

Linoleic acid metabolite levels and transepidermal water loss in children with atopic dermatitis

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Background: It has been suggested that atopic dermatitis (AD) is associated with impaired δ -6 desaturase activity and the subsequent altered composition of n-6 essential fatty acids (EFAs).

Objective: To investigate whether n-6 EFA deficiency accounts for AD by affecting transepidermal water loss or the immune response.

Methods: Serum levels of n-6 EFAs were measured using gas chromatography–mass spectrometry in a well-defined group of 35 children with AD (IgE level >150 U/mL); 35 age-matched children with allergic rhinitis, asthma, or both (IgE level >150 U/mL); and 31 nonatopic controls (IgE level <100 U/mL). Skin barrier function was evaluated by measuring transepidermal water loss and severity of AD by computing the Scoring Atopic Dermatitis (SCORAD) index.

Results: Atopic children had higher levels of linoleic acid (LA) and lower levels of its metabolites. Furthermore, γ -linolenic acid to LA and dihommo- γ -linolenic acid to LA ratios were significantly reduced in atopic patients. Transepidermal water loss and the SCORAD index were negatively correlated with serum levels of LA metabolites. There was no correlation between the SCORAD index and IgE level ($P = .51$) or between n-6 EFA concentrations and IgE level ($P > .10$).

Conclusions: Deficits in n-6 EFAs were correlated with the severity of AD by affecting skin barrier function and cutaneous inflammation. The link between impaired n-6 EFA metabolism and IgE level could not be defined.

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INTRODUCTION

Atopic dermatitis (AD) has been thought to be associated with impairment of n-6 essential fatty acid (EFA) metabolism.¹ Synthesis of the n-6 EFA series from linoleic acid (LA) (C18:2) involves alternate steps of desaturation and elongation. It is subsequently converted into γ -linolenic acid (GLA) (C18:3), dihommo- γ -linolenic acid (DGLA) (C20:3), and arachidonic acid (AA) (C20:4).² As early as 1937, lower concentrations of AA were reported in the serum of children with AD.³ More recently, some studies have shown higher concentrations of LA and substantially lower concentrations of its metabolites in the blood of these patients. This suggested reduced conversion of LA to GLA, possibly as a result of impaired δ -6 desaturase activity.⁴ δ -6 Desaturase, which catalyzes the formation of GLA from LA, is the rate-limiting enzyme in n-6 EFA metabolism.² On the basis of these studies, it has been suggested that patients with AD might benefit from a dietary supplement of LA metabolites, such as GLA.⁵

The skin lesions of AD may be attributable to n-6 EFA deficiencies that lead, in part, to loss of normal skin barrier function, inflammatory imbalances, and initiation but not maintenance of immunologic abnormalities.^{5–7} If so, the inflammatory effect and the effect at the skin level may be correctable by means of n-6 EFA supplementation.⁸ However, the effect on maturation and sensitization of the immune system (ie, the immunologic abnormalities) may not be reversible using supplementation after immune maturation.⁹ In this model of pathogenesis, if there is a relationship between impaired n-6 EFA metabolism and immune hyperactivity, a detectable deficit in LA metabolites would be expected in atopic children with AD and in atopic children with allergic rhinitis, asthma, or both. The purpose of this study was to investigate whether n-6 EFA deficits account for AD by acting at the level of the skin or the immune system.

PARTICIPANTS AND METHODS

Participants

We collected data from 3 groups of participants aged 2 to 17 years between September 2004 and August 2005: (1) children with AD but not asthma or allergic rhinitis (AD group); (2) children with asthma, allergic rhinitis, or both without AD (AS or AR group); and (3) controls. The AD group consisted of inpatients and outpatients at National Taiwan University Hospital chosen according to well-defined criteria that included flexural eczema; a chronic, relapsing course; and absence of allergic asthma or allergic rhinoconjunctivitis. The

