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REVIEW ARTICLE

Vitamin D and the Skin: An Update for Dermatologists

Elio Kechichian[1,2] · **Khaled Ezzedine**[1,3]

Abstract Vitamin D plays a key role in skeletal and cardiovascular disorders, cancers, central nervous system diseases, reproductive diseases, infections, and autoimmune and dermatological disorders. The two main sources of vitamin D are sun exposure and oral intake, including vitamin D supplementation and dietary intake. Multiple factors are linked to vitamin D status, such as Fitzpatrick skin type, sex, body mass index, physical activity, alcohol intake, and vitamin D receptor polymorphisms. Patients with photosensitive disorders tend to avoid sun exposure, and this practice, along with photoprotection, can put this category of patients at risk for vitamin D deficiency. Maintaining a vitamin D serum concentration within normal levels is warranted in atopic dermatitis, psoriasis, vitiligo, polymorphous light eruption, mycosis fungoides, alopecia areata, systemic lupus erythematosus, and melanoma patients. The potential determinants of vitamin D status, as well as the benefits and risks of vitamin D (with a special focus on the skin), will be discussed in this article.

Key points

Latitude, season, time spent outdoors, sex, Fitzpatrick skin type, alcohol intake, physical activity, body mass index, and single nucleotide polymorphisms of the vitamin D-binding protein are all potential determinants of vitamin D status.

Normal average daily sunscreen applications did not affect 25-hydroxyvitamin D levels in the real-life setting.

Vitamin D status has been linked to infections, cancers, and dermatological disorders such as atopic dermatitis, psoriasis, vitiligo, polymorphous light eruption, mycosis fungoides, alopecia areata and systemic lupus erythematosus.

1 Introduction

Vitamin D is a pro-hormone that plays a central role in skeletal health [1]. A growing evidence base suggests that it is also implicated in cardiovascular health [2, 3], cancers [4, 5], nervous system diseases [6, 7], reproductive diseases [8, 9], infections [10, 11], autoimmune diseases [12, 13] and pain [14]. The two main sources of vitamin D are exogenous dietary supplementation and endogenous production from skin exposure to sunlight. Most vitamin D is obtained from ultraviolet radiation (UVR) exposure of the skin [15, 16] and, more, specifically UVB [17]. Ergocalciferol (vitamin D2) is sourced from UV irradiation of

✉ Khaled Ezzedine
Khaled.ezzedine@aphp.fr

[1] Department of Dermatology, Hôpital Henri Mondor, 51 Avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France

[2] Faculty of Medicine, Saint Joseph University, Beirut, Lebanon

[3] EA EpiDermE (Epidémiologie en Dermatologie et Evaluation des Thérapeutiques), UPEC-Université Paris-Est Créteil, 94010 Créteil, France

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ergosterol, whereas epidermal 7-dehydrocholesterol (7-DHC), or provitamin D3, absorbs UVB and transforms into previtamin D3 [18]. This reaction is an obligate step in the synthesis of the biologically active product 1,25-dihydroxyvitamin D (calcitriol). Previtamin D3 is then converted to vitamin D. Afterwards, hydroxylation reactions occur in multiple tissues, such as the liver, where 25-hydroxylase transforms vitamin D into 25-hydroxyvitamin D3, and the kidney, where 1α-hydroxylase produces the final calcitriol, or 1,25 dihydroxyvitamin D3 [1, 19]. UVR exposure seems to be a determinant step in epidermal vitamin D synthesis. Due to increasing knowledge about the overall health benefits of vitamin D, reaching and maintaining an optimal vitamin D status now seems necessary. Hypovitaminosis D remains a major concern worldwide [20, 21], and public health authorities encourage sun exposure to maintain optimal vitamin D status [22]. Patients practicing daily photoprotection for various photosensitive dermatological disorders often have low vitamin D status [23]; however, excessive UV exposure has multiple detrimental effects. The WHO estimates that UVR is associated with 60,000 premature deaths per year, a loss of 1.5 million disability-adjusted life-years, 12.8 million non-melanoma skin cancers, and 200,000 melanomas [24]. Limited evidence exists for weighing risk against benefit when considering insufficient 25-hydroxyvitamin D levels and overexposure to UVR [24], and the effect of vitamin D on malignancies, infections, and dermatological disorders is still debated.

The objective of this article was to review the current evidence for the beneficial role of vitamin D in skin cancer and immunity and the potential risks of vitamin D. The effects of photoprotection on 25-hydroxyvitamin D levels, and the role of sun exposure and oral supplementation in maintaining adequate vitamin D will also be discussed.

