

Comorbidity of Vitamin A and Vitamin D Deficiency Exacerbates the Severity of Atopic Dermatitis in Children

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Keywords

Atopic dermatitis · Vitamin D · Vitamin A · Comorbidity · Severity

Abstract

Background: Several studies have suggested that vitamin D (VD) deficiency (VDD) is associated with atopic dermatitis (AD). However, little is known about the relationship between AD and vitamin A (VA). The interaction between VA and VD on AD requires further study. **Objective:** We detected serum levels of VA and VD in children with AD to explore how VA deficiency (VAD) and VDD affect AD severity. **Methods:** We assessed the SCORing Atopic Dermatitis (SCORAD) index, total immunoglobulin E levels and peripheral blood eosinophil counts. VA and VD levels were determined with high-performance liquid chromatography. Correlations among variables were investigated with Pearson's correlation analysis. **Results:** The VD and VA levels were significantly lower in children with AD than in normal children ($p < 0.001$, $p = 0.0423$). Both VD and VA levels were negatively correlated with SCORAD scores. The SCORAD scores were significantly higher in AD patients with both VDD and VAD (co-deficiency) than in other AD patients. Significant inverse

correlations were observed between peripheral blood eosinophil counts and serum VA and VD levels. **Conclusions:** VA and VD co-deficiency may exacerbate AD symptoms in children, but the specific mechanism underlying this relationship requires further study. These findings may indicate the need for studies evaluating the use of VD and VA as potential treatments for AD patients.

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Introduction

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disorder that is characterized by recurrent eczematous lesions, itching and dry skin. Some children with AD may exhibit an increasing risk of allergic rhinitis, asthma or allergic conjunctivitis with age. The incidence of AD in children has increased over time. Its global incidence is approximately 10–20% (only 3–5% in adults). [1, 2], and it has become an important chronic disease that affects the health of children and adolescents. Previous studies have suggested that the pathogenesis of AD is multi-complex and not yet fully understood. These studies have mainly focused on gene-environmental interac-

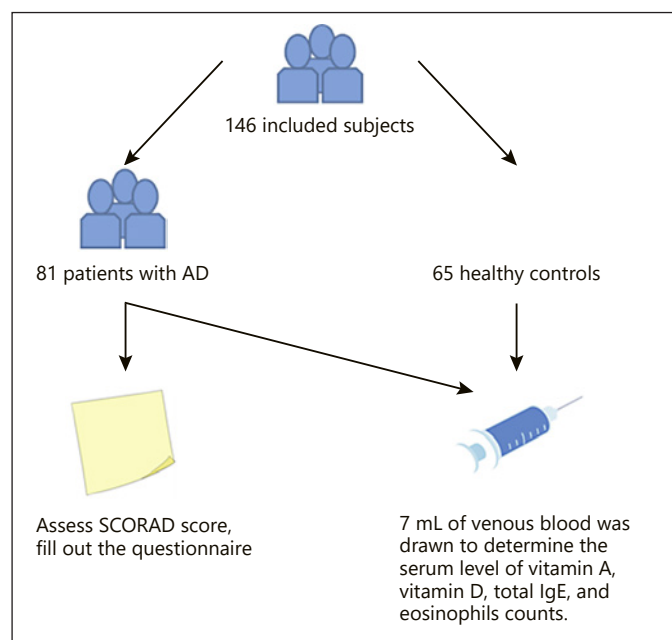


Fig. 1. Flowchart of Materials and Methods. Methodology synopsis. AD, atopic dermatitis.

tions, skin barrier dysfunction, abnormal immune responses, etc. [3].

