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Serum Vitamin D levels and Vitamin D supplementation do not correlate with the severity of chronic eczema in children

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IgE chronic eczema; Not-IgE chronic eczema; Serum vitamin D levels; Vit D supplementation

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Summary

Background: *Eczema is one of the most common chronic inflammatory skin diseases, affecting about 20% of children. The pathogenic mechanisms of eczema are still not fully understood, and current treatment of moderate-severe eczema is often difficult. Recently, it has been suggested that Vitamin D plays a key role in this disease, even if mechanisms are only partially known.* ***Objective:*** *The purpose of our study was to assess the 25-Hydroxyvitamin D serum levels in a pediatric population suffering from chronic eczema (IgE-mediated and non-IgE-mediated), and to correlate these phenotypes with the SCORAD severity and selected clinical and biological parameters. Moreover, we aimed to evaluate whether a supplementation of Vitamin D3 could affect the same clinical and laboratory parameters.* ***Methods:*** *89 children with chronic eczema were enrolled in the study. Severity of eczema was assessed with the SCORAD index. Past and present history was taken, and patients were divided into two groups according to the state of sensitization. According to a randomization schedule, the enrolled children were assigned to the following groups: supplementation group, which received a daily oral Vitamin D3 supplementation (2000 IUs) for 3 months; control group which received no supplementation.* ***Results:*** *Vitamin D concentrations in patients with moderate and severe eczema were not statistically different from Vitamin D concentration detected in the serum of patients with mild eczema. Furthermore, we did not find any correlation between Vitamin D levels, total IgEs and SCORAD index, both in the Sensitized and in the Not-Sensitized group. The Vitamin D3 supplementation did not influence the SCORAD severity or the total IgEs concentration.* ***Conclusion:*** *To our knowledge, our study is the first one that shows no correlation between serum levels of Vitamin D, eczema severity and IgE sensitization in a pediatric population suffering from chronic eczema.*

Introduction

Eczema is one of the most common chronic inflammatory skin diseases, affecting about 20% of children and 3% of adults (1). It is a frustrating condition for both patients and caregivers, as intractable pruritus can cause sleep disturbance with important physical and psychological implications. Indeed, current treatment of moderate-severe eczema is often difficult (2,3).

Genetic and environmental factors, other than innate and adaptive immune defects, affect the development of eczema, although the pathogenic mechanisms are still not fully understood (4,5).

Recently, it has been shown that Vitamin D (Vit D) plays a key role in the innate and adaptive immunity (6). In the innate immune system, Vit D appears to improve antimicrobial

defences in general. Vit D induces endogenous expression of the antimicrobial peptide cathelicidin. This can be seen in the skin, in monocytes, and in the lung. Because cathelicidin has been found in multiple experimental systems to be essential for defence against a variety of microbial infections, it has been proposed that Vit D can enhance resistance to infections (7). Epithelial cells may express the Vit D receptor, and its activation implies a different expression of an array of target genes which, in turn, can interfere with the inflammation process and immune defence, possibly affecting those immune disorders characterized by an altered Th1/Th2 cytokines balance. The cutaneous production of cathelicidin can inhibit the production of IL-12. In this way the Th1 cell response is downregulated, and the Th2 cell response is upregulated with an IL-4 and IL-5 increase (6-8). This may explain the growing body of evidence connecting Vit D to the allergic disease, even if mechanisms are only partially known.

The purpose of our study was to assess the 25-Hydroxy Vit D (25-OH-D) serum levels in a pediatric population suffering from chronic eczema, both IgE-mediated and non-IgE-mediated type, and to correlate these two phenotypes with the SCORAD severity and selected clinical and biological parameters (allergic diseases, total and specific IgEs). Moreover, we aimed to evaluate whether, independently from baseline levels of Vit D, a daily 2000 IUs supplementation of Vit D3 (*cholecalciferol*) for 3 consecutive months could affect the same clinical and laboratory parameters.

