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The role of vitamin D in atopic dermatitis

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Abstract

The skin is a central organ for vitamin D metabolism, representing both the site of its synthesis and a target organ. Vitamin D regulates both proliferation and differentiation of keratinocytes. Vitamin D is also involved in regulating the synthesis of ceramides, a key component of the corneocyte lipid envelope, which acts as an epidermal barrier, protecting the skin from chemical, physical and microbiological agents. Vitamin D also carries out several actions on the skin's immune system. Among these there is the induction of the synthesis of antimicrobial peptides such as hCAP18/LL-37 and β-defensin and it inhibits antigen presentation by Langerhans cells, whilst inducing the formation of regulatory T lymphocytes. Atopic dermatitis (AD) is the most common inflammatory skin disease, affecting up to 20% of the paediatric population and 5% of the adult population. Several epidemiological studies have shown an inverse correlation between AD prevalence and latitude, reduced exposure to sunlight and hypovitaminosis D. Most observational studies and meta-analyses have shown that vitamin D levels are lower in adults and children with AD than in controls. Vitamin D supplementation, either oral or secondary to exposure to UV radiation, is generally associated with an improvement in AD. Serum vitamin D dosing is recommended for patients affected by AD.

PHYSIOLOGICAL FEATURES OF VITAMIN D IN NORMAL SKIN

Vitamin D is a secosteroid known primarily for the regulation of the metabolism of calcium and phosphorus and the maintenance of normal skeletal architecture. The skin is a central organ for vitamin D metabolism, representing both the site of its synthesis and a target organ. Vitamin D can be taken through food or through supplementation in the form of vitamin D_2 (ergocalciferol) or D_3 (cholecalciferol) and is synthesised in the skin. The vitamin D precursor, 7-dehydrocholesterol (pro-vitamin D) is contained in the membranes of keratinocytes of the basal and spinous layers. The action of UVB radiation (290-315 nm) opens the B-ring of 7-dehydrocholesterol to generate pre-vitamin D_3 or cholecalciferol [1]. In temperate zones, UVB radiation may be insufficient for adequate vitamin D synthesis, especially during winter. Other factors that may inhibit cutaneous vitamin D synthesis include advanced age, dark phototypes, limited exposure of skin surface area and/or the use of sunscreens [2]. To become metabolically active, vitamin D undergoes two hydroxylation reactions in the liver and kidneys by enzymes of the cytochrome P450 family, generating 25-hydroxyvitamin D [25(OH)D], which is the main serum index of vitamin D repletion, and 1,25-dihydroxyvitamin D [1,25(OH)2D], the active form of vitamin D. Keratinocytes themselves already contain all the enzymes necessary for vitamin D metabolism, namely CYP27A1 and CYP27B1.

Vitamin D's physiological effects are mediated by the nuclear vitamin D receptor (VDR), which, after activation, interacts with the retinoid X receptor to form heterodimeric complexes that bind specific regions in the promoter of target genes [1]. There is also a non-genomic mechanism of action, mediated by a membrane receptor, which results in the transduction of multiple signalling pathways, including the regulation of intracellular calcium levels and the activation of phospholipase C-γ1. Therefore, keratinocytes respond to vitamin D in both an autocrine and paracrine manner.

In vitro studies have shown that vitamin D has a dose-dependent effect on the proliferation and differentiation of keratinocytes. Low concentrations of vitamin D promote keratinocyte

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Conflict of interest
Francesco Bellinato and Paolo Gisondi declare that they have no conflicts of interest.