2 Sources and Potential Determinants of Vitamin D Status

Sun exposure and Fitzpatrick skin type are two important factors that influence vitamin D status (Table 1) [25, 26]. Summer season, along with lower latitude and higher amounts of sunshine and sun exposure, have been associated with a lower risk of vitamin D deficiency [24, 26, 27], while time spent outdoors has been shown to be directly proportional to 25-hydroxyvitamin D levels [5]. Usual practices of sun exposure, including intensity, frequency, duration, and protection habits, were compiled into a validated score [24, 28, 29]. Improvement of 25-hydroxyvitamin D levels was observed, with relatively low scores reflecting daily-life sun exposure. Low summer-sun exposure confers vitamin D sufficiency in light-skinned people, along with minimal DNA damage, while the same amount of exposure produces low-level DNA damage but less vitamin D in dark-skinned people [30]. At higher latitude, greater solar zenith angles result in less favorable conditions for vitamin D production [31, 32], and, during the winter season, vitamin D synthesis significantly decreases at these higher latitudes [31, 33].

Oral intake contributes to maintaining adequate vitamin D status (Fig. 1). Primary sources include fortified products and foods [34]. The recommended daily intake in infancy is estimated to be 400 IU/day; however, after 1-year of age, the recommended daily intake is 600 IU/per day, and, after 71 years of age, the recommended daily intake reaches 800 IU/day [35]. Tripkovic et al. found that vitamin D3 is more efficacious at raising serum 25-hydroxyvitamin D concentrations than vitamin D2 [18]. The doses in oral supplements of vitamin D are often enough to prevent gross bone diseases such as osteomalacia or rickets, but not enough to prevent osteoporosis or other diseases that are thought to be linked to vitamin D [36]. Ekwaru et al. identified lower 25-hydroxyvitamin D levels in overweight patients and concluded that vitamin D supplementation was two–threefold higher for obese subjects and 1.5-fold higher for overweight subjects relative to normal-weight subjects [37].

Other potential determinants of vitamin D status include sex, body mass index (BMI), physical activity, alcohol intake, and genetic polymorphisms [24], with women being at higher risk of vitamin D deficiency [24, 38, 39]. Old age, even in countries with adequate sun exposure, is negatively correlated with vitamin D status [40]. A high BMI [41–43] and low level of physical activity are also associated with low 25-hydroxyvitamin D levels [44–46]. Interestingly, Touvier et al. found that the correlation with physical activity remained statistically significant, even after adjusting for sun exposure during activities such as outdoor hobbies or sports [24]. Therefore, increased physical activity by itself is associated with a better vitamin D status.

Kimlin et al. evaluated the contribution of solar UVR exposure and other determinants to serum 25-hydroxyvitamin D levels in over 1000 Australian adults and found that the skin surface exposed to solar radiation was the single strongest contributor to 25-hydroxyvitamin D levels, followed by geographic location, season, vitamin D supplementation, body mass, and physical activity [47]. Excessive alcohol intake has been associated with vitamin D deficiency [48]; however, moderate consumption was positively correlated with vitamin D status in several relatively recent studies [24, 43–45, 49, 50].

Single nucleotide polymorphisms (SNPs) of genes seemed to influence vitamin D status and calcium metabolism [24, 51, 52]. Of particular interest is the *GC* gene

Table 1 Potential determinant of vitamin D status

Variable	Outcome	References (year)
Oral intake and sun exposure	Higher 25-hydroxyvitamin D levels	Autier et al. (2014) [85]
Latitude	Higher vitamin D levels at lower latitudes	Major et al. (2013) [26]
		Holick (2007) [27]
		Touvier et al. (2015) [24]
Season	Higher 25-hydroxyvitamin D levels during the summer season	Terushkin et al. (2010) [31]
Fitzpatrick skin type	Lower 25-hydroxyvitamin D levels in darker skin	Harris and Dawson-Hughes (1998) [58]
		Young (2010) [59]
		Powe et al. (2013) [54]
Time spent outdoors and sun-exposure practices	Higher 25-hydroxyvitamin D levels with increased time spent outdoors	Brot et al. (2001) [5]
Gender	Lower 25-hydroxyvitamin D levels in females	Hintzpeter et al. (2008) [38]
		Mithal et al. (2009) [39]
		Touvier et al. (2015) [24]
BMI	Lower 25-hydroxyvitamin D levels with higher BMI	Greene-Finestone et al. (2011) [41]
		Daly et al. (2012) [42]
		Bertrand et al. (2012) [43]
Physical activity	Higher 25-hydroxyvitamin D levels with increased physical activity	Touvier et al. (2015) [24]
Alcohol intake	Higher 25-hydroxyvitamin D levels with moderate intake	Bertrand et al. (2012) [43]
	Lower levels with excessive intake	Shirazi et al. (2013) [49]
		Thuesen et al. (2012) [44]
		Engelman et al. (2013) [45]
		Lee (2012) [50]
		Touvier et al. (2015) [24]
Genetic polymorphism	Higher 25-hydroxyvitamin D levels with rs7041, and lower vitamin D levels with rs4588	McCullough et al. (2009) [55]

