Report

Evaluation of dietary intake of vitamin E in the treatment of atopic dermatitis: a study of the clinical course and evaluation of the immunoglobulin E serum levels

Evridiki Tsoureli-Nikita, MD, Jana Hercogova, MD, Torello Lotti, MD, and Giovanni Menchini, MD

From the Institute of Dermosciences, University of Siena, Siena, Italy, Department of Dermatology, Charles University, Prague, Czech Republic, and Department of Dermatologic Sciences, University of Florence, Florence, Italy

Correspondence
Evridiki Tsoureli-Nikita, MD
Department of Dermatologic Sciences
Via Alfani 37
50125 Florence
Italy
E-mail: tlotti@unifi.it

Abstract

Background Vitamin E (VE) is a potent antioxidant that can improve the immune macrophage-mediated response, decrease the production and/or release of prostaglandins in humans, and decrease the serum levels of immunoglobulin E (IgE) in atopic subjects.

Aim To compare the effects of placebo (PL) and VE intake (400 IU/day) on subjective symptoms and serum IgE levels in 96 subjects with atopic dermatitis.

Materials and methods A single-blind clinical analysis was performed on 96 subjects randomly divided into two groups. Fifty subjects were given orally 400 IU (268 mg) of VE of natural origin, once a day for 8 months, and 46 took PL for the same period. Complete blood count, serum IgE levels, radioallergosorbent test (RAST) score, antinuclear antibodies (ANA), and biochemical analysis were obtained at the time of enrollment and every 15 days during the 8 months of the study. To evaluate VE therapy, a questionnaire was sent to each subject for completion at the end of the study.

Results The results were as follows: (A) four subjects treated with VE worsened, compared to 36 in the PL group; (B) six subjects in the VE group and five in the PL group showed no change; (C) slight improvement was observed in 10 subjects in the VE group and four in the PL group; (D) 23 of the 50 subjects treated with VE showed great improvement, compared to only one in the PL group; and (E) there was almost complete remission of atopic dermatitis in seven of the 50 subjects in the VE group, but none in the PL group. Females showed less progression of atopic dermatitis than males in both groups and a higher percentage of almost complete remission (five females and two males). The range of serum IgE levels varied markedly from 1005 to 490 IU/mL in the VE group and from 1239 to 812 IU/mL in the PL group over 8 months. Subjects with great improvement and near remission of atopic dermatitis in the VE group demonstrated a decrease of 62% in serum IgE levels based on initial conditions, while, in subjects taking PL, the difference was approximately 34.4%. No complications were observed in either group. A remarkable improvement in facial erythema, lichenification, and the presence of apparently normal skin was reported. Eczematous lesions healed mostly as a result of decreased pruritus.

Conclusions The correlation between VE intake, IgE levels, and the clinical manifestations of atopy indicates that VE could be an excellent therapeutic tool for atopic dermatitis.

Introduction

Atopic dermatitis (AD) is a well-known, chronic, pruritic, inflammatory skin disease frequently seen in subjects with a personal and/or family history of atopy, such as asthma and allergic rhinitis. Its etiology and pathogenesis are still unclear, although a possible altered immune regulation, with the development of immunoglobulin E (IgE) and IgG antinuclear antibodies (ANA), has recently been demonstrated.[1,2] Due to the lack of specific laboratory diagnostic tests, the diagnosis depends entirely on the recognition of the major and minor clinical features suggested by Hanifin and Rajka.[3,4] Intense itching and a chronically relapsing course are seen in all cases. In addition, owing to their resistance to conventional therapies, AD subjects present a high incidence of recurrence and complications after discharge from hospital and face serious clinical and social problems.[5] Many subjects feel discouraged after trying different, more or less aggressive treatments,

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including antimicrobials, antihistamines, corticosteroids, and cyclosporin A, and present to our clinic asking for less aggressive treatments or just to be reassured about their condition. Vitamin E (VE), well known for its potent antioxidant properties, appears to be protective against common health conditions, such as heart disease,[6] cataract,[7] cancer, and strokes.[8] Recent data have shown that VE can be considered to be a safe and active treatment for murine nasal allergy,[9] and can reduce serum levels of IgE in atopic subjects.[10] In the last 12 months, from the many subjects who asked for less "active" treatments, we selected a group to be treated with VE (400 IU/day) (50 subjects) and placebo (PL) (46 subjects).

Patients and methods

Ninety-six subjects (ratio of males to females, 2 : 1), aged 10–60 years, with AD (according to the diagnostic features reported by Hanifin and Rajka[3,4]) were enrolled in this study. All the subjects manifested uncontrollable itching resulting in exacerbated eczematous lesions, and were admitted to our clinic and treated with topical ointments and antihistamines or antiallergic drugs between 1996 and 1998. The clinical assessment of pruritus was performed by the SCORAD index,[11] a cumulative index which combines objective (extent and intensity of lesions) with subjective (daytime pruritus and sleep loss) criteria. Total body photographs were taken of each patient and they were reviewed at the final evaluation. The patients enrolled demonstrated lesions (including crusts and lichenifications) of moderate/severe intensity involving 30–70% of the body surface.