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proliferation, whilst high concentrations inhibit it and promote epidermal differentiation [3].
This anti-proliferative action arises from the repression of cyclin D and the induction of cell cycle inhibitors such as p21cip and p27kip. Vitamin D-mediated epidermal differentiation requires VDR binding with the joint participation of two specific coactivators: DRIP and SRC. Keratinocyte differentiation is promoted through the increased synthesis of the K1 and K10 keratins and other proteins involved in barrier function, including filaggrin, involucrin, loricrin and transglutaminase [4]. Vitamin D is also involved in regulating the synthesis of very-long-chain glucosylceramides and their transport into the lamellar bodies. These lipids form a component of the corneocyte lipid envelope with an important barrier function [5]. Vitamin D also performs several actions on the skin's immune system. One of the most important of these is induction of the synthesis of antimicrobial peptides, such as hCAP18/LL-37 and β-defensin in keratinocytes and sebocytes, either through direct transcriptional induction or indirectly through the regulation of KLK5 and KLK7 serine proteases. Antimicrobial peptides alter bacterial membranes and virus envelopes and stimulate the innate immune response [6]. Vitamin D and its analogue, calcipotriol, exert an immunosuppressive effect on the skin by inhibiting antigen presentation by Langerhans cells and inducing regulatory T lymphocytes [7]. A serum concentration of approximately 30 ng/mL of 25(OH)D is the estimated cut-off value for defining an adequate level of vitamin D. Vitamin D requirements range from 1,500 IU/day for healthy adults to 2,300 IU/day for the elderly. Vitamin D deficiency affects about half of all young patients in the winter and nearly the entire elderly population. Vitamin D3 supplementation is useful for the treatment and prevention of hypovitaminosis D. In cases of severe deficiency, cumulative doses of between 100,000 and 300,000 IU are given over a period of 1-4 weeks. In general, after adequate correction of the vitamin deficiency, a daily preventive dose of between 800 and 2,000 IU/day can be set, depending on age and exposure to sunlight. Many studies have confirmed that daily doses of up to 4,000 IU are safe and there are no reports of intoxication at this dosage [8].

ATOPIC DERMATITIS

Atopic dermatitis (AD) is the most common inflammatory skin disease, affecting up to 20% of the paediatric population and 5% of the adult population [9]. AD is a complex disease with a multifactorial aetiology. Patients with AD show genetic and acquired alterations in the formation and regulation of the skin barrier and dysregulation of the immune response [9]. Among the abnormalities in the barrier function of keratinocytes, there is also a filaggrin deficiency, increased serine protease enzyme activity and reduced levels of total lipids and ceramide fractions of their cell membranes [10]. The pathogenesis of AD is dominated by an immunological imbalance of Th2 and Th22, and an increased release of IL-4 and IL-13, which are also involved in the regulation of IgE synthesis. IL-4, and to a lesser extent IL-13, stimulate the switch to IgE production by B lymphocytes and also reduce the production of ceramides, loricrin, involucrin, desmoglein 3 and filaggrin. An increased Th2 type inflammatory response also leads to a reduced production of antimicrobial peptides. Th1 and Th17 type responses modulate the development and progression of the disease in chronic phases [9]. The distinctive features of AD are eczematous lesions, intense itching, and a chronic, relapsing progression with periodic exacerbations. Acute AD lesions are erythematous and vesicular and become chronically reddened, scaly and lichenified. Lesion topography characteristically changes with age [9]. At onset, AD in infants may present as cradle cap of the scalp, which then spreads to the extensor surfaces of the extremities and face with exudative lesions, which characteristically spare the mid-facial region. In children and adolescents there is a typical localization in the folds (flexural eczema), commonly associated with involvement of the face, neck and upper part of the trunk (Fig. 1). In adults, AD most often manifests as chronic eczema of the hands or face with characteristic involvement of the eyelids and neck (Fig. 2) [9].
The objective of treating AD is to achieve and maintain clinical remission and to prevent relapses. Treatment comprises a remission induction phase and a maintenance phase. For mild to moderate forms, topical anti-inflammatory therapy with corticosteroids or topical calcineurin inhibitors, tacrolimus and pimecrolimus, may be sufficient and can be used with a "proactive" maintenance treatment schedule, usually twice a week. Systemic treatments are indicated for more severe and widespread forms or when there is involvement of sensitive or visible areas (face), for forms that are made more severe by significant itching or that cause a major impact on the quality of sleep or the quality of life. Systemic drugs currently available include systemic corticosteroids, cyclosporine and dupilumab, a fully human monoclonal antibody directed against the IL-4 and IL-13 α receptors. Dupilumab is the first biologic approved for the treatment of AD. It has an excellent efficacy and safety profile, and is indicated in cases of intolerance, ineffectiveness and/or contraindication to cyclosporine. In especially severe and treatment-resistant cases, azathioprine, methotrexate and mycophenolate mofetil may also be used. Phototherapy may be useful in treating moderate forms. In patients over 12 years of age, broadband UV (UVA + UVB = 290-400 nm), narrowband UVB (311-313 nm) and UVA1 (340-400 nm) can be used with benefit. The use of emollients as an integral part of AD therapy is strongly recommended by all major international guidelines. However, some

