

ORIGINAL ARTICLE

Vitamin D effects in atopic dermatitis

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Background: Because vitamin D has immunomodulatory properties and immunologic mechanisms play a role in the pathogenesis of atopic dermatitis (AD), it is possible that vitamin D may influence the activity of AD.

Objective: The aim of the study was to correlate vitamin D concentrations in patients who had AD with clinical, immunologic, constitutional, and environmental factors, and to determine if vitamin D supplementation affects the clinical manifestations of AD.

Methods: Clinical and laboratory parameters of 95 patients with AD and 58 control subjects were measured. Severity of AD was assessed with the SCORAD index.

Results: The mean serum concentration of 25(OH)D₃ in patients with AD was not statistically different from control subjects. The frequency of bacterial skin infections was higher in patients with AD who had lower 25(OH)D₃ levels. No statistical associations between vitamin D levels and other multiple laboratory and clinical parameters were found. After supplementation both mean objective SCORAD and SCORAD index were significantly lower ($P < .05$).

Limitations: All study patients were Caucasians and only one supplemental vitamin D dose and treatment duration were assessed.

Conclusion: The results from this study indicate that vitamin D supplementation may help ameliorate clinical signs of the disease and can be considered as a safe and well-tolerated form of therapy. (J Am Acad Dermatol 10.1016/j.jaad.2013.03.014.)

Key words: atopic dermatitis; vitamin D; 25(OH)D₃.

Atopic dermatitis (AD) is a common skin disease that is influenced by genetic and other factors including environmental conditions, diet, infections, and stress.

Recently there have been several reports that vitamin D plays a role in the pathogenesis of many diseases including AD.¹⁻³ Considering the purported immunologic mechanisms that contribute to AD, it is possible that vitamin D may influence this disorder through its immunomodulatory properties.⁴⁻⁷ Schaubert et al⁸ demonstrated that the active form of vitamin D [1,25(OH)₂D₃] enhanced expression of antibacterial peptides, and thus

Abbreviations used:

AD:	atopic dermatitis
BMI:	body mass index
25(OH)D ₃ :	25-hydroxy-vitamin D ₃
SCORAD:	Scoring Atopic Dermatitis
1,25(OH) ₂ D ₃ :	1,25 dihydroxy vitamin D ₃

prevented skin infections. Liu et al^{9,10} demonstrated a link between vitamin D-mediated activation of Toll-like receptors, the production of cathelicidin, and diminished sensitivity to bacterial infections. Depending on the concentration, vitamin D can

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stimulate or inhibit keratinocyte differentiation.¹¹ The presence of CYP27B1, which is responsible for the active form of vitamin D production in keratinocytes, supports this hypothesis.¹² In addition, vitamin D stimulates protein synthesis, such as filaggrin, that is necessary for stratum corneum barrier formation.¹³

Therefore, vitamin D deficiency might exacerbate AD via disturbed epidermal barrier function and immunologic dysregulation, with subsequent impaired defense against infections. Clinical observations indicate that the disease usually worsens in winter season, perhaps as a result of less exposure to solar radiation. Epidemiologic investigations have shown a higher prevalence of AD in countries with higher geographic latitude.¹⁴ Sidbury et al¹⁵ previously addressed the therapeutic influence of vitamin D supplementation on the course of the AD.

AIM OF THE STUDY

The aim was to measure vitamin D levels in patients with AD and to correlate the levels to selected parameters, including clinical, immunological, constitutional, and environmental factors. Moreover, we evaluated the influence of oral vitamin D supplementation on the clinical manifestations of AD.

METHODS

Cross-sectional-study

The study was conducted in Poland and covered 95 patients with AD, aged between 18 and 50 years, mean 29.9 ± 8.5 years. The diagnosis was based on the classification of Hanifin and Rajka.¹⁶ Characteristics of the examined group are shown in Table I.

