REVIEW ARTICLE

Role of vitamin D in skin diseases: A review article

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ABSTRACT

Background: Vitamin D is a fat-soluble steroid that works like a prohormone and performs a central role in skeletal health, cardiovascular diseases, neurological disorders, reproductive diseases, cancers, infections, autoimmune and dermatological diseases. Vitamin D has a role in several skin functions involving keratinocyte apoptosis, keratinocyte differentiation and proliferation, barrier function, and Immunomodulatory effect. Also, vitamin D offers a therapeutic option for multiple skin diseases.

Objectives: To provide a brief outline of the metabolism of vitamin D, its function in skin physiology and cutaneous disorders.

Methods: A literature review was conducted by searching in PubMed, UpToDate, and the Cochrane Library. All randomized controlled studies, meta-analysis studies, cohort studies, case-control studies, and reviews relevant to vitamin D and skin diseases administered by any route and published in english were identified.

Conclusion: Low vitamin D levels were related to multiple diseases, including dermatological disorders. However, further randomized clinical research is necessary to establish the vitamin D impact and its analogs as a treatment option in dermatological disorders.

KEY WORDS: Vitamin D, calcitriol, skin diseases, wound healing, psoriasis, atopic dermatitis, vitiligo, scleroderma, bullous pemphigoid, pemphigus vulgaris, ichthyosis, skin cancer, acne, and rosacea

INTRODUCTION

Vitamin D is a fat-soluble steroid, works like a prohormone and perform a central role in skeletal health, heart diseases, neurological diseases, reproductive diseases, tumors, infections, autoimmune and dermatological diseases.[1, 2] The skin is the target organ for the vitamin D active form, which acts as producing this vitamin.[1] Vitamin D is generated in the skin via sunlight and is found in dietary supplementation.[2] The majority of vitamin D is obtained by skin exposed to ultraviolet radiation [UVR] and, more specifically, ultraviolet B-rays [UVB].[2] Vitamin D has endocrine, autocrine, and paracrine functions.[3,4] The endocrine function of vitamin D controls calcium concentrations in the blood by regularly enhancing the absorption of phosphorus and calcium from the gut or enhancing calcium out of bones.[5] The autocrine and paracrine functions of vitamin D are based on genetic transcription, which is considered specific to the type of cell expressing nuclear vitamin D receptors [VDR].

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The possible impacts involve suppressing cell propagation, inducing cell distinction, and apoptosis, that might have a role in immunity, cancer, and several human body systems.[5] Vitamin D has a role in many skin functions, involving keratinocyte distinction and propagation, keratinocyte apoptosis, barrier function, and Immunomodulatory effect.[1] Also, vitamin D offers a therapeutic option for multiple skin diseases.[1,6]

Objectives: Our research will provide a brief outline of the metabolism of vitamin D, vitamin D role in skin physiology, and cutaneous conditions.

METHODS

A review was conducted by searching in PubMed, UpToDate, and the Cochrane Library during the fourth week of June 2020. Keywords searched included vitamin D, calcitriol, skin diseases, wound healing, atopic dermatitis, psoriasis, vitiligo, scleroderma, ichthyosis, skin cancer, and rosacea. The number of research screened was 250, and the number of studies involved was 183 with preference to the studies conducted within the past 30 years, whether studies conducted for humans or animals. All randomized controlled studies, meta-analysis studies, cohort studies, case-control studies, and reviews relevant to vitamin D and skin diseases administered by any route and published in english were identified. The research was also included in the review if they discussed the metabolism and vitamin D sources, vitamin D role in skin physiology, and skin diseases. All procedures followed were under the ethical standards of the responsible committee on human experimentation [institutional and national] and with the Helsinki Declaration of 1964, as revised in 2013. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

REVIEW OF LITERATURE

1.Vitamin D

1.1 Vitamin D: Synthesis and Functions

Vitamin D is a lipophilic steroid prohormone. There are two primary vitamin D forms: vitamin D2 or ergocalciferol and vitamin D3 or cholecalciferol. Ergocalciferol is derived from plants, and cholecalciferol is generated in the skin from 7-dehydrocholesterol beneath the ultraviolet light effect. The primary vitamin D source is skin production by sunlight. In the skin, 7-dehydrocholesterol on exposure to ultraviolet radiation B is turned to the Pre-vitamin D3 which is then isomerized to vitamin D3. Finally, vitamin D3 is transferred to the bloodstream. In the hepatocytes, vitamin D3 is hydroxylated to 25-hydroxyvitamin D3 [25(OH)D3] through D 25-hydroxylase, which is used to measure vitamin D. However, 25-hydroxyvitamin D3 [25(OH)D3] is inactive biologically and needs more hydroxylation. Thus, in the kidney, the 25-hydroxyvitamin D3 [25(OH)D3] is hydrolyzed by 1α-hydroxylase to 1,25-dihydroxyvitamin D or calcitriol, which is a vitamin D active form.[1,7,8]

The vitamin D impact in controlling cell differentiation, apoptosis, proliferation, and Immunomodulatory is interfering with the vitamin D receptor [VDR]. After the VDR stimulates, they react with the retinoid X receptor to create a heterodimeric complex. The genomic action of vitamin D is when the RXR/VDR complex is selected for the vitamin D response elements [VDREs] in specific gene promoters to control their expression. In opposite the non-genomic

action that is direct vitamin D affects many signaling pathways.[1]

1.2 Role of vitamin D in skin physiology

The keratinocytes are considering the primary source of vitamin D, and they also have the enzymatic machinery to metabolize the vitamin D generated to the active form [1,25-dihydroxy vitamin D]. Besides, the keratinocytes express the VDR; thus, they respond in a paracrine and autocrine route to the 1,25-dihydroxyvitamin D.[1,9] Vitamin D and the differentiation and proliferation of the epidermis. The vitamin D impact on epidermal differentiation and proliferation occurs directly or by its reaction with calcium. Calcitriol promotes the differentiation of keratinocytes by excess the expression of loricrin [LOR], involucrin [IVL], filaggrin [FLG], and transglutaminase [TG] of the cornified envelope while suppressing the proliferation. The impact of vitamin D in the differentiation is in a portion of the ability of calcitriol to elevate the intracellular Ca2+ levels due to stimulation of calcium receptors and increase the expression of phospholipase C-γ1. The differentiation of keratinocyte is controlled via vitamin D through reaction with VDR. Mice lacking the vitamin D receptor show disturbed epidermal differentiation, indicating low levels of involucrin, profilaggrin, and loricrin.[1,5,10,11]

Vitamin D and barrier function

Vitamin D impact on the skin barrier occurs by enhancing the formation of structural proteins of the cornified envelope. Also, the long-chain glycosylceramide processing, which is vital for lipid barrier formation, is controlled through the effect of vitamin D and its receptor.[1,12] Hong S et al. 2010 conducted a study to examine the calcitriol impact on antimicrobial barrier function and epidermal permeability, made defective by topical corticosteroids. The results show the efficacy of topical calcitriol to restore the antimicrobial barrier and epidermal permeability, which is declined through topical corticosteroids.[13]

