in Dermatology: Cambridge University Press; 2006.
106. Finch J, Munhutu MN, Whitaker-Worth DL. Atopic dermatitis and nutrition. Clinics in Dermatology. 2010; 28[6]: 605-14.
107. Al Shobaili HA. The pattern of skin diseases in the Qassim region of Saudi Arabia: What the primary care physician should know. Annals of Saudi Medicine. 2010; 30[6]: 448-53.
108. Alakloby OM. Pattern of skin diseases in Eastern Saudi Arabia. Saudi Medical Journal. 2005; 26[10]: 1607-10.

109. Al-Saeed WY, Al-Dawood KM, Bahnassy AA, Bukhari IA. Prevalence and pattern of skin disorders among female schoolchildren in Eastern Saudi Arabia. Saudi Medical Journal. 2006; 27[2]: 227-34.
110. Alsuwaida AO, Al Sayyari AA, Mousa DH, Alhejaili FF, Al-Harbi AS, Housawi AA, et al. Prevalence of vitamin D deficiency in Saudi adults. Saudi Medical Journal. 2013; 34[8]: 814-8.
111. Elsammak MY, Al-Wossaibi AA, Al-Howeish A, Alsaeed J. High prevalence of vitamin D deficiency in the sunny Eastern region of Saudi Arabia: a hospital-based study. East Mediterr Health J. 2011; 17[4]: 317-22.
112. Oren E, Banerji A, Camargo CA. Vitamin D and atopic disorders in an obese population screened for vitamin D deficiency. 2008. p. 533-4.
113. Camargo Jr CA, Rifas-Shiman SL, Rich-Edwards JW, Kleinman K, Gillman MW, Litonjua AA, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. American Journal of Clinical Nutrition. 2007; 85[3]: 788-95.
114. Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN, et al. Maternal vitamin D status during pregnancy and child outcomes. European Journal of Clinical Nutrition. 2007; 62[1]: 68.
115. Stenberg B. Does Vitamin D Intake During Infancy Promote the Development of Atopic Allergy? Acta Dermato-Venereologica. 2009; 89[1]: 28-32.
116. Okita H, Ohtsuka T, Yamakage A, Yamazaki S. Polymorphism of the vitamin D 3 receptor in patients with psoriasis. Arch Dermatol Res. 2002; 294[4]: 159-62.
117. Dayangac-Erden D, Karaduman A, Erdem-Yurter H. Polymorphisms of vitamin D receptor gene in Turkish familial psoriasis patients. Founded in 1869 as Archiv für Dermatologie und Syphilis. 2007; 299[10]: 487-91.
118. Mee JB, Cork MJ. Vitamin D Receptor Polymorphism and Calcipotriol Response in Patients with Psoriasis. 1998. p. 301-2.
119. Reichrath J, Schilli M, Kerber A, Bahmer FA, Czarnetzki BM, Paus R. Hair follicle expression of 1,25-dihydroxyvitamin D3 receptors during the murine hair cycle. Br J Dermatol. 1994; 131[4]: 477-82.
120. Li YC, Pirro AE, Meuse J, Demay MB, Amling M, Baron R, et al. Normalization of mineral ion homeostasis by dietary means prevents hyperparathyroidism, rickets, and osteomalacia, but not alopecia in vitamin D receptor- ablated mice. Endocrinology. 1998; 139[10]: 4391-6.

121. Malloy PJ, Feldman D. The role of vitamin D receptor mutations in the development of alopecia. Molecular and Cellular Endocrinology. 2011; 347[1]: 90-6.
122. Finlay AY, Khan GK. Dermatology Life Quality Index [DLQI]—a simple practical measure for routine clinical use. Clinical and Experimental Dermatology. 1994; 19[3]: 210-6.
123. Resources 2016 [Available from: http://www.nottingham.ac.uk/homeforeczema/resources.aspx.