Vitamin D (VD) is a unique vitamin with endocrine-hormone functions that has received an increasing amount of attention in recent years. Vitamin D deficiency (VDD) has become a public health issue both in developed and developing countries [4–6]. It is estimated that more than 1 billion people have suffered from VDD [7]. VDD causes a variety of disorders that include but are not limited to calcium and phosphorus metabolism disorder, infection, autoimmune disease, tumours and allergic disease [8–10]. A potential link between VD and the development of allergic disease (the so-called “vitamin D hypothesis”) first emerged when higher rates of allergic disease were observed in people residing at higher latitudes, where VDD is common [11]. Although many clinical studies have found that 25(OH)D3 levels are significantly lower in patients with AD and negatively correlated with the severity of the disease [12–14], this view has remained controversial. Recently, additional studies have indicated that VD plays an important role in the pathogenesis of AD by regulating antimicrobial peptides, modulating immunity, and affecting skin barrier functions [15, 16]. The mechanisms underlying these interactions are not fully understood.

Vitamin A deficiency (VAD) is one of four major nutritional deficiencies recognized by the World Health Or-

ganization (WHO). VAD causes approximately 1–2.5 million deaths worldwide each year; approximately 500,000 pre-school children are blind, and more than 10 million people suffer from xerophthalmia as a result of VAD [17]. In China, the prevalence of VAD in children under 6 years of age is 11.7%, while that of vitamin A (VA) insufficiency is 39.2% [18]. VA plays a regulatory role in immune functions and skin integrity. Cellular retinoic acid (RA) bioavailability has been shown to determine epithelial integrity by inducing the epidermal cells to differentiate into subtypes with distinct specializations, which is essential to maintain the homeostasis of the skin barrier [19]. VAD can cause epithelial cell growth, migration and apoptosis disorders, leading to impairment of skin barrier function. Disorder of the skin barrier plays an important role in the pathogenesis of AD. However, few reports have explored the correlation between AD and VA to date. Oh et al. [20] reported that the incidence of AD was negatively correlated with the intake of antioxidant nutrients (including retinol and β -carotene), and Mihály et al. [21] found decreased retinoid concentration and retinoid signalling pathways in human AD patients. Our previous studies demonstrated that VA and VD co-deficiency may exacerbate the symptoms of children with autism spectrum disorders [22]. No studies have reported the serum levels of VA in children with AD or explored whether there is a synergistic effect between VD and VA in AD patients. In this study, we propose that VAD and VDD may be risk factors for and may aggravate the condition of children with AD. To test our hypothesis, we examined serum VA and VD levels in children with AD and analysed whether VA and VD co-deficiency exacerbates clinical symptoms in children with AD.

Materials and Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000496603 for all online suppl. material) (Fig. 1).

Results

Patient Characteristics

The mean objective SCORing Atopic Dermatitis (SCORAD) score in the AD patients was 45.48 ± 13.36 (22–74.36). In this group, 33 (40.7%) had moderate and 48 (59.3%) had severe AD. Out of the 81 patients diagnosed with AD, 9 cases (11.11%) had asthma, 14 (17.28%) had allergic rhinitis, and 6 (7.41%) had allergic conjunc-

Table 1. General data of patients with atopic dermatitis and healthy controls

	AD (<i>n</i> = 81)	HCs (<i>n</i> = 65)	<i>p</i> ^a
Age, years	5.08±3.19	5.29±3.27	0.5845
Sex (M/F)	49/32	37/28	0.572
Height, cm	109.3±15.92	112.2±14.55	0.2515
Weight, kg	19.84±6.78	21.19±6.80	0.2343
BMI	16.21±1.28	16.45±1.87	0.3603
Onset (<2 years old)	63 (77.78)	–	–
Breastfeeding (≥6 months old)	32 (39.51)	23 (35.38)	0.6788
SCORAD	45.48±13.36 (22–74.36)	–	–
Compliance			
Asthma	9 (11.11)	None	–
Allergic rhinitis	14 (17.28)	None	–
Allergic conjunctivitis	6 (7.41)	None	–

Values are shown as *n* (%) or mean ± SD. AD, atopic dermatitis; HCs, healthy controls. ^a The χ^2 test was used for categorical variables, and the *t* test was used for continuous variables.