We included only patients with normal hepatic and renal function. Patients taking vitamin, mineral, and fatty acid supplementations, oral contraceptive pills, steroid hormones (orally or injected), antiepileptic agents, and anticoagulants; those using ultraviolet B or solar irradiation; patients who applied photoprotection within 6 months before the enrollment; and pregnant or nursing mothers were excluded from the study. In addition, patients with hypercalcemia, sarcoidosis, and tuberculosis were excluded. The patients enrolled used only routine

treatment of AD including emollients, topical corticosteroids, and oral antihistamines. Patients with AD and concomitant asthma were allowed to take inhaled steroids.

The control group consisted of 58 age- and gender-matched healthy individuals. All examined persons were Caucasians with the skin phototype II or III according to Fitzpatrick classification. The project was approved by the local ethics committee.

Clinical evaluation and laboratory analysis, including total IgE and 25(OH)D₃ serum concentrations, were collected between March and April 2010 in Poland.

25(OH)D₃ serum concentrations were compared with a control group and correlated with parameters listed in Table I.

Severity of AD in 95 patients was assessed by the same dermatologist (Z. S.) using the SCORAD index.¹⁷

Twenty patients with the lowest vitamin D levels who had histories of skin infections and winter exacerbations based on a patient survey and medical record documentation were selected. The presence of yellow crusts on eczema skin lesions; folliculitis, furunculosis, well-defined erythema with fever; and antibiotic use for skin infection were all regarded as manifestations of bacterial skin infections. This group consisted of 7 women and 13 men aged 21 to 43 years, mean age 30.5 years. All of them fulfilled inclusion criteria from March to April 2010. In 1 of 20 (5%) asthma coexisted, in 4 of 20 (20%) rhinitis coexisted, and in 5 of 20 (25%) asthma and rhinitis were diagnosed simultaneously.

To evaluate the effect of vitamin D supplementation on AD, the patients were given an oral dose of 2000 IU cholecalciferol (Devikap solution, Medana Pharma Terpol Group SA, Sieradz, Poland) daily for 3 consecutive months (January to March).

In this selected group, 25(OH)D₃ and total IgE concentrations, along with SCORAD index and objective SCORAD (Table II) were measured before and after 3 months of oral supplementation.

The effect of the oral supplementation was assessed by the same dermatologist (Z. S.) using the objective SCORAD,¹⁸ which lacks assessment of itch and sleeplessness, so the maximum possible objective SCORAD is 83 points. To help minimize bias, the evaluator (Z. S.) was unaware of vitamin D

CAPSULE SUMMARY

- Vitamin D has immunomodulatory properties that may influence atopic dermatitis (AD).
- Our study explores the relationship between vitamin D levels and AD-related factors, and indicates that vitamin D supplementation may provide therapeutic benefit for patients with AD.
- Vitamin D supplementation is a beneficial adjunctive treatment for patients with AD.

Table 1. Characteristics and 25(OH)D₃ of patients with atopic dermatitis

Patients with AD		25(OH)D ₃ concentration $\pm$ SD ng/mL, when statistically significant
Female	n = 51 (53.7%)	25.9 $\pm$ 14.5*
Male	n = 44 (46.3%)	19.55 $\pm$ 10.9
Duration of AD	5-49.7 y, mean 21.9 y	NS
Personal history of atopy	n = 74 (77.9%)	NS
Asthma	n = 25 (26.3%)	
Allergic rhinitis	n = 42 (44.2%)	
Asthma and allergic rhinitis	n = 7 (7.4%)	
Exacerbation during spring/summer	n = 15 (15.7%)	NS
Exacerbation during autumn/winter	n = 74 (77.9%)	
Exacerbation regardless of season	n = 6 (6.4%)	
Eczema located mainly on usually covered skin	n = 74 (77.9%)	20.64 $\pm$ 9.9 [†]
Eczema located on usually sun-exposed skin	n = 21 (22.1%)	31.87 $\pm$ 21.68
Secondary bacterial infections	n = 51 (53.6%)	20.46 $\pm$ 12.03 [‡]
No secondary bacterial infections	n = 44 (46.4%)	26.51 $\pm$ 14.4
SCORAD index	18-102, mean 47.1	NS
Extent, % of body area	10-95, mean 42.1	
Intensity	4-18, mean 9.1	
Subjective symptoms	2-20, mean 10.3	
SCORAD index severity		NS
Mild <25	n = 21 (22.1%)	
Moderate 25-50	n = 29 (30.5%)	
Severe >50	n = 45 (47.4%)	
Objective SCORAD	16-82, mean 36.7	NS
BMI	16.6-36.4, mean 23.1	NS
Total IgE UI/mL	6.6-12,000, mean 1318	NS
$\leq$ 100 UI/mL	n = 44 (46.3%)	
>100 UI/mL	n = 51 (53.7%)	
Special elimination diet [§]	n = 51 (53.6%)	NS