Vitamin D and keratinocyte apoptosis

Calcitriol [1,25(OH)2D] was observed to enhance ceramide production by prompt neutral Mg2+-dependent sphingomyelinase to convert the sphingomyelin to ceramide. Thus, ceramide prompts the pro-differentiating impact of calcitriol [1,25(OH)2D] on keratinocytes. Also, ceramide has a critical role in enhancing apoptosis in keratinocytes. The physiological levels of 1,25[OH]2D start cell death in cultured keratinocytes but, in contrast block the proapoptotic effect of ceramides, UV radiation, and TNF-α. In opposite, the pharmacological levels of 1,25[OH]2D [≥ 10-6 M] induce a proapoptotic impact on keratinocytes.[14,15]

Immunomodulatory effects on the skin

Vitamin D receptors [VDR] are present on immune cells, like monocyte, B and T lymphocytes, macrophage, dendritic cells, mast cells, and natural killer cells. These cells express VDR and have the enzymatic machinery [cytochrome P450 family 27 subfamily B member 1 [CYP27B1] for the local formation of calcitriol. The local production of calcitriol in immune system cells is very significant for regulating and controlling the immune response.[6,16]

In innate immunity, in dendritic cells, calcitriol suppresses maturation and enhances the phenotype, which induces tolerance and suppresses immunity after stimulation with antigen. Calcitriol also inactivates the expression of major histocompatibility complex MHC class II molecules, and co-stimulatory molecules CD80, CD86, and

CD40 also inhibit the production of interleukin-12 [IL-12] and interleukin-10 [IL-10], causing the suppression of T-cell activation.[6,17]

In adaptive immunity, the activation of B and T lymphocytes increases the activity of cytochrome p450 27B1 [CYP27B1]. Calcitriol suppresses adaptive immunity via limiting the differentiation and proliferation of B cells into plasma cells. Calcitriol is an inhibitor of T helper-17 and T helper-1 function and propagation but induces T helper-2 and regulatory T cells.[6]

Calcitriol and its new analogs with immunomodulatory effects are promising new drugs for inflammatory skin diseases.[14]

2. Vitamin D and cutaneous disorders

2.1 Vitamin D and wound healing

The skin's epidermis forms a protective barrier that holds back vital fluids of the body. In mediator between the body and surroundings, the skin is permanently exposed to physical trauma and needs to be prepared to heal the wounds in response to injury.

Wound healing is a multi-step process in which different cell types and processes are involved. In the skin, an injury induces an acute inflammatory reaction through which the innate immunity contributes both to protecting against invasive organisms and inducing inflammatory cell invasion in the damaged area.[18-20] The first step include blood clotting and anti-inflammatory response.

These cells release various cytokines and growth factors that induce the migration and propagation of epidermal and dermal cells to close the wound. Once the skin is damaged, the keratinocytes multiply, migrate, and differ to regenerate the epidermis.[21]

In particular, the type of wound activates the interfollicular epidermis [IFE] and hair follicles [HF] stem cells to multiply and their offspring to reproduce again. For this activation process, the calcium and calcium labels are important.[18]

The epidermal stem cells of the skin are important for epidermal regeneration. When the skin is injured, the stem cells replicate and then migrate and divide to regenerate the epidermis. Vitamin D receptors [VDRs] are required for the initiation of these mechanisms. VDR is needed for epidermal stem cells and their progeny to self-renew, emigrate, and differentiate during wound healing.[22] Epidermal stem cells [SCs] locating in the skin have important roles for maintenance[23] and regeneration of the epidermis during wound heal.[24,25] The skin epithelia is created from the ectoderm throughout embryonic development and separate into the hair follicle [HF], the interfollicular epidermis [IFE] and the sebaceous gland [SG]. Following birth, adult SCs located in various sites are important for SG, IFE, and HF regeneration. To preserve IFE, the putative epidermal stem cells [eSCs] located in the basal layer of IFE are controlled, at least partly, by β-catenin signaling.[24] SCs locating in the HF [bSCs] bulge region defined by CD34 expression are in charge of HFs.[26] Once the skin is injured, eSCs[23,25] and bSCs[27] are first activated to multiplicate.

Afterwards, the progeny migrates and differentiates to re-epithelize the wounds, resulting in the regeneration of the intact epidermis. Numerous signaling pathways, such as calcium and β-catenin, control the epidermal SCs and progeny throughout wound repair regeneration mechanisms.[26] Vitamin D receptors [VDRs] and their ligand, 1,25[OH]2D3, are well-characterized regulators of epidermal propagation and distinction.[10] The role of VDR and its ligand in

epidermal SCs, particularly in the aspect of epidermal regeneration throughout wound repair, has received less attention. The VDR functions by regulating β-catenin signaling in the skin, that is critical for epidermal SC maintenance, like CD34+bSCs.[28,29] and eSCs.[23] The VDR binds directly to β-catenin in the AF2 domain and promotes transcription of aim genes.[30,31] Even so, the hypothesis that VDR with sufficient dietary calcium regulates epidermal SC enhancement by the interaction with β-catenin signaling and epidermal distinction by adherens junction signaling.

2.2 Vitamin D and atopic dermatitis

AD, alternatively referred to as atopic eczema, is a chronically recurrent inflammatory skin disease that influences more than 20% of children in most advanced nations and is also growing in a spread in developing nations.[32] AD is common in adolescents and children while spreading in adults is between 1% and 3%.[33] AD is characterized by pruritus and inflamed lesions that including certain parts of the body and causing generalized xerotic skin.

2.2.A Relation between Vitamin D and atopic dermatitis

The possible role of low vitamin D levels in AD development consists of several research findings.[34] The finding of vitamin D receptors [VDRs] in the majority of cells and the existence of enzymes that generate the active form of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)2D], in non-renal tissues, including the skin, has renewed interest in its roles.[15,35] Especially, its function in reducing the risk of infectious conditions, carcinomas, cardiovascular diseases, and autoimmune disorders. Vitamin D is a vital subject for dermatologists due to its cutaneous production and role in treating many more common skin diseases like psoriasis. Vitamin D's function as an immunomodulator has paved the way for more research into its therapeutic effects in psoriasis, atopic dermatitis, and skin cancer.[36]

Vitamin D supplementation can aim as a treatment agent for atopic dermatitis owing to its capacity to inhibit inflammatory responses, improve antimicrobial peptide function and maintain the permeability barrier integrity. The function of vitamin D in the pathogenesis of atopic dermatitis is not yet fully understood. An observational study of 138 Norwegian patients with atopic dermatitis showed no relation between the severity of clinical disease and low dietary vitamin D.[37] Vitamin D supplementation was observed to have a non-significant effect on seasonal atopic dermatitis in a small pilot study.[38] According to one study, a high intake of vitamin D through early life is related to a high prevalence of atopic manifestations. This was on the side with previous studies that suggest that vitamin D intake during childhood has a role in the development of atopic allergy in later childhood.[39] On the other hand, some epidemiological research found that individuals with atopic dermatitis consume less vitamin D than controls. Several studies have found that vitamin D's immunomodulatory effects contribute to the pathogenesis of atopic dermatitis. J. Schauber et al. shown that the active form of vitamin D [1,25 (OH) 2 D3] improved antibacterial peptide expression and thus protected against skin infections.[40] Liu et al. showed a relation among the vitamin D-mediated activation of toll-like receptors, decreased susceptibility to bacterial infections, and cathelicidin production.[41] Based on the level, vitamin D can activate or inactivate

keratinocyte differentiation[42] and activate the proteins synthesis like filaggrin, which are important for the formation of the stratum corneum barrier.[43] Additionally, vitamin D analogs have been shown to inhibit *in vitro* immunoglobulin E [IgE] production and IgE-mediated skin reactions.[44] Ong et al. found that acute and chronic atopic dermatitis lesions immunostaining significantly less for cathelicidin [LL-37] than psoriatic skin lesions.[45] This result can help to understand why cases with these two diseases develop different types of skin infections. Cathelicidin levels are substantially lower in cases with atopic dermatitis cases with a history of herpes simplex virus [HSV] superinfection. Cathelicidin has been shown to have activity against the herpes simplex virus [HSV] in antiviral assays.[46]

Some research on the function of vitamin D in atopic dermatitis has demonstrated that vitamin D supplementation can be used therapeutically with a good safety profile. Although, more research with larger sample sizes and longer treatment durations is necessary to determine the efficacy of vitamin D as a treatment method for atopic dermatitis.

