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Randomized controlled trial using vitamins E and D supplementation in atopic dermatitis

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Abstract

Background: Atopic dermatitis is a chronically relapsing, highly pruritic and inflammatory skin disease. This study was done to assess the effects of vitamins D and E supplementation on the clinical manifestation of atopic dermatitis. *Methods*: Forty-five atopic dermatitis patients were included in a randomized, double-blind, placebo-controlled trial. They were randomly divided into four groups and treated for 60 days: group P ($n = 11$), vitamins D and E placebos; group D ($n = 12$), 1600 IU vitamin D_3 plus vitamin E placebo; group E ($n = 11$), 600 IU synthetic all-*rac*-α-tocopherol plus vitamin D placebo; and group DE ($n = 11$), 1600 IU vitamin D_3 plus 600 IU synthetic all-*rac*-α-tocopherol. Serum 25(OH) vitamin D and plasma α-tocopherol were determined before and after the trial. The clinical improvement was evaluated with SCORing Atopic Dermatitis (SCORAD). Data were analyzed by analysis of variance (ANOVA) and Kruskal-Wallis tests. *Results*: SCORAD was reduced after 60 days in groups D, E and DE by 34.8%, 35.7% and 64.3%, respectively ($p = 0.004$). Objective SCORAD also showed significant improvement. There was a positive correlation between SCORAD and intensity, objective, subjective and extent ($p < 0.001$). We found a significant negative association between plasma α-tocopherol and SCORAD, intensity, objective and extent ($p = 0.02$). *Conclusion*: This study supports the contributing and beneficial effects of vitamins D and E in the treatment of atopic dermatitis.

Key words: *atopic dermatitis, SCORAD, vitamin D, vitamin E*

Introduction

Atopic dermatitis (AD) is a chronically relapsing, highly pruritic and inflammatory skin disease (1). The prevalence of this disease has tripled during the previous three decades (2). Its prevalence is 10–20% in children and 1–3% in adults (1). AD is the most prevalent occupational skin disease in adults (2).

Owing to chronic symptoms, AD substantially disturbs quality of life in such a way that its impact is bigger than diabetes (3). It is estimated that the national cost of managing AD reaches several hundreds of dollars annually in the United States (3).

Emollients are the principal maintenance therapy for AD. Topical corticosteroids are the first-line treatment for AD flare-ups. Topical corticosteroids do not cure AD; moreover, their long-term usage is associated with local and systemic adverse effects (4).

One of the treatment options with fewer adverse effects is ultraviolet (UV) phototherapy, which may be beneficial for severe cases (4). It seems that UV causes

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some alleviation through immune suppression and production of vitamin D (5).

Vitamin D also inhibits the adverse effects of UV on the skin (6–9). Vitamin D induces cathelicidin production. Cathelicidins are involved in defense against skin infections, which are one of the exacerbating factors and causes of resistance to steroid therapy in AD (8,10). Topical vitamin D shows an inhibitory effect on immunoglobulin E (IgE)-mediated cutaneous reaction (11).

Moreover, AD is exacerbated in adults and also in children during the winter, which seems to be due to vitamin D under-production (5). Epidemiological studies suggest that climate influences the prevalence of AD (12). A pilot study has shown the beneficial effects of vitamin D supplementation on AD (13).

It is assumed that reactive oxygen species (ROS) participate in the pathogenesis of allergic inflammation. Therefore, it seems that increments of ROS production would be one of the contributing factors in AD (14). In AD, urine 8-hydroxydeoxyguanosine is higher than in healthy people. It is the product of DNA oxidation by free radicals. Accordingly, it seems that free radicals are involved in AD (14).

Vitamin E is an essential nutrient that is receiving growing attention in the skin care industry because of its antioxidant properties (15). Vitamin E is also the predominant physiological barrier antioxidant in human skin (15). It has been shown that there is an inverse relationship between dietary intake of vitamin E and the serum IgE level (16,17). Epidemiological studies have reported an association between dietary antioxidants and atopic disease (18). Some studies have shown an improvement and near remission of AD after vitamin E supplementation (19). Therefore, it seems that oral vitamin E could be an excellent therapeutic adjunct for this disease (15).