Methods

Study design

We designed a randomized clinical trial. The power was set at 80%, confidence interval at 95%, the sample size was 78 patients for a risk/prevalence rate of approximately 5 (Fleiss).

This randomized open study was carried out in the Pediatric Allergy Unit, Research Centre, S. Peter Hospital, Fatebenefratelli, Roma, Italy, from January 2012 to March 2013.

Eighty-nine consecutive children with chronic eczema (48 boys) with a median age of 68 months (range 6-195 months), diagnosed according to the Hanifin and Rajka criteria (9), were enrolled in the study. Past and present medical history including food allergy, respiratory symptoms and cutaneous infections was taken from patients. Eczema was considered chronic if it lasted at least 6 months. The severity of eczema was evaluated by the same operator (EG) according to the SCORAD method (10). Patients with a SCORAD value less than 25 were considered as having a mild eczema, those with a score from 25 to 50 as having a moderate eczema and those with a SCORAD value greater than 50 as suffering from a severe eczema (**table 1**).

None of the enrolled children suffered from other chronic diseases or were taking topical or oral steroids, vitamins, minerals, fatty acids supplementation or immunosuppressive therapy at the time of investigation and in the last 6 months.

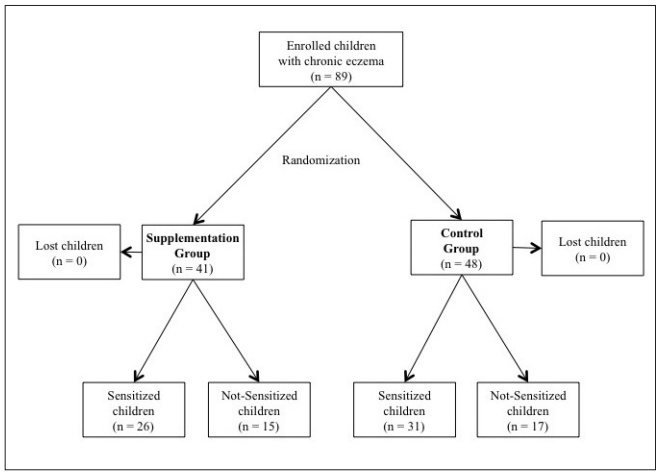
Seventy-one out of 89 patients did not have special dietary restrictions, and everyone enjoyed exposure to sun and ordinary outdoor activities.

After a descriptive analysis, the enrolled children were assigned to one of the 2 following groups according to a randomization schedule: supplementation group (SG) composed by 41 children (median age 91 months, range 11-195 months, 22 males) who were given a daily oral Vit D3 (*cholecalciferol*) supplementation (2000 IUs) for 3 months, in fat soluble form; and a control group (CG) composed by 48 children (median age 57.5 months, range 22-180 months, 26 males) who received no Vit D3 supplementation. The study design is depicted in **figure 1**.

Table 1 *- Characteristics of the 89 enrolled children with chronic eczema.*
RR: Relative Risk; NS: Not Significant; NA: Not Applicable