Vitamin D3 is known to contribute to the function of the skin barrier by modulating structural proteins of the keratinized dermis layer and regulating glycoceramides that are required for moisturizing the protective lipid barrier that maintains the skin moist.[47] It modulates innate immunity by producing antimicrobial peptides [AMPs], defensin, and cathelicidin, that could help decrease the risk of skin infections.[1] Additionally, Amon et al showed that vitamin D inhibits dendritic cell activity, and monocyte production [via toll-like receptors], and increases the release of interleukin-10 at dendritic cell.[48] Additionally, they discussed how vitamin D inhibits the release of IgE by reducing B cell function and reduces the release of proinflammatory cytokines from T helper type 1 [Th1] cells.[34] Theoretically, these mechanisms can help in the reduction of chronic inflammation in the skin.

2.2.B Vitamin D levels and the severity of atopic dermatitis

As the low levels of an antimicrobial peptide in atopic dermatitis, impairing congenital immunity, a recent study questioned if supplementing with vitamin D will increase the production of antimicrobial peptide and thus improve the ability of patients with atopic dermatitis to prevent viral and bacterial skin infections.[45] Vitamin D has been studied with the severity of atopic dermatitis. For instance, many studies applied the Scoring Atopic Dermatitis [SCORAD] to determine the severity of atopic dermatitis.[49,50] The oral vitamin D supplementation function has also been expressed in the scientific literature. Despite conflicting results, most research indicates that vitamin D protects against atopic dermatitis.[51] On the other hand, many reports have shown an association between low levels of vitamin D in mothers and the development of atopic dermatitis in offspring.[52,53] However, we have reports that have not shown a significant link between atopic dermatitis and vitamin D levels.[54]

2.3 Vitamin D and psoriasis

Psoriasis is a chronic immune-mediated inflammatory skin disease that has complex pathogenesis,[55] clinically presented with scaly erythematous plaques due to the hyperproliferative epidermis and dermal cell infiltrates. The skin provides both a biosynthesis site of vitamin D and a target organ for vitamin D activity.[55] Data suggests that vitamin D has a function in terminal

differentiation and inhibiting keratinocytes from proliferating abnormally. Abnormal metabolism of vitamin D can contribute to psoriasis pathogenesis.[1,56] There is conflict about the vitamin D role in psoriasis as a causative factor, but more reports are required to ensure its role.

Masoud Maleki et al. did research to assess serum 25-OH vitamin D level in psoriatic cases and compared it with a control group to see if the serum level of vitamin D has a role in developing psoriasis. The result showed: The mean serum level of vitamin D was 14.92 ± 6.31 ng/mL in psoriatic cases and 12.52 ± 4.54 ng/mL in the control group; this difference was statistically non-significant [P = .06].[57] The prevalence of vitamin D deficiency [<20 ng/mL] in psoriatic cases was 84.0%, and 93.0% in the control group, and this difference was non-significant statistically [P = .21].[57] Also, they found that serum level of 25-OH vitamin D does not link with a nail or joint psoriasis, but it correlates links more with the female and higher PASI score.

Similarly, Michelle A. Ingram, et al performed a randomized double-blind placebo-controlled trial to determine the impact of vitamin D oral supplementation in the management of psoriasis. The cases in the treatment group were administered 200,000 IU of vitamin D3 at the baseline, then 100,000 IU monthly for 11 months. This study used a computer-generated program to randomize the study participants; cholecalciferol was given as a monthly mega-dose [200,000 IU at baseline, followed by 100,000 IU/month a gelatin capsule]. The study of both groups demonstrated statistically significant improvement in mean Psoriasis Area and Severity Index [PASI] score: the vitamin D group demonstrated a trend toward a significant difference from baseline at 6 months [p=.06], and the Psoriasis Area and Severity Index [PASI] score was significantly lower than baseline at 9 and 12 months.[58]

On the other hand, Lee et al conducted a meta-analysis to study the connection between vitamin D level and the severity of psoriasis. They used the EMBASE, MEDLINE, and Cochrane databases to search for studies related to this subject up to December 2016; the 25-OH vitamin D level in the cases having psoriasis was low more in the studies done in western countries but not in Asia or South America. The study showed that circulating 25-OH vitamin D levels were negatively linked to the severity of psoriasis, as evaluated by PASI score.[59] The result showed that the level of vitamin D is much lower in the serum of patients with psoriasis, a small but statistically significant negative association presents between psoriasis severity and 25-OH vitamin D levels. It highlighted the possible role of vitamin D in the pathogenesis of psoriasis, but more research is needed to evaluate this matter. The limitation of this meta-analysis is that majority of the reports included have a small sample size, small numbers of the study highlight the association between vitamin D level and psoriasis. The reports included have a different patient's ethnicity and clinical feature of psoriasis. The other contributors to low levels of vitamin D in psoriasis cases, such as low intake of vitamin D are not mentioned in all reports included.[59]

Amon et al. conducted a retrospective study for 1,532 patients visiting the dermatology clinic for screening measures of serum vitamin D; the median 25-OH vitamin D value of subgroup A was 22.97 ng/mL [range 2.61–96.0] and was 41.6 ng/mL in subgroup B.[48]

They also subdivided the group into common

skin disorders: atopic dermatitis, psoriasis, acne, alopecia, and hand eczema. They found that cases with psoriasis tend to have lower serum levels of vitamin D than those with atopic dermatitis, but it was statistically not significant. They found that 45.1% of psoriasis cases had a serum level of 25-OH vitamin D below 20 ng/mL.[48]

To support the important role of vitamin D in psoriasis, maybe the recent information in which psoriasis cases have a significantly increased risk for fractures (vertebral fractures) would be relevant.[60] In conclusion: Amon et al. found that the level of vitamin D is low in most skin diseases, including psoriasis. Further study is needed to support their result.

Mohammed Saleh Al-Dhubaibi conducted an exploratory study to assess the function of low vitamin D levels in the development of autoimmune disorders like psoriasis. By searching electronically published studies using Google Scholar, Saudi Digital Library, Ovid MEDLINE, and PubMed from July 2016 to October 2016.[61] Only 20 articles met the criteria for the study, which summarized the association between vitamin D and psoriasis. The sample size of these 20 articles involved: 6508 healthy controls, 2046 psoriatic cases with or without arthritis, and 167 cases with rheumatoid arthritis.[61]Fourteen re search agrees on the association of low levels of vitamin D and psoriasis; the remaining six studies deny any relation.