BMI body mass index

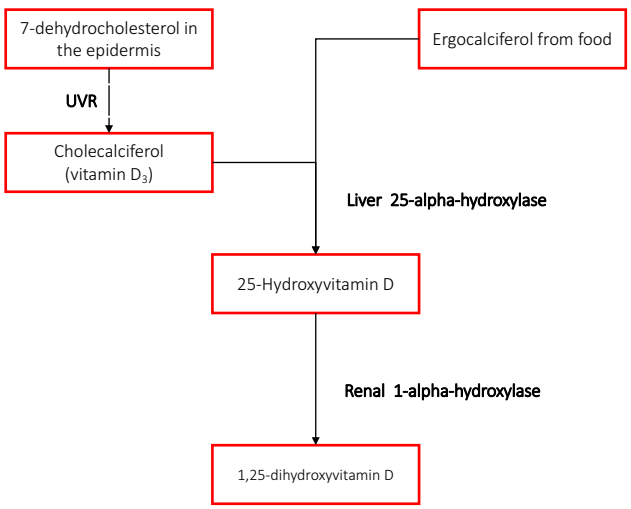

Fig. 1 Vitamin D pathway and synthesis. *UVR* ultraviolet radiation

coding for the vitamin D-binding protein. Serum 25-hydroxyvitamin D levels are dependent on the concentration of vitamin D-binding protein and variations in vitamin D-binding affinity for specific vitamin D metabolites [53]. Different gene polymorphisms produce a slightly different vitamin D-binding protein in terms of affinity for vitamin D metabolites [54]. Multiple non-synonymous SNPs are contained in the *GC* gene, two of which are relatively common—*rs7041* and *rs4588* [55]. A strong and independent correlation was found between these two polymorphisms and vitamin D status [24, 45, 56, 57]. *Rs7041* was associated with a lower risk of vitamin D deficiency, whereas *rs4588* was associated with a higher risk of vitamin D deficiency [24, 45, 56, 57].

2.1 Fitzpatrick Skin Type and Vitamin D

White skin produces vitamin D more efficiently than dark skin [58–60]. The northern European climate provided an evolutionary challenge for modern human beings who first colonized the continent following the ice age [25]. In Europe, the scarcity of sunlight compared with tropical Africa enabled efficient use to be made of short sunny periods. Moreover, white skin is able to synthesize vitamin

D even with less sunlight at the beginning and end of the summer season, as well as on cloudy days [25].

Low 25-hydroxyvitamin D levels are related to less reproductive capacity, probably due to infantile rickets with a deformed pelvis, and increased risk of tuberculosis [10, 11]. These two factors probably contributed to the strong selection pressure that determined skin-color genes, favoring a greater synthesis of vitamin D [10, 11].

African American patients had lower levels of 25-hydroxyvitamin D but higher bone mineral density compared with Caucasian patients, with racial differences in genetic polymorphisms. These differences may be related to biological and environmental modifiers, as well as genetic variation found in European American and African American adults [61].

Sun exposure for optimal vitamin D status is indicated for Fitzpatrick skin type II, with multipliers for other skin types, based on the average minimal erythematous dose [60].

In a recent systematic review regarding skin pigmentation and vitamin D production, Xiang et al. concluded that evidence on the effectiveness of vitamin D production for different skin types with different doses of UV radiation was lacking, as well as information regarding optimal sun exposure for vitamin D sufficiency [60].

3 Photoprotection, Phototherapy and Vitamin D

Photoprotection is an additional potential determinant of vitamin D status that is of particular concern in the field of dermatology and public health. In order to prevent photoaging, skin cancer, or flares of photosensitive disorders, sun-protective behaviour and other photo-protective measures have been advocated by dermatologists over the last few decades. Vitamin D deficiency was reported in patients practicing daily photo-protection, including the use of sunscreens and sun avoidance [23, 62]. The effects of clothing and sunscreens on vitamin D status have been studied in healthy individuals [63, 64], patients with photosensitive disorders [23, 62], and renal transplant patients [65, 66].

