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Vitamin D Supplementation Modulates the Immune System and Improves Atopic Dermatitis in Children

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Key Words
Children · Atopic dermatitis · Vitamin D · SCORAD index · Cytokines

Abstract
Background: Vitamin D seems to influence the evolution of atopic dermatitis (AD) in children. ***Methods:*** We tested the vitamin D serum levels of 39 children with AD (AD group t_0) and of 20 nonallergic healthy controls (C group). AD severity was evaluated using the AD scoring system (SCORAD index). Cytokine serum levels (IL-2, IL-4, IL-6, IFN-γ, TNF-α) and atopy biomarkers were also measured. The patients were then treated with vitamin D oral supplementation of 1,000 IU/day (25 mg/day) for 3 months. We then reevaluated the vitamin D serum levels, AD severity and cytokine serum levels in all of the treated children (AD group t_1). ***Results:*** The cross-sectional analysis on patients affected by AD (AD group t_0) showed that the initial levels of all the tested cytokines except for TNF-α were higher than those of the healthy control group (C group), falling outside the normal range. After 3 months of supplementation the patients had significantly increased vitamin D levels (from 22.97 ± 8.03 to 29.41 ± 10.73 ng/ml; $p = 0.01$). A concomitant significant reduction of both the SCORAD index (46.13 ± 15.68 at the first visit vs. 22.57 ± 15.28 at the second visit; $p < 0.001$) and of all the altered cytokines (IL-2, IL-4, IL-6, IFN-γ) was also found. ***Conclusions:*** This study showed vitamin D supplementation to be an effective treatment in reducing AD severity in children through normalization of the Th1 and Th2 interleukin serum pattern.

Introduction

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases, affecting more than 25% of children and 1–3% of adults worldwide [1].

AD often occurs in early childhood: 45% of all cases begin within the first 6 months of life, 60% during the first year and 85% within 5 years. More than 50% of affected children do not have any evidence of IgE-mediated sensitization in the first 2 years of life, but sensitization can occur later in life. More than 70% of these children have a spontaneous remission before adolescence [2].

The imbalance of the Th2 and Th1 pathways and their associated cytokines is an important pathogenic mechanism in AD. In the skin of patients with AD, there is an

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increase in Th2 cells and a decrease in Th1 cells. However, important changes in T-cell populations occur depending on whether the patient is in the acute or chronic phase of the disease. In the acute phase, Th2 cells and the associated cytokines (IL-4, IL-5, IL-13) are predominant, whereas in the chronic phase, Th1 cells, releasing mostly IFN-γ and other cytokines like IL-5 and IL-12, play a central role [2].

The vitamin D receptor is widely distributed throughout the body. It is well represented in the skin as well as in the immune system, suggesting a central role in regulating these two tissues. However, it is also known to play a larger role in modulating many other functional activities of the human body. In particular, the importance of vitamin D in calcium homeostasis and skeletal development in children has been well documented. Some authors have not found any correlation between vitamin D deficiency and asthma or other allergic diseases. For example, a recent study including 120 children diagnosed with asthma and 74 children with no evidence of allergic disease has suggested that vitamin D levels were not significantly different in patients with asthma, reporting vitamin D deficiency in the asthmatic children as well as in the control group [3].

However, several studies have suggested a possible influence of vitamin D on the development of allergic diseases and AD, but both positive and negative correlations have been found. The first hypothesis suggests that higher serum vitamin D levels (vitamin D supplementation in pregnant women and neonates or high vitamin D intake during the first year of life) are responsible for the increased prevalence of asthma and allergy [4, 5]. In contrast, the second hypothesis supposes that lower levels may contribute to the increased prevalence of the allergic diseases, which is supported by studies that have shown vitamin D supplementation during pregnancy prevents the development of asthma and allergic rhinitis [6] and that pregnant mothers with low vitamin D dietary intake [7] or low fish consumption [8] have a higher risk of having children who develop AD.