Kincse et al. conducted a study including 72 psoriatic patients, psoriatic arthritis and both found that an inverse relation exists between the severity of psoriasis and vitamin D3 levels. In addition, the activity of psoriatic arthritis was significantly higher in cases with insufficient vitamin D3 status.[62]

Chandrashekar et al., in their study, compared serum 25-hydroxy vitamin D concentrations in 43 psoriatic cases with sex and age-matched 43 healthy controls and noticed that psoriatic cases had smaller levels of 25-hydroxy Vitamin D in contrast to controls, and the difference was statistically significant ($P < 0.002$).[63]

Similarly, Orgaz-Molina et al., in their study that including 44 psoriatic patients, found that the 25-OH vitamin D levels were markedly lower in cases with psoriasis in comparison to the control group.[64]

Ricceri et al., in their study comparing serum 25-hydroxy vitamin D levels in 68 chronic plaque psoriasis cases and 60 healthy controls noticed that psoriatic cases had significantly ($P < 0.05$) lower levels of 25-OH vitamin D than healthy controls.[65]

El-Moaty Zaher et al. conducted a case-control study that showed that their 48 psoriatic cases had poorer readings of 25-hydroxy vitamin D than 40 healthy controls, and the difference was statistically significant.[66]

In a study of 5841 individuals in total (148 reporting psoriasis and 5693 participants without psoriasis), Wilson found no difference in serum levels of Vitamin D between cases without and with psoriasis.[67]

A comparative study of 34 psoriatic cases and 24 healthy controls found no significant difference in the mean basal values of 25(OH)D and 1,25(OH) 2D between controls and psoriatic cases.[68]

Rudi Chandra et al. conducted a cross-sectional pilot study using immunohistochemistry on 28 psoriasis vulgaris cases to see the expression of VDR (vitamin D receptors) and the psoriasis severity. The study showed there was a significant

strong negative link between PASI score and immunohistochemistry expressions of VDR. While there was a significant moderate negative link between duration of disease in psoriasis and immunohistochemistry expressions of VDR.[69] From 28 cases with psoriasis vulgaris, only 16 cases (57%) showed a strong immunohistochemistry expression of VDR, 11 cases(39.3%) showed moderate expression, and only one case (3.6%) has mild expression of VDR.[69]

Visconti et al. conducted a study that reported that the mean percentage of keratinocytes with positive immunohistochemistry expression of VDR was 41.9% lower in psoriatic skin than in healthy skin (80%).[70] Another study also reported that immunohistochemistry expressions of VDR were five times lower in psoriatic skin than in healthy skin ($P<0.001$).[71] In conclusion: Psoriasis can be initiated as a response to abnormalities of VDR, either due to low levels of VDR or genetic factors due to genetic mutations that encode their expression or receptor downregulation due to viral or bacterial infection.[70,72]

2.4 Vitamin D and vitiligo

Vitiligo is presented clinically as a depigmented whitish patch, symmetrically distributed over the body due to melanocyte destruction. It is considered an autoimmune disease although the pathogenesis is not fully understood.[73] There is a correlation with other autoimmune diseases like pernicious anemia, systemic lupus, alopecia areata, and thyroid problems has been established.[74]

Diala M. Alshiyab et al. conducted a case-control study, where they compared 100 vitiligo cases with 100 vitiligo-free individuals as a control group, and it was done in Jordan from May to December 2018. Serum 25 hydroxyvitamin D3 level was measured for each group.[73] Also, they studied if there was a possible connection between the different types of the disease presentation and serum vitamin D level or different responses to treatment attributed to serum vitamin D level. They could not find any connection between them. The result showed low serum levels in both disease and control groups, and they contributed it due to the Jordanian lifestyle, especially women by wearing hijab and covering their entire bodies, or due to darker skin complexion compared to Europe.

They concluded there is no connection between serum vitamin D and vitiligo neither in the presentation nor in management.

Many studies investigating the connection between serum vitamin D and the pathogenesis of vitiligo, but the result was nonconformity.[75,76]

Beheshti et al. conducted a study that revealed a low serum level of vitamin D in vitiligo cases; although, no control group was involved.[76]

A Chinese study involved 114 children with vitiligo who showed lower vitamin D levels and was linked to the onset of vitiligo.[77] On the other hand, other studies showed no significant differences in vitamin D levels between vitiligo cases compared to controls;[78-80] however, these research examined a limited number of cases.

Ebru Karagün et al. researched the serum concentration of vitamin D among vitiligo cases and compared it with healthy controls; the result showed that all of the cases having vitiligo vulgaris with a male predominance have no significant difference serum vitamin D level comparing to healthy control.[78]

A case-control study of 150 Saudi Arabian patients with vitiligo compared to 150 healthy controls of matched gender and age, was done to

found the connection between serum vitamin D and vitiligo cases.[81] The study showed, there are no significant differences among vitiligo group and healthy controls; there was no difference in serum vitamin D level between the two groups and also no seasonal variation. Low vitamin D levels in vitiligo cases revealed a significant association with younger age [P =.01], male gender [P =.01], positive family history of vitiligo [P =.04], and a long period of vitiligo [P =.00].[81] No association was seen between the serum level of vitamin D and vitiligo types, body surface area [BSA] involvement, or the presence of other autoimmune disorders.[81] No difference was noticed regarding sunscreen using and serum level of vitamin D, but a larger scale study is needed to confirm or deny the association between vitamin D and vitiligo.[81]

2.5 Vitamin D and hair loss

Vitamin D exerts its action through the vitamin D receptor [VDR].[82] VDR is expressed in a variety of cell populations involving the hair follicle. The two primary cells in hair follicle expressing this receptor are the mesodermal dermal papilla cell and epidermal keratinocytes.[83,84] VDR expression is essential for normal hair follicle cycling,[85] and its deficiency may suppress keratinocyte differentiation and interrupt the normal hair cycle.[84,86,87]

A study showed that cases with vitamin D-dependent rickets type 2A [VDDR2A] have alopecia at 1-3 months of age along with dental caries, osteomalacia, hyperparathyroidism, and electrolytes disturbance like hypocalcemia and hypophosphatemia.[87,88] Histologically, patient with VDDR2A showed the presence of dermal cysts and irregular epidermal structures in the lower part of the hair follicle.[88] This same histological changes were also observed in another disorder called atrichia with papular lesions [APL].[88] Atrichia with papular lesions [APL] is described as total alopecia and milia-like growths that developed after birth. Therefore, it has been hypothesized that the Hairless [Hr] and the VDR genes could be part of the same genetic pathway that regulates postnatal hair cycling.[88,89]

Therefore, vitamin D role was investigated in many studies. Herein, the authors focused on vitamin D function in non-scarring alopecia.