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AS or AR group included patients with typical clinical features of allergic diseases diagnosed by a physician at National Taiwan University Hospital. The inclusion criteria for atopic individuals (the AD and AS or AR groups) were multiple allergic sensitizations, as indicated using the multiple antigens simultaneous test (Hitachi Chemical Diagnostics Inc, Mountain View, California),¹⁰ and serum IgE levels greater than 150 U/mL using an ImmunoCAP system (CAP-FEIA; Pharmacia, Uppsala, Sweden). The controls had no personal history of atopic disease and were not taking medications at the time of the study. Their inclusion criteria were a negative response to multiple antigens simultaneous testing and a serum IgE level less than 100 U/mL. The exclusion criteria for all the participants included previous therapy with specific fatty acid preparations, malnutrition, metabolic disease, liver dysfunction, renal disease, and adherence to a special diet, such as a vegetarian diet. Finally, these criteria were met by 35 patients with AD (21 boys and 14 girls; mean age, 8.1 years), 35 patients with AS or AR (24 boys and 11 girls; mean age, 7.9 years), and 31 controls (17 boys and 14 girls; mean age, 10.6 years). Written informed consent was provided by the children's parents or legal guardians before any study-related procedures. The study protocol was approved by the ethics committee of National Taiwan University.

Blood Sampling and Analysis of Lipid Composition

Overnight fasting blood samples were collected by means of venous puncture, and the sera were separated within 1 hour of collection and then immediately stored at -70°C until further analysis. Immediate separation and freezing prevent changes in the fatty acid composition of serum lipids. Lipids were extracted from 0.5 mL of serum using methanol and chloroform (1/1 vol/vol). The total lipids, together with pentadecanoic acid (40 $\mu\text{mol/L}$) added as an internal standard, were transmethylated using methanol/3N hydrochloride.^{11,12} After transmethylation, fatty acid methyl esters were analyzed using gas chromatography-mass spectrometry (Gas Chromatograph 5890/Mass Selective Detector 5972; Hewlett Packard Co, Palo Alto, California).¹³

Determination of Transepidermal Water Loss

Transepidermal water loss (TEWL) reflects cutaneous barrier function and the integrity of the stratum corneum against passive water loss by means of diffusion.¹⁴ The *in vivo* effects of n-6 EFAs on skin barrier function were evaluated by measurement of TEWL on the right volar forearm of patients with AD, approximately 4 cm distal to the bend of the elbow.¹⁵ The TEWL values were determined using a Tewameter TM300 (Courage-Khazaka Electronics, Koln, Germany), and the measuring principle of the TM300 is the diffusion law discovered by Adolf Fick in 1855. Air convection, noise in the room, and talking during the recording were restricted. Furthermore, TEWL was measured between 9 and 11:30 AM to avoid intrinsic variation in evaporation water loss due to circadian differences.¹⁶ The TEWL values are given as loss of grams of water per square meter of skin per hour.

Evaluation of the Severity of Dermatitis

Severity of dermatitis was scored by 1 dermatologist (Y.-S.D.) using objective clinical criteria (ie, the Scoring Atopic Dermatitis [SCORAD] criteria). The size of the affected area (A); the intensity of the dermatitis based on 5 criteria (erythema, edema or papulation, oozing or crusting, excoriation, and lichenification [B, each with score of 0–3]); and the intensity of pruritus or insomnia (C, each with a score of 0–10 estimated by the patient or a relative) were used to compute the SCORAD index as follows: $A/5 + (7 \times B)/2 + C$.^{17,18}

Statistical Analysis

Nonparametric tests (Mann-Whitney and Wilcoxon tests) were used to evaluate differences between the AD group and the AS or AR group, the AD group and controls, and the AS or AR group and controls. $P < .05$ was chosen as the minimum level of significance. Simple linear regression and the Spearman rank correlation test were calculated to evaluate the correlation between n-6 EFA composition and TEWL, between n-6 EFA composition and the SCORAD index, between n-6 EFA composition and IgE level, and between IgE level and the SCORAD index. Statistical significance was set at $P < .05$, 2-tailed.

RESULTS

In total, 101 participants (35 patients with AD, 35 patients with AS or AR, and 31 controls) were included. Fourteen and 21 patients with AD had SCORAD index scores of at least 50 and less than 50, respectively. The basic demographic and clinical data are summarized in Table 1.

n-6 EFA Levels in Serum Lipids

Serum lipid n-6 EFA levels are summarized in Table 2. There were no between-age group differences in serum levels of n-6 EFAs (verified by Mayo Medical Laboratories, Rochester, Minnesota). Compared with controls, atopic children (the AS or AR and AD groups) had higher LA levels and lower AA levels, although not statistically significantly, and patients with AS or AR also had lower GLA and DGLA levels ($P > .05$ for both). Furthermore, GLA and DGLA levels were significantly lower in patients with AD than in controls ($P = .04$ and $P = .03$, respectively). There were no significant differences in the serum levels of n-6 EFAs between patients with AS or AR and patients with AD (Fig 1). Consequently, GLA:LA, DGLA:LA, and AA:LA ratios were significantly lower in patients with AD than in controls, and GLA:LA and DGLA:LA ratios were significantly lower in patients with AS or AR than in controls ($P < .05$ and $P = .01$, respectively). The AA:LA ratio also tended to be lower in patients with AS or AR (Fig 2).