Peroni et al. [9] found that vitamin D serum levels were higher in children with milder dermatitis, as determined by the SCORAD index, in contrast to another study that observed that a clinical improvement of AD (evaluated using SCORAD) after 60 days was significant in the groups receiving vitamin D or E or both. In addition, Amestejani et al. [10] published a randomized, double-blind, placebo-controlled trial in which 30 patients affected by AD received vitamin D (1,600 IU/day) and 30 patients received placebo. After 60 days, the group treated with vitamin D improved significantly (according to SCORAD and TIS value index), while in the placebo group the improvement was not significant.

In general, taking into consideration all the support given by these studies, the second hypothesis, stating that lower vitamin D levels increase the risk of allergy-related disease, is more accepted over the first hypothesis, probably because it is supported by the effects of vitamin D on the skin such as suppression of the inflammatory response, the increase of antimicrobial peptides (AMPs) and the promotion of skin barrier integrity [11]. In AD, the skin barrier function is deficient and cathelicidin levels are altered. An altered cytokine microenvironment may be the reason for the decreased expression of AMPs. Specifically, the Th2 cytokines such as IL-4 and IL-13 suppress the induction of AMP [12]. Vitamin D decreases local and systemic inflammation, thus modulating cytokine production and inhibiting T-helper cell (Th1) proliferation, as well as Th17 cells [13]. Calcitriol, the active form of vitamin D, seems to significantly decrease the secretion of IL-2 and IFN-γ by Th1 clones and that of IL-4 by Th2 clones, as demonstrated by some investigators [14].

The aim of this study was to investigate the correlation between AD and vitamin D deficiency and to examine the possible effect of vitamin D oral supplementation on AD evolution in children through the modulation of the immune system, influencing Th1 and Th2 lymphocyte subpopulations.

Materials and Methods

Study Population and Design

This was a single-center, prospective and longitudinal study. To prevent the influence of the season on vitamin D serum values, all patients were enrolled during the winter (from November to February). We included 39 children (aged 4 ± 3.15 years) affected by AD (AD group) who were referred to the Allergy Unit of the Pediatric Department between the years 2011 and 2013.

Inclusion criteria for the AD group were the following: (1) clinical diagnosis of AD (erythema, edema and papulation, oozing, excoriation, lichenification, dryness, and pruritus) by a single pediatric allergist and (2) prepubertal stage (stage 1 of Tanner). Exclusion criteria for the AD group were as follows: (1) vitamin D supplementation in the previous 6 months and (2) administration of calcineurin inhibitors in the previous 2 weeks or systemic anti-inflammatory therapy in the previous 6 months.

The AD group was evaluated at the time of recruitment (t_0) and after 3 months of vitamin D supplementation of 1,000 IU/day (t_1).

During the first visit (t_0) the following parameters were examined: (1) baseline vitamin D serum level, (2) AD severity using the

SCORAD index and (3) cytokine serum concentration (IL-2, IL-4, IL-6, IFN-γ, TNF-α). Every patient in the AD group at the recruitment time (t_0) received a diary in which they documented any administration of adjunctive therapy (topical or oral) in the case of disease exacerbation. Supplementation with oral vitamin D (1,000 IU/day or 25 mg/day) was prescribed for 3 months for all patients.

The second visit was performed after 3 months of vitamin D supplementation (t_1) – from February to May between the years 2012 and 2014. This visit was performed on 26 of the initial 39 patients, 22 of whom declared that they adhered to oral vitamin D supplementation (AD group t_1) – 4 patients were not included in the analysis because, although they completed the second visit (t_1), they declared that they did not follow the recommended therapy with vitamin D, and 13 patients did not complete the follow-up.

All 22 subjects in the AD group t_1 were tested for the following: (1) vitamin D serum level after the oral supplementation, (2) AD severity using the SCORAD index and (3) cytokine serum concentration (IL-2, IL-4, IL-6, IFN-γ, TNF-α).

