VITAMIN D
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The role of vitamin D in dermatological diseases

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INTRODUCTION

Vitamin D is also of great interest in dermatology. Indeed, there is a dual relationship between it and the skin. On the one hand, it is synthesised by keratinocytes in response to sun exposure and, on the other, it works actively on the skin itself. This two-way process has been named the photoendocrine system of vitamin D [1].

From a biochemical perspective, the skin synthesises the prohormone vitamin D_3 (cholecalciferol) through the interaction between 7-dehydrocholesterol and ultraviolet light. This process can meet up to 80% of our daily needs.

Many factors influence the skin's ability to synthesise vitamin D. Amongst the most important are latitude, seasonality, phototype and means of sun exposure [2]. A minority percentage of the requirement, 20%, is taken up through the food supply in the form of vitamin D_2 (ergocalciferol), found in fruit and vegetables, and vitamin D_3, contained in high amounts especially in salmon and herring. The biologically-inactive vitamin D_3 is converted in the liver into 25-hydroxy-vitamin D_3 (calcifediol), the form most commonly found in the systemic circulation. Calcifediol is again hydrosilylated in the kidney into 1,25-dihydroxy-vitamine D_3 (calcitriol) which, by interacting with specific nuclear receptors called *Vitamin D Receptors* (VDRs), is the main driver of the biological effects of this molecule (Fig. 1) [3].

Vitamin D plays a fundamental role for bone tissue, regulating phospho-calcium homeostasis whilst a deficiency causes osteomalacia, osteoporosis and increased susceptibility to bone fractures.

However, the effects of this vitamin are not limited to the skeleton. There is growing evidence of its ubiquitous antiproliferative and immunomodulatory properties. Vitamin D deficiency has been documented in various cardiovascular, oncological, neurological, autoimmune and infectious diseases [2-4].

Of particular interest are the multiple functions that vitamin D performs in the body. By acting on the keratinocytes through an autocrine and paracrine mechanism, it controls their differentiation and proliferation whilst stimulating their production of ceramides, which are essential lipids for maintaining skin hydration[1]. Vitamin D also plays an important role in the defence against skin infections by inducing the production of antimicrobial peptides, such as cathelicidin LL-37 and beta-defensin [5]. Vitamin D exerts a relevant immunomodulatory function by inhibiting antigen presentation by Langerhans cells and the proliferation of both B- and T-lymphocytes, inducing an overall shift from a Th1 response to a Th2. This inhibits the production of proinflammatory cytokines such as IL-1, -6, -8, -12, TNF-alpha and interferon-gamma, whilst inducing the production of anti-inflammatory cytokines, such as IL-10, and the differentiation of regulatory T-cells [1].

The main dermatological diseases associated with vitamin D deficiency include both skin neoplasms and some of the most frequent immune-mediated diseases, like atopic dermatitis, psoriasis and vitiligo.

CUTANEOUS NEOPLASMS

Vitamin D is involved in cell differentiation, maturation and cellular senescence and has an inhibitory effect on neoangiogenesis and oncogenesis [6]. However, the association between vitamin D deficiency and skin neoplasms is controversial since data from the studies is conflicting [3]. Sun exposure is both a major risk factor for this type of neoplasm and the main source of cholecalciferol. For the same reason, photoprotection recommended by dermatological guidelines with the aim of preventing photoageing and photocarcinogenesis could theoretically lead to lower vitamin D production in the skin [1]. Current evidence seems to suggest that this phenomenon is unlikely with common sun filters. No good studies are available that have defined the relationship between sun exposure, photoprotection, vitamin D levels and neoplasia risk [2].

Vitamin D may be involved in the development of *Non-Melanoma Skin Cancer* (NMSC), tu-