Correlations With the Skin Variable

There were significantly negative correlations between TEWL and GLA level ($r = -0.627$; $P < .001$) and between TEWL and DGLA level ($r = -0.896$; $P < .001$) (Fig 3) and a less robust negative correlation between TEWL and AA

Table 1. Basic Demographic and Clinical Data for the 3 Study Groups

	Controls (n = 31)	AS or AR group (n = 35)	AD group (n = 35)
Age, mean $\pm$ SD, y	10.6 $\pm$ 3.2	7.9 $\pm$ 3.5	8.1 $\pm$ 3.8
Sex, M/F, No.	17/14	24/11	21/14
IgE, mean $\pm$ SD, IU/mL	37.2 $\pm$ 27.6	624 $\pm$ 380	1,237 $\pm$ 715
Family history of atopy, No.	11	28	26
TEWL, mean $\pm$ SD, g/m ² /h	NA	NA	9.1 $\pm$ 3.2
SCORAD index, mean $\pm$ SD			
Overall	NA	NA	43.8 $\pm$ 18.4
≥ 50 (n = 14)	NA	NA	62.8 $\pm$ 8.4
<50 (n = 21)	NA	NA	31.1 $\pm$ 10.4

Abbreviations: AD, atopic dermatitis; AS or AR, asthma, allergic rhinitis, or both; NA, not applicable; SCORAD, Scoring Atopic Dermatitis; TEWL, transepidermal water loss.

Table 2. Serum Lipid n-6 EFA Levels in the 3 Study Groups^a

n-6 EFA	Controls (n = 31)	AS or AR group (n = 35)	AD group (n = 35)
C18:2, μ mol/L	2,902.65 $\pm$ 742.25	3,250.71 $\pm$ 1,025.52	3,206.57 $\pm$ 657.78
C18:3, μ mol/L	22.07 $\pm$ 15.65	16.37 $\pm$ 7.54	12.65 $\pm$ 3.25
C20:3, μ mol/L	47.52 $\pm$ 22.45	37.72 $\pm$ 18.49	33.17 $\pm$ 19.59
C20:4, μ mol/L	511.00 $\pm$ 151.56	488.37 $\pm$ 99.36	445.31 $\pm$ 133.92
C18:3/C18:2, %	0.73 $\pm$ 0.47	0.52 $\pm$ 0.25	0.45 $\pm$ 0.16
C20:3/C18:2, %	1.66 $\pm$ 0.73	1.20 $\pm$ 0.63	1.08 $\pm$ 0.65
C20:4/C18:2, %	18.01 $\pm$ 4.88	15.66 $\pm$ 3.37	13.94 $\pm$ 3.85

Abbreviations: AD, atopic dermatitis; AS or AR, asthma, allergic rhinitis, or both; EFA, essential fatty acid.

^a Results are expressed as mean $\pm$ SD.

level ($r = -0.322$; $P = .06$) (data not shown). However, there was no correlation between TEWL and LA level ($r = -0.123$; $P = .48$).

Clinical Variables

The negative correlations between the SCORAD index and GLA ($r = -0.677$; $P < .001$) and DGLA ($r = -0.873$; $P < .001$) levels were strong (Fig 4), but that between the SCORAD index and AA level was not ($r = -0.316$; $P = .06$) (data not shown). In contrast, the SCORAD index did not correlate with LA level ($r = -0.094$; $P = .59$). Although a good correlation between the SCORAD index and TEWL was found ($r = 0.866$; $P < .01$), none was found between the SCORAD index and IgE level ($r = 0.115$; $P = .51$), TEWL and IgE level ($r = 0.068$; $P = .70$), and the levels of all n-6 EFAs and IgE level ($r < 0.3$; $P > .10$).