To compare the vitamin D concentration and cytokine levels of the AD group at each time point (t_0 and t_1), these variables were measured in the winter period (from November to February between the years 2011 and 2013) in a healthy control group of 20 patients (C group) matched for age (4 ± 2.5 years) and sex with the AD group (online suppl. tables 1 and 2; for all online suppl. material, see www.karger.com/doi/10.1159/000371350).

Written informed consent was obtained from all parents and verbal consent was obtained from all children. The study was approved by the Ethics Committee of the University of Chieti.

Assessment of AD Severity

AD severity was determined by the same operator using the SCORAD index and each patient was classified as follows: SCORAD <25: mild AD, SCORAD 25–50: moderate AD or SCORAD >50: severe AD [15, 16].

Laboratory Tests

The cytokines serum concentration was determined by the flow cytometric method using the BD™ Cytometric Bead Array human Th1/Th2 cytokine kit. The vitamin D status was determined through the ELISA technique LIAISON® 25-OH Vitamin D Assay Kit (DiaSorin), with a measurement range between 7.0 and 150 ng/ml. Blood levels of total and specific IgE to inhalant and food allergens were measured using the ImmunoCAP (Phadia, Thermo Scientific), which detects specific IgE in the range between 0 and 100 kUA/l. For eosinophils, a range from 1 to 6% was considered normal.

Statistical Analysis

The results were expressed as mean ± standard deviation. $p < 0.05$ was considered statistically significant. A paired sample t test was used to compare the cytokine values, the SCORAD index and vitamin D levels between the two visits (AD group t_0 vs. AD group t_1). The independent sample t test was used to compare cytokines and vitamin D levels between the asthmatic patients at the two time points (AD group t_0 and AD group t_1) and the control group (C group). The correlation between vitamin D change and the SCORAD change in the AD group was evaluated by Pearson's correlation test. Graphs were represented as means ± SEM. SPSS 17 software (SPSS Inc.) was used for the statistical analysis.

Results

The study participants were comparable for age, gender and pubertal stage. In the AD group t_0, 15/39 children (38.4%) had familiarity for asthma, and 34/39 children (87.1%) had familiarity for allergy. None of the children had a medical history of neonatal disease. In addition, 13/39 patients (33.3%) were affected by asthma, and 13/39 (33.3%) had a history of rhinitis.

All patients had chronic AD. In the AD group t_0, 3 children (7.7%) had mild AD, 18 (46.1%) had moderate AD and 18 (46.1%) had severe AD. Allergy status was evaluated by the skin prick test, total IgE and specific IgE for inhalant and food allergens. Total IgE was increased in 35 children (about 89.7%; mean value expressed in online suppl. table 3), and specific IgE was increased in 31 children (79.4%); 9 children were positive for food allergens only and 8 children for inhalants only, while 14 children were positive for both. The most frequent sensitizations were for dust mite (15/39 children) and eggs (17/39 children); the skin prick tests were positive in 31/39 children, according to the results of specific IgE.

The families were strongly encouraged not to use oral or topical steroids during vitamin D supplementation to avoid this as a confounding factor in data interpretation. None of the patients used oral steroid therapy during the follow-up; 6 patients used sporadic doses of topical steroid.

In the AD group t_0, only 7/39 patients (17.9%) had sufficient vitamin D serum levels; 29/39 patients (74.3%) had insufficient vitamin D serum levels, and 3/39 patients (7.6%) had deficient vitamin D serum levels.

The mean value of serum vitamin D levels was insufficient and comparable between the AD group t_0 and the C group (22.97 ± 8.03 vs. 20.08 ± 3.23), showing that this deficit is a very common condition, regardless of AD (online suppl. table 1).