In 1999, we undertook a single-blind pilot study of the dietary intake of VE by 50 subjects (VE group). At the time of admission, all other treatments were suspended, topical steroids included, on both facial and trunk lesions. Only topical creams/ointments containing petrolatum or vaseline were permitted. Antihistamines were also forbidden.

The international literature demonstrates that clinical studies should concentrate on dosages of at least 400 IU/day to ascertain the effects of VE on coronary heart disease,[6] cataract formation,[7] cancer chemoprevention,[8] and dermatologic disorders (i.e. discoid lupus erythematosus).[12] Consequently, VE pills (400 IU) were given orally to 50 subjects with AD once a day for 8 months, and 46 subjects were given PL for the same period of time (Fig. 1). The active ingredient, dissolved in an oily solution and obtained by the distillation of vegetable oils, is a natural isomer of VE, R,R,R-α-tocopherol, with a much higher biological activity than synthetic forms. Each pill (400 IU) contained 268 mg of R,R,R-α-tocopherol and 132 mg of soya oil. PL had exactly the same composition as the test formulation (except for the active ingredient) and was similar in appearance and taste.

All subjects were routinely screened for complete blood count, serum IgE levels using enzyme-linked immunoabsorbent assay (ELISA), radioallergosorbent test (RAST) score, ANA, and

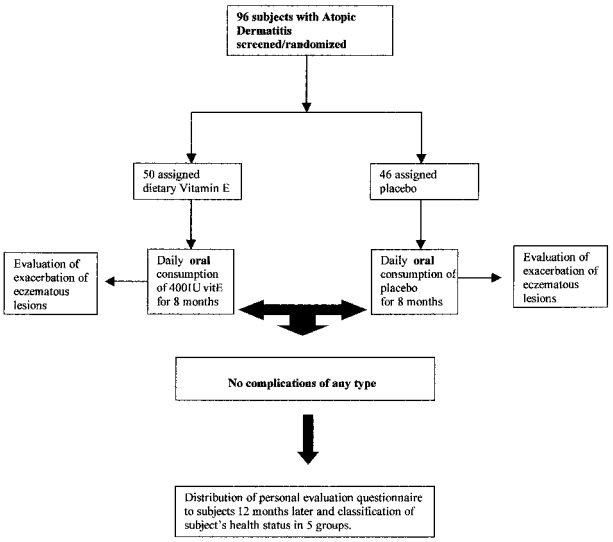

Figure 1 Trial profile for the evaluation of dietary intake of vitamin E in the treatment of atopic dermatitis

biochemical analysis at the time of enrollment and every 15 days during the 8 months of the study. Clinical follow-up of symptoms and drug accountability (measured by pill counting) were also performed at the same visit every 15 days. Bacterial colonization analysis was performed with samples from the skin, tonsils, and/or nostrils. Patch testing with ointments and hair care products and phototesting (UV sensitivity) were performed if they were considered to be exacerbating factors. Subjects with suspected food allergies were scratch tested with the corresponding allergens, and restriction and provocation tests were performed. Finally, all patients underwent ophthalmologic examination, as eye complications are quite common in patients with AD.[13]

A questionnaire was sent to each patient at least 12 months after the end of the study to obtain a personal subjective evaluation of the treatment, exacerbating factors, and the types of remedies used. In particular, the subjects were asked if: (A) the condition had worsened compared to the beginning of the study; (B) no changes were seen compared to the initial conditions; (C) there was slight improvement; (D) there was great improvement; and (E) the subject had experienced almost complete remission of symptoms. The patients were visited after the first 6 months and no complications or recurrences were observed.

Data were analyzed for statistical significance using Student's *t*-test and chi-squared test.

Results

The results are shown in Figs 2–4.

Figure 2 shows the clinical distribution pattern of all the subjects in the two groups after the evaluation of symptoms at the end of 8 months. In summary: (A) only four subjects

