Atopic dermatitis and vitamin D

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VITAMIN D
UpDates
2024;7(4):76-79
https://doi. org/10.30455/2611-2876-2024-7e

By the term 'barrier organ' we mean the set of epithelia in the body, on whose integrity our survival depends. Numerous components contribute to the constitution of the barrier. In fact, there is a chemical, immunological, micro-biological and a physical barrier. The latter, at skin level, is much more complex than in other epithelia and is regulated by a well-defined set of molecules involved in the metabolism of filaggrin, the formation of the stratum corneum, the synthesis of intercellular lipid lamellae, the organisation of corneodesmosomes, desquamation and the formation of tight junctions (TJs), which reduce the intercellular spaces between epithelial cells until they disappear. In particular, it is the stratum corneum and the TJs, which are present in it, especially in the compact layer [1], that are responsible for permeability [2-5], which in other epithelia is provided by the TJ system. In addition, recent investigations have shown that partial or total inhibition of TJ proteins modifies epithelial permeability by interfering in the metabolism of filaggrin and lipids with abnormal formation of the stratum corneum [1,2].

In two inflammatory skin diseases, namely psoriasis and atopic dermatitis, barrier disruption appears to play an important role in their pathogenesis.

In fact, a series of investigations we conducted on psoriasis showed that vitamin D, in addition to its known functions, plays a role in the expression of some of the proteins making up the TJs. Starting from the observation that psoriasis improves with exposure to sunlight and that the skin, irradiated by the sun, synthesises vitamin D, we investigated the role of this vitamin. In particular, we have shown that in psoriasis patients, vitamin D is reduced and inversely correlates with PASI (Psoriasis Area Severity Index) [6] and with the blood level of T lymphocytes reg [7]; VDRs (Vitamin D Receptor) in psoriatic lesions are reduced by 50% compared to healthy skin; VDRs present polymorphisms that correlate with clinical [8]; finally, reduced VDRs are associated with reduced expression of certain TJ constituent proteins, in particular claudin-1, occludin and zonulin-1 [9]. In conclusion, in psoriasis, there is a correlation between vitamin D deficiency and altered TJ and, therefore, altered skin permeability. Based on these results, we turned our attention to atopic dermatitis (AD). Dermatosis is the cutaneous manifestation of atopy, a polygenic hereditary trait with high prevalence that can affect other epithelia (allergic rhinitis, asthma, etc.) in which, as already mentioned, the integrity of the barrier is also guaranteed by the TJ. It is more frequent in the paediatric age with a prevalence of between 10 and 30% and decidedly less frequent in adults (5-7%). It is an inflammatory disease characterised by altered permeability of the barrier due to filaggrin deficiency, the gene of which is mutated in 30-50% of patients. A Th2-type immunological response is predominant in AD with an increase in certain cytokines, such as IL-4, IL-5 and IL-13, which play an essential role in eosinophil recruitment and IgE synthesis. In this respect, it should be noted that two forms of AD are recognised: the extrinsic form, which is much more frequent and characterised by increased circulating IgE, and the intrinsic form, which accounts for approximately 20 % of cases, with normal IgE values. Finally, it must be remembered that AD is burdened with certain co-morbidities, such as psoriasis [10].

Moreover, AD also improves with exposure to sunlight [11]. In fact, exposure to artificial sources of UV radiation is considered among the possible treatments for this dermatosis [12]. The work of Napolitano et al. [13], in particular, shows that 6 out of 10 adults with AD improve after exposure to UV radiation. Various hypotheses have been put forward to explain this phenomenon: the immunomodulatory action of UV rays inducing apoptosis of inflammatory cells, inhibiting Langerhans cells and modifying cytokine production [14]; the direct action of UV rays reducing the colonisation of *Staphylococcus aureus*, but also the effect of sunlight exposure on vitamin D synthesis must be considered. In addition, studies have shown a correlation between severity of AD and the haematic concentration of vitamin D without being able to prove a link between these variables. Furthermore,

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Conflict of interest
The Author declares no conflict of interest.

How to cite this article: Calvieri S. Atopic dermatitis and vitamin D. Vitamin D – Updates 2024;7(4):76-79. https://doi.org/10.30455/2611-2876-2024-7e

different clinical trials on vitamin D supplementation in children have given contradictory results.