Table 2. Serum levels of vitamin D and vitamin A in children with atopic dermatitis and healthy controls

Vitamins	Status	AD	HCs	<i>p</i>
Vitamin D, nmol/L	Deficient	26.14±3.50 (37)	26.71±1.74 (6.2)	0.7513
	Insufficient	38.13±5.02 (59.3)	38.67±5.46 (41.5)	0.6681
	Normal	56.39±6.90 (3.7)	63.08±10.25 (52.3)	0.2209
	Total	34.37±8.52	50.70±15.65	<0.001
Vitamin A, μ mol/L	Deficient	0.55±0.08 (27.2)	0.60±0.09 (13.8)	0.1969
	Insufficient	0.89±0.10 (46.9)	0.89±0.10 (53.8)	0.8181
	Normal	1.17±0.08 (25.9)	1.22±0.18 (32.4)	0.7917
	Total	0.87±0.25	0.96±0.24	0.0423

Values are shown as mean ± SD (with percentages in parentheses). AD, atopic dermatitis; HCs, healthy controls.

tivitis, consistent with atopic march. The general information related to the included subjects is shown in Table 1.

VD and VA Levels in Patients and Healthy Controls

The average serum VD levels were significantly lower in children affected by AD (34.37 ± 8.52 nmol/L) than those of healthy controls (HCs) (50.70 ± 15.65 (*p* < 0.0001)). The mean serum VA value of AD children was significantly different from that of the control subjects (0.87 ± 0.25 vs. 0.96 ± 0.24 μ mol/L) (*p* = 0.0423). Further analysis showed that the rate of deficiency/insufficiency of VD was higher than that of VA (96.3 and 74.1%, respectively), and 57 children (70.4%) in the AD group suf-

fered from both VA and VD deficiency (For more details, see Table 2.)

Serum Levels of VD and VA in Children with Different Severities of AD

The results suggest that the serum levels of VA and VD are markedly lower in patients with severe AD than in those with moderate AD. There were 30 (90.9%) individuals with insufficient VD levels in the moderate group. Among these, 9 (27.3%) were deficient, and 21 (63.6%) were insufficient. Only 3 had adequate VD levels. The mean VD levels in deficient, insufficient and normal individuals were 27.47 ± 1.78 nmol/L, 40.14 ± 5.14 nmol/L and 56.39 ± 6.90 nmol/L, respectively. In the severe AD

Table 3. Serum levels and distribution of vitamin A and vitamin D in children with moderate and severe atopic dermatitis

		Moderate AD	Severe AD	<i>p</i>
Vitamin D, nmol/L	Normal	56.39±6.90 (9.1)	0	
	Insufficient	40.14±5.14 (63.6)	36.57±4.41 (56.2)	0.0129
	Deficient	27.47±1.78 (27.3)	25.56±3.91 (43.8)	0.1740
	Total	38.17±9.28	31.75±6.91	0.0006
Vitamin A, µmol/L	Normal	1.166±0.0849 (39.4)	1.186±0.0853 (16.7)	0.6066
	Sufficient	0.8948±0.1108 (42.4)	0.8948±0.0955 (50)	1.0000
	Deficient	0.5084±0.1351 (18.2)	0.5524±0.0925 (33.3)	0.3907
	Total	0.9312±0.2587	0.8292±0.2412	0.0730

Values are shown as mean ± SD (with percentages in parentheses). AD, atopic dermatitis.

group, all patients had abnormal VD levels, with 21 patients (43.8%) exhibiting VD deficiency (mean value, 25.56 ± 3.913 nmol/L) and 27 (56.2%) exhibiting insufficiency (mean value, 36.57 ± 4.41 nmol/L).

In children with moderate and severe AD, the serum VA levels were 0.9312 ± 0.2587 and 0.8292 ± 0.2294 µmol/L, respectively. There was no significant difference between the two groups ($p = 0.0730$). In the moderate AD group, the serum VA levels were deficient, insufficient and sufficient in 6 (18.2%), 14 (42.4%) and 13 (39.4%) children, respectively. The mean serum VA levels in the same groups were 0.5084 ± 0.1351 , 0.8948 ± 0.1108 and 1.166 ± 0.0849 µmol/L, respectively. Among patients with severe AD, 16 (33.3%) were classified as VA-deficient (average value, 0.5524 ± 0.0925 µmol/L), 24 (50%) were classified as VA-insufficient (mean value, 0.8948 ± 0.0995 µmol/L), and 8 children (16.7%) had normal VA levels (mean value, 1.186 ± 0.0853 µmol/L) (for more details, see Table 3).