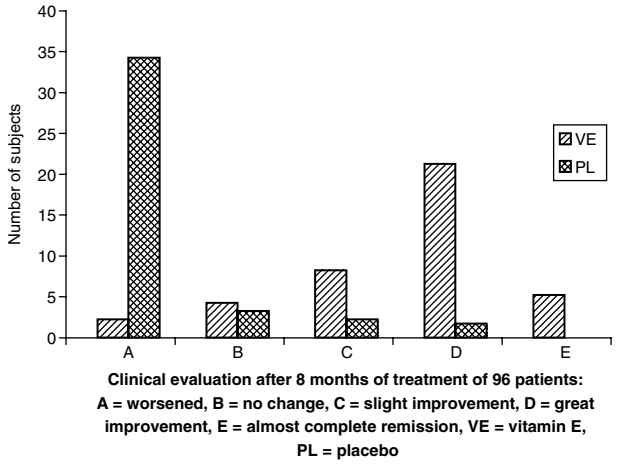

Figure 2 Results of treatment of atopic dermatitis with vitamin E

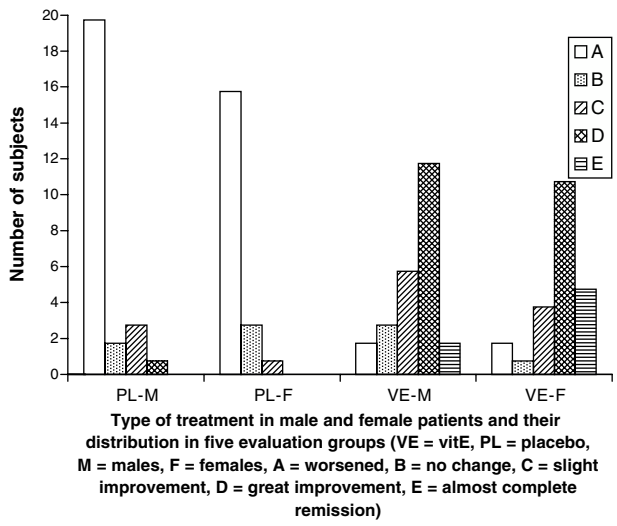

Figure 3 Comparison of response to treatment (vitamin E and placebo) in males and females

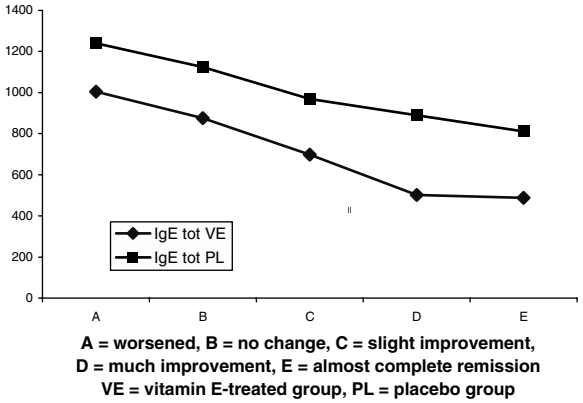

Figure 4 Modification of serum immunoglobulin E (IgE) levels in 50 subjects treated with vitamin E and 46 subjects given placebo at the end of the study

treated with VE worsened, compared to 36 in the PL group; (B) six subjects treated with VE and five receiving PL showed no change compared to their initial conditions; (C) slight improvement was observed in 10 subjects in the VE group and four in the PL group; (D) 23 of the 50 VE subjects showed great improvement, compared to only one PL subject; and (E) there was almost complete remission of AD in seven of the 50 VE subjects, but none of the PL subjects. Pruritus and generalized skin lesions had totally disappeared in the group with total remission treated with VE; great improvement was defined as good control of pruritus and only traces of lichenification on the limbs. Females showed less progression of AD than males in both groups and a higher percentage of almost near remission than males (five females and two males) (Fig. 3).

No significant differences were observed in eosinophil count and ANA and RAST score in the two groups, except for a higher prevalence of elevated RAST scores for inhalant and food allergens in the PL group. Exacerbating factors, such as emotional stress, followed by sweating and uncontrollable pruritus (monitored by the SCORAD index[13]), induced worsening of initial conditions, with exacerbated eczematous lesions, mainly in the PL group. One prominent feature was the remarkable decrease in serum IgE levels in the VE group (Fig. 4). The range of serum IgE varied markedly from 1005 to 490 IU/mL in the VE subjects and from 1239 to 812 IU/mL in the PL group. Subjects with great improvement (D) and near remission (E) of AD in the VE group demonstrated a 62% decrease in serum IgE levels compared to initial conditions, while in PL subjects the difference was 34.4%. No side-effects were observed in any case.