The cross-sectional analysis of the AD group t_0 showed that the mean values of IL-2, IL-4, IL-6, and IFN-γ were higher compared to the normal values. In contrast, the mean value of TNF-α was not increased. The mean values of these cytokines in the healthy control group (C group) were within the normal range (online suppl. table 1).

After 3 months of vitamin D supplementation, it was found that in the AD group t_1 (online suppl. table 4) vitamin D values were significantly higher compared to the starting levels (29.41 ± 10.73 vs. 22.97 ± 8.03 ng/ml; $p = 0.01$). At the same time, a reduction in the SCORAD index was observed (46.13 ± 15.68 at the first visit vs. 22.57 ±

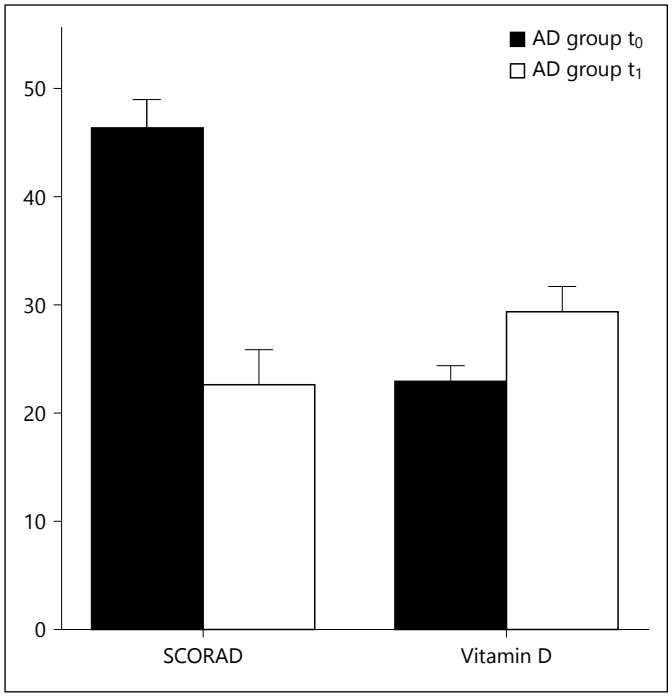

Fig. 1. After 3 months of vitamin D supplementation in the AD group it was found that vitamin D values were significantly higher (29.41 ± 10.73 ng/ml) compared to the starting levels (22.97 ± 8.03 ng/ml; p = 0.01). At the same time, a statistically significant reduction in the SCORAD index was found (46.13 ± 15.68 at t_0 vs. 22.57 ± 15.28 at t_1; p < 0.001).

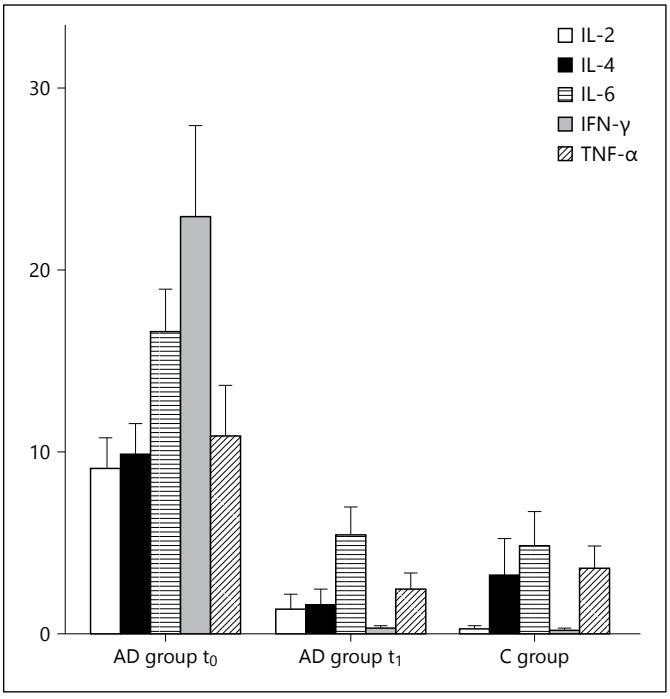

Fig. 2. A statistically significant reduction of IL-2, IL-4, IL-6, and IFN-γ was found; no statistically significant reduction of TNF-α was found. The cytokine values decreased and approached the healthy control group values back within the normal range.