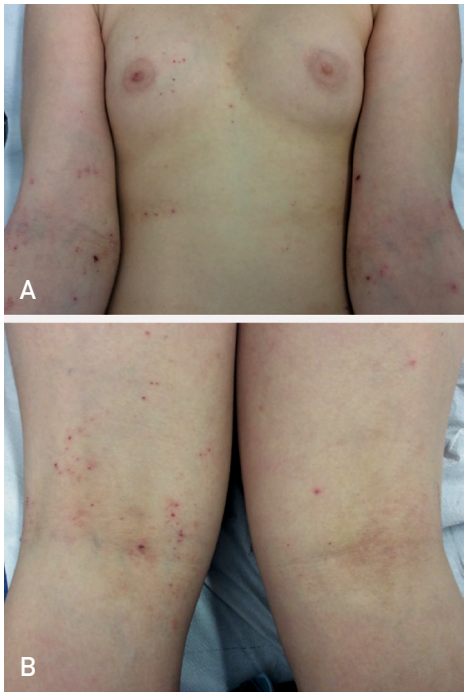

FIGURE 1.
Typical eczematous lesions on the chest and on the antecubital (A) and popliteal (B) fossa in a adolescent female patient with atopic dermatitis.

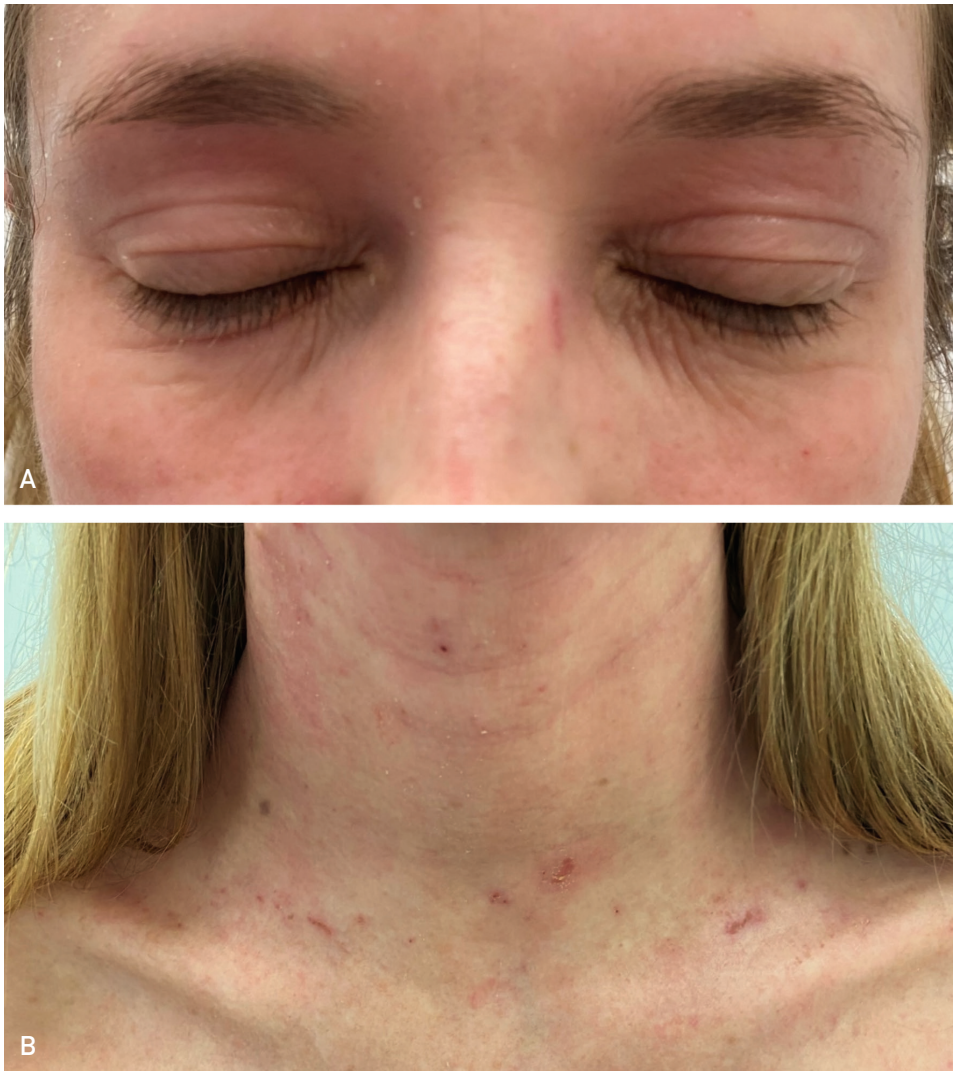

FIGURE 2.
Typical eczematous lesions on the eyelids (A) and neck (B) in a young woman with atopic dermatitis.

patients are reluctant to adhere to this recommendation due to the discomfort caused by the greasy sensation that some products leave on the skin as well as their cost [11].