2.5.A Vitamin D role in alopecia areata

Alopecia areata is an autoimmune disease known for patchy hair loss in any hair-bearing area.[90] A percentage of cases with Alopecia Areata [AA] exhibit vitamin D deficiency in comparison to healthy subjects. The deficiency showed an inverse association with disease severity and duration.[91,92] Manju et al. reported that VDR expression in alopecia areata [AA] skin biopsies was reduced, and the reduction was inversely correlated with inflammation histologically. But, did not correlate with serum vitamin D levels, duration, or severity of the disease.[91] Aksu Cerman et al. revealed that serum 25-OH vitamin D levels were inversely correlated with the alopecia areata severity by using the Severity of Alopecia Tool [SALT] Score.[83] Similarly, Bakry et al.,[93] Ghafoor et al.,[94] and Attawa et al.[95] showed the same correlations.

However, Yilmaz et al. did not find any correlation between vitamin D level and the extent of alopecia areata disease progression, disease duration, nail involvement, and the number of patches.[96] This study was supported by Darwish et al.[97] and d'Ovidio et al.[98] studies.

Interestingly, the observed differences between these studies are probably because of the differ-

ent sample sizes, inclusion criteria, and the seasonal variation in serum 25[OH] D levels in each study.[99]

Some reports studied the topical application of vitamin D analogue as a treatment choice in alopecia areata. Kim et al. observed a complete hair regrowth in a 7-year-old boy after applying topical calcipotriol solution [50 mcg/mL] for three months, with no hair loss within six months follow up. VDR lacked in the affected hair follicle histologically before initiation of the therapy but then regained after hair regrowth.[86] Similar results are shown in adult populations in other studies.[100,101]

In conclusion, decreased serum vitamin D levels in alopecia areata cases suggest its function in the pathogenesis of the disease.

2.5.B Vitamin D role in Female Pattern Hair Loss and Telogen Effluvium

Female pattern hair loss (FPHL) is a common form of hair loss in females characterized by diffuse hair thinning.[102] Telogen Effluvium (TE) is characterized by diffuse hair shedding after three months to varying triggers like stress, post-partum, febrile illness and is usually self-limiting.[103] There is a possible association between low serum 25(OH) vitamin D and female pattern hair loss (FPHL) in published reports.[104,105] Moreover, other reports yield the opposite results.[106] Large-scale trials are necessary to study the vitamin D role in FPHL and TE.[107]

2.6 Vitamin D and Autoimmune blistering disease

2.6.A. Role of vitamin D on Pemphigus Vulgaris

Pemphigus Vulgaris [PV] is a Th-2 autoimmune blistering disorder due to IgG autoantibodies purposing keratinocytes desmoglein [Dsg] 3 and 1 antigen resulting in epidermal erosions and blisters in the mucous membrane and skin.[108,109] The vitamin D role has been involved in different autoimmune diseases because of its immunomodulatory impacts on adaptive and innate responses.[110]

Upon B cell activation, B cell vitamin D receptor expression is upregulated, then it will express 25[OH]D3 1-alpha-hydroxylase, which is essential in the activation of 25[OH]D.[111] *In vitro*, vitamin D suppresses B cell proliferation and increases its apoptosis. Moreover, vitamin D may also suppress plasma cell differentiation and immunoglobulin synthesis.[112,113] There are data that showed that vitamin D is able to suppress Th-2 cell differentiation.[114] Additionally, Gniadecki et al. showed that 1,25[OH]D2 could lead to adherence junctions assembly in cultures keratinocytes.[115] The study suggests that the low calcium level used in their report may not have been enough to stabilize desmosome assembly.[115] So, it is suggested that the low levels of vitamin D might aggravate PV by many mechanisms.[116] Marzano et al. showed low serum vitamin D in thirteen cases newly diagnosed with pemphigus compared to healthy control.[117] Similarly, Elkomy et al. evaluated vitamin D status in thirty-four Pemphigus Vulgaris cases and twenty healthy individuals. The study revealed that 25[OH]D was significantly lower in the PV cases than in the control.[116] In 2014 another Iranian study supported these findings.[118] However, Moravvej et al. enrolled fifty-two cases with pemphigus and fifty-six matched healthy controls and revealed no differences in serum concentrations of vitamin D among the cases and the control groups. Probably because of hypovitaminosis D in the healthy Iranian population and even globally.[119]

Moreover, Moravvej et al. study included only cases with newly diagnosed pemphigus or cases that have relapsed after discontinuing their treatment for more than six months. In contrast to El-Komy et al., where they include PV cases with severe and active disease on prednisolone treatment (which contribute to their low vitamin D levels).[119] Additionally, Moravvej et al. study showed an inverse connection between Vitamin D level and PV severity.[119]

Neha Joshi et al. support Moravvej et al. finding, where they noticed no significant differences in serum vitamin D level between cases and controls. The study documented vitamin D level alone cannot account for disorder pathogenesis but is likely to be one of several factors contributing to the disease.[110]

2.6.B. Role of vitamin D on Bullous pemphigoid

Bullous pemphigoid (BP) is a common autoimmune subepidermal blistering skin disorder characterized by autoantibodies against hemidesmosomal BP 230 and BP180.[120]

In vitro, Tukaj et al. investigated the impact of calcitriol on human keratinocytes treated with autoantibodies from a patient with bullous pemphigoid. The study showed calcitriol protects from bullous pemphigoid IgG-induced inflammatory process *in vitro*, thus favoring it's in treating bullous pemphigoid.[121]

Marzano et al. studied 15 cases with bullous pemphigoid [seven males and eight females], 13 consecutive inpatients with untreated active PV [six males and seven females], and 28 matched controls. They assessed 25[OH]D concentrations and the existence of vertebral fractures on spinal x-ray on all subjects. Cases with BP showed lower 25[OH]D concentrations and a higher prevalence of severe hypovitaminosis D (73%) than the control. BP cases even had a higher probability of fractures than control.[117]

In 2015 Marzano et al. extended their study to include 39 additional cases (17 BP and 22 PV). Where the total studied cases became 67 (35 PV,32 BP). Serum 25[OH]D, calcium, alkaline phosphatase (ALP) were measured. Along with bone mineral density (BMD). The intensity of disease was determined using autoimmune bullous skin disorder intensity score (ABSIS). The study supported the previous finding and showed that BP and PV cases had increased hypovitaminosis D and vertebral fracture prevalence. Besides, they conclude that 25[OH]D concentrations are inversely linked to disease severity.[122]

In contrast, Tukaj S and M. Kasperkiewicz et al. investigated 25[OH]D in the serum of 12 cases with BP (seven hospitalized patients with active disease and receiving therapy, and five outpatients in clinical remission on maintenance therapy, age 71.6 ± 20.9 years) with their similar matched healthy blood donors. They found no alternation in vitamin D status between BP and their control group.[120] The contrasting results between Tukaj S. et al. and Marzano et al. contributed to different methods used to measure serum vitamin D, the heterogeneity in disease activity, and therapeutic status in each study.[120]

There are case reports linking psoriasis and autoimmune blistering disorders, so the role of topical vitamin D applications (which is an essential therapeutic tool in psoriasis) should be encouraged through further research and more clinical trial on PV and BP cases.[123]

2.6.C Role of vitamin D in other autoimmune blistering diseases

Several case reports mentioned that Hailey-

Hailey disorder (also known as familial benign chronic pemphigus) could be controlled with vitamin D analogue either orally[124] or topically.[125,126] Vitamin D role was investigated in epidermolysis bullosa acquisita (EBA), an anti-type VII collagen autoantibody-induced skin blistering disease. Oral intake of calcitriol (active vitamin D) decreases disease severity and dermal neutrophil infiltration in both an antibody transfer and immunization induced EBA mouse model.[127] The study's findings promote the use of vitamin D derivatives for cases with EBA.[127]