	BASIC ANALYSIS						
	Whole population	Enrolled children divided according to allergic sensitization			After randomization to Supplementation or Control group		
Variables	Total children (n = 89)	Not-Sensitized children (n =32)	Sensitized children (n =57)	p [RR]	Supplementation group (n = 41)	Control group (n = 48)	p
Demographic parameters							
Age, months, median (range)	68 (6-195)	62 (6-195)	74 (6-192)	NS	91 (11-195)	57.5 (22-180)	p = 0.003
Male, *n* (%)	48 (53.9%)	13	35	NS [RR=1.51 (0.95-2.41)]	22	26	NS
Clinical parameters							
SCORAD score, mean (±SD)	17.5 (±17.2)	16.5 (±16.5)	18.1 (±17.7)	NS	12.2 (±11.1)	22.1 (±20.1)	p = 0.006
Mild (< 25)	66 (74.2%)	22 (68.8%)	44 (77.2%)	NS	7.121 (+3.814)	9.879 (±5.952)	p = 0.029
Moderate (25-50)	17 (19.1%)	8 (25.0%)	9 (15.8%)	NS	29.29 (±1.89)	39.5 (+6.09)	p = 0.000
Severe (> 50)	6 (6.7%)	2 (6.3%)	4 (7.0%)	NS	0	3	NA
Duration of eczema, months, median (±SD)	63	58.41 (±34.89)	65.18 (±38.92)	NS	72.71 (±38.28)	54.23(±34.92)	p = 0.019
Staphylococcal infections	38 (42.7)	3 (9.4%)	35 (61.4%)	p < 0.0001 [RR = 6.55 (2.19-19.61)]	19 (46.3%)	19 (40.4%)	NS
Personal history of atopy	44 (49.4%)	13 (40.6%)	31 (54.4%)	NS [RR=1.34 (0.82-2.16)]	23 (56.1%)	21 (44.7%)	NS
Rhinitis	29 (32.6%)	7 (21.9%)	22 (38.6%)	NS [RR=1.76 (0.84-3.67)]	17 (41.5%)	12 (25.5%)	NS
Asthma/wheezing	34 (38.2%)	9 (28.1%)	25 (43.9%)	NS [RR=1.56 (0.83-2.92)]	16 (39.0)	18 (38.3%)	NS
Food allergy	18 (20.2%)	5 (15.6%)	13 (22.8%)	NS [RR=1.46 (0.57-3.72)]	11 (26.8)	7 (14.9%)	NS
Basic laboratory parameters							
Total IgE (IU/ml), mean (±SD)	376.3 (±837.5)	18.9 (±9.7)	577.0 (±994.0)	p = 0.002	547.5 (±1104.5)	230.2 (±477.2)	NS
25(OH)D3 (ng/ml), mean (±SD)	48.3 (±40.6)	48.8 (±39.3)	48.0 (±41.6)	NS	56.0 (±53.5)	41.6 (±23.4)	NS
Vit D sufficiency (> 30 ng/ml)	48 (53.9%)	18 (56.3%)	30 (52.6%)	NS [RR=0.94 (0.63-1,38)	21 (51.2%)	2 (4.2%)	p = 0.0001
Vit D insufficiency (12-30 ng/ml)	31 (34.8%)	11 (34,4%)	20 (35.1%)	NS [RR=1.66 (0.95-2.91)	12 (29.3%)	19 (39.6%)	NS
Vit D deficiency (< 12 ng/ml)	10 (11.3%)	3 (9.3%)	7 (12.3%)	NS [RR=1.31 (0.36-4.72)	8 (19.5%)	27 (56.3%)	NS

Figure 1 *- Study design.*



Skin prick tests

Skin prick tests (SPTs) were performed on the volar aspect of the forearm for some foods (cow's milk, hen's egg white, wheat, peanut, soy and fish) and common aeroallergens (house dust mites, animal dander, molds and grass pollens). The reaction was read at 15 minutes and SPTs were considered positive if the wheal diameter was at least 3 mm greater than the negative control.

Isolation and identification of bacteria

Swabs were taken from the most severe skin lesion and from the non lesional skin only at the start of the trial. The swabs were plated on to blood agar and cultured. Colonies were grown for 24 h at 37°C. Staphylococcus aureus was identified by testing typical colonies for coagulase activity.