Clothing worn for cultural reasons can interfere with 25-hydroxyvitamin D levels and its health outcomes. When comparing 25-hydroxyvitamin D levels in orthodox and non-orthodox Jewish patients, Mukamel et al. found a higher prevalence of vitamin D deficiency among the orthodox patients who wore thicker layers of clothing [63]. Similarly, Allali et al. found that post-menopausal Moroccan women who wore a veil had a higher risk of osteoporosis [64]. Therefore, when thick clothing is worn, even in sunny countries, other sources of vitamin D are needed.

Vitamin D status has been studied in patients with photosensitive disorders who took different photoprotective measures, including the daily use of sunscreens. Sollitto et al. monitored vitamin D levels in eight xeroderma pigmentosum (XP) patients [67] and found that patients had consistently low 25-hydroxyvitamin D levels during the 6-year study period, with lower values in winter than in the summer season. Similarly, Querings and Reichrath reported low 25-hydroxyvitamin D levels in three XP patients and one basal cell nevus syndrome patient [68]. Additionally, Cusack et al. measured 25-hydroxyvitamin D levels in 52 biopsy-confirmed cutaneous lupus erythematosus patients and found lower 25-hydroxyvitamin D levels in patients who applied sunscreens all year round compared with those who applied sunscreen during the summer months only or not at all [23]. A study of 201 erythropoietic protoporphyria patients revealed that 63% of patients had vitamin D deficiency that was inversely proportional to the time of onset of symptoms following sun exposure [62]. Renal transplant patients are also at risk of vitamin D deficiency due to various photoprotection methods, such as clothing, sun avoidance, and sunscreens [65, 66].

Sunscreen application has been shown to affect vitamin D status, even in healthy individuals [69]. Holick stated that daily application of sunscreen on all sun-exposed body parts reduced 25-hydroxyvitamin D levels by 90% [27]. Even though sunscreen was proved to suppress vitamin D synthesis in laboratory settings, real-life evidence failed to link sunscreen use to lower vitamin D production. When studying vitamin D status in 113 healthy Australian subjects, Marks et al. found that the serum vitamin D concentration was similar in patients who applied an SPF 17 sunscreen and those who applied a placebo cream [70]; however, they did not recommend sunscreen use over all sun-exposed areas, only on the face, hands, and arms. Similarly, Farrerons et al. found that typical use of sunscreens did not decrease bone mass in 10 sunscreen users compared with 18 controls [71]. An analysis of data from 5920 adults in the National Health and Nutrition Examination survey revealed that sunscreens did not decrease 25-hydroxyvitamin D levels. Avoiding the sun and wearing long sleeves were associated with vitamin D deficiency, whereas applying sunscreen and wearing hats were not. The authors noted that the lack of association between sunscreens and low 25-hydroxyvitamin D levels might be due to the fact that the application of sunscreen was associated with prolonged sun exposure and sunburns.

Sunscreens do not completely block cutaneous absorption of UVR; a minor fraction of UVB radiation penetrates the skin, even with high-SPF sunscreens [72]. Moreover, sunscreens are rarely applied at the tested concentration of 2 mg/cm^2. In this context, Norval and Wulf commented

that very strict photoprotection blocked vitamin D production, but the inadequate application of sunscreen by average users did not result in vitamin D deficiency [73].

Narrowband (NB) UVB therapy was shown to increase 25-hydroxyvitamin D levels in psoriasis [74–76], atopic dermatitis [74, 77], vitiligo [78], and polymorphic light eruption patients [79]. Several studies compared UVB exposure with vitamin D supplementation in the treatment of vitamin D deficiency. Barth et al. revealed a significantly higher improvement of 25-hydroxyvitamin D levels with suberythemal doses of total-body NB UVB three times weekly compared with a daily 400 IU dose of oral vitamin D3 among institutionalized elderly patients [80]. Similarly, Karppinen et al. showed that a suberythemal NB-UVB dose every other week maintained and even increased serum 25-hydroxyvitamin D levels during winter [81]. Interestingly, total-body NB-UVB exposure three times weekly was shown to be more efficient in treating vitamin D deficiency than a daily 1600 IU dose of vitamin D3 [82]. Due to its potential carcinogenic effect, UVB exposure should not be considered as a first-line treatment for hypovitaminosis D; however, it could be an attractive option in patients with severe malabsorption diseases, or non-compliant patients, to rapidly replenish vitamin D stores. Continued exposure to low-dose simulated sunlight conferred vitamin D sufficiency without causing an accumulation of DNA damage [30].