2.7 Vitamin D and scleroderma

Scleroderma is a rare connective tissue disorder characterized by cutaneous sclerosis with variable systemic involvement.[128] Two categories of scleroderma are known: systemic sclerosis manifested by skin fibrosis and visceral organ inclusion, and localized scleroderma (morphea), which exclusively involves the skin and the underlying tissues.[128]

Plenty of studies show a link between vitamin D deficiency and systemic sclerosis (SSc).[129-132] Studies document that the pathogenesis of SSc is connected to vitamin D's function in regulating cytokine transforming growth factor (TGF-β), an essential inducer of fibroblast collagen production.[133] Interestingly, the profibrotic cytokines TGF-β1 increased in the serum of vitamin D deficient subjects.[134] Additionally, enhancement of vitamin D receptor (VDR) via paricalcitol (synthetic vitamin D analogue) decreases fibroblast TGF-β stimulation.[135]

Arnson et al. collected 327 sera samples from European patients with systemic sclerosis and 141 samples from matched controls to assess vitamin D levels and other parameters. The study revealed that cases with systemic sclerosis had significantly lower serum vitamin D levels than healthy controls (13.5 ng/ml vs. 21.6). Moreover, fibrosis of cutaneous tissue was inversely linked to vitamin D level.[136]

Oral calcitriol taking showed a promising result in treating scleroderma and generalized morphea cases in some open-label studies.[137-140] However, a randomized, double-blind, placebo-controlled study for nine month's duration with six months follow up was done in the department of Dermatology, Leiden University Medical Center, Leiden, Netherlands. A sum of 27 cases (seven subjects with SSc, twenty with morphea) was selected. Every case received calcitriol 0.75 microgram/day for 6 months plus 1.25 microgram/day for 3 months or placebo for 9 months. The cases were followed up on using the following parameters: measurement of collagen synthesis, skin score, and degradation markers besides oral aperture measurement, lung function tests, and esophageal mobility in cases with SSc. The study revealed no significant difference between the calcitriol and placebo group in morphea cases. And no conclusions regarding calcitriol efficacy in SSc because of the small sample size.[141]

Alicia et al. demonstrated that topical calcipotriol application on sclerotic mice's skin showed antifibrotic effects.[142]

2.8 Vitamin D and ichthyosis

Ichthyosis is a cutaneous disorder characterized by skin thickening due to keratinocytes hyperkeratosis. It is mostly congenital; however, acquired cases have been reported. Congenital ichthyosis is the collective name of a group of disorders of cornification that may be associated with systemic illness.[143]

There are several studies linking ichthyosis and rickets. Calcitriol suppresses keratinocyte prolif-

eration and plays a role in the mineralization of new bones by increasing intestinal phosphorus and calcium absorption. Thus, ichthyosis, which is known as keratinocyte alternation, can also be linked with abnormal vitamin D metabolism resulting in osteomalacia and rickets. Although it still must be determined whether this connection is causative or concurrent.[144]

Several reasons lead to rickets in a case with ichthyosis, like thick epidermal keratinocytes layers leading to poor sunlight penetration, sun avoidance, epidermal cholesterol metabolism abnormalities, or associated vitamin D rickets.[145]

Nine patients with severe congenital ichthyosis [congenital (nonbullous) ichthyosiform erythroderma (CIE) and lamellar ichthyosis (LI)] were enrolled in a prospective study.[146] Three of them were north African; Six were European. Calciotrophic hormones, calcium and phosphorus, bone remodeling factors, and bone mineral density (BMD) were measured before and, in some cases, after summer months. All the cases had a deficiency in 25[OH]D concentration; the study observed that North African cases had more deficiency than European cases, probably due to skin pigmentation differences.[146] After sun exposure, only one case showed improvement in vitamin status. The study concluded, pigmented skin cases with congenital ichthyosis have a severe deficiency of vitamin D, and care should be given to protect their skeletons.[146] Similarly, Sethuraman et al. reported a high prevalence of vitamin D deficiency rickets in kids with congenital ichthyosis.[147] They reported that children with serum levels of 25[OH]D ≤8 ng/ml and parathyroid hormone ≥75 pg/ml are more prone to develop rickets. So, vitamin D supplements would be an effective treatment for congenital ichthyosis.[147] Other published reports support these results.[148-152] The finding could be due to altered vitamin D metabolism, secondary keratinization disorders, patient's sun avoidance, calcium loss through the skin, or retinoid induce calcium deficiency.[149] However, another study in 1993 on sixty-five cases with keratinization diseases did not find any connection between secondary hyperparathyroidism and vitamin D deficiency or retinoid intake.[153]

Sethuraman et al. reported incidental observation of the dramatic response of skin scaling in 7 children with congenital ichthyosis and severe vitamin D deficiency (and /or rickets) after short term high oral dose vitamin D supplementation.[154] Five of those cases had autosomal recessive congenital ichthyosis, and two with epidermolytic ichthyosis. All patients had severe vitamin D deficiency (serum 25[OH]D <4 ng/ml), and secondary hyperparathyroidism, six cases had clinical and radiological evidence of rickets. The cases were given 60000 IU of oral cholecalciferol daily for ten days under supervision, then continued daily allowance of 400 to 600 IU of cholecalciferol.[154] Significant improvement in skin scaling was revealed by day 5, with more improvement by day 10, in 6 of seven patients. At one month, the skin was almost healthy in all autosomal recessive congenital ichthyosis patients, with an observed decrease in skin rigidity in all children.[154]

Tom D Thacher et al. documented that 1 of 2 children treated with topical calcipotriene revealed improvement in the treated parts of the skin. The study stated," calcipotriene can be effective in improving the severity of skin disease in children with ichthyosis".[155] Additional studies should be encouraged to verify whether

topical calcipotriene can prevent vitamin D deficiency in ichthyosis cases.[15]

Elkhateeb et al. recorded a case of hypocalcemic vitamin D-resistant rickets (HVDRR) and bullous congenital ichthyosiform erythroderma in an 8-year-old boy. HVDRR is a specific type of rickets due to vitamin D receptor defects rather than vitamin D deficiency. However, the connection might be coincidental, the authors hypothesized the connection could be because of the close genetic localization of both conditions on the long arm of chromosome 12.[156]

2.9 Vitamin D and Skin cancer (MF, Melanoma, BCC, and SCC)

Skin is one of the main organs for vitamin D production and absorption. A protective effect of vitamin D has been shown in recent laboratory studies against skin cancer and UV radiation-induced DNA damage. Numerous researchers indicated that oral vitamin D could help minimize the risk of skin cancer. Recognizing the function of vitamin D in the etiology of skin cancer in humans is highly complicated because exposure to the sun induces both vitamin D production and skin cancer.[157]