Correlation between Serum Vitamin Levels and the Severity of AD

To further explore the relationship between vitamins and disease, we analysed the correlation between serum concentrations of vitamins and SCORAD scores. The results showed that in children with AD, serum VD levels were negatively correlated with the severity of the disease ($r = -0.3880$, $p = 0.0004$), consistent with the results of previous studies [19, 22, 23] (Fig. 2a). Interestingly, in children with AD, VA levels were not only significantly lower than those observed in the controls but also negatively correlated with the severity of the disease ($r = -0.4203$, $p = 0.0001$) (Fig. 2b).

Analysis of AD Severity in Children with VDD and Different Levels of VA

According to the serum level of VA, 78 AD patients with VDD or VD insufficiency were further divided into the following three subgroups: VA-deficient (22 cases), VA-insufficient (36 cases) and VA normal (20 cases). The SCORAD scores in the three groups were 50.86 ± 14.85 , 46.03 ± 11.96 and 40.02 ± 12.76 , respectively. The SCORAD scores both in the VAD group and the VA-deficient/insufficient group were significantly higher than those in the VA normal group ($p = 0.0312$, Fig. 3a; $p = 0.0236$, Fig. 3b). When compared with the sufficient/insufficient group, the SCORAD score in VAD group was still significantly higher ($p = 0.0388$, Fig. 3c). These results suggest that AD severity is greater in patients with both VD and VA co-deficiency than in AD patients in the VA normal group (Fig. 3).

Relationship among Vitamins, Serum Immunoglobulin E Levels and Peripheral Eosinophil Counts in Children with AD

Total serum immunoglobulin E (IgE) concentrations were significantly higher in AD patients (308.1 ± 403.9 IU/L) than in HCs (31.91 ± 36.68 IU/L) and positively correlated with AD severity ($p = 0.0011$) (Fig. 4a). There was no correlation between vitamin levels and IgE levels ($p = 0.44$, $p = 0.9298$) (Fig. 4b, 4c). The average number of peripheral blood eosinophils was significantly higher in children with AD ($0.69 \pm 0.41 \times 10^9$) than that in HCs. Interestingly, there was a negative correlation between serum VD/VA levels and eosinophil counts in patients with AD ($p = 0.0367$, $p = 0.0264$) (Fig. 4d, e).

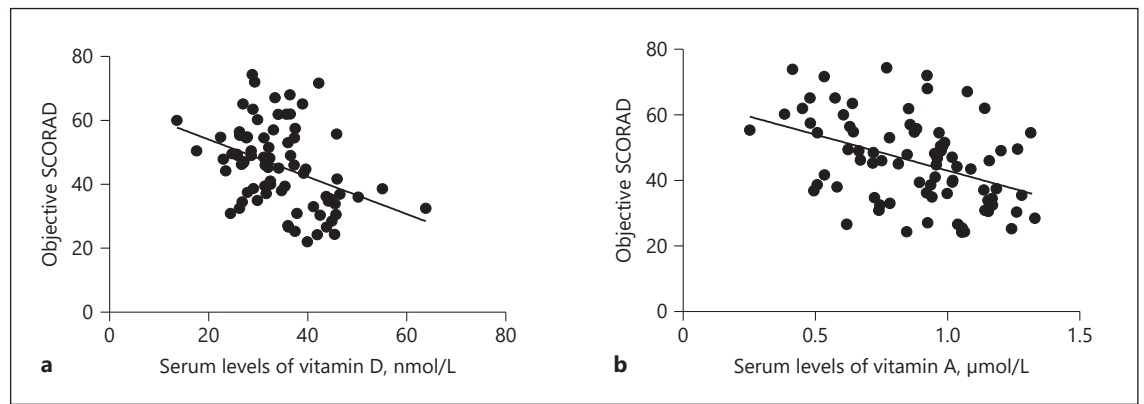


Fig. 2. Correlation analysis of the severity of atopic dermatitis (AD) with serum levels of vitamin D (a) and vitamin A (b).