15.28 at the second; p < 0.001; fig. 1). A statistically significant reduction of IL-2 (8.22 ± 7.39 vs. 1.24 ± 4.06; p < 0.001), IL-4 (9.01 ± 7.05 vs. 1.36 ± 4.26; p < 0.001), IL-6 (15.11 ± 9.13 vs. 6.81 ± 9.60; p = 0.007), and IFN-γ (20.05 ± 22.84 vs. 0.19 ± 0.79; p = 0.019) was documented (online suppl. table 4). In contrast, TNF-α reduction was not significant (8.85 ± 11.09 vs. 2.33 ± 4.27). All the tested cytokines approached the healthy control group values back within the normal range (fig. 2; online suppl. table 2).

Taking into consideration all 22 patients in the AD group t_1, we found no significant correlation between the vitamin D change and the SCORAD change between the second and the first visit. Otherwise, excluding from the analysis 6 patients who declared they adhered to the vitamin D supplementation but were unable to increase vitamin D levels between the first and the second visit (meaning the supplementation was not sufficient to improve their vitamin D levels), we found a significant negative correlation between the vitamin D change and the SCORAD change (r = –0.49; p = 0.02), strongly supporting the hypothesis that the positive clinical effect was mostly due to vitamin D effective supplementation (online suppl. fig. 1).

Overall, 17 individuals did not adhere to the 3 months of vitamin D supplementation, and only 4 of those attended the second visit. Despite the small size of the sample, it was interesting to note that, without supplementation, there was not a significant change in these 4 children between the first and second visit in the following: (1) vitamin D levels (22.8 ± 3.5 vs. 22.9 ± 6.6), (2) SCORAD (31.9 ± 13.2 vs. 22.8 ± 10.2) and (3) cytokine levels.

Discussion

AD is characterized by local and systemic immune dysregulation. The cutaneous inflammation displays a biphasic pattern of T-cell activation. In the acute phase of lesion development, there is a predominance of Th2 cytokines (especially IL-4 and IL-13) which promotes immunoglobulin isotype switching to IgE production and induces the expression of vascular cell adhesion molecules (e.g. VCAM1), which may suggest a role for these Th2 cytokines in regulating eosinophilic infiltration in the skin [17]. Moreover, IL-4 and IL-13 inhibit the de-

struction of *Staphylococcus aureus* by keratinocytes in patients with AD. In the chronic phase of AD there is a shift to the Th1 pattern, with a predominant production of IFN-γ [18–20].

In this study, Th1 and Th2 cytokine levels (IL-2, IL-4, IL-6, IFN-γ) were higher in patients affected by AD compared to the healthy control group. In contrast, the mean value of TNF-α was not increased compared to the controls. Our finding fits with the literature, showing immune system activation with increased levels of Th1 and Th2 cytokines. Because our population was composed of patients with chronic AD, the predominant lymphocyte phenotype (according to the cytokine pattern) was the Th1 subpopulation, with levels of IFN-γ 100 times higher than the normal values and the control group [21].

IL-10 is a critical anti-inflammatory cytokine whose expression is induced after proinflammatory mediators. It is produced by numerous cell types, including Th2 cells. Data from studies examining IL-10 in subjects with AD are conflicting. Plasma levels of IL-10 inversely correlate with the severity of AD. In contrast, other studies have shown elevated IL-10 levels in peripheral blood mononuclear cells isolated from AD patients or in lesional skin. Elevated numbers of CD4+ and CD8+ cells expressing IL-10 were also observed in patients with AD. In this study, IL-10 levels were not tested due to technical problems of our laboratory [22].