The most common cancer that afflicts humans is skin cancer. These cancers involve melanomas and two types of malignant keratinocytes: carcinomas of basal cells (BCC) and carcinomas of squamous cells (SCC). Related to the incidence of these cancers is UV light exposure. On the other hand, the skin is the main source of cholecalciferol, and UV light is necessary for its development. Keratinocytes that convert vitamin D-3, 1, 25 dihydroxyvitamin D3 [1,25(OH)2D3] (calcitriol) to its hormonal form. 1,25[OH]2D3, in turn, induces keratinocyte differentiation and raises the hope that 1,25[OH]2D3 may prevent the malignancies development in these cells. Vitamin D has been linked with a lower risk of many cancer, including colorectal, breast, and kidney cancers. However, its association with the risk of skin cancer, involving melanoma and keratinocyte carcinoma (KC, previously defined as non-melanoma skin cancer), the most prevalent cancer in the USA, is still uncertain.[158]

There is a controversial debate about how much sunlight is suitable to balance solar UV exposure's positive and negative effects in many scientific and public communities. Unquestionably, UV exposure causes skin cell DNA destruction and is a significant environmental risk factor for all forms of skin cancers. Geographically speaking, living in areas of the world with elevated erythemic UV or high average annual bright sun leads to an increased skin cancer risk, with the highest incidence of squamous cell carcinoma, followed by basal cell carcinoma and then melanoma. On the other hand, sunlight has beneficial impacts on human health, which are partly mediated by UV-B-mediated cutaneous vitamin D photosynthesis.[159]

In many studies, Park et al. discovered that vitamin D administered orally did not do any protective impact against the development of skin cancer. Increased vitamin D intakes from food and supplements were linked with increased risk of BCC of the skin, while a non-significant increased risk was found with SCC and melanoma. These trends persisted despite efforts to minimize the confounding by sun exposure. When vitamin D-rich foods were tested individually, consumption of cereal, skim milk, and fish were significantly correlated with BCC risk in both cohorts.[160]

There is evidence that insufficiently repaired

DNA damage resulted from UVA and UVB along with UV-induced immune suppression also contributes to melanoma pathogenesis, especially on skin that is exposed to the sun.[161]

Inadequately repaired melanocyte DNA damage may result in mutations or amplifications of genes included in a variety of growth and survival pathways, like cyclin D, BRAF, and kit.

At present, there is an ongoing discussion about the amount of vitamin D we need to achieve protection against cancer and other disorders. Adults may require 1,000 IU daily, according to some experts in the field, to be sufficiently protected from some cancers, bone fractures, and derive other broad-ranging health advantages. Although, some experts suggested that oral doses of 2,000 IU each day may not provide the amount of vitamin D that may be optimal. To assess potential risks that may be related to supplementation of vitamin D, one must first look at the human skin's physiological ability to synthesize vitamin D.[162]

2.10 Vitamin D and infection

2.10.A Vitamin D and bacterial infections:

Liu et al. proved how vitamin D might provoke innate immunity.[41] This group exhibits that the excitement of macrophage-bound Toll-like receptor 2/1 complex by *M tuberculosis*-derived antigens will upregulate the expression of both VDR and CYP27b1, an enzyme that converts 25-hydroxyvitamin D(25-OHD) to its active form 1,25-dihydroxyvitamin D(1,25-[OH]2D). Intracellular 1,25-(OH)2D produced an action of CYP27b1; after that, it will interact with the VDR and lead up to the initiation of the destruction of the intracellular *M tuberculosis* and antimicrobial peptide cathelicidin.[41] In the case of vitamin D insufficiency, the affected macrophage is powerless to make adequate 1,25-(OH)2D upregulate the cathelicidin production. These techniques confirm only while macrophage is affected with *M tuberculosis*. The cathelicidin has a broad-spectrum effect against various pathogens like bacteria, viruses, and fungi.[163] Also, have other antimicrobial peptides with several actions within the immune system, known as managing the expression of β-defensin.[164] Some studies in humans confirm that after infection of *Helicobacter pylori*, gastric mucosa secretes β-defensin,[165] which has the main part of immunity protection against *H.pylori* at the mucosal surface. Other research showed that vitamin D might lead to the upregulation of the oxidative burst in stimulated macrophages,[166] according to other multi-role techniques of bacterial killing. Reports of VDR polymorphisms in the human race promote the hypothesis that variations in vitamin D situation and host genes encoding vitamin D-responsive elements influence the immune response to pathogenic bacteria other than *M tuberculosis*.[167,168] However, more research is necessary in order to assist this data in other clinical settings.

2.10.B Vitamin D and viral infections:

Vitamin D adjusts the cytokine profiles of autoimmune disorders in animal models by restricting the excessive production of pro-inflammatory cytokines, for instance, interleukin-12 (IL-12), and tumor necrosis factor-α (TNF-α), consequently causing repression of the inflammation.[169] The connection between the human immunodeficiency virus (HIV) infection and vitamin D is catching more interest in modern literature. Thus, it is unsure if vitamin D state is related to specific results of HIV-related disease and the potential for immunologic recovery with antiretroviral

treatment. Although, new reports demonstrate that there might be an increased prevalence of vitamin D deficiency in HIV-infected cases compared to healthy persons, while this information stays discordant.[170,171] Laboratory models of HIV infection have demonstrated that pretreatment of human monocytes and macrophages with 1,25-(OH)2D inhibits HIV infection in specific cell lines [172] while raising HIV replication in others.[173] Other modern studies demonstrated that cathelicidin, the antimicrobial peptide organized in part by vitamin D, could directly inhibit the duplication of HIV.[174] Accordingly, the association between HIV illness, HIV treatment, and metabolism of vitamin D seems complex, and extra investigations are necessary to assist interpret the clinical significance of thus-far conflicting information on this subject.

2.11 Vitamin D and acne

Acne is a multifactorial disease including modification in the keratinization pattern within pilosebaceous follicles, causing the formation of the comedo, increased sebum production, the proliferation of *Propionibacterium acnes*, and peri-follicular inflammation.[175,176] Acne propionibacterium cases have been appeared to advance the creation of inflammatory cytokines like TNF-α, IL-1β, and IL-8.[177] Lately, identified the sebocytes like bioactive vitamin D- reacting target cells, indicating that they might be effectively treating acne.[178] Lee et al. examined the vitamin D effectiveness on the indication of inflammatory biomarkers from sebocytes (TNF-α, IL-8, IL-6, and IL-1β) and the role of the Th17 cells in acne.[179] They revealed that *P. Acnes* is a powerful induction of IL-22 and IL-17 in acne lesions. Treatment with vitamin D reduces the indication of matrix metalloprotein-9, IL-8, IL-6, and IL-17 in cultured sebocytes. Finally, they suggest the vitamin D could be the option for the treatment of acne and other Th17-mediated skin diseases.[179]

2.12 Vitamin D and rosacea

Rosacea is a common chronic inflammatory disorder marked by temporary or constant erythema, papules, telangiectasia, and pustules that are affecting the facial skin. The etiology until now unidentified but proposes many factors. Vitamin D has the reason for the induction of cathelicidin and thymic stromal lymphopoietin. Dramatic illness has various pathogenesis, as well as psoriasis and rosacea linked with cathelicidin dysfunction.[180] Cathelicidins within the first families of antimicrobial peptides (AMPs) were observed on the skin.[181] AMPs have an antimicrobial action that functions as enzyme inhibitors, chemokines, neuropeptides, and enzymes. Vitamin D performs an important part in the innate immunity in the production of AMP.[35] Ekiz et al., based on this supposition, found an elevation in vitamin D concentrations in rosacea patients, and they propose that elevation can lead to the development of rosacea. However, the connection between rosacea and vitamin D is still unclear.[182]