DISCUSSION

In this study patients with AD tended to have higher levels of LA and lower levels of GLA and DGLA than controls. Although these data show that there was no significant difference in the concentration of AA between patients with AD and controls, it may be speculated that the decreased DGLA levels possibly have lead to an up-regulation of δ -5 desaturase activity and a resultant increase in conversion of DGLA to AA. The observation of higher concentrations of LA and lower concentrations of its metabolites suggests that AD is associated not with the defect of n-6 EFA intake but with abnormal metabolism of LA.¹ We also found that GLA:LA, DGLA:LA, and AA:LA ratios were significantly lower in

patients with AD. It has been well established that the product to substrate ratio of fatty acids could be estimated as an index of enzyme activity.^{19,20} Thus, the GLA:LA ratio was considered to reflect the activity of δ -6 desaturase.^{21,22} Although the DGLA:LA and AA:LA ratios should reflect the combined activities of δ -6 desaturase, the elongation enzymes, or δ -5 desaturase, in fact, the activities of the elongation enzymes and δ -5 desaturase are relatively rapid, and δ -6 desaturase is the rate-limiting factor and, therefore, the prime determinant of these ratios.²³ Hence, lower ratios of GLA:LA, DGLA:LA, and AA:LA in these patients with AD could implicate, but not confirm, a relationship between impaired δ -6 desaturase activity and the pathogenesis of AD. Excessive consumption of the metabolites that could not be compensated by the rate-limiting enzyme may be another explanation for these findings.

The GLA:LA and DGLA:LA ratios were also significantly lower in patients with AS or AR. Besides, there was no significant difference in the serum levels of n-6 EFAs between atopic children with AD and atopic children with AS or AR in this study. The finding is consistent with previous research that showed similar changes in n-6 EFA levels in atopic patients with AD and atopic patients with asthma.²⁴ Hence, it was suggested that all atopic diseases, not only AD, may be associated with a deficit in LA metabolites.^{4,5}

Normal human epidermis lacks the capacity to transform LA into GLA (absence of epidermal δ -6 desaturase activity) or DGLA into AA (absence of epidermal δ -5 desaturase activity) but has the capacity to elongate fatty acids (elongase