Serum 25-Hydroxy Vit D3, total and specific IgEs

In all the enrolled children 2 peripheral venous blood samples were collected: the first at the beginning of the protocol, and the second after 3 months. Blood samples were centrifuged and serum was stored at -20°C. For each serum sample total and specific IgEs (for the same allergens tested with SPTs) and serum 25-Hydroxy Vit D3 (25-OH VitD3) were determined. Total and specific serum IgEs were measured with a commercially available fluorometric enzyme-linked immunosorbent assay system ImmunoCAP (Thermo Scientific).
Circulating levels of 25-Hydroxy Vit D (25(OH)D) are considered to be the most reliable measure of overall Vit D status (11). Serum 25-OH VitD3 levels were measured by a competitive protein-binding assay with the 25 OH Vit D direct ELISA (DRG International, Inc. USA). Data were analysed by Manta MMaine5 software. For purposes of analyses, the prevalence of Vit D deficiency was based on the proposed definition of < 30 nmol/L (< 12 ng/ml), and cut-off values of 30-75 nmol/L (12-30 ng/ml) and > 75 nmol/L (> 30 ng/ml) were used to describe overt Vit D, insufficiency and sufficiency (12).
In our study, sensitized children have: total IgE > 40 UI/ml, at least 1 positive SPT and/or positive serum specific IgE. Not-sensitized children are those who did not have any positive SPT results and total IgE ≤ 40 UI/ml (**table 1**).

Ethical Concerns

The ethics committee of our hospital approved this study as a part of a registered protocol. The ethical procedures for the study protocol included informed consent of all parents or caregivers for scientific reporting of research findings based on the study protocol.

Statistical Analysis

The sample size was calculated using OpenEpi 3.01. Normality of variables has been tested with the Shapiro-Wilk test. The correlation between the variables examined was made with the Pearson test for continuous variables, and with Spearman test for non-parametric variables. Comparisons were one-tailed, and $p < 0.05$ was considered to be statistically significant. The Student's T test was used to compare the mean values of clinical and laboratory parameters. Statistical analysis was performed using SPSS (version 21.0).
Relative risk was computed using Epiinfo 7.1.2

Results

Descriptive analysis

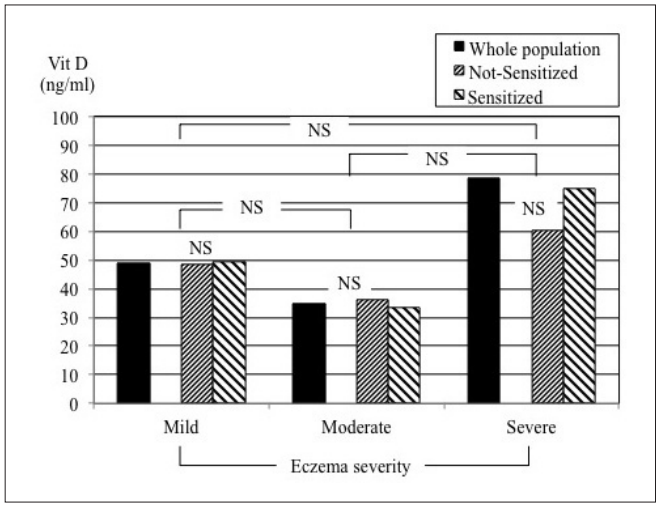
Eighty-nine children (48 males, 53.9%) with chronic eczema were enrolled in the study (**figure 1**). The demographic and clinical data of the whole enrolled population are depicted in **table 1**.

(Whole population)

The majority (53.9%) of the enrolled children had Vit D sufficiency (> 30 ng/ml) and 34,8% presented Vit D insufficiency (12-30 ng/ml). Only 11.3% of children had Vit D deficiency (< 12 ng/ml) (**table 1**).
The mean serum Vit D concentration (78.3 ng/ml ± 71,0) in the patients (77 out of 89) with severe eczema and the mean Vit D concentration (34.9 ng/ml ± 20,0) in the patients (17 out of 89) with moderate eczema were not statistically different from the mean Vit D concentration (49.06 ng/ml ± 40,2) detected in the serum of the patients (66 out of 89) with mild eczema (**figure 2**, black bars).

In the whole enrolled population there was no correlation between Vit D levels and total IgE, food allergy and the frequency of skin impetigo with positive cultures of Staphylococcus aureus (data not shown).