Therefore, in order to clarify a possible role of vitamin D, we enrolled 43 adults with moderate or severe AD who had not been on systemic therapy for at least three months and from who, after collecting anamnestic data, blood samples have been taken and skin biopsies have been done in the lesional (LS) and nonlesional (NLS) areas. In addition, EASI (Eczema Area Severity Index) was assessed for each of them and all of them have done the prick tests (STP) (Tab. I). PCR (Polymerase Chain Reaction) evaluations were carried out to study certain VDR polymorphisms (Tab. II) on blood, and histochemical examinations to study the expression of VDRs, occludin, claudin and ZO-1 on both NLS and LS and their gene expression. Multivariate logistic regression was used to explore the association between various VDR polymorphisms (dependent variables) or TJ proteins (dependent variables) and clinical and pathological characteristics of AD patients (independent variables). In this article, we will report the part of the results relating to the VDR [15] polymorphisms because not all of them have yet been published. The results of this cross-sectional study identify a link between VDR polymorphisms, VDR and TJ protein expression and clinical characteristics in a cohort of AD patients. Specifically, we observed a lower OR for the occurrence of AD in individuals with the hetero-zygote VDR polymorphism A1012G, whereas homozygous cumulative VDR polymorphisms ≥ 2 (Tab. III) were linked to an increased likelihood of developing allergic reactions. Among the constituent proteins of TJs, claudin and ZO-1 were those most expressed. VDR protein expression was associated with the presence of generalised AD lesions, whereas claudin showed a significant association with a positive SPT. While previous studies have investigated differences in the frequency of VDR polymorphism and the expression levels of VDR and TJ between AD patients and healthy control groups, the aim of our study was to characterise the interrelationships between SNPs (single-nucleotide polymorphism), VDR and TJ protein expression in skin biopsies from this cohort of AD patients and associate them with their clinical features. To date, no work has correlated VDR polymorphisms with the clinical characteristics

TABLE I.
Clinical and laboratory data.

Gender, no. (%)	
• Male	17 (39,5)
• Female	26 (60,5)
Age	
• < 60 years	36 (83,7)
• ≥ 60 years	7 (16,3)
Age of disease onset no. (%)	
• Childhood/adolescence	28 (65,1)
• Adults	15 (34,9)
Body Mass Index (BMI)	
• < 30 kg/m^2	35 (81,4)
• ≥ 30 kg/m^2	8 (18,6)
Location no. (%)	
• Flexure	9 (20,9)
• Generalised	18 (41,9)
• Head/neck	14 (32,6)
• Hands	2 (4,7)
EASI score	
• Mild (EASI < 16)	5 (11,6)
• Moderate-to-severe (EASI ≥ 16 or < 16 with involvement of the face and hands)	38 (88,4)
Asthma, no. (%)	
• Present	8 (18,6)
• None	35 (81,4)
Rhinoconjunctivitis, no. (%)	
• Present	14 (32,6)
• None	29 (67,4)
Skin prick test, no. (%)	
• Positive	20 (46,5)
• Negative	23 (53,5)
Total IgE (IU/ml), no. (%)	
• < 100 IU/ml	18 (41,9)
• ≥ 100 IU/ml	25 (58,1)
25(OH)D	
• ≥ 30 ng/ml	15 (34,9)
• < 30 ng/ml	28 (65,1)

of dermatosis. Our results suggest that VDR polymorphisms may indeed be associated with the clinical features of AD. We found that individuals with heterozygous A1012G status had significantly lower odds of developing AD early (OR: 0,046, IC 95%: 0.004-0.510, p = 0.012), suggesting a potential protective effect of this polymorphism on disease onset. Moreover, Richetta et al. reported a lower risk of developing psoriasis when this polymorphism, either in heterozygosity or homozygosity, was present compared to the wild-type gene [16].

We also observed that the presence of ApaI in homozygosity showed a tendency towards a higher probability (OR of 5.99) of developing the disease early, indicating a potential risk associated with this polymorphism. Interestingly, ApaI (rs7975232) is associated with lower levels of expression and reduced stability of mRNA VDR [17], and low levels of vitamin D are associated with AD. Moreover, Heine et al. [18] demonstrated an association between the ApaI polymorphism and severe forms of AD.

Our results showed a statistically significant association between the presence of homozygous cumulative polymorphism > 2 of the VDR and a positive SPT (10/20, 50%) compared to negative SPT (1/23, 4.3%; p = 0.0003). To support this observation, it has been reported that a low vitamin D level is associated with higher IgE levels in atopic patients [19,20].