Based on the results of previous studies, we hypothesized that vitamins E and D could cause some improvement in the clinical manifestation of AD. Thus, we designed a randomized, double-blind, clinical trial to evaluate our hypothesis.

Patients and methods

We conducted a randomized, double-blind, placebo-controlled clinical trial on 52 AD patients, aged 13–45 years old. This report is part of that trial. AD was diagnosed based on Hanifin and Rajka's criteria (20). The patients participated from private clinics and Razi Hospital (a teaching hospital, Tehran, Iran). We included only patients with objective SCORing Atopic Dermatitis (SCORAD) from 10 to 70 with normal hepatic and renal functions. Patients taking vitamin, mineral and fatty acids supplements, oral contraceptive pills, steroid hormones (oral or parenteral), anti-epileptic agents, anticoagulant drugs, as well as pregnant or nursing mothers, were excluded. However, the patients could use the prescribed routine treatments of AD including emollients, topical corticosteroids and oral anti-histamines, depending on the severity of their disease and their physician's prescription.

We completely explained the purposes, procedures and possible hazards of the trial to the participants. They were free to leave the trial at any time. All of the patients signed a written informed consent before entering the trial. In the case of patients under 18 years old, a parent signed the written informed consent. The ethics committee of the Tehran University of Medical Sciences (TUMS) approved the research protocol.

The patients were interviewed about past medical history, medications and age. The severity of their eczema was evaluated based on SCORAD (21) by the same trained physician before and after the trial. To determine intensity we chose an area that was representative of the whole body.

After 12–14 hours of overnight fasting, 10 ml of blood from the antecubital vein was drawn into two tubes, with and without EDTA as an anticoagulant before and after the trial. Samples were centrifuged at 3000 rpm for 10 minutes. The separated plasma and serum were immediately stored at –80°C until analysis. We randomly assigned subjects to one of four groups in permuted randomized block design. The randomization was done by a third person who was not involved in the trial. The randomization codes were only broken at the end of the study. Therefore, the assignments were concealed from both participants and physicians.

The four groups were as follows: Group D, 1600 IU cholecalciferol (vitamin D_3) and vitamin E placebo; Group E, 600 IU synthetic all-*rac*-α-tocopherol in two softgels (400 and 200 IU) and vitamin D placebo; Group DE, 1600 IU cholecalciferol (vitamin D_3) and 600 IU synthetic all-*rac*-α-tocopherol in two softgels (400 and 200 IU); and Group P, vitamin D and E placebos. Therefore, each patient took one capsule and two softgels for 60 days. The placebos were identical to supplements in size, color and shape. The vitamin E placebo was filled with mineral oil and it was identical to vitamin E softgels in size and color. The vitamin D placebo was filled with starch and it was identical to vitamin D capsules in size and color. The supplements and placebos were delivered to the patients in identical blisters and boxes with no labels. The patients were told to take the capsules with meals and to take vitamins D and E separately.

To evaluate the efficacy of vitamin D and vitamin E supplementation on AD patients, serum 25-hydroxy vitamin D_3 [25(OH)D_3] was determined by radioimmunoassay with a BioSource kit (cat no.KIP19161; BioSource Europe S.A., Belgium) following the manufacturer's instructions (22). Plasma α-tocopherol was determined by high-performance liquid chromatography (HPLC) as described by Sanz (23). We analyzed all samples from each individual (before and after treatment) in the same analytical run to minimize the influence of analytical variation.

Topical corticosteroidal usage was recorded in times per day irrespective of its potency and extent of usage.

Statistical analysis

All values are expressed as mean ± standard error (SE). The Kolmogorov-Smirnov test was performed on variables to test their normal distribution. We compared four groups by one-way analysis of variance (ANOVA) in the case of continuous variables and chi-squared test for categorical data. In the case of non-normal distribution, we compared four groups by the Kruskal-Wallis test. Post hoc comparisons were performed with the Tukey test. To exclude the baseline values from after-intervention values, analysis of covariance (ANCOVA) was used. To determine no intention to treat, we calculated the percent of improvements supposing no improvements in excluded patients. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was carried out with the Statistical Package for the Social Sciences (SPSS) (version 16; SPSS Inc., Chicago, IL, USA).