Figure 2 - *Correlation between eczema severity (SCORAD) and Vit D levels in the whole population and when children were divided in Not-Sensitized (total IgEs < 40UI/ml) and Sensitized (total IgEs ≥ 40UI/ml) groups. All correlations were not significant.*



(Not-Sensitized versus Sensitized children)

When the enrolled population was divided according to sensitization - sensitized children (n = 57, 64%) having at least one positive SPT and total IgE > 40 UI/ml - we found no significant differences between Not-Sensitized and Sensitized children for age, sex, SCORAD score, duration of eczema, personal history of atopy, allergic rhinitis, asthma and/or wheezing, food allergy and Vit D concentration. In particular, male sex, personal history of atopy, allergic rhinitis, asthma and/or wheezing and food allergy tended to be a relative risk for the eczema associated to sensitization, but they did not reach the statistical significance (**table 1**).
Moreover, eczema severity did not differ between Not-Sensitized and Sensitized children when they were sub grouped according to the SCORAD severity (mild, moderate or severe eczema) (**figure 3**).
No significant difference was found in Vit D serum levels when children were analysed according to sensitization and severity of eczema (**figure 2**, right bars).
In particular, Vit D levels were sufficient in 18/32 (56.3%) of the Not-Sensitized children and in 30/57 (52.6%) of the Sensitized children; insufficient in 11/32 (34.4%) versus 20/57 (35.1%) and deficient in 3/32 (9.3%) versus 7/57 (12.3%). Also this analysis did not reveal any statistical differences between Not-Sensitized and Sensitized children (**figure 4**).
Furthermore, we did not find any correlation between Vit D levels, total IgEs and SCORAD index, both in the Sensitized and in the Not-Sensitized group (**tables 2** and **3**).
The only parameter strongly associated to eczema in Sensitized children (3/32, 9.4%) with respect to Not-Sensitized (35/57, 61.4%) children were skin staphylococcal infections ($p < 0.0001$ and RR = 6.65 [2.19-19.61]) (**table 1**).

Table 2 - *Relationships between Vit D serum levels, SCORAD index and total IgE in Sensitized children with chronic eczema (57/89 children).*

	Mean (±SD)	p (one-tailed)	
Vit D	48.0 (±41.6)	0.41	0.94
Total IgEs	577.0 (±994.0)		
SCORAD	18.1 (±17.7)	0.55	

Table 3 - *Relationships between Vit D serum levels, SCORAD index and total IgE in Not-Sensitized children with chronic eczema (32/89 children).*

	Mean (±SD)	p (one-tailed)	
Vit D	48.8 (±39.3)	0.994	0.15
Total IgEs	18.9 (±9.7)		
SCORAD	16.5 (±16.5)	0.409	

Intervention analysis

After randomization, 41 children were assigned to the SG (that was given a daily oral Vit D3 supplementation for 3 months), and 48 to the CG. Apart from the enrolment visit, all children were visited again 3 months later and there were no dropouts (**figure 1**). At the second visit, the operator was not aware to which group the subject belonged.
The SG and CG were not homogeneous for either age, SCORAD score or duration of eczema. On the other hand, they were homogeneous for the other parameters considered (sex, secondary bacterial infections, personal history of atopy, asthma and/or wheezing, food allergy, total IgEs and Vit D concentrations) (**table 1**).
In table IV the Vit D serum level, the SCORAD score and total IgE before and after 3 months of cholecalciferol supplementation in the SG (41 children) are compared with data of the CG

Table 4 *- Vit D serum level, SCORAD score and total IgE in children with eczema before and after 3 months of Vit D supplementation (Supplementation Group) or without Vit D supplementation (Control Group).*

	Supplemetation Group (n = 41)		Control Group (n = 48)	
	Time 0	After 3 months (Vit D supplementation)	Time 0	After 3 months (NO Vit D supplementation)
	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)
Vit D	56.0 (±53.5)	105.9 (±76.9)	41.6 (±23.4)	42.0 (±22.4)
	p < 0.001		NS	
SCORAD	12.2 (±11.1)	12.0 (±11.0)	22.1 (±20.1)	20.8 (±18.6)
	NS		NS	
Total IgE	547.5 (±1104.5)	416.9 (±694.9)	230.2 (±477.2)	239.7 (±538.4)
	NS		NS	