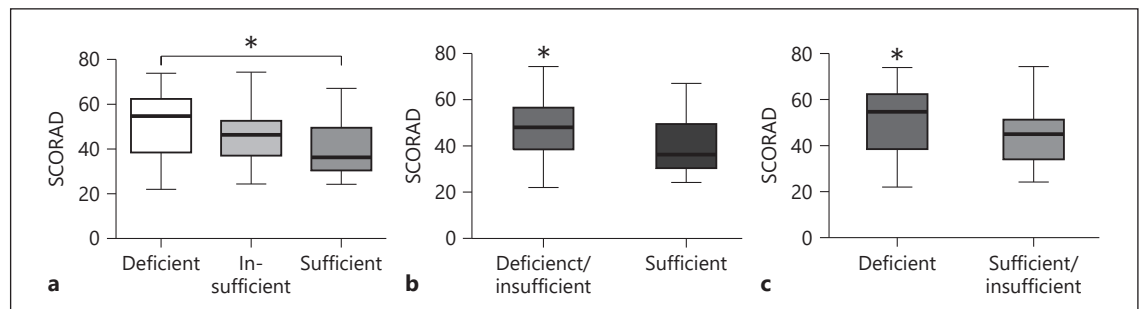


Fig. 3. a SCORAD scores for different vitamin A (VA) levels in patients with vitamin D deficiency (VDD) and atopic dermatitis. b SCORAD scores for the VA-deficient/insufficient group and the sufficient group. c SCORAD scores for the VAD group and the sufficient/insufficient group.

Discussion

This is the first study to explore the dual effects of VD and VA on the severity of AD. Our results show that serum levels of VD and VA were significantly lower in children with AD than in HCs. The serum levels of both VD and VA were negatively correlated with AD severity, and AD severity was even more extreme in patients in whom VD and VA were co-deficient than in other AD patients.

Previous results have shown that VD plays an important role in regulating immune functions, inhibiting cell proliferation, promoting cell differentiation and maintaining skin barrier integrity. VDD has been implicated in several allergic disorders, including AD. Peroni et al. [12] were the first to reveal the relationship between VD and AD by showing that VD levels were significantly lower in patients with AD and negatively correlated with the severity of the disease. These results were consistent with

epidemiological findings [29]. Akan et al. [13] found the same relationship, especially in children with allergic sensitization, and the results of our study also support this finding. All of these data seem to indicate that VDD may be a risk factor for the development of AD. In addition, several clinical trials demonstrated that VD supplementation can help improve the clinical symptoms of AD and significantly increase the serum levels of VD [30, 31], providing further support for the notion that VD may play a protective role in AD. Although the majority of previous studies have indicated that there is an inverse relationship between serum VD levels and the severity of AD, overall, their results have not been consistent. Samochocki et al. [32] found that the mean serum concentration of 25(OH) D3 was not significantly different between patients with AD and control subjects. Studies by Chiu et al. [33] and Han et al. [34] showed that although VD levels were lower in AD patients than in HCs, there was no correlation