4 Vitamin D and Infections

Mycobacterial growth [10, 13, 83], viral response in hepatitis C infection [84], upper respiratory tract infections [85], CD4 counts in HIV patients [85], acute infectious mononucleosis [86], and eczema herpeticum [87] were all found to be linked to vitamin D status. Vitamin D exerts an antimicrobial activity by different mechanisms. It inhibits mitogen-activated protein kinases (MAPKs) and nuclear factor (NF)-kB signaling, therefore inhibiting interleukin (IL)-1b, IL-6, IL-8, IL-12p40, IL-23, interferon (IFN)-γ, and tumor necrosis factor (TNF) and inducing the anti-inflammatory cytokine IL-10. Similarly, vitamin D also inhibits chemokines CXCL9 and CXCL10. Therefore, the severity and mortality of infections are decreased by the reduction of the overall inflammatory state. T-helper (Th) 1 proliferation is reduced and differentiation of naive T cells into FoxP3-expressing regulatory T cells (Tregs) is induced [88].

In parallel, vitamin D boosts innate immunity in Mycobacterium tuberculosis infections by inducing expression of the cathelicidin antimicrobial peptide (CAMP) gene. The protein produced by this gene, LL-37, directly inhibits mycobacteria in liquid culture [89, 90]. Cathelicidin binds and punctures the bacterial cell wall phosphatidylglycerol monolayers [91]. Similarly, the membranes of viruses such as influenza A virus, papillomavirus, and respiratory syncytial virus (RSV) can be damaged by the LL-37 protein [92, 93]. Moreover, the cathelicidin pro-peptide, hCAP18, restricts in vitro HIV-1 replication in macrophages by promoting phagosome-lysosome fusion [94].

To test the effect of vitamin D on bacterial skin infections, Muehleisen et al. put mice on dietary vitamin D3 restriction [95] and demonstrated that vitamin D and parathyroid hormone (PTH) both affected the expression of CAMP and the capacity of mice to resist Streptococcus A. Vitamin D3 metabolism, PTH1 receptor expression, and pattern receptor activation were all intricate factors that contributed to the vitamin D-related immunity boost.

Vitamin D also increases the production of antimicrobial peptide human β-defensin-2 (HBD2). HBD2 decreases RSV viral entry into host cells [96], and, similarly, decreases HIV infectivity by directly binding to the virus and downregulating its co-receptor, the CXCR4 expression on CD4+ T cells [97].

Albenali et al. found that children with atopic dermatitis with eczema herpeticum had lower LL-37 levels than children with uncomplicated atopic dermatitis, and that the 25-hydroxyvitamin D levels directly correlated with LL-37 levels. The children were supplemented with vitamin D for 2 months and the atopic dermatitis scores improved significantly, with a notable increase in LL-37 levels, suggesting a causal relationship [87]. Although not randomized, this study concluded that maintaining a vitamin D status within the normal range could be of benefit to children with atopic dermatitis.

5 Vitamin D and Dermatological Disorders

Vitamin D status was proven to be linked to several dermatological disorders, such as atopic dermatitis, psoriasis, vitiligo, mycosis fungoides (MF), systemic lupus erythematosus (SLE), systemic sclerosis, alopecia areata, and polymorphic light eruption (Table 2).

Vitamin D receptor polymorphisms are increased in atopic dermatitis patients compared with healthy controls, suggesting a crucial role of vitamin D in the pathogenesis of the disease [98, 99].

Atopic dermatitis is a common inflammatory skin disorder that involves proinflammatory chemokines and cytokines with over activation of T lymphocytes, mast cells, eosinophils, keratinocytes, dendritic cells, and macrophages [100]. LL-37 is usually overexpressed in skin injury to induce re-epithelialization, and patients with atopic dermatitis often have low LL-37 levels [101].