AD, Atopic dermatitis; BMI, body mass index; NS, not statistically significant; SD, standard deviation.

* $P < .05$.

[†] $P = .01$.

[‡] $P = .03$.

[§]17/51 (33.3%) fish, 37/51 (72.5%) milk/egg, 29/51 (56.8%) citrus, 25/51 (49.01%) chocolate, 16/51 (31.3%) vegetables, 10/51 (19.6%) fruits, 7/51 (13.7%) nuts.

levels and did not access patients' records during the clinical assessment. The evaluator (Z. S.) was not involved in the treatment of these patients. Patients were selected after SCORAD assessments, when the vitamin D levels became available for the whole group. The severity of AD was classified as: mild, less than 25; moderate, 25 to 50; and severe, greater than 50 points according to SCORAD index versus less than 15, 15 to 40, and greater than 40, respectively, in objective SCORAD.¹⁹

To perform a subjective evaluation of the AD course after supplementation, examined patients compared their general status with the last winter season using the linear Patient Global Assessment scale (0 = no difference and 1 = slight, 2 = mild, and 3 = great improvement; conversely, -1 = slight, -2 = mild, and -3 = great worsening).

Body mass index (BMI) was calculated according to the formula BMI = body weight (kg)/height² (m).

Laboratory determination

Total IgE concentration was evaluated using enzyme-linked immunosorbent assay method, fluorometer UniCAP (Pharmacia, Stockholm, Sweden). Serum 25(OH)D₃ levels were determined with Roche Diagnostic reagents (Mannheim, Germany) by electrochemiluminescence immunoassay in the automated analyzer Elecsys 2010 (Roche Diagnostic). Both interassay and intraassay variations were less than 15%. Levels less than 10 ng/mL = deficit (insufficiency), between 10 and 20 ng/mL = deficiency, and between 20 and 30 = hypovitaminosis. Values between 30 and 80 ng/mL were regarded as normal range.²⁰

Statistical analysis

Statistical analysis was performed using software (Statistica, Version 9.0, Statsoft, Krakow, Poland). Data estimation with Shapiro-Wilk test did not confirm

Table II. SCORAD and its components, total IgE, and 25(OH)D₃ level in 20 patients with atopic dermatitis before and after cholecalciferol supplementation

	Before		After		P value
	Range	± SD	Range	± SD	
SCORAD index	26-78	45.12 ± 16.07	10-49	25.70 ± 11.10	.001
Extent %	10-80	30.35 ± 23.48	10-20	19.90 ± 18.64	.01
Intensity	4-15	8.55 ± 2.85	2-9	4.05 ± 2.11	.001
Erythema	0-3	1.3 ± 0.73	0-2	0.5 ± 0.76	.01
Edema/papulation	1-3	1.35 ± 0.58	0-1	0.15 ± 0.36	.001
Oozing/crust	0-2	0.6 ± 0.68	0	0	.01
Excoriation	0-3	0.85 ± 0.67	0-2	0.2 ± 0.52	.01
Lichenification	1-3	2.05 ± 0.82	1-3	1.9 ± 0.78	NS
Dryness	1-3	2.4 ± 0.75	1-3	2.0 ± 0.72	.05
Subjective symptoms	2-18	7.80 ± 3.96	0-13	4.20 ± 3.08	.001
Pruritus	1-10	5.50 ± 2.52	1-7	2.85 ± 1.92	.001
Sleeplessness	0-8	2.25 ± 2.29	0-6	1.45 ± 1.66	.05
Objective SCORAD	18-68	37.09 ± 15.17	9-44	20.85 ± 9.94	.001
Total IgE level, IU/mL	6.6-7100	1147.56 ± 1883.85	6.3-6150	994.86 ± 1680.71	.001
25(OH)D ₃ level, ng/mL	4.0-15.0	7.43 ± 3.34	5.01-23.87	13.05 ± 5.49	.001