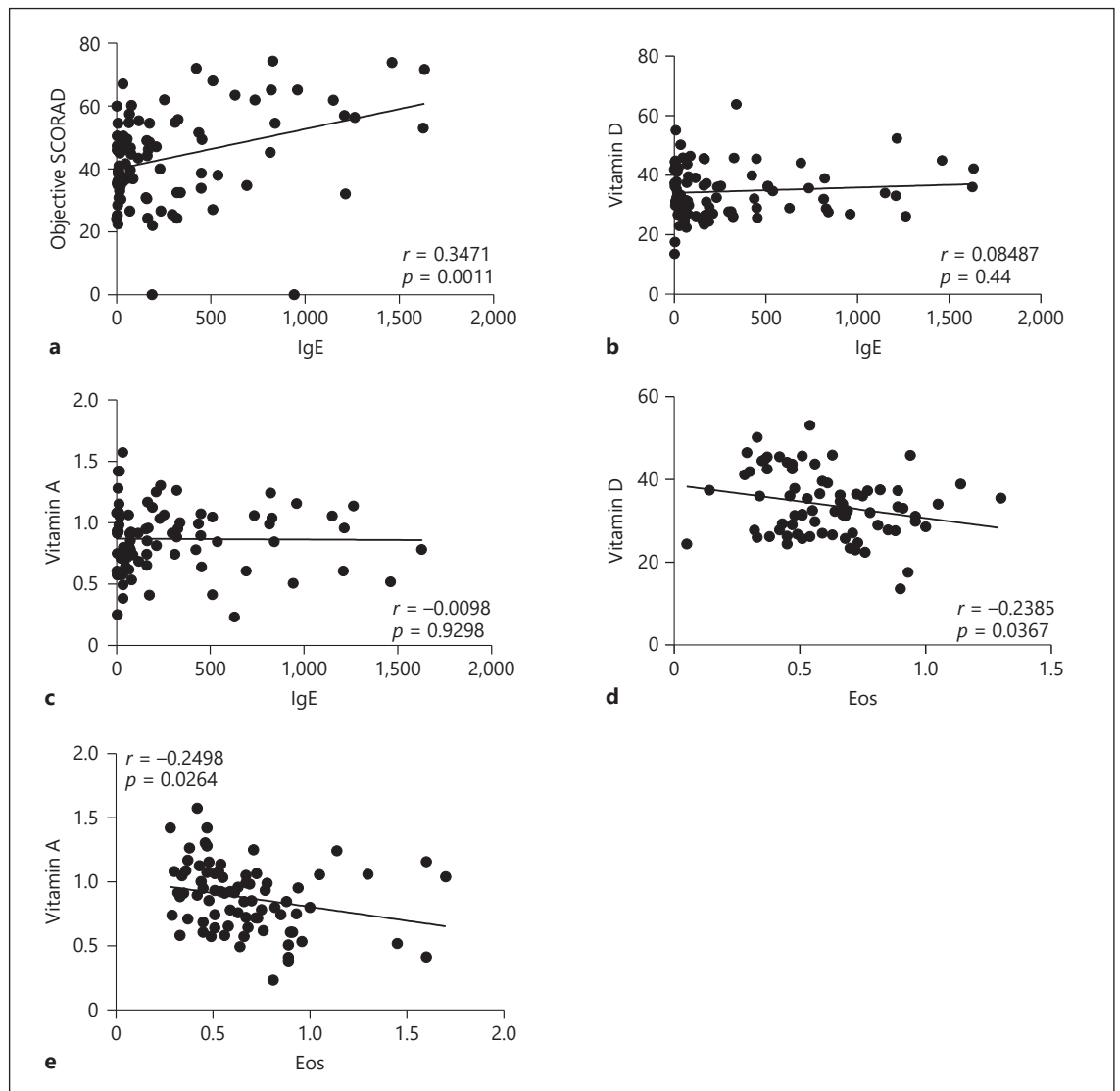


Fig. 4. Correlation analysis of serum IgE levels and disease severity (a), serum IgE and vitamin D levels (b), and serum IgE and vitamin A levels (c) in children with atopic dermatitis. Correlation analysis of peripheral blood eosinophil (Eos) counts and vitamin D levels (d) and peripheral blood Eos counts and vitamin A levels (e).

between VD levels and AD. A few plausible explanations have been suggested to explain these contrary results about the relationship between VD and AD. For example, Mallbris et al. [35] showed that cathelicidin production could be induced in keratinocytes by the VD₃ pathways in atopic skin. In addition, Hata et al. [36] showed that the expression of cathelicidin was increased in skin affected by AD after oral VD supplementation. It is widely accepted that cathelicidin is one of the key protective factors in the skin barrier [37]. Thus, in AD, increasing VD₃ levels not only in the serum but also in the skin may help to

strengthen innate defensive barrier function to prevent cutaneous infections by triggering skin inflammation.