Results

Forty-five of 52 patients completed the 60-day trial, as shown in the flowchart (Figure 1). One subject was excluded due to phototherapy, two patients due to oral or parenteral corticosteroids and two more patients due to immunosuppressive drugs. Finally, two patients were not willing to continue the trial. The four groups were not different in age, sex, SCORAD index and topical corticosteroidal usage at baseline (Table I). There were no significant differences between the two sexes in plasma level of α-tocopherol. However, serum levels of 25(OH)D in female subjects were significantly lower than in males (9.6 versus 17.7, $p = 0.001$). At baseline, the plasma level of α-tocopherol was no lower than the deficient level (< 5 μg/ml) in any of the patients (24).

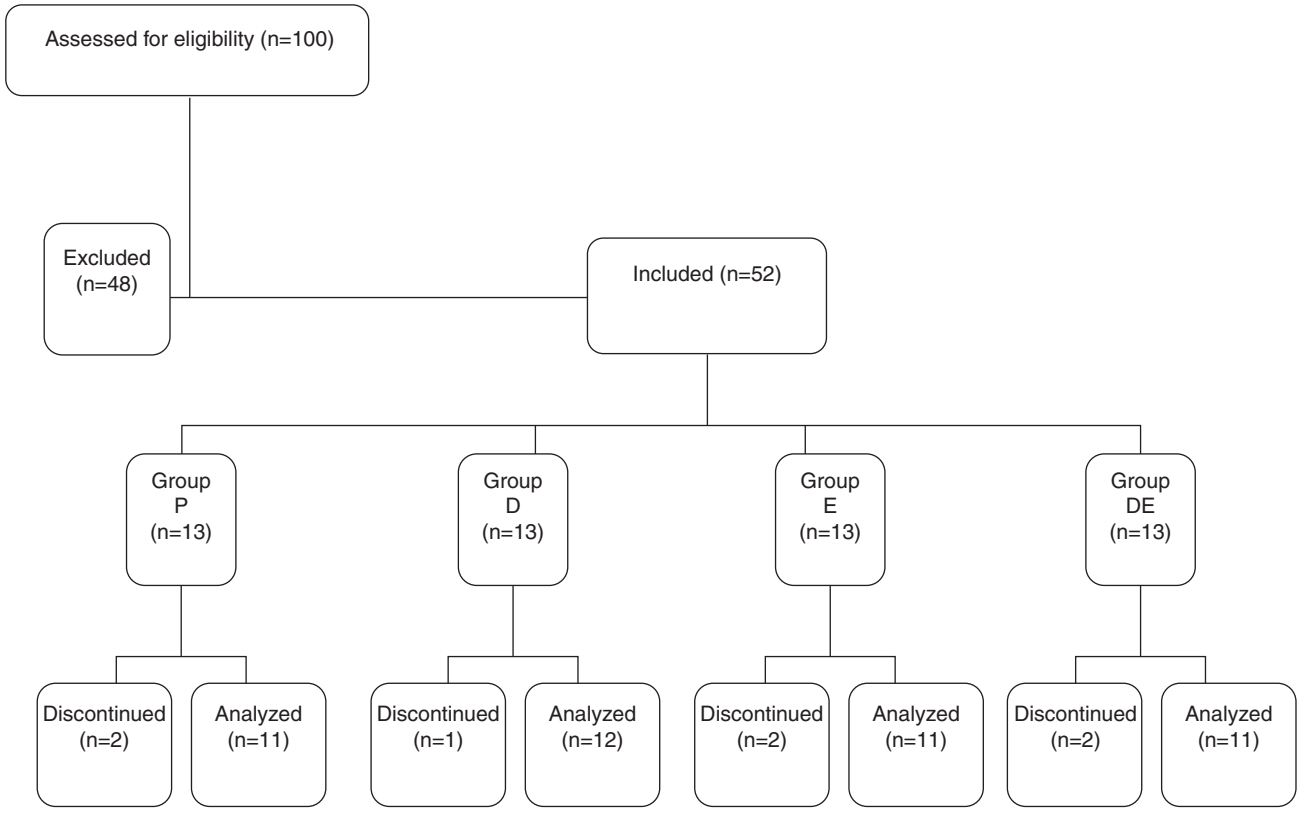

Figure 1. Flowchart of the clinical trial.