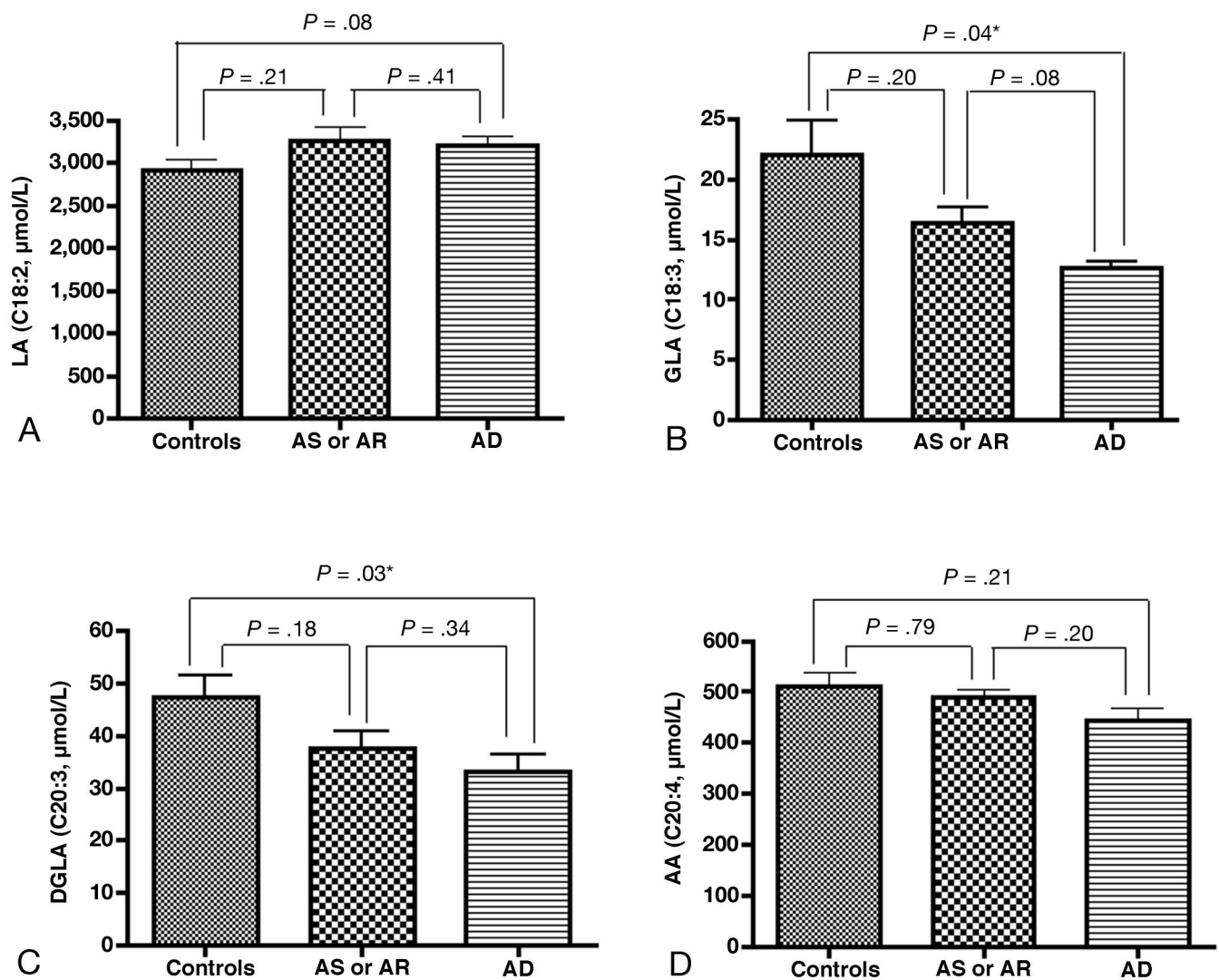


Figure 1. Comparison of mean serum n-6 essential fatty acid levels in controls, patients with asthma or allergic rhinitis (AS or AR), and patients with atopic dermatitis (AD). A, Linoleic acid (LA). B, γ -Linolenic acid (GLA). C, Dihomo- γ -linolenic acid (DGLA). D, Arachidonic acid (AA). Error bars represent SD. Statistical analysis was performed using the Mann-Whitney test. *Significant difference at $P < .05$.

activity).²⁵ This suggests that the GLA, DGLA, and AA present in epidermal phospholipids are biosynthesized endogenously elsewhere and transported by the bloodstream to the epidermis, where phospholipid esterification takes place. So serum levels of n-6 EFAs presumably reflect their epidermal concentrations.

This study found significant negative correlations between TEWL and serum GLA level and between TEWL and serum DGLA level in patients with AD. A negative correlation between TEWL and serum AA level trended similarly but was not significant. The results indicate that LA metabolites are involved in maintenance of the epidermal water barrier. Similarly, it has been reported that

dietary supplementation with GLA-rich borage seed oil, by compensating for the loss of δ -6 desaturase activity with aging, reduced TEWL in 29 healthy elderly individuals.¹⁵ This finding may explain the beneficial effects of n-6 EFAs on the skin epidermis. Dry skin and itch are typical symptoms in patients with AD, and dry skin correlates with disturbed epidermal barrier function.²⁶ Thus, dietary or topical supplementation with LA metabolites may improve skin water content in patients with AD.²⁷

In addition, this study shows significant negative correlations between the SCORAD index and GLA and DGLA levels and between the SCORAD index and AA level, although the latter was not statistically significant. The SCO-