Figure 3 *- Mean eczema severity (SCORAD) in the whole population (left side) and % of mild, moderate and severe eczema in Not-Sensitized and Sensitized children with chronic eczema (right side).*

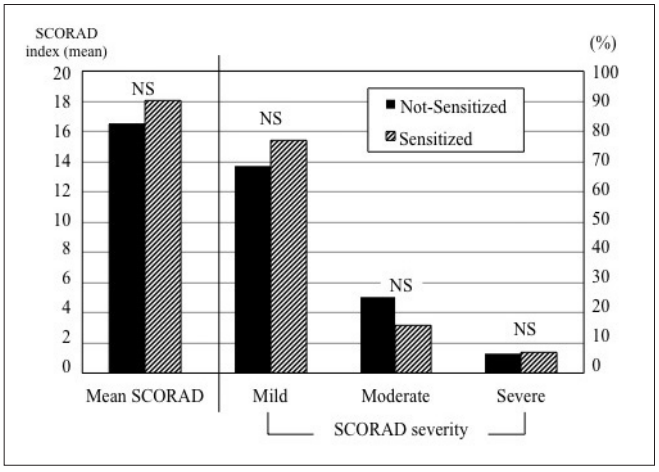
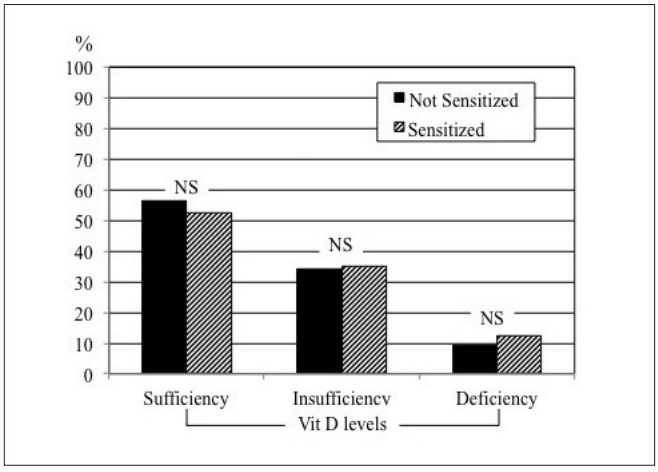


Figure 4 *- Vit D levels (classified as sufficient, insufficient and deficient in Not-Sensitized (total IgE < 40 UI/ml) and Sensitized (total IgE ≥ 40UI/ml) children with chronic eczema.*



(48 children). The daily cholecalciferol supplementation (2000 IUs for 3 months) significantly increased the Vit D levels in the SG with respect to the CG, as expected. Instead, it did not influence the severity SCORAD, or the total IgEs concentrations.

Discussion

In the past ten years, eczema research has focused on the barrier and the innate immune defects, especially in correlation to staphylococcal infections (13). Moreover, it has been suggested that Vit D plays a pivotal role in the innate and adaptive immunity (6). Furthermore, Liu et al. highlighted the connection between Vit D-mediated activation of Toll-like receptors, production of the antimicrobial peptide cathelicidin and human susceptibility to bacterial infections (14). The active form of Vit D - 1.25-$(OH)_2$D - induces the expression of antimicrobial peptides that help in preventing skin infection and possesses immunosuppressive properties in the skin. Moreover, some Authors have shown that it promotes immune tolerance (15,16). Thus, Vit D deficiency could contribute to the hallmark signs of eczema as altered barrier function, immune dysregulation and inadequate bacterial defence (17).

Recently, some of the studies aimed at assessing the impact of Vit D on allergic diseases with a focus on eczema (18,19), and some of them have assessed the prevalence and the severity of eczema in Vit D-deficient patients (20-22).

Furthermore, some Authors suggested the potential role of Vit D only in selected sub-groups of patients with eczema. Indeed, the results of Lee et al. (23) suggest that Vit D deficiency might be related to the severity of eczema only if accompanied by food sensitization, while Akan et al. (24) showed that Vit D might

affect the severity of eczema only in children with allergic sensitization. Finally, Chiu et al. (25) in a cross-sectional study of 94 children with eczema found instead no correlation between serum Vit D concentration and eczema severity.