In addition to its classical role in calcium homeostasis, recent studies demonstrated the influence of vitamin D in immunomodulation and cell differentiation. Although a definitive role for vitamin D in the pathogenesis of AD has not been explained, its levels seem to be related to AD severity [8]. Therefore, vitamin D is increasingly used in the management of diseases such as AD, psoriasis, vitiligo, acne, and rosacea [23, 24].

In this study, an insufficient level of vitamin D was found in 82% of children (32/39) with AD. However, vitamin D deficiency has also been documented in healthy subjects despite reports of abundant solar exposure [25]. The prevalence of this deficit is very common even in the healthy population, as confirmed by the healthy control group.

Vitamin D serum levels after 3 months of supplementation were significantly higher, going from insufficient to sufficient vitamin D levels. At the same time, SCORAD reduction was observed, demonstrating a clinical status improvement. Confirming that this effect was mostly due to the vitamin D supplementation, we found a negative significant correlation between the SCORAD change and vitamin D change in the subgroup of patients in which the supplementation was able to increase vitamin D levels. In addition, the treatment with vitamin D was effective in normalizing the serum levels of all the altered cytokines (IL-2, IL-4, IL-6, IFN-γ). Their levels after 3 months of treatment were comparable to the control group and within the normal range, confirming the effect of vitamin D in modulating the immunological status of the patient.

At the skin level, vitamin D acts through the suppression of the inflammatory response, increasing AMPs and promoting the integrity of the cutaneous barrier [11]. It may reduce both local and systemic inflammatory responses, modulating cytokine production and reducing Toll-like receptor activation [26]. It has been shown that vitamin D also inhibits T-helper cell (Th1) proliferation (consequently the production of IL-2, TNF-α and IFN-γ decreases) [13].

According to the literature, IFN-γ and IL-2 serum levels decrease in the treated group. This fact can be explained by the vitamin D inhibitory effect on the acquired immunity, resulting in a reduction of Th1 cell activation [27]. Moreover, the IFN-γ reduction would lead to a decreased expression of other cytokines such as IL-31 and IL-33 [28] and to the improvement of clinical features such as spongiosis. In fact, IFN-γ is implicated in keratinocyte apoptosis, which leads to eczema and spongiosis in patients with AD [29].

Vitamin D antimicrobial activity and the negative effects of its deficiency on the general well-being and on the longevity of patients have been previously demonstrated. It may reduce the risk of infection through multiple mechanisms, improving the efficiency of innate immunity by modulating the production of AMPs (such as cathelicidin and β-defensin 2 [30, 31]) and cytokine response.

AMPs are effectors of skin innate immunity ('endogenous antibiotics'), killing bacteria, viruses and fungi. They contribute to the formation of a chemical barrier on the skin surface and trigger a host immune response ('alarming activity'). Therefore, from an antimicrobial viewpoint, vitamin D is able to reduce the infection susceptibility in patients with AD and regulate local immune and inflammatory responses [32].

The potential role of vitamin D in suppressing inflammatory responses, enhancing AMP activity and promoting the integrity of the skin, is clear. Its supplementation has a possible therapeutic role for many skin diseases such as AD.

An important weakness in our study was the small sample size. It would be desirable to design a multicenter

case-control study that would help to decrease the bias due to many variables such as the genetic background, the environment and other confounding factors.

Conclusions

The existing literature on the influence of vitamin D on the development of allergic diseases, in general, is contradictory. It is an issue that needs to be further investigated. There is growing interest in vitamin D supplementation in patients with AD. Many studies have confirmed that vitamin D supplementation has a positive effect on AD severity. This study highlight how the correction of the vitamin D deficit in children is able to improve the clinical evolution of AD, most likely through negative modulation of the immune system, involving Th2 but primarily Th1 lymphocyte populations.

Disclosure Statement

The authors declare no conflict of interests.

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