Table I. SCORAD and its components in four groups before and after intervention.

	Group P (Placebo)	Group D (Vitamin D)	Group E (Vitamin E)	Group DE (Vitamins D, E)	*p*-value
n	11	12	11	11	
Male/female	1/10	3/9	3/8	3/8	NS
Age (years)	26.1 ± 2.8	21.2 ± 1.6	29.0 ± 2.09	27.5 ± 2.3	NS
SCORAD					
Before	31.7 ± 3.5	36.0 ± 3.7	33.3 ± 3.6	35.6 ± 3.7	0.82
After	22.3 ± 3.0	23.3 ± 2.8	20.4 ± 2.4	12.5 ± 2.3	0.01
Topical steroid (times per day)					
Before	1.10 ± 0.2	0.66 ± 0.17	0.66 ± 0.18	0.80 ± 0.21	0.34
After	0.54 ± 0.13	0.23 ± 0.11	0.20 ± 0.09	0.12 ± 0.09	0.05
Extent					
Before	11.0 ± 2.9	9.3 ± 2.6	12.9 ± 3.2	11.2 ± 2.8	0.85
After	5.4 ± 1.6	4.5 ± 1.8	4 ± 1.1	3.1 ± 1.4	0.69
Intensity					
Before	6.1 ± 0.8	7.4 ± 0.7	5.7 ± 0.6	7.0 ± 0.8	0.37
After	4.5 ± 0.7	4.5 ± 0.5	4.3 ± 0.5	2.6 ± 0.4	0.04
Subjective symptoms					
Before	8.2 ± 0.7	8.0 ± 1.2	10.6 ± 1.5	8.7 ± 1.6	0.48
After	4.6 ± 0.7	6.4 ± 1.3	4.8 ± 1.0	3.0 ± 1.0	0.18
Objective SCORAD					
Before	23.6 ± 3.4	27.9 ± 2.8	22.7 ± 2.8	26.9 ± 3.1	0.56
After	15.3 ± 1.8	17.2 ± 1.9	15.5 ± 1.8	1.2 ± 1.7	0.01

Values are expressed as means ± SE.
ANOVA was used to test the differences between baseline and after-intervention values of four groups.
NS = not significant.

In six patients (13.3%), the serum 25(OH)D level was higher than the deficient level (20 ng/ml) (25). The serum 25(OH)D level of 17 patients (37.7%) was between 10 and 19.9 ng/ml. Twenty-two subjects had serum 25(OH)D levels lower than 10 ng/ml. The prevalence of vitamin D deficiency was 72.7%, 91.7%, 81.8% and 100% in groups P, D, E and DE, respectively.

At the beginning of the trial, the plasma level of α-tocopherol and the serum level of 25(OH)D were similar in the four groups (ANOVA). After 60 days' supplementation, patients taking vitamin E (groups E and DE) had a significant increase in plasma α-tocopherol ($p = 0.011$ for group E and $p < 0.001$ for group DE (paired *t*-test)). Patients who had taken vitamin D had a significant increase in serum 25(OH) D ($p < 0.001$ for groups D and DE (paired *t*-test)).

As Table I shows, the differences in the SCORADs after intervention were significant. Despite this, the difference between groups P and D was not significant. Compared with baseline SCORAD, groups D, E and DE showed a significant reduction of 34.8%, 35.7% and 64.3%, respectively ($p = 0.004$). The reduction was 28.9% in group P. Based on SCORAD, two patients showed no change: one in group P and one in group D. The disease was exacerbated in two patients: one in group P (11.7%) and one in group E (27.7%). The disease went into remission in one person in group DE. The two patients whose disease had been exacerbated showed improvements in objective and extent in groups D and E. The change in objective symptoms were 31.04%, 38.2%, 30.1% and 64.3% for groups P, D, E and DE, respectively ($p = 0.002$). The change in intensity was 25.2%, 36.8%, 23% and 62% for groups P, D, E and DE, respectively ($p = 0.001$).