Discussion

VE is an essential fat-soluble vitamin that was discovered in 1922 by Evans and Bishop, who demonstrated that diet deficiency in certain lipids resulted in reproductive failure in rats; the missing substance was characterized and named vitamin E.[14] VE refers to a group of eight naturally occurring compounds – α-, β-, γ- and δ-tocopherols and tocotrienols.[15] α-Tocopherol, especially the naturally occurring D-α-tocopherol, has the highest biological activity. Despite its low concentration in cell membranes (approximately one VE molecule for 1000 lipid molecules), VE is the major chain-breaking antioxidant in body tissues and is considered to be the first line of defense against lipid peroxidation, protecting cell membranes at an early stage of free radical attack through its free radical-quenching activity. Deficiency results

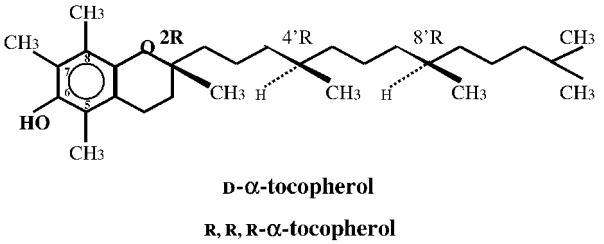

Figure 5 Chemical formula of the natural isomer of vitamin E – R,R,R-α-tocopherol (D-α-tocopherol)

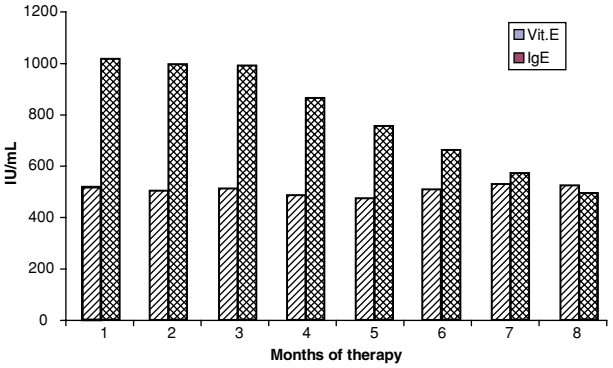

Figure 6 Relationship between serum immunoglobulin E (IgE) levels and vitamin E during the treatment of 50 subjects with atopic dermatitis

in muscle weakness, decreased vibratory sense, and may cause a decrease in immune function.[16]

The primary source of VE for humans is plant oils. In the intestine, VE is absorbed by passive diffusion requiring a micelle (formed from bile salts and pancreatic juices). In general, the recommended intake is 6–10 mg/day.[17] VE is the exception to the paradigm that synthetic and natural vitamins are equivalent because their molecular structures are identical (Fig. 5). The biological potency of natural forms of VE (R,R,R-α-tocopherol or D-α-tocopherol) is higher than that of synthetic forms (all-rac-α-tocopherol, also known as D,L-α-tocopherol), based on animal bioassays and human studies. Physiological differences between natural and synthetic VE relate to the preferential retention of D-α-tocopherol in blood and tissues compared to other tocopherols.[18]

There are at least two mechanisms by which VE increases the immune response. One mechanism is that, as an antioxidant, it protects macrophage cell membranes from oxidative damage. Another mechanism that may account for the immune-enhancing effect of VE could be its ability to decrease the production of prostaglandins. International studies have demonstrated that VE increases humoral and cell-mediated immunity and infectious disease resistance in laboratory animals, farm animals, and humans.[19,20]

There was a significant inverse relationship between serum IgE levels and VE levels in the 50 subjects treated (Fig. 6). The mean level of VE during the 8-month treatment period was 400 ± 124 IU/mL, whereas the IgE level decreased by 12% in each of the last 4 months of therapy, with a total decrease of 62% at the end of the study compared to the initial serum levels. Even though absolute normalization of serum IgE levels was not achieved, the mean of 490 IU/mL is interesting given the normal range of serum IgE of 236 ± 148 IU/mL in the normal population. These levels were found in subjects in evaluation groups D and E (great improvement or nearly complete remission of AD), who demonstrated remarkable improvement in facial erythema, lichenification, and areas of normal skin.

IgE hyperproduction is considered to be an important factor in the pathogenesis of AD, but the precise mechanisms of its influence are still unclear. Recent studies in transgenic Nc/nga mice have suggested that the enhanced phosphorylation of the Janus kinase (JAK3) of B cells, highly sensitive to CD40L and interleukin-4 (IL-4), may be related to IgE hyperproduction in Nc/nga mice and also in subjects with AD.[10,21] Evidence from other animal studies suggests that VE suppresses *in vitro* oxidant-induced IgE production and also inhibits total serum IgE, nasal responsiveness, and sneezing responses in a mouse model of allergy.[9]

Noh and Lee,[22] in a recent study, considered serum IgE as a predictor for the prognosis of AD treatment, and demonstrated that AD patients with clinical improvement treated with interferon-γ showed significantly decreased serum IgE levels. The correlation of serum IgE with disease severity has also been observed in AD patients treated with stellate ganglion block when, after a series of treatment was stopped, clinical symptoms worsened and serum IgE levels increased once again.[23]

Our findings suggest that VE may play an important role in IgE-mediated atopic responses in humans by significantly decreasing the serum IgE levels. This leads to an improvement in clinical symptoms, offering patients a better quality of life and dermatologists a safe tool for the treatment of AD.

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