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Conflict of interest
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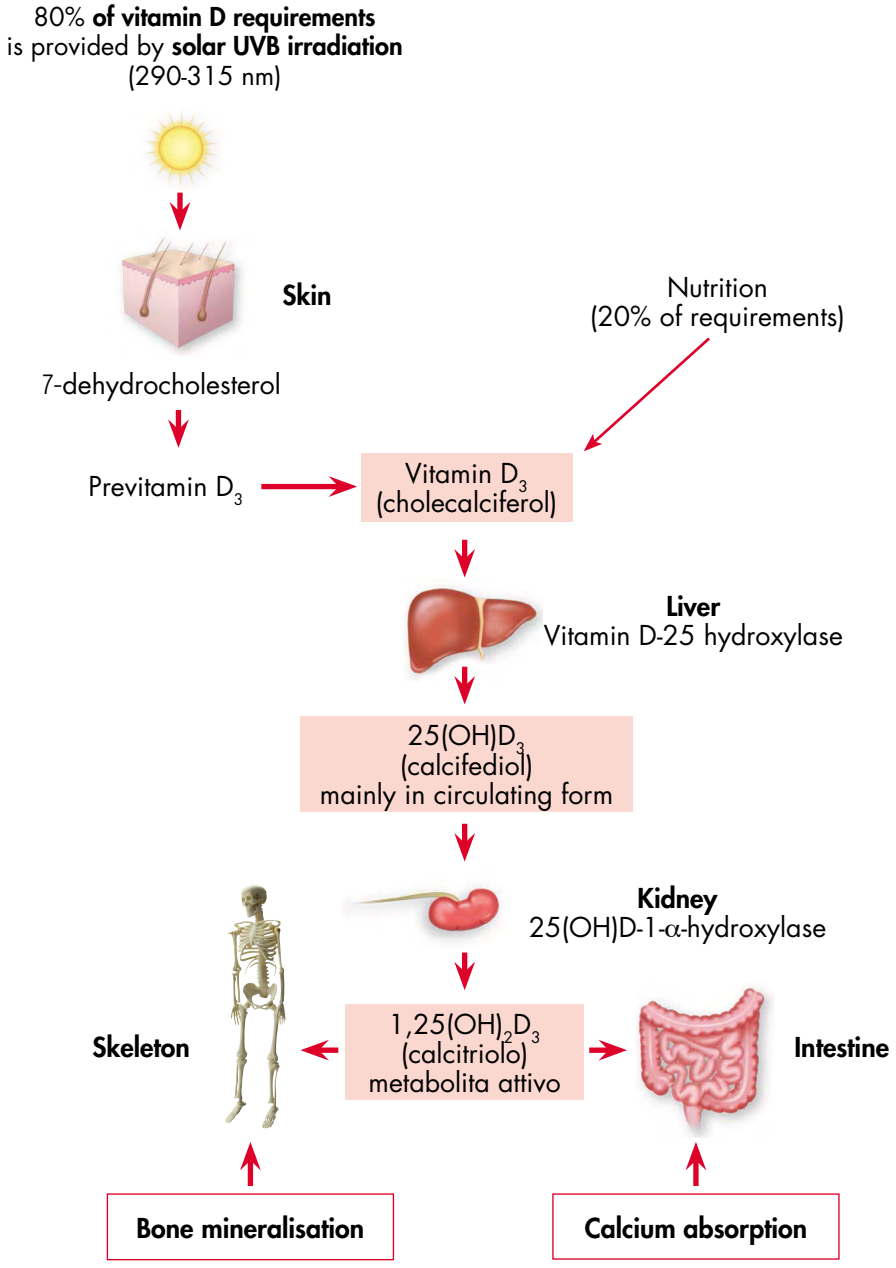

FIGURE 1.
Vitamin D synthesis and metabolism [3].

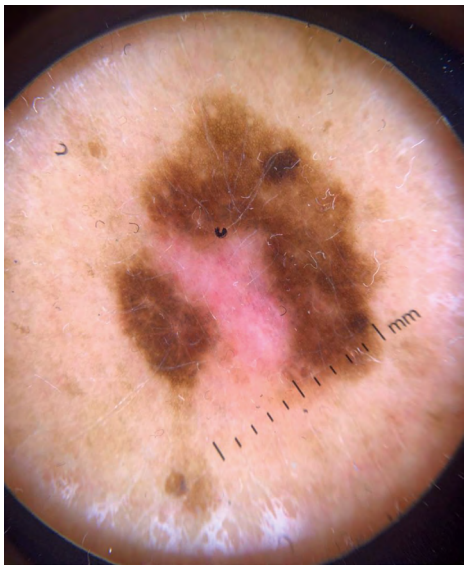

FIGURE 2.
Malignant melanoma of the skin. Epiluminescence image (10X optical magnification).

mours that have keratinocyte as their cell of origin and manifest as erythematous, sometimes ulcerated nodules, usually in photo-exposed areas (face, scalp, back). More specifically, it has been observed that vitamin D has the property of inhibiting the Hedgehog signalling pathway, which plays a key role in the development of basal cell carcinomas (BCC) [2]. Clinical data in the literature is all conflicting, sometimes positively and sometimes negatively associating serum vitamin D levels and incidence of Non-Melanoma Skin Cancer (NMSC), both Basal Cell Carcinoma (BCC) and squamous cell carcinomas (SCCs). A positive association was even observed between NMSC and high serum levels of vitamin D, yet not between NMSC and oral supplementation [7].