Table 2 Dermatological disorders associated with vitamin D status

Disease	Type of association	References (year)[a]	Level of evidence[b]
Atopic dermatitis	Low 25-hydroxyvitamin D levels in severe disease	Heine et al. (2013) [98]	2
	Vitamin D supplementation reduced disease severity	Kiliç et al. (2016) [99]	
		Camargo et al. (2014) [102]	
		Hata et al. (2010) [101]	
Psoriasis	Low 25-hydroxyvitamin D levels associated with the disease	Bergler-Czop et al. (2016) [166]	1
	Topical vitamin D treated the disease	Schlager et al. (2017) [167]	
Vitiligo	Low 25-hydroxyvitamin D levels associated with the disease	Upala and Sanguankeo (2016) [108]	1
Systemic sclerosis	Low 25-hydroxyvitamin D levels associated with the disease	Giuggioli et al. (2017) [116]	2
Alopecia areata	Low 25-hydroxyvitamin D levels in severe disease	Aksu Cerman et al. (2014) [118]	2
	Topical vitamin D treated the disease	Kim et al. (2012) [122]	
		Aksu Cerman et al. (2014) [118]	
Systemic lupus erythematosus	Low 25-hydroxyvitamin D levels in severe disease	Wu et al. (2009) [110]	2
		Mok et al. (2012) [111]	
		Amital et al. (2010) [112]	
Polymorphic light eruption	Topical 25-hydroxyvitamin D treated the disease	Gruber-Wackernagel et al. (2012) [79]	3
Cutaneous bacterial infections	Low 25-hydroxyvitamin D levels associated with increased risk in vitro	Muehleisen et al. (2012) [95]	5

[a]Only references from the last 10 years are listed

[b]Level of evidence from the Center of Evidence-Based Medicine: 1. Meta-analysis, systematic review or randomized trials; 2. Randomized trial or observational study with dramatic effect; 3. Non-randomized controlled cohort/follow-up study; 4. Case-series, case–control studies, or historically controlled studies; 5. Mechanism-based reasoning

Vitamin D supplementation increased LL-37 expression in skin biopsies of atopic dermatitis patients [101] and was shown to reduce disease severity in randomized controlled trials [102, 103].

Keratinocyte proliferation and abnormal differentiation, along with immune-cell infiltration into the epidermis and dermis, are the hallmarks of psoriasis [104]. Calcitriol controls increased proliferation and regulates keratinocyte differentiation [16]. Vitamin D inhibits the secretion of IL-2, IL-6, IL-8, and IFN-γ and increases IL-10 production, and, by doing so, it reduces T-cell proliferation and induces regulatory T-cell differentiation [105]. It also inhibits the production of psoriasin and koebnerisin, two antimicrobial peptides, and increases the expression of LL-37 and HBD2, thereby controlling inflammation in psoriasis. These anti-inflammatory and antiproliferative effects of vitamin D have led to the clinical use of topical vitamin D analogs in the treatment of psoriasis [15].

Vitiligo is a relatively common skin disease that affects up to 2% of the general population and results in immune destruction of melanocytes in the epidermis [106]. The etiology of this disorder is thought to be autoimmune as it is associated with other autoimmune diseases such as pernicious anemia, Hashimoto thyroiditis, and hyperthyroidism [107]. Vitiligo patients are often instructed to avoid sun, which might hinder vitamin D production [108]. A recent meta-analysis of observational studies revealed an association between low vitamin D and vitiligo [108]; however, it remained unclear whether or not low vitamin D was involved in the pathogenesis of vitiligo. The association of UVA or UVB therapy with topical vitamin D analogs was shown to be effective in treating vitiligo [109]. Monitoring 25-hydroxyvitamin D levels in vitiligo patients is essential to prevent other complications of vitamin D deficiency.

SLE activity was found to be associated with vitamin D status. Three large studies with sample sizes of 378, 290, and 181 patients showed a strong correlation between low 25-hydroxyvitamin D levels and SLE disease activity scores [110–112]. Mok et al. found that vitamin D deficiency is a marker of SLE activity, with a specificity comparable to anti-double-stranded DNA and anti-C1q [111]. These studies were observational; therefore, concluding a causal interference was impossible. Vitamin D status was also found to be associated with renal [113] and cardiovascular [114, 115] disorders in SLE patients. These findings need to be evaluated rigorously in large randomized controlled trials. Nevertheless, monitoring and correcting 25-hydroxyvitamin D levels in SLE is warranted.

Vitamin D deficiency is extremely common in systemic sclerosis patients, with rates as high as 90% [116].

Furthermore, less than one-third of supplemented systemic sclerosis subjects reached normal 25-hydroxyvitamin D levels [116].