ROLE OF VITAMIN D IN ATOPIC DERMATITIS

Several epidemiological studies have shown an inverse correlation between the prevalence of AD and latitude, reduced exposure to sunlight and hypovitaminosis D. Bryemo et al. observed an improvement in AD in Norwegian children who were moved to a sub-tropical country for 4 weeks [12]. Most observational studies have shown that 25(OH)D levels were lower in AD patients (both adults and children) than in the controls. For example, a Korean study involving more than 15,000 adults observed significantly lower vitamin D levels in AD patients compared with healthy controls [13]. A meta-analysis of eleven studies described a mean difference of 14 nmol/L (95% CI 25-2) between AD patients and healthy controls and 16 nmol/L (95% CI 31-1) in the paediatric population [14]. Other studies have described the association between hypovitaminosis D and increased disease severity, elevated IgE levels, allergic sensitisation and risk of food allergy, although the results do not overlap completely [15].
In particular, some studies have described this association only in children with AD but not in adults, whilst others have confirmed that there is an association between hypovitaminosis D and disease severity, but only in the presence of allergic sensitisation. On the other hand, Quirk et al. reported significantly higher vitamin D levels in children and adolescents with AD compared with controls [15]. It is likely that some methodological limitations in the studies may have influenced the variability of these results, including the failure to assess exposure to sunlight, vitamin D supplementation, and the fact that a single severity score assessment will not reflect long-term disease severity. Genetic polymorphisms in the VDR gene and in the enzymes involved in vitamin D metabolism could account for the variability of the observations [15].
Specifically, Heine et al. estimated the frequency of VDR gene polymorphisms in patients with severe AD, highlighting the increased prevalence of four specific haplotypes, which could affect disease severity by regulating the skin barrier and the local immune response [16]. Weber et al. reported that vitamin D deficiency is associated with superinfection by the more virulent strains of S. aureus and that vitamin D supplementation reduces colonisation by this bacterium, which is responsible for re-exacerbations of the disease [6].
Whilst topical application of vitamin D or its analogues may have an irritative effect on eczematous lesions, most studies indicate that oral vitamin D supplementation, at doses between 1,600 and 2,000 IU/day, have been associated with an improvement in AD, as measured by SCORAD and EASI scores [15].
Several hypotheses have been formulated to explain the beneficial effects of vitamin D supplementation on AD. These include normalisation of IL-2, IL-4, IL-6 and IFN-γ levels, an inhibitory effect on allergic responses with suppression of IgE production, normalisation of the barrier defect and increased production of antimicrobial peptides such as LL-37 [1]. In a double-blind randomised controlled trial in Mongolia with 104 children with AD, vitamin D supplementation (1,000 IU/day) was associated with improvement in AD as measured by EASI and IGA scores after one month [17]. Similar results have been shown in other randomised controlled trials. However, a Swedish prospective cohort study observed an increased risk of developing AD at six years of age in children who received a high dietary intake at between 5 and 10 months [18]. Finally, numerous studies have been conducted to

determine whether there is an association between maternal vitamin D levels and risk of AD in the unborn child, but with conflicting results [15].

CONCLUSIONS

Vitamin D may play an important role in the homoeostasis of healthy skin and in the pathogenesis of certain inflammatory and immune-mediated skin diseases such as AD. Hypovitaminosis D is an emerging risk factor for AD and is associated with well-known extra-cutaneous consequences on mineral metabolism and bone homoeostasis. Therefore, the serum dosage of 25(OH)D in AD patients is recommended, especially in winter, when its levels are expected to be lower especially in those patients who have been taking systemic and/or topical corticosteroids for a long time. In case of hypovitaminosis D, supplementation with vitamin D3 is recommended.

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