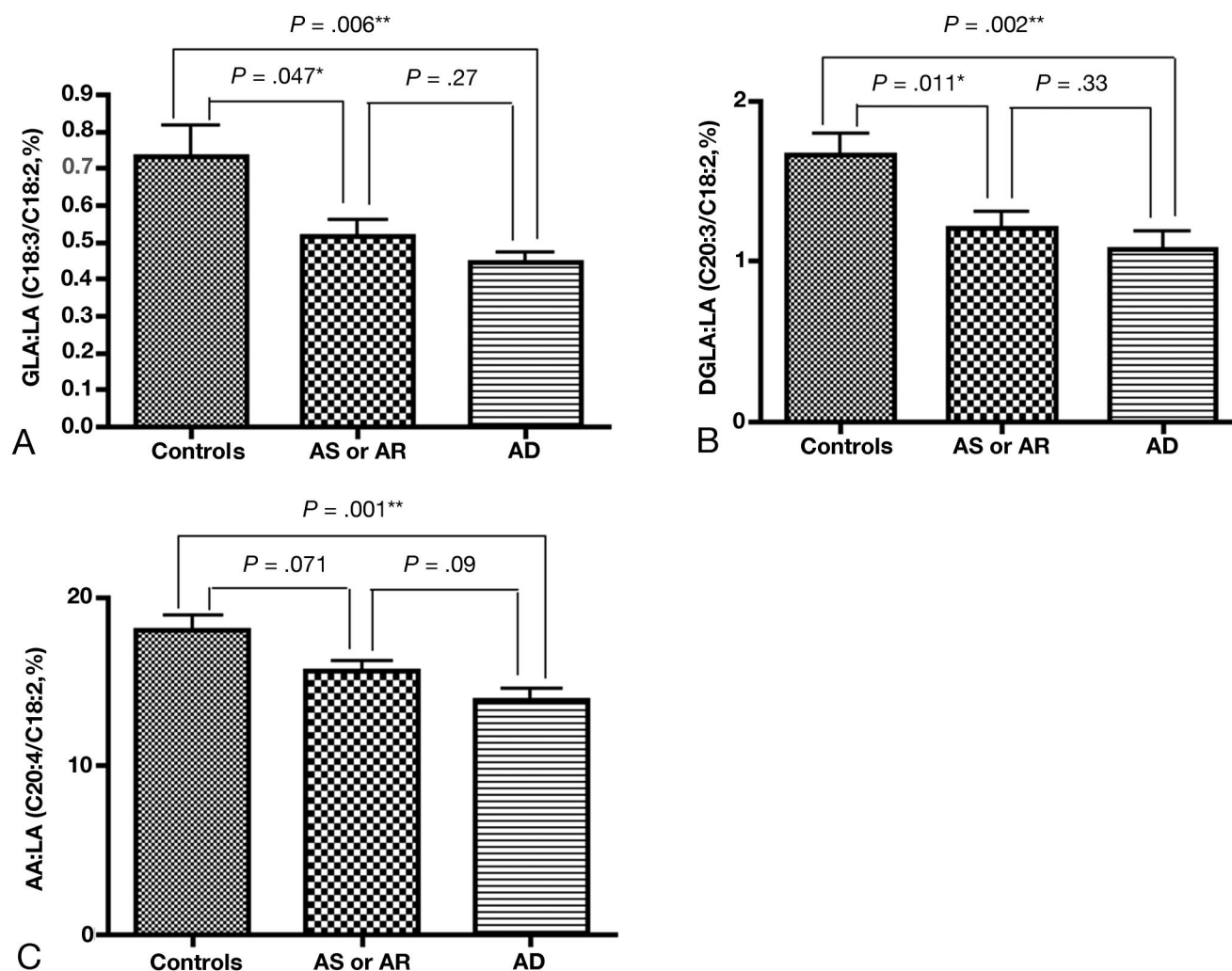


Figure 2. Comparison of the mean γ -linolenic acid (GLA) to linoleic acid (LA) (A), dihommo- γ -linolenic acid (DGLA) to LA (B), and arachidonic acid (AA) to LA (C) ratios in controls, patients with asthma or allergic rhinitis (AS or AR), and patients with atopic dermatitis (AD). Error bars represent SD. Statistical analysis was performed using the Mann-Whitney test. Significant difference at $*P < .05$ or $**P < .01$.

RAD index has been documented to be positively correlated with several variables of skin inflammation and thus can be regarded as a useful inflammatory scale for assessing the severity of AD.^{28–30} The present findings demonstrate that reduced serum levels of LA metabolites, ie, GLA, DGLA, and AA, may result in prolonged cutaneous inflammation, presenting as a high SCORAD index. Otherwise, LA metabolites may have a beneficial effect on the skin inflammation of patients with AD. Some previous studies have shown that DGLA-derived prostaglandin E_1 (PGE_1)³¹ and 15-hydroxy-eicosatrienoic acid⁶ exert anti-inflammatory and antiproliferative effects on the skin. PGE_1 inhibits the mobilization of AA from membrane phospholipids.³² Thus, PGE_1 suppresses eicosanoid synthesis and, thereby, diminishes the release of PGE_2 , leukotriene B₄ (LTB₄), and LTC₄ from blood leukocytes of atopic individuals.³³ PGE_1 activates

adenylate cyclase, which increases cyclic adenosine monophosphate levels of mast cells and basophils, thereby leading to dose-dependent inhibition of histamine release.³⁴ The significantly reduced pruritus in patients with AD given evening primrose oil (rich in GLA) might be explained by PGE_1 -mediated inhibition of histamine release from mast cells and basophils.³⁵ Although AA is metabolized via the cyclooxygenase pathway into PGE_2 and $PGF_{2\alpha}$ (which exert potent proinflammatory effects), 15-lipoxygenase is very active in the epidermis and catalyzes the transformation of AA into predominantly 15-hydroxy-eicosatetraenoic acid, which has been reported as an inhibitor of the generation of proinflammatory LTB₄ from polymorphonuclear cells and basophils.³⁶ The results of this study seem consistent with those of previous studies, mentioned previously herein, that LA metabolites have anti-inflamma-