To our knowledge, our study is the first one that shows no correlation between serum levels of Vit D and eczema severity, IgE sensitization and skin staphylococcal infections in a pediatric population suffering from chronic eczema.

In fact, Vit D levels and the SCORAD index were not correlated in the whole study group of 89 children (**figure 2**) and we did not find any correlation between serum Vit D concentration and eczema severity SCORAD when the whole population was sub grouped according to sensitization (**figure 2** and **tables 1, 2, 3**).

Moreover, our data show there was no correlation between Vit D serum levels and total IgEs neither in the whole study group, nor when the Sensitized and Not-Sensitized subgroups were evaluated separately (**figure 4, tables 1** and **2**).

As for Vit D levels in children with chronic eczema, our data differ from the results previously reported as 53.9% of the enrolled children had sufficient levels of Vit D (> 30 ng/ml) (**table 1**). Further studies are necessary to determine whether Vit D deficiency is really more prevalent in these children or whether other factors such race, geographic or diet can contribute.

Even if Sensitized and Not-Sensitized children may have identical clinical characteristics, they must have some different pathophysiologic mechanisms. Our series, however, shows that Vit D does not express a specific role in modulating the clinical presentation of eczema, despite its proven effects on the immune system (reducing and/or preventing inflammation) (6,16).

So far, there are only a few studies investigating the effects of Vit D supplementation in the treatment of eczema (26-31), and some of these reports found a beneficial effect on eczema although this improvement was not always statistically significant. For this, in our opinion, they should be regarded with caution.

In the present study, 41/89 children with chronic eczema were randomly given a daily Vit D(*cholecalciferol*) oral supplement of 2000 IUs for 3 consecutive months.

After supplementation, serum levels of Vit D have increased significantly ($p < 0.001$), but this had no influence on the severity of the disease measured by the SCORAD method (**table 4**), unlike other studies that have showed an improvement in the SCORAD index after the administration of lower doses of Vit D (27-29).

Even if the small number of participants is a limitation of this study, in our opinion it has the merit of being one of the few that dealt with pediatric only population. Nevertheless, it confirms that at present there are no certainties in this field due to differences in age, population geography, type of Vit D and schedules of administration. In particular, important questions need to be answered regarding the dosage of Vit D required, which may vary between sexes and between individuals, and the optimal timing and duration of such intervention. Randomized controlled trials adequately designed are still needed in order to establish optimal dosage and duration of treatment for the relative effect of Vit D supplementation.

In view of the phenotypic complexity of eczema, we believe that the current state of knowledge lacks large-scale prospective and randomized studies, which are needed to clarify the actual role of Vit D in this complex disease.