Cutaneous melanoma (Fig. 2) is a tumour that results from the neo-plastic transformation of melanocytes that, together with keratinocytes, are part of the epidermis and are responsible for producing melanin, a pigment that protects against the damaging effects of the sun's ultraviolet rays. With regard to melanoma, ongoing studies have shown that vitamin D and its metabolites are able to inhibit the proliferation of melanoma cells in both animal and human models [6]. This effect appears dependent in part on the expression of VDR within neoplastic cells and the presence of specific single nucleotide polymorphisms at coding gene level [6]. Although sometimes conflicting, the results seem to suggest a clinical association between low serum levels of vitamin D and the onset, progression and outcome of melanoma [8,9]. In particular, hypovitaminosis appears to play a significant role in melanomas arising in non-photo-exposed sites, which often have a worse prognosis. This result could be due not only to a diagnostic delay but also to a vitamin D-mediated protective effect on the photo-exposed areas [10].

Conclusive data on possible preventive effects of skin neoplasias by oral vitamin D supplementation is not yet available [1,2].

ATOPIC DERMATITIS

Atopic Dermatitis (AD) is the most common inflammatory skin disease. It is characterised by a multifactorial aetiology including factors of genetic predisposition, altered skin barrier function, along with a filaggrin defect and Th2 immune response. Vitamin D possesses not only an immunomodulatory capacity but also the ability to stimulate filaggrin production. AD has been associated with hypovita-

minosis D in both adults and children [5]. This is consistent with the epidemiological finding that both of these conditions have a higher incidence with increasing latitude and consequently with reduced sun exposure. It has also been observed that children with AD show clinical improvement after migration to lower latitudes [11]. Poor exposure to sunlight during the winter months may partly explain disease exacerbations that commonly occur in the cold months, whereas AD generally tends to improve in summer. Moreover, AD presents an increased risk of *Staphylococcus aureus* infections related to lower skin levels of LL-37 peptide, the synthesis of which is induced by vitamin D [2]. In AD, oral supplementation showed an improvement in disease severity indices and also a decrease in cutaneous colonisation by *Staphylococcus aureus* [5].

PSORIASIS

Psoriasis is a chronic inflammatory skin disease whose distinctive anatomopathological features are excessive keratinocyte proliferation, abnormal keratinocyte differentiation and the presence of a major inflammatory infiltrate (Fig. 3). These are all processes in which vitamin D plays a biologically-important role [12]. Numerous studies have identified an association between low serum calcifediol levels and psoriasis with a statistically significant inverse correlation between the magnitude of the deficiency and the severity of the psoriasis [12,13]. Other studies have found a downturn in the risk of developing psoriasis with increasing serum levels of vitamin D [14]. Its therapeutic effect on this disease has been known for decades, with topical vitamin D analogues such as calcipotriol and calcitriol commonly used in the local treatment of psoriasis, often in combination with a corticosteroid. These drugs have the property of not only inhibiting proliferation and increasing the differentiation of keratinocytes but also modulate the immune response, acting directly on the etiopathogenesis of plaque psoriasis on several levels [1]. The evidence that oral vitamin D supplementation may be of benefit to a psoriatic patient is still debated [12].