We also observed significant differences in lichenification and pruritus (Table II). We also found a negative correlation between the plasma level of α-tocopherol and SCORAD ($r = -0.33$, $p = 0.025$) before intervention (Table III). The correlation between the plasma level of α-tocopherol and most of the SCORAD items was negative. No association was found between serum 25(OH)D_3 and SCORAD and any of its items.

Table II. Intensity and subjective items, before and after intervention.

	Group P (Placebo)	Group D (Vitamin D)	Group E (Vitamin E)	Group DE (Vitamins D, E)	*p*-value
Erythema					
Before	1.4 ± 0.2	1.4 ± 0.1	1.3 ± 0.2	1.7 ± 0.2	0.67[a]
After	1.1 ± 0.09	0.9 ± 0.1	1.1 ± 1.1	0.6 ± 0.1	0.09[a]
Edema					
Before	0.7 ± 0.1	1.1 ± 0.2	1.0 ± 0.2	1.3 ± 0.2	0.19[a]
After	0.5 ± 0.2	0.4 ± 0.1	0.4 ± 0.1	0.1 ± 0.1	0.21[a]
Oozing					
Before	0.18 ± 0.1	0.5 ± 0.2	0.36 ± 0.1	0.4 ± 0.1	0.61[a]
After	0.18 ± 0.1	0.2 ± 0.1	0.0	0.0	0.13[a]
Excoriation					
Before	1.2 ± 0.2	1.3 ± 0.1	1.1 ± 0.1	1.3 ± 0.2	0.69[a]
After	0.7 ± 0.2	0.8 ± 0.1	0.8 ± 0.1	0.4 ± 0.1	0.19[a]
Lichenification					
Before	1.1 ± 0.3	1.3 ± 0.2	0.8 ± 0.2	1.1 ± 0.1	0.52[a]
After	0.9 ± 0.2	1.0 ± 0.1	0.3 ± 0.1	0.5 ± 0.2	0.03[a]
Dryness					
Before	1.2 ± 0.2	1.5 ± 0.2	1.4 ± 0.2	1.4 ± 0.1	0.68[a]
After	1.2 ± 0.1	1.0 ± 0.08	1.0 ± 0.1	0.9 ± 0.1	0.4[a]
Pruritus					
Before	7.0 ± 0.5	5.7 ± 0.6	6.2 ± 0.7	5.5 ± 1.0	0.52[b]
After	4.0 ± 0.6	5.0 ± 0.8	3.4 ± 0.5	2.0 ± 0.5	0.009[b]
Sleeplessness					
Before	1.1 ± 0.3	2.3 ± 0.7	4.3 ± 0.9	3.2 ± 0.7	0.07[a]
After	1.0 ± 0.4	1.4 ± 0.6	1.3 ± 0.5	1.0 ± 0.6	0.85[a]

Values are expressed in means ± SE.
[a]Kruskal-Wallis test; [b]ANOVA.

To exclude the intent of treatment, the improvements of lost patients were assumed to be zero. Analyzing SCORAD before intervention showed no difference (p = 0.9). After omitting the effects of baseline SCORADs, the groups were compared by ANCOVA (p = 0.021). In this case, the improvements were 24%, 32%, 30% and 54.4% for groups P, D, E and DE, respectively (p = 0.032).

Topical corticosteroidal usage was significant between groups after intervention (p = 0.05). The percent of decrease in topical corticosteroidal usage was 37.5%, 66.8%, 70.2% and 88.7% for groups P, D, E and DE, respectively.