Interestingly, our study found for the first time that 74.1% of the AD patients had VA deficiency/insufficiency, and serum VA levels were significantly lower in affected children and negatively correlated with AD severity. When VD and VA were both deficient, the AD condition was more serious. Hence, our results indicate that VA may have synergistic effects with VD in AD. It is widely accepted that VA and its derivative, RA, influence a wide variety of essential physiological processes, includ-

ing growth and development, vision, and the health of the immune system and skin barrier functions [38, 39]. Although a great deal of effort has been put into promoting the importance of VA supplementation, VAD is one of the most common micronutrient deficiencies in the world, especially in developing countries such as China, and it causes many disordered conditions. Previous studies have shown that RA has a dual effect on immune homeostasis and inflammatory conditions [40] and plays a central role in eliciting Tregs to create a tolerogenic environment at the cost of Th17 cells [41, 42]. Conversely, when stimulated by the RA receptor, RA rapidly and directly suppresses Th1 development and directly enhances Th2 development [43, 44]. VA is thought to induce epidermal cells to differentiate into subtypes with distinct specializations, and this function is essential to maintaining the homeostasis of the skin barrier [45]. Impairment of the skin barrier and imbalance in the ratios of Th1/Th2 and Tregs/Th17 are key contributors to the pathogenesis of AD, suggesting a potential link between VA and AD. Recently, Oh et al. [20] found that serum VA concentrations are lower in children with AD, regardless of the level ingested from food or found in the serum, and that AD was negatively associated with the intake of antioxidant-related nutrients (including VA and β -carotene). Their findings suggested that VAD increases the risk of AD, consistent with our own conclusions. Moreover, Mihály et al. [21] found that in patients with AD, retinoid transport, synthesis, concentrations and signalling were markedly abnormal in both affected and non-affected skin. However, there were no differences in the serum concentrations of all trans-RA and retinol between AD patients and HCs, suggesting that AD exerts a general intrinsic influence on skin retinoid signalling pathways. In this study, we found that in patients suffering from VDD, comorbid VAD worsened the severity of AD.

Total IgE levels and eosinophil counts have long been considered important indexes for AD diagnosis, and elevated total IgE and higher eosinophil counts are commonly observed in patients affected by AD [46]. In this study, the total IgE level was significantly higher in AD patients than in HCs and positively correlated with disease severity, in accordance with previous studies [47]. Total IgE levels were correlated with neither VD nor VA. Cheng et al. [48] and Wang et al. [49] showed that in AD patients, there is an inverse relationship between total IgE levels and serum levels of VD. Studies have also shown that VD receptor agonists inhibit the production of IgE in cultured human B cells and allergic mice models [50]. However, in our study, we found no correlation between

IgE levels and VD levels in either atopic or non-atopic AD, consistent with the results of other studies [31, 32]. Unexpectedly, we found that the absolute eosinophil count in peripheral blood was negatively correlated with serum levels of VD and VA. Previous studies have reported that VDD is associated with higher eosinophil counts [51]. These data suggest that eosinophils may be a new target of VA and VD in the pathogenesis of AD.

Conclusions

In summary, our results demonstrate that VDD and VAD are more prevalent in AD patients than in HCs and that serum levels of VD and VA are negatively correlated with the severity of AD and peripheral blood eosinophil counts. The severity of AD was greater when both VD and VA were deficient. We described these phenomena in the current study, but further supplementary clinical trials are needed to confirm this association and determine the underlying mechanism.

Key Message

Vitamin D and vitamin A co-deficiency may exacerbate the severity of atopic dermatitis.

Acknowledgements

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Statement of Ethics

An informed written consent was signed by all individuals (or their parents) to participate in this work. The study was approved by the Clinical Research Ethics Committee of the Children's Hospital of Chongqing Medical University.

Disclosure Statement

The authors declare no conflict of interest.

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