NS, Not statistically significant; SD, standard deviation.

a gaussian distribution. Therefore, nonparametric Mann-Whitney U test was used to compare interval variables between 2 groups. Fisher exact test or χ^2 test was used to assess associations between dichotomic variables. Pearson correlation coefficient was used to assess correlations. To find the best predictor of vitamin D status among such variables as age, BMI, and disease duration, multiple regression analysis was performed. In all calculations *P* less than .05 was regarded as statistically significant.

RESULTS

The mean serum concentration of 25(OH)D₃ in 95 patients with AD (23.05 ± 13.37 ng/mL) was not statistically different (*P* > .05) from that of 58 control subjects (23.81 ± 12.78 ng/mL).

Levels of 25(OH)D₃ were detected as normal in 16 of 95 (16.8%) patients with AD and in 14 of 58 (24.1%) control subjects; insufficient in 16 of 95 (16.8%) versus 7 of 58 (12.1%); deficient in 25 of 95 (26.4%) versus 16 of 58 (27.6%); and hypovitaminosis in 38 of 95 (40.0%) versus 21 of 58 (36.2%). Results in both groups were comparable, without statistical differences (*P* > .05) (Fig 1).

Mean serum concentration of 25(OH)D₃ in 44 male patients with AD (19.55 ± 10.9) was significantly lower (*P* < .05) than in 51 female patients (25.9 ± 14.5 ng/mL) (Table I).

In 74 patients with AD, who had skin lesions located mainly in body regions usually covered by clothing, mean concentration of 25(OH)D₃ was significantly lower (*P* = .01) than in 21 patients with skin lesions located on usually sun-exposed areas

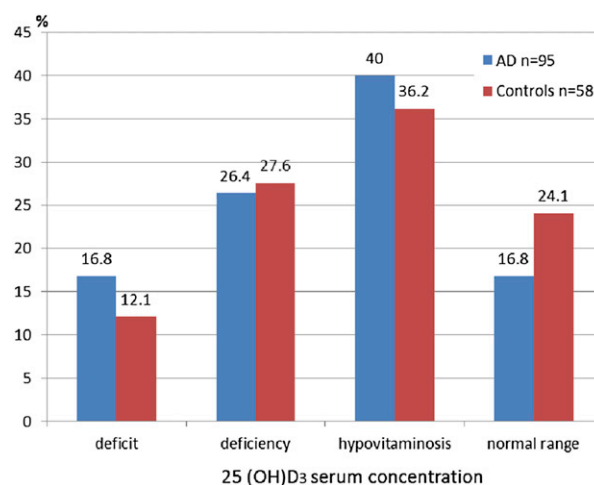


Fig 1. Percentage of patients with atopic dermatitis (AD) and healthy control subjects with vitamin D deficit (insufficiency), deficiency, hypovitaminosis, and normal levels, based on 25(OH)D₃ serum concentrations.

(20.64 ± 9.9 vs 31.87 ± 21.68 ng/mL, respectively) (Table II).

The frequency of bacterial skin infections was higher in patients with AD who had low 25(OH)D₃ levels: 42 of 51 (82.4%) patients with levels less than 30 ng/mL compared with 9 of 51 (17.6%) patients with levels 30 ng/mL or higher (*P* = .03). In 51 patients with AD prone to bacterial skin infections, the 25(OH)D₃ mean concentration (20.46 ± 12.03 ng/mL) was significantly decreased (*P* = .03) in comparison with the 44 without such susceptibility (26.51 ± 14.4 ng/mL) (Table I).