Discussion

The results of this research showed considerable improvement in AD patients taking vitamins D and/or E, which was consistent with our hypothesis. The negative association between SCORAD and the plasma level of α-tocopherol could imply its influence in improvement. It also supports the positive correlation between dietary vitamin E and serum IgE (17). Although we found considerable improvement in patients taking vitamin D, no association was found between serum 25(OH)D_3 and SCORAD. Groups D and E showed 34.5% and 35.7% reduction in SCORAD, respectively. Their improvements were clinically important. Meanwhile, group DE showed a very considerable improvement (64.3%). It could be the result of synergistic effects of both vitamins. Plasma levels of α-tocopherol were different in groups E and DE (17.1 versus 22.3, p = 0.03), which could also explain such an improvement. However, to draw a confident conclusion more studies are needed. In the supplementation groups, we did not observe any exacerbation except one in group E. Therefore, it seems that these vitamins could not have negative effects on AD.

Table III. Correlations between SCORAD and its items and plasma α-tocopherol, before and after intervention.

	Plasma α-tocopherol before	SCORAD before		Plasma α-tocopherol after	SCORAD after
SCORAD before	–0.33[a,c]	–	SCORAD after	–0.39[a,c]	–
Intensity before	–0.32[a,c]	0.91[a,d]	Intensity after	–0.36[a,c]	0.93[a,d]
Extent before	–0.33[b,c]	0.55[b,d]	Extent after	NS	0.68[b,d]
Subjective before	NS	0.59[a,d]	Subjective after	NS	0.7[a,d]
Objective before	–0.34[a,c]	0.93[a,d]	Objective after	–0.39[a,c]	0.93[a,d]
Erythema before	NS	0.62[b]	Erythema after	NS	0.61[b,d]
Edema before	NS	0.71[b,d]	Edema after	NS	0.62[b,d]
Oozing before	NS	0.59[b,d]	Oozing after	–0.3[b,c]	0.38[b,c]
Excoriation before	–0.5[b,d]	0.63[b,d]	Excoriation after	NS	0.77[b,d]
Lichenification before	NS	NS	Lichenification after	–0.42[b,c]	0.57[b,d]
Dryness before	NS	0.5[b,d]	Dryness after	NS	NS
Pruritus before	NS	0.51[a,d]	Pruritus after	–0.36[a,c]	0.7[a,d]
Sleeplessness before	NS	0.48[b,c]	Sleeplessness after	NS	0.56[b,d]

[a]Pearson correlation; [b]rho Spearman; [c]p-value < 0.05; [d]p-value < 0.001.
NS = not significant.

The significant correlation between SCORAD and objective, subjective and intensity imply the consistent evaluation. It could be the result of a single examiner. Fairris et al. did not use SCORAD to evaluate clinical improvement (26). The SCORAD is the major outcome measure for follow-up in trials (27). It also is one of the best validated systems and is suited for clinical trials (28). Moreover, Fairris et al. used vitamin E with selenium, which made it difficult to draw a certain conclusion about vitamin E effects.

Our findings are consistent with those of Tsoureli-Nikita (19). They gave 400 IU of vitamin E to their patients. Their study was single blind in comparison with our double-blind study. The duration of their intervention was 8 months, which was much longer than ours. Despite that, they observed four exacerbations. They studied 96 patients, which was a greater sample size than ours. They suspended the other treatments but we did not discontinue the routine treatment of patients, even antihistamines due to ethical consideration.

Sidbury et al. studied the effects of vitamin D supplementation on winter-related AD in children (13). They gave 1000 IU of ergocalciferol to the patients, which was lower than ours, and they continued the supplementation for only 30 days. Their sample size was only 11 patients. To measure severity they used the eczema area and severity index (EASI). They observed some improvement, which is consistent with our study.

Moreover, we measured the plasma level of α-tocopherol and serum level of 25(OH)D to evaluate the efficacy of supplementation. As a confounder, we recorded the topical corticosteroidal usage in times per day, but we did not record the potencies of topical corticosteroids. Therefore, it could be one of the limitations of this study, although they did not have much variation. Anyway, studies with a larger sample size are needed to draw a conclusion. It is necessary to control the treatments as much as possible to decrease confounders.

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