VDR polymorphisms were also correlated with receptor expression in lesional skin biopsies (LS) from our cohort of AD patients. We observed a positive association for the ApaI polymorphism when in the heterozygous state with the expression of VDR. This result is in contrast to other results that report that polymorphisms in ApaI are associated with reduced messenger RNA stability and lower levels of expression [21,22]. However, another study in Turkish children described a significant link between ApaI in heterozygosity and risk of asthma [23]. It should be noted that functional studies on the association between ApaI polymorphisms and VDR protein expression are lacking.

With regard to the investigation of TJ constituent proteins, we observed that claudin and ZO-1 were the most highly expressed in skin biopsies of lesions from AD patients, whereas VDR and occludin were the lowest. No studies have reported the expression levels for these proteins. Only

TABLE II.
Target polymorphisms

Gene	Polymorphism	SNP ID	Position on chromosome 12 (assembly hg38)	Genomic location (NM 000376	ATG position in VDR (NM_000376)
VDR	A-1012G	rs4516045	47906043	VDR promoter	c.-1172A>G
VDR	FokI	rs2228570 rs107365810	47879112	Exon 3 (encoding)	c.2T>C
VDR	BsmI	rs1544410	47846052	Intron 9	c.1024+283G>T
VDR	ApaI	rs7975232	47845054	Intron 9	c.1025-49G>T
VDR	TaqI	rs731236	47844974	Exon 10 (encoding)	c.1056T>C

TABLE III.
Frequency of specific genotypes for different single nucleotide polymorphisms of the VDR in AD patients.

Polymorphism	Number of cases (%)
rs4516035 A1012G	
Genotype	N (%)
AA (wild type)	15 (34,9)
AG (heterozygous)	23 (53,5)
GG (homozygous)	5 (11,6)
rs2228570 FokI	
Genotype	N (%)
TT (wild type)	5 (11,6)
TC (heterozygous)	17 (39,5)
CC (homozygous)	21 (48,8)
rs1544410 BsmI	
Genotype	N (%)
GG (wild type)	18 (41,9)
GT (heterozygous)	20 (46,5)
TT (homozygous)	5 (11,6)
rs7975232 ApaI	
Genotype	N (%)
GG (wild type)	10 (23,3)
GT (heterozygous)	19 (44,2)
TT (homozygous)	14 (32,6)
rs731236 TaqI	
Genotype	N (%)
TT (wild type)	19 (44,2)
TC (heterozygous)	19 (44,2)
CC (homozygous)	5 (11,6)

case-control studies can be found in the literature. Furthermore, our work revealed a negative correlation between vitamin D and the expression of ZO-1 (rho = -0.43; p = 0.0058). In a study by Yuki et al. [24], TJ protein levels were quantified in the epidermal tissues of three AD patients and three normal subjects. Skin biopsies were taken from non-lesional sites of AD (NLS) and lesional skin sites (LS). In the NLS of DA, claudin-1, occludin and ZO-1 proteins detected conditions similar to those of normal skin. However, in LS, the signal intensities of claudin-1 and ZO-1 were markedly reduced. These data seem to be in contrast to our results, although only three patient samples were examined and our analysis was limited to LS.

Meckel et al. [25] observed a reversed correlation between serum 25(OH)D concentrations and mucosal inflammation in 230 subjects with ulcerative colitis, together with altered protein expression of VDR, occludin and decreased protein expression of ZO-1.

These results are in line with our results. We also found a positive association between ZO-1 expression and BMI (body mass index) ≥ 30. Zonulin is considered the only physiological mediator known to regulate intestinal permeability in a reversible manner by modulating intercellular TJs and obesity and has been associated with increased intestinal permeability and absorption [26].

We also observed a higher level of claudin expression in patients with positive SPT. De Benedetto et al. [27] reported reduced claudin-1 expression in DA NLS, while Gruber et al. [28] and Yuki et al. [24] showed that claudin-1 was over-regulated in the NLS of subjects with AD. Taken together, these results suggest a complex and context-dependent role of claudin-1 in AD, influenced by genetic factors and environmental considerations.

In conclusion, in our study of Italian AD patients, we identified significant associations between VDR polymorphisms, VDR expression, TJ proteins and clinical features of AD. These results provide important information on the complex interplay between genetic factors, vitamin D deficiency and TJ proteins in the pathology of AD, emphasising the complex nature of the pathophysiology of this dermatosis and the identification of potential markers for the early diagnosis of AD.

Finally, despite some similarities with psoriasis that we have highlighted, such as the protective role of heterozygous A1012G, the reduced expression of VDR, etc., differences emerge that, if correctly interpreted, could further clarify the role of vitamin D in the complex mechanisms regulating epithelial permeability.

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