No statistical associations among 25(OH)D₃ levels, duration of the disease, coexistence of other

atopic diseases, seasonal exacerbations, SCORAD index and objective SCORAD, extent and intensity of skin lesions, subjective symptoms, diet, BMI, and total IgE level were found in the 95 patients with AD (Table I).

In 20 of 95 patients selected for the supplementation part of the study, 25(OH)D₃ mean concentrations were very low, between 4 and 15 ng/mL. After 3 months of supplementation a statistically significant ($P < .001$) increase in 25(OH)D₃ mean level from 7.43 ± 3.34 to 13.05 ± 4.49 ng/mL was observed. However, none of the patients achieved the recommended range (Table II). After supplementation a statistically significant decrease in the number of patients with an insufficiency of vitamin D was observed in 5 of 20 (25%) versus 16 of 20 (80%) ($P < .02$).

After supplementation both mean objective SCORAD (28.85 ± 9.94) and SCORAD index (25.7 ± 11.1) were significantly lower than before (37.09 ± 15.17 and 45.12 ± 16.07 , respectively; $P < .001$) (Table II). Before supplementation the degree of AD severity was: mild = 0; moderate = 13 of 20 (65%); and severe = 7 of 20 (35%). After 3 months of supplementation most patients' vitamin D levels switched from insufficiency to deficiency. Seven of 20 (35%) patients had mild, 12 of 20 (60%) had moderate, and 1 of 20 (5%) had severe disease. The decreases in the disease severity, after supplementation, were statistically significant ($P < .05$).

Similarly, after supplementation, all SCORAD parameters, except lichenification, were significantly decreased (Table II).

For the whole supplemented group the subjective Patient Global Assessment parameter was between 0 and 3 points (mean 1.9). Eighteen of 20 patients reported improvement after vitamin D supplementation and Patient Global Assessment was evaluated as a mild improvement in 5, moderate improvement in 7, and great improvement in 6 patients (mean 2.1 points). They did not report bacterial skin infections during the supplementation period.

However, in 2 patients no improvement was recorded, but objective SCORAD and SCORAD index diminished slightly. In these 2 patients the objective SCORAD/SCORAD index before and after supplementation were: patient 1: 19.5 of 27 and 16 of 24.5; and patient 2: 32 of 36 and 28.5 of 31.5.

After 3 months of supplementation, the mean total IgE level was significantly lower than before (994.86 ± 1680.71 vs 1147.56 ± 18.83 IU/mL, $P < .001$) (Table II).

No adverse events during supplementation were observed.

DISCUSSION

A previous report found low vitamin D levels in patients with AD.²¹ In our study, about 80% of patients with AD had low serum concentrations of 25(OH)D₃, below 30 ng/mL, however, a similar distribution of D₃ hypovitaminosis was found in age- and sex-matched healthy control subjects. This is consistent with other observations that inhabitants of urban countries at high latitudes often have low vitamin D levels.²² Javanbakht et al²³ revealed that additional factors, besides geographic locations, may influence vitamin D level in patients with AD. Peroni et al²⁴ found an inverse correlation between serum concentration of vitamin D and severity of the disease expressed by SCORAD index in children. However, others reported no association between serum 25(OH)D₃ concentration and objective SCORAD including any of its parameters in patients with AD.²³ Our results also did not prove such a correlation in SCORAD index and any of its parameters. This finding could be explained by the influence of other environmental factors on the course of the disease in adult subjects.

It was interesting to find that those individuals with eczema mostly in sun-protected areas had lower 25(OH)D₃ levels than patients with skin lesions located mainly on sun-exposed areas. Perhaps other extrinsic factors, such as sweat or clothing, can irritate and exacerbate skin inflammation in a setting of low vitamin D levels. Moreover, it is possible that in some patients prone to AD, a deficiency in vitamin D is responsible for the most intensive skin lesions localized on body regions not exposed to sun. Vitamin D is poorly produced by cloth-covered skin, which suggests a possible local beneficial effect of vitamin D generated in the skin to protect against the development of AD lesions.