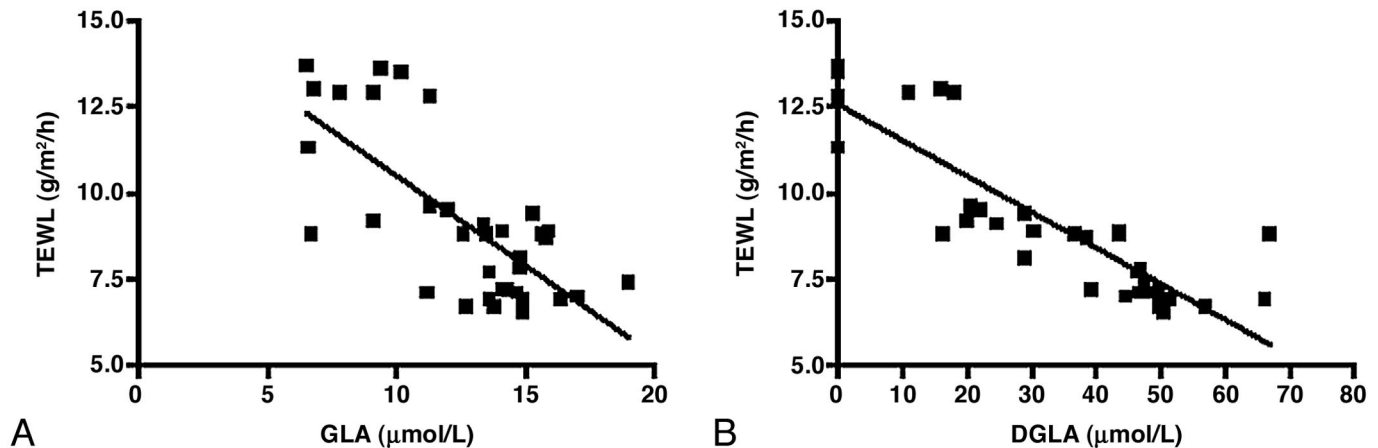


Figure 3. Correlations between transepidermal water loss (TEWL) and serum γ -linolenic acid (GLA) level (A) and serum dihommo- γ -linolenic acid (DGLA) level (B). The TEWL was negatively correlated with GLA level ($r = -0.627$; $P < .001$) and DGLA level ($r = -0.896$; $P < .001$).