VITILIGO

Vitiligo is an acquired disease of an autoimmune nature that targets epidermal melanocytes. It manifests as achromic maculae, without melanic pigment (Fig. 4). Vitamin D_3 increases tyrosinase activity and melanogenesis via the nuclear hormone receptor – the vitamin D receptor in melanocytes. Tyrosinase catalyses the oxidative transformation of thyroxine into dihydroxyphenylalanine, from which melanins are then formed. It has additionally been reported that the active form of vitamin D decreases apoptotic activity in melanocytes induced by ultraviolet type B radiation. Like many other autoimmune diseases, vitiligo is also associated with low levels of vitamin D, although the mechanism behind it is not yet clear [1,15]. A direct correlation between vitamin D deficiency and the severity and/or extent of vitiligo on the body surface has not been demonstrated. Yet, it was observed that vitamin D supplementation in patients with vitiligo with a vitamin D deficiency led to a reduction in lesion size after 6 months of treatment compared to the control, so patients who only received topical cortisone therapy. Preliminary data suggests that topical application of vitamin D analogues may exert a therapeutic effect in patients with vitiligo. Indeed, it has been observed that the additional use of topical calcipotriol or tacalcitol over NB-UVB may exert a synergistic therapeutic effect on vitiligo [16].

Other possible associations between cutaneous diseases and vitamin D are being investigated, such as systemic lupus erythematosus, systemic sclerosis, alopecia areata, mycosis fungoides, polymorphous light eruption and ichthyosis [1].

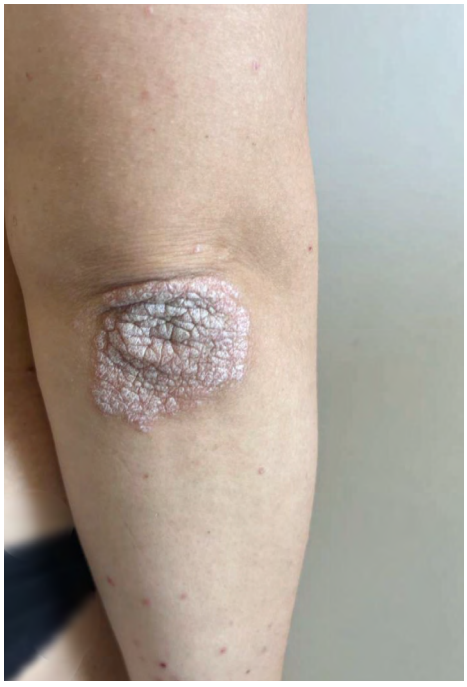

FIGURE 3.
Erythematous-squamous plaque with clear-cut margins in a patient with psoriasis.

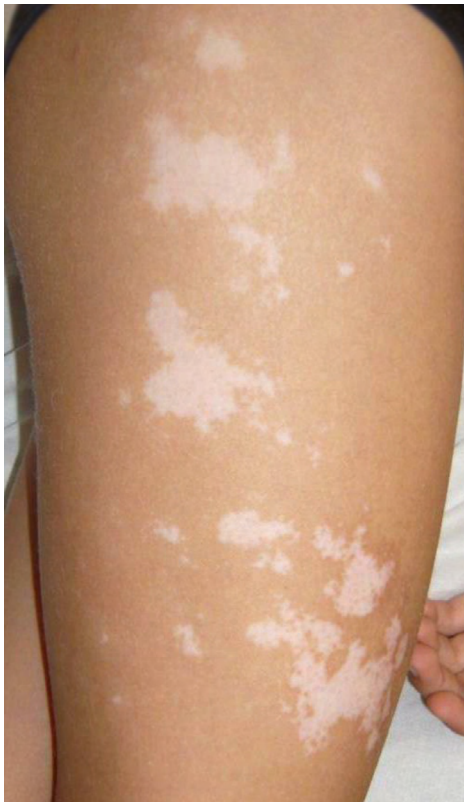

FIGURE 4.
Sharp-edged achromic maculae on the right thigh to be attributed to vitiligo.

CONCLUSIONS

Vitamin D plays a key role in skin health and its deficiency may contribute to the pathogenesis of some skin diseases, both neoplastic and immune-mediated [14].

Exposure to the sun can certainly increase vitamin D levels but is also a risk factor and thus photoprotection remains a key element in preventing skin cancer [2]. Sun exposure is a useful tool if used correctly, through the use of sunscreens and avoiding the resulting erythema, which is a known marker of DNA damage [2].

Vitamin D deficiency is associated with significantly worse overall survival in melanoma patients. Five-year survival is 90% if serum vitamin D levels exceed the 10 ng/ml threshold but drops to 84% if levels fall below the threshold.

Studies with eczemas, such as AD, are also particularly interesting because they are very

common in the adult and paediatric population. High levels of vitamin D in umbilical cord blood have been associated with a reduced prevalence of eczema at/near the age of one year [17]. Oral vitamin D supplementation is indicated for the correction and prevention of hypovitaminosis D in the general population and in patients with skin diseases. To date, there is no established data confirming its role in the treatment of dermatological diseases in the absence of a documented deficiency [12].