Sex-related differences in vitamin D levels are controversial and may be an incidental or spurious finding. In this study males had a lower mean serum concentration of vitamin D₃ compared with females and it was lowest in patients with a prevalence of inflammatory AD lesions in the sun-protected areas. In contrast to our results, Javanbakht et al²³ reported that male patients with AD had higher concentrations of 25(OH)D₃ than female patients. But this difference might be explained by different lifestyles between Iranian and European women. Iranian women expose less skin in public than Polish women, because of the way Muslim women dress.

Literature data indicate that obesity is associated with vitamin D deficiency.²⁵ This is because body fat acts as a sink for vitamin D, which is deposited in an almost irreversible manner and is not bioavailable. Moreover, people with high BMI are not so eager to expose their skin to the sun.²⁶ In our study we did not notice any correlation between BMI and 25(OH)D₃ levels.

We found 25(OH)D₃ deficiency in AD to be correlated with bacterial infections, winter exacerbations of AD, and the presence of more active lesions in sun-protected areas. Thus, vitamin D supplementation in these patients became the second goal of our study.

Twenty patients who exhibited these manifestations, along with a 25(OH)D₃ level below 15 ng/mL, were selected for the vitamin D supplementation portion of the study. Three months of 2000 IU of oral cholecalciferol daily, which is regarded to be a safe and efficient dose,^{20,27} almost doubled the mean 25(OH)D₃ concentration in these most deficient patients with AD; however, none of them reached normal vitamin D concentration above 30 ng/mL. Marked improvement of skin lesions was observed in 90% of supplemented patients with AD, who had SCORAD reduction, as a result of both lower area of skin involvement and reduction in intensity of inflammatory parameters of this index.

There were fewer bacterial infections in our patients during supplementation. The fact that vitamin D stimulates keratinocytes to produce antimicrobial peptides may help explain this finding and helps explain why skin infections may occur more often during the winter season.⁸

This conclusion is in agreement with the placebo-controlled double-blind study performed by Javanbakht et al,²³ who supplemented children and adults with AD using 1600 IU/day for 60 days, and by Sidbury et al¹⁵ in a pilot study using 1000 IU/day for 1 month. In another study, 3-week supplementation with 1000 IU/day vitamin D resulted in an increased expression of cathelicidin belonging to antimicrobial peptides family.²⁸ These authors observed a switch of objective SCORAD toward minor disease activity index, with a decrease in mean index for lichenification and pruritus, and reduction of AD severity evaluated by Eczema Area and Severity Index (EASI). More recently Amestajani et al²⁹ have similarly shown improvement in the SCORAD scores in vitamin D-treated patients with AD in a randomized, double-blind, placebo-controlled study. A medical literature search has not revealed studies using topical vitamin D formulations such as calcitriol or calcipotriene (Dovonex, Leo Pharma AS, Balleup, Denmark) in AD.

A slight, but statistically significant, decrease in total IgE from 1148 to 995 IU/mL could not be easily explained. Possibly, it demonstrates a regulatory effect of vitamin D on the immune response. Vitamin D stimulates production of antimicrobial peptides in the epidermis and, in turn, reduces skin colonization by *Staphylococcus aureus*.⁸ In patients with AD, superantigens of these bacterial species are known to generate superantigen-specific IgE,³⁰ whose concentration correlated with SCORAD.³¹ Activation of basophils and mast cells in IgE-mediated mechanism may initiate IgE-mediated inflammation.³²

Literature data and our observations indicate that patients with AD, especially with low vitamin D level, may benefit from ultraviolet B maintenance treatment not only to suppress function of Langerhans cells or inflammatory cells infiltrating the skin, but also to diminish the risk of bacterial infections, which in part may result from ultraviolet B-induced vitamin D synthesis. This should be considered especially in the winter season in patients living under Northern geographic latitudes.

In conclusion, vitamin D may influence the course of AD. The results from this study indicate that vitamin D supplementation may ameliorate clinical signs of the disease and can be considered as a safe and well-tolerated form of therapy. However, additional studies on larger groups are needed.

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