Vitamin D-resistant rickets is a rare genetic disease caused by vitamin D receptor mutations [117]. Patients affected by this disorder also develop alopecia due to the fact that the vitamin D receptor plays an important role in the normal hair follicle cycle [117]. Patients with alopecia areata had significantly lower levels of vitamin D compared with vitiligo patients and healthy controls [118]. Vitamin D receptor and 1α-hydroxylase expression by immune cells, such as dendritic cells, T-lymphocytes, and macrophages, suggest that vitamin D affects different aspects of the innate and adaptive immune systems. It suppresses Th1-mediated autoimmune diseases by polarizing the immune response towards the Th2 phenotype and enhancing the production and function of Tregs [119, 120]. Alopecia areata is a CD8+ T-cell-mediated, organ-specific disease in which autoreactive cytotoxic T cells and IFN-γ-secreting natural killer cells target the hair follicle [121]. Immune modulation induced by vitamin D might play a role in alopecia areata. Topical calcipotriol application on the affected areas improved hair growth in mild to moderate alopecia areata patients [122, 123]; however, oral supplementation with vitamin D has not been rigorously studied in the treatment of alopecia areata.

Vitamin D status was found to be linked to polymorphic light eruption, and topical vitamin D analogs seemed to play a role in treating and preventing polymorphous light eruption (PLE). Activation of the receptor activator of NF-κB (RANKL), Treg induction, and dendritic cell differentiation inhibition are all intricate factors implicated in calcipotriol-mediated protection in PLE [124]. Interestingly, photohardening, an established PLE treatment method, increased 25-hydroxyvitamin D levels in affected patients [124].

6 Cancer and Vitamin D

Vitamin D status has been repeatedly evaluated in cancer patients. In 2014, Autier et al. conducted a meta-analysis regarding vitamin D and ill health [85]. They assessed all the published data regarding 25-hydroxyvitamin D levels and nine different cancers: breast, colon, prostate, esophageal, endometrial, kidney, ovarian, bladder, and non-Hodgkin lymphoma. No significant association was found between most of these neoplastic diseases and vitamin D concentrations, with the only statistically significant association found between decreased incidence of colon cancer and increased 25-hydroxyvitamin D levels. The available data for the remaining cancers yielded mixed results [85]. Pre-existing local inflammation favors the occurrence and progression of cancer in the surrounding tissue [125], while inflammatory markers are associated with rapid cancer progression and poor prognosis [126]. Non-steroidal anti-inflammatory drugs reduced the risk of colorectal cancer and melanoma [127, 128]. Low vitamin D concentrations could be associated with inflammatory diseases such as chronic colitis, predisposing to an increased risk of cancer or progression of pre-cancerous lesions such as adenomatous polyps [85].

6.1 Skin Cancers and Vitamin D

In the cutaneous tissue, vitamin D inhibits keratinocyte proliferation in vitro [129] and regulates keratinocyte differentiation [130]. Furthermore, hyperproliferative keratinocytes that lacked a vitamin D receptor exhibited a reduced rate of apoptosis [131]. Vitamin D receptor polymorphisms were linked to the development of actinic keratosis [132]. Vitamin D enhanced the DNA repair process [133] and reduced UVR-induced cyclobutane pyrimidine dimer (CPD) formation in vitro [134, 135].

Basal cell carcinoma tumors also expressed vitamin D receptors [136]. Vitamin D inhibited a key tumor pathway in the development of basal cell carcinoma, i.e. the hedgehog signaling pathway [137]. Clinical studies regarding the relationship between vitamin D status, vitamin D supplementation, and basal cell carcinoma yielded conflicting results. Eide et al. revealed that higher 25-hydroxyvitamin D levels were associated with an increased risk of keratinocyte carcinomas (formerly known as non-melanoma skin cancers) in a prospective cohort [138]. In contrast, a negative correlation was found between basal cell carcinomas and vitamin D status in multiple studies [139, 140], which might be explained by the positive correlation between UV exposure, vitamin D synthesis, and keratinocyte carcinoma, with sunlight exposure being a confounding factor.

As in basal cell carcinomas, squamous cell carcinoma cells lacked vitamin D receptors [131]. Similarly, in vitro protection from UV-related DNA damage might prevent squamous cell carcinoma development [131]. To date, epidemiologic studies evaluating the effect of vitamin D on squamous cell carcinoma in a real-life setting are lacking. Although animal studies suggest a link between vitamin D and keratinocyte cancers, a definitive causal relationship in humans is difficult to demonstrate. In this context, Park et al. conducted a prospective study on vitamin D intake and the development of skin cancer in a sample of 63,760 women and 41,530 men with 20,840 basal cell carcinomas, 2329 squamous cell carcinomas, and 1320 melanoma cases [141]. They found that oral vitamin D intake increased the risk of basal cell carcinoma without affecting the incidence of squamous cell carcinoma and cutaneous melanoma;

however, residual confounding by sun exposure, which was hard to accurately measure, was not totally excluded.