N. Akdogan et al. have a study in rosacea cases. The study including, study protocol and participants, this case-control study selected cases from the Dermatology outpatient clinic of Ankara Numune between October 2016 and February 2017. Incorporation rules involved the age ≥ of 18 years and consented to partake. Exclusion measures were pregnancy/lactation, utilization of medications identified to influence serum nutrient D3 levels, and any set of experiences of fiery skin sickness. Altogether, 120 members (60 cases with rosacea and 60 sex-and age-coor-

dinated HCs) were selected. Segment information involving sex, age, individual, and family clinical history were reported for all participants. Sub-atomic investigations were done at the Bioscience and Genetics labs of Ufuk University Medical Faculty. All rosacea cases had their conclusion affirmed as per the rules of the National Rosacea Society Expert Committee, and the infection subtype, length, beginning, and localization, alongside past and current treatments and encouraging elements, were assessed.[183]

Preparation of serum and analyses: A venous blood test (10 mL) was collected from every member, utilizing 4 distinctive anticoagulant tubes "2 (13 9 75 mm 9 3.0 mL every; BD Vacutainer K - EDTA 5.4 mg, BD, Plymouth, Cornwall UK) to investi-door serum 25(OH)D3 levels and VDR polymorphisms after fasting for 8 h. All the members were tried throughout the colder time of year duration (November, December, and January) in light of the possible occasional variety in nutrient D status. A serious electrochemiluminescence protein test (Roche Diagnostics, Mannheim, Germany) was the strategy utilized to gauge serum 25(OH)D3 levels. Nutrient D inadequacy was characterized as serum 25(OH) D3 esteems < 30 ng/mL, while insufficiency was characterized as qualities < 20 ng/mL. Members that were nutrient D-inadequate or - lacking at standard were permitted to receive supplements containing nutrient D.[183]

Molecular analysis of vitamin D receptor polymorphisms: After extraction of DNA from fringe blood leucocytes, the five VDR SNPs (Cdx2, FokI, BsmI, ApaI, and TaqI variations) were broke down. A groundwork expansion-based strategy (SNaPshot" Multiplex System; utilized Biosystems Inc./Life Technologies, Foster City, CA, USA) was utilized to recognize the separate polymorphisms, utilizing in-house planned preliminaries. Section examination was carried out on hereditary analyzer (ABI 3130; Applied Biosystems Inc./Life Technologies), and then going with programming (GeneMapper" Software v4.0; utilized Biosystems Inc./Life Technologies) was utilized for information investigation.[183]

Statistical analysis: All measurable investigations were made utilizing IBM SPSS Statistics for Windows (v21.0; IBM Corp., Armonk, NY, USA). Genome-wide affiliation examines were conducted with the SNP affiliation bundle in the R delicate product program. A Shapiro-Wilk test was utilized to test mathematical factors for ordinary conveyance. Information was communicated as mean SD or middle interquartile range (IQR) as suitable. Segment and clinical attributes of the examination populace were dissected utilizing distinct measurements. All out factors were portrayed with frequencies and rates. The Mann–Whitney U-test was utilized to analyze serum 25(OH)D3 levels, and the v2 test was utilized to think about allele and genotype frequencies among gatherings. Canister are strategic relapse examination was utilized to decide if the factors nutrient D3 and VDR SNPs were a risk factor for rosacea. Various calculated relapse examination was utilized to explore the connection among rosacea and the alleles. The strength of the relationship between rosacea hazard and the VDR quality polymorphisms was evaluated by OR compared to 95% CI. Tough Weinberg balance was utilized to think about allele frequencies. The contrasts among passive and predominant models were depicted. The Kruskal–Wallis test was utilized to evaluate the connection be-

tween illness length and VDR SNPs. P < 0.05 was considered genuinely critical.[183]

Results: Participants: The investigation selected 60 cases (M/F: 14/46) and 60 sex-and age-coordinated HCs (M/F: 14/46). Age (mean SD) was 4811 years for the two gatherings, and infection length (middle IQR) was 36 72 months.[183]

Vitamin D deficiency: Of the 60 cases, 52 (87%) displayed nutrient D3 inadequacy, and 59 (98%) showed nutrient D3 insufficiency. The whole benchmark group was both nutrient D-lacking and - inadequate. Serum 25(OH)D3 concentrations (middle IQR) were higher in rosacea cases (12.9 6.8 ng/mL) contrasted and HCs (10.5 3.7 ng/mL) (P < 0.001). Subjects with high serum 25(OH)D3 concentrations had a 1.36-crease expanded rosacea hazard (95% CI 1.17–1.58).[183]

Nucleotide polymorphisms: There were no critical contrasts in Cdx2, FokI, or BsmI nucleotide polymorphisms among HCs and cases, though TaqI and ApaI polymorphisms were significantly unique between the two gatherings. Contrasted and the wildtype ApaI polymorphisms, heterozygous and freak ApaI polymorphisms expanded rosacea hazard by 5.26-overlap (P < 0.01, 95% CI 1.51–18.35) and 3.69-crease (P = 0.02, 95% CI 1.19–11.48), separately. Freak TaqI polymorphisms diminished rosacea hazard nu 4.69 occasions contrasted and wildtype TaqI polymorphisms (P = 0.01, 95% CI 1.37–16.67). These outcomes uncovered that heterozygous and freak type ApaI polymorphisms expanded rosacea hazard, though freak TaqI polymorphisms were protective against rosacea. No significant hazard or defensive impact on rosacea was noticed for either BsmI or FokI alleles in any model correlation. In any case, a few alleles of TaqI, ApaI, and Cdx2 nucleotides were demonstrated to be fundamentally connected with rosacea in certain models. The outcomes indicated that heterozygosity for Cdx2 alleles expanded rosacea hazard, though wildtype ApaI and freak TaqI alleles diminished it.[183]

Clinical subtypes: There were no critical contrasts among the clinical subtypes of rosacea as far as VDR SNPs, illness term, or serum 25(OH) D3 levels in the patient gathering. AA, amino corrosive; dbSNP, Database of Single Nucleotide Polymorphisms; MAF, freak allele recurrence; RFLP, limitation section length polymorphism; SNP, single nucleotide polymorphism.[183]

Conclusion: As far as anyone is concerned, this is the principal report on the association of these five SNPs of the VDR quality with rosacea. This report recorded a relationship between rosacea danger and nutrient D and VDR SNPs, demonstrating a potential part of nutrient D and VDR pathways in rosacea. Albeit the connection between nutrient D concentrations and rosacea may not be straightforwardly causal, it is conceivable that rosacea and raised nutrient D concentrations are both initiated by UV openness yet by discrete and inconsequential systems. More planned examinations disposing of perplexing components and surveying more cases from various ethnic populaces are needed to decide if VDR SNPs and nutrient D assume a part in hereditary helplessness to rosacea. The association among RXR polymorphisms and rosacea must likewise be evaluated for its possible job in cathelicidin articulation.[183]

CONCLUSION

In conclusion, low vitamin D levels have been linked to multiple disorders, including dermatological disorders. However, further randomized

clinical studies are necessary to establish the effect of vitamin D and its analogs as a treatment option in dermatological disorders.

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