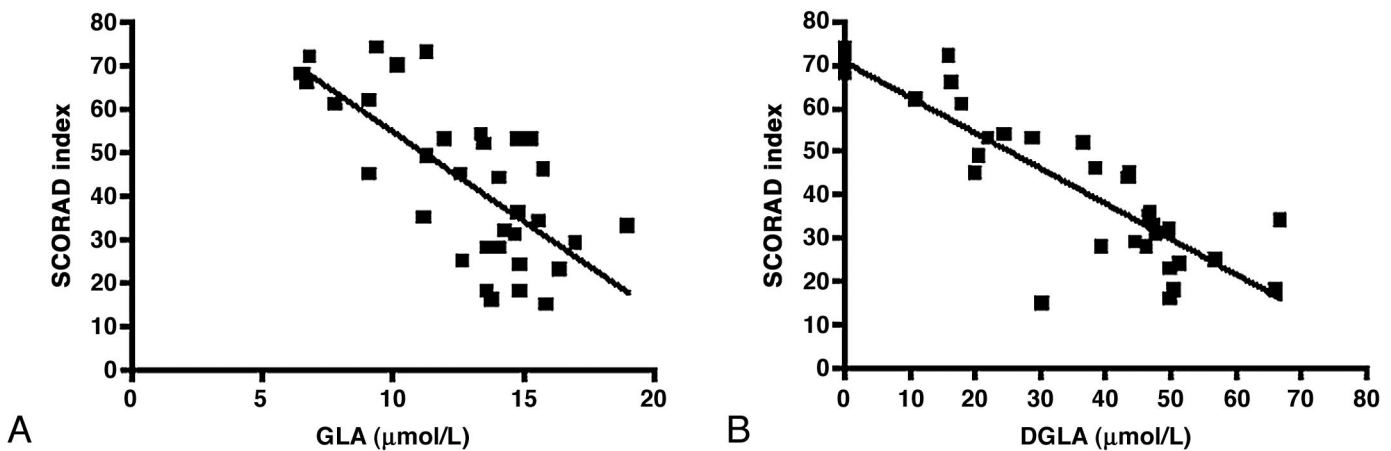


Figure 4. Correlations between the Scoring Atopic Dermatitis (SCORAD) index and serum γ -linolenic acid (GLA) level (A) and serum dihommo- γ -linolenic acid (DGLA) level (B). The negative correlations between the SCORAD index and GLA ($r = -0.677$; $P < .001$) and DGLA ($r = -0.873$; $P < .001$) levels were strong.

tory beneficial effects on the skin. Furthermore, these anti-inflammatory effects of LA metabolites on the epidermis may contribute to the stability of the skin barrier. As in the present results, a significant positive correlation between TEWL and the SCORAD index was observed.

The absence of a correlation between the severity of AD (SCORAD index) and serum IgE level in this study also indicates that different components are implicated in the pathogenesis of AD. This finding is consistent with those of a previous study³⁷ that showed that GLA supplementation has an anti-inflammatory beneficial effect, which does not include the effect on its IgE-mediated component, in AD. n-6 EFAs are thought to play a role in the maturation of the immune system and in IgE synthesis.³⁸ The immunoregulatory effects of n-6 EFAs are mediated through PGE₁.³⁹ PGE₁ is present in the thymus and exerts thymic hormone-like activities in promoting T-lymphocyte maturation and func-

tion, especially suppressor T-cell function.⁷ The deficient T-cell function and the subsequent uncontrolled B-cell responses with exaggerated IgE synthesis might be explained by inadequate formation or availability of GLA, DGLA, and its biologically active product PGE₁ in atopic patients.⁵ Although this study shows no correlation between n-6 EFA concentrations and serum IgE level, the immunoregulatory effects of n-6 EFAs in AD cannot be excluded. Four aspects of this reasoning must be pointed out. First, n-6 EFAs may have a role, but are not the only factor, in IgE synthesis. Many genes and environmental factors may contribute to the end level of IgE.⁴⁰ For example, the levels of interleukin 6, interleukin 10, and transforming growth factor β have been proposed to be involved in IgE synthesis.^{41,42} Hence, the correlations between the level of IgE and δ -6 desaturase products are often weak or do not achieve statistical significance. Second, n-6 EFA concentrations were detected in

patients aged 2 to 17 years but not in the first year (ie, before immune maturation). One study⁴³ suggested that the fatty acid composition of cord blood might even be predictive of later development of atopic disease (IgE mediated). Third, these data showed that a deficit in LA metabolites was noted in atopic patients (the AD and the AS or AR groups had elevated IgE levels) and, therefore, that n-6 EFAs may play a role in the pathogenesis of IgE-mediated allergy. Finally, IgE level was elevated (IgE level >150 U/mL) in all allergic patients enrolled in this study, and n-6 EFA concentrations were not evaluated in patients with AD or AS or AR and normal IgE levels. If n-6 EFA concentrations should be found to be the same in patients with elevated vs normal IgE levels, then n-6 EFAs should be thought to contribute to allergic reactions mediated by inflammatory or other components as yet undetected rather than by IgE.

In conclusion, this study indicates that the pathogenesis of AD can be related to deficiency in n-6 EFAs that are required for (1) normal skin barrier function and (2) protection against inflammatory changes in the skin. For this reason, n-6 EFA supplementation is expected to ameliorate AD symptoms in children even after immune maturation. We have shown that n-6 EFA deficits, thought to be associated with impaired n-6 EFA metabolism, are noted in atopic children with AD and with AS or AR. Thus, n-6 EFAs may play a role in IgE-mediated allergic reactions. We distinguish between the atopic (IgE-mediated) and other inflammatory components of allergic reactions. This study has shown that LA metabolites, ie, GLA and DGLA, have anti-inflammatory beneficial effects in children with allergic diseases. Future studies should be performed to determine whether deficiencies in n-6 EFA metabolism contribute to the atopic (IgE-mediated) component of AD. If disordered n-6 EFA metabolism is associated with hyperactivity in the immune system, treatment with n-6 EFAs could be beneficial in the first year before significant immunologic sensitization.

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