References

1. Flohr C, Mann J. New insights into the epidemiology of childhood atopic dermatitis. Allergy. 2014:69:3-16.
2. Meglio P, Galli E, Maiello N. Atopic dermatitis In ERS Handbook: Paediatric Respiratory Medicine, eds. Eber E., Midulla F. 2013;363-9.
3. Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. J Allergy Clin Immunol. 2013;131:295-9.
4. De Benedetto A, Kubo A, Beck LA. Skin barrier disruption: a requirement for allergen sensitization? J Invest Dermatol. 2012;132:949-63.
5. Park CO, Noh S, Jin S, et al. Insight into newly discovered innate immune modulation in atopic dermatitis. Exp Dermatol. 2013:22:6-9.
6. Hewison M. Vitamin D and innate and adaptive immunity. Vitam Horm. 2011;86:23-62.
7. Muehleisen B and Gallo RL. Vitamin D in allergic disease: shedding light on a complex problem. J Allergy Clin Immunol. 2013;131:324-329.
8. Von Gunten S, Cortinas-Elizondo F, Kollarik M, et al. Mechanisms and potential therapeutic targets in allergic inflammation: recent insights. Allergy. 2013;68:1487-98.
9. Hanifin JM, Rajka G. Diagnostic features of atopicdermatitis. Acta Dermatol Venereol. 1980;92:44-7.
10. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology. 1993;186:23-31.
11. Misra M, Pacaud D, Petryk A, et al. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics. 2008;122:398-17.
12. Thacher TD, Clarke BL. Vitamin D insufficiency. Mayo Clin Proc. 2011;86:50-60.
13. Jinnestål CL, Belfrage E, Bäck O, et al. Skin barrier impairment correlates with cutaneous Staphylococcus aureus colonization and sensitization to skin-associated microbial antigens in adult patients with atopic dermatitis. Int J Dermatol. 2014;53:27-33.
14. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science. 2006;311:1770-3.
15. Hollams EM. Vitamin D and atopy and asthma phenotypes in children. Curr Opin Allergy Clin Immunol. 2012;12:228-34.
16. Roider E, Ruzicka T, Schauber J. Vitamin D, the cutaneous barrier, antimicrobial peptides and allergies: is there a link? Allergy Asthma Immunol Res. 2013;5:119-28.
17. Benson AA, Toh JA, Vernon N, et al. The role of vitamin D in the immunopathogenesis of allergic skin diseases. Allergy. 2012;67:296-301.

18. Mutgi K, Koo J. Update on the role of systemic vitamin D in atopic dermatitis. Pediatr Dermatol. 2012;30:303-7.
19. Mesquita Kde C, Igreja AC, Costa IM. Atopic dermatitis and vitamin D: facts and controversies. An Bras Dermatol. 2013;88:945-53.
20. Peroni DG, Piacentini GL, Cametti E, et al. Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children. Br J Dermatol. 2011;164:1078-82.
21. Heimbeck I, Wjst M, Apfelbacher CJ. Low vitamin D serum level is inversely associated with eczema in children and adolescents in Germany. Allergy. 2013;68:906-10.
22. Wang SS, Hon KL, Kong AP, et al. Vitamin D deficiency is associated with diagnosis and severity of childhood atopic dermatitis. Pediatr Allergy Immunol. 2014;25:30-5.
23. Lee SA, Hong S, Kim HJ, et al. Correlation between serum vitamin D level and the severity of atopic dermatitis associated with food sensitization. Allergy Asthma Immunol Res. 2013;5:207-10.
24. Akan A, Azkur D, Ginis T, et al. Vitamin D level in children is correlated with severity of atopic dermatitis but only in patients with allergic sensitizations. Pediatr Dermatol. 2013;30:359-63.
25. Chiu YE, Havens PL, Siegel DH, et al. Serum 25-hydroxyvitamin D concentration does not correlate with atopic dermatitis severity. J Am Acad Dermatol. 2013;69:40-6.
26. Hata TR, Kotol P, Jackson M, et al. Administration of oral vitamin D induces cathelicidin production in atopic individuals. J Allergy Clin Immunol. 2008;122:829-31.
27. Sidbury R, Sullivan AF, Thadhani RI, et al. Randomized controlled trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. Br J Dermatol. 2008;159:245-7.
28. Javanbakht MH, Keshavarz SA, Djalali M, et al. Randomized controlled trial using vitamins E and D supplementation in atopic dermatitis. J Dermatol Treat. 2011;22:144-50.
29. Amestejani M, Salehi BS, Vasigh M, et al. Vitamin D supplementation in the treatment of atopic dermatitis: a clinical trial study. J Drugs Dermatol. 2012;11:327-30.
30. Hata TR, Audish D, Kotol P, et al. A randomized controlled double-blind investigation of the effects of vitamin D dietary supplementation in subjects with atopic dermatitis. J Eur Acad Dermatol Venereol. 2014;28:781-9.
31. Samochocki Z, Bogaczewicz J, Jeziorkowska R, et al. Vitamin D effects in atopic dermatitis. J Am Acad Dermatol. 2013;69:238-44.