Vitamin D deficiency has been incriminated in MF [142, 143]. The prevalence of vitamin D deficiency among cutaneous T-cell lymphoma patients was close to other cancer patients compared with healthy controls [142], while aberrant clones of T cells were found to express the vitamin D receptor [144]. Vitamin D receptor polymorphism, and more specifically FokI polymorphism, was found to be significantly correlated to MF [143]. Vitamin D deficiency leads to decreased antimicrobial peptides with a higher rate of colonization by Staphylococcus aureus and sepsis that is frequent in patients with cutaneous T-cell lymphomas [145]. Staphylococcal superantigen stimulation can initiate and promote T-cell activation and aberrant clone formation [146]. Rasheed et al. did not find a significant correlation between vitamin D status and clinical variants or duration of MF [143], and concluded that vitamin D might play a role in triggering MF rather than determining the duration and extent of the disease.

Several studies have reported an association between vitamin D status and melanoma. Vitamin D receptor expression and vitamin D receptor polymorphisms have been found to be associated with melanoma [147–149], while vitamin D inhibited tumor invasion, angiogenesis, and metastasis [39, 150]. Newton-Bishop et al. found an inverse relationship between 25-hydroxyvitamin D levels at the time of diagnosis and tumor thickness, as well as the risk of melanoma relapse [151]. Ulceration was proved to be independently associated with low 25-hydroxyvitamin D levels and poorer melanoma specific survival [152]. Nürnberg et al. revealed that stage IV melanoma patients had lower 25-hydroxyvitamin D levels than stage I melanoma patients [153], and specific SNPs of the vitamin D-binding protein were independently associated with poorer outcome in melanoma patients [154, 155]. Furthermore, melanoma relapse was more common among patients with low levels of vitamin D [156]. However, Randerson-Moor et al. failed to find a relationship between vitamin D status and melanoma [157]. Furthermore, data regarding the dietary intake of vitamin D and the development of melanoma yielded conflicting results [158, 159]. To the best of our knowledge, all the published studies are observational. At present, there is currently insufficient evidence to determine the optimal serum 25-hydroxyvitamin D levels in melanoma patients. Laboratory evidence suggests a possible role for vitamin D in melanoma development and progression; however, further research is needed to identify the potential mechanisms underlying the association between vitamin D and skin cancers.

7 Potential Risks of Vitamin D

Vitamin D over supplementation leads to adverse events. The main source of vitamin D is sun exposure, and patients who excessively expose themselves to solar radiation to replenish vitamin D stores are overexposed to UVR and have an increased risk of cancer [160]. Skin erythema was shown to be a good surrogate marker of UV-induced DNA damage [160]. Therefore, advice regarding 'safe sun exposure' is based on the avoidance of erythema when exposed to solar radiation. Petersen et al. evaluated 25-hydroxyvitamin D levels and DNA damage (thymine dimers) in Danish holiday sun-seekers to investigate the simultaneous harmful and beneficial effects of UVR [161], and found that vitamin D levels and DNA damage were significantly correlated, indicating that the adverse effects of UVR were inevitable when obtaining vitamin D while on holiday [161]. Felton et al. found that low-dose sun exposure can help replenish 25 hydroxyvitamin D levels without causing severe DNA damage [30]. Relying on supplementation rather that intentional sun exposure combined with sunscreen application is a useful alternative source of vitamin D, along with 'safe sun exposure'.

Vitamin D intoxication leads to non-specific symptoms such as nausea, vomiting, constipation, weight loss, and weakness [162, 163]. Furthermore, if the excess vitamin D results in severe hypercalcemia, cardiac arrhythmia and neurological manifestations can occur [162]. Pooling of 10 National Cancer Institute cohorts showed that chronic 25-hydroxyvitamin D levels over 40 ng/mL were associated with a greater risk of pancreatic cancer [164]; hence, over supplementation with vitamin D and/or excessive sun exposure to replenish vitamin D stores can lead to significant adverse events. The Endocrine Society Practice Guidelines recommend up to 10,000 IUs daily [165].

8 Conclusions

Vitamin D plays an important role in inflammation, directly affecting lymphocyte function and cytokine secretion. Low 25-hydroxyvitamin D levels are associated with multiple dermatological disorders, systemic infections, and cancers. Appropriate dose supplementation and safe sun exposure with sunburn avoidance are warranted to prevent the adverse effects of excessive UVR and vitamin D toxicity. Further trials are needed to explore the therapeutic role of vitamin D and its analogs on the aforementioned associated diseases.

Compliance with Ethical Standards

Conflict of interest Elio Kechichian and Khaled Ezzedine have no conflicts of interest to declare.

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