Bibliography

1 Bergqvist C, Ezzedine K. Vitamin D and the skin: what should a dermatologist know? G Ital Dermatol Venereol 2019;154:669-680. https://doi.org/10.23736/S0392-0488.19.06433-2

2 Kechichian E, Ezzedine K. Vitamin D and the skin: an update for dermatologists. Am J Clin Dermatol 2018;19:223-235. https://doi.org/10.1007/S40257-017-0323-8

3 Gisondi P, Romanelli M, Dini V, et al. Deficit di vitamina D in dermatologia - Linee guida e raccomandazioni Sidemast. Published online 2015.

4 Autier P, Mullie P, Macacu A, et al. Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials. Lancet Diabetes Endocrinol 2017;5:986-1004. https://doi.org/10.1016/S2213-8587(17)30357-1

5 Bellinato F, Gisondi P. The role of vitamin D in atopic dermatitis. Vitamin D UpDates 2021;4:4-7. https://doi.org/10.30455/2611-2876-2021-1e

6 Paolino G, Moliterni E, Corsetti P, et al. Vitamin D and melanoma: state of the art and possible therapeutic uses. G Ital Dermatol Venereol 2019;154:64-71. https://doi.org/10.23736/S0392-0488.17.05801-1

7 Liang G, Nan H, Qureshi AA, et al. Pre-diagnostic plasma 25-hydroxyvitamin D levels and risk of non-melanoma skin cancer in women. PLoS One 2012;7(4). https://doi.org/10.1371/JOURNAL.PONE.0035211

8 Ombra MN, Paliogiannis P, Doneddu V, et al. Vitamin D status and risk for malignant cutaneous melanoma: recent advances. Eur J Cancer Prev 2017;26:532-541. https://doi.org/10.1097/CEJ.0000000000000334

9 Caini S, Boniol M, Tosti G, et al. Vitamin D and melanoma and non-melanoma skin cancer risk and prognosis: a comprehensive review and meta-analysis. Eur J Cancer 2014;50:2649-2658. https://doi.org/10.1016/J.EJCA.2014.06.024

10 Paolino G, Moliterni E, Didona D, et al. Clinicopathological features, vitamin D serological levels and prognosis in cutaneous melanoma of shield-sites: an update. Medical Oncology 2015;32:1-7. https://doi.org/10.1007/S12032-014-0451-4/METRICS

11 Byremo G, Rød G, Carlsen KH. Effect of climatic change in children with atopic eczema. Allergy 2006;61:1403-1410. https://doi.org/10.1111/J.1398-9995.2006.01209.X

12 Barrea L, Savanelli MC, Di Somma C, et al. Vitamin D and its role in psoriasis: an overview of the dermatologist and nutritionist. Rev Endocr Metab Disord 2017;18:195-205. https://doi.org/10.1007/s11154-017-9411-6

13 Lee YH, Song GG. Association between circulating 25-hydroxyvitamin D levels and psoriasis, and correlation with disease severity: a meta-analysis. Clin Exp Dermatol 2018;43:529-535. https://doi.org/10.1111/CED.13381

14 Ren Y, Liu J, Li W, et al. Causal associations between vitamin D levels and psoriasis, atopic dermatitis, and vitiligo: a bidirectional two-sample mendelian randomization analysis. Nutrients 2022;14:5284. https://doi.org/10.3390/NU14245284/S1

15 Upala S, Sanguankeo A. Low 25-hydroxyvitamin D levels are associated with vitiligo: a systematic review and meta-analysis. Photodermatol Photoimmunol Photomed 2016;32:181-190. https://doi.org/10.1111/PHPP.12241

16 Liu X, Yao Z, Wang Y, Chai L, Zhou X. Vitamin D analogs combined with different types of phototherapy in the treatment of vitiligo: A systematic review of randomized trials and within-patient studies. Int Immunopharmacol 2022;109:108789. https://doi.org/10.1016/j.intimp.2022.108789

17 Liu YY, Zhou XJ, Li YC. The relationship between vitamin D levels in umbilical cord blood and infantile eczema. J Obstet Gynaecol 2022;42:2813-2817. https://doi.org/10.1080/01443615.2022.2109948