

Increased FADS2-Derived n–6 PUFAs and Reduced n–3 PUFAs in Plasma of Atopic Dermatitis Patients

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Key Words

Atopic dermatitis · Lipid enzymes · n–3 polyunsaturated fatty acids · n–6 polyunsaturated fatty acids · Fatty acid desaturase 2

blood of AD patients, might be responsible for higher levels of FADS2-derived n–6 PUFAs and lower n–3 PUFA levels in patients.

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Abstract

Fatty acid concentrations, in particular n–3 and n–6 polyunsaturated fatty acids (PUFAs), have been described to be dysregulated in atopic dermatitis (AD) patients. The role of genetic polymorphisms of fatty acid enzymes in AD is controversial. We determined in a Hungarian cohort of healthy volunteers (n = 20) and AD patients (n = 20) triglyceride-, sterol- and phospholipid-bound fatty acids in the plasma, mRNA expression of fatty acid desaturase 2 (FADS2) and stearoyl-coenzyme A desaturase 1 in peripheral blood mononuclear cells (PBMCs) and FADS2 concentrations in plasma. We observed higher levels of monounsaturated fatty acids, 16:1 versus 16:0 ratios in phospholipids, triglycerides and sterol esters in patients compared to healthy subjects. In addition higher levels of the FADS2-derived n–6 PUFAs γ-linolenic acid and dihomogamma-linolenic acid were observed in PBMCs of patients as well as lower levels of n–3 PUFAs. We conclude that the increased expression of FADS2 in PBMCs, as a representative tissue accessible from human

Introduction

n–3 and n–6 polyunsaturated fatty acids (PUFAs) are essential lipids for human health [1]. Various plant-derived oils contain linoleic acid (LA, 18:2 n–6), which is the primary member of the n–6 family and a precursor of arachidonic acid (AA, 20:4 n–6). α-Linolenic acid (ALA, 18:3 n–3) found in plant oils is the essential fatty acid of the n–3 family and is also a limited precursor of the n–3 PUFAs eicosapentaenoic acid (EPA, 20:5 n–3) and docosahexaenoic acid (DHA, 22:6 n–3). Marine oils such as fish oil are important sources of EPA and DHA [2]. AA and EPA are the precursors of various bioactive substances known as eicosanoids/docosanoids. These include prostaglandins, thromboxanes and leukotrienes [3], respectively lipoxins, protectins and resolvins [4]. Eicosanoids are pivotal to health due to their role in modulating immune responses and inflammation. AA-derived eicosanoids have been shown to elicit mainly pro-inflam-

matory effects, while EPA-derived eicosanoids are mainly anti-inflammatory/pro-resolving derivatives [5].

Several epidemiological studies have shown that altered dietary intake of n-3 PUFAs is associated with an increased prevalence of atopic diseases [6]. Therefore, it has been hypothesized that altering PUFA profiles by dietary supplementation may be beneficial in established allergic diseases, such as asthma and atopic dermatitis (AD) [7, 8]. Thus, supplementation with EPA and DHA in human clinical trials of established autoimmune-related diseases has shown beneficial effects by reducing inflammatory responses [9–11]. Furthermore, our own supplementation studies in adults with atopic diseases [12] and the work of others in children with atopic diseases [13] and in pregnant women [14] have shown that n-3 PUFAs are molecules which transit/mediate anti-inflammatory effects. Nevertheless, there is still controversy on how effective dietary manipulation is as some studies have shown little or no effect of n-3 supplementation in asthma [15] and AD [16]. Thus, the response to supplementation may be susceptible to individual variations which may be linked to a specific genetic makeup.

AD is a chronically relapsing eczematous disorder of the skin associated with cutaneous hyperreactivity to environmental triggers. It appears in patients at all ages, but it is predominantly present in infancy and childhood [17]. Genetic susceptibility is generally a condition for the development of AD. Polymorphisms in enzymes responsible for PUFA metabolism may be involved in the development of AD [18].

Fatty acid desaturase 2 (FADS2) plays an important role in the biosynthesis of PUFAs, since it catalyzes the desaturation of LA and ALA which is needed for the biosynthesis of longer PUFAs [19]. FADS2 polymorphisms have been identified as genetic contributors to PUFA concentrations in several population-based studies [20, 21] in adults. Furthermore, adult carriers of the minor alleles of nucleotide polymorphisms proved to have a lower prevalence of allergic diseases [22]. However, cohort studies in children carrying FADS2 alleles are contradictory as they confirm the association between FADS2 and PUFA concentrations but weak or no associations between PUFA and eczema [23].

Stearoyl-coenzyme A desaturase 1 (SCD1) catalyzes the $\Delta 9$ desaturation of saturated fatty acyl-coenzymes A, and these monounsaturated fatty acids (MUFAs) are the substrates for the synthesis of triglycerides, sterol esters and phospholipids [24, 25]. Animal studies have shown that suppression of SCD1 expression is associated with increased inflammatory responses. These may be linked

Table 1. Clinical and basic demographic data of healthy volunteers and AD patients

	Healthy volunteers	AD patients	p value
Age, years	21±1	20±5	–
Gender female, %	70	60	–
SCORAD	0±0	35.2±16.9	<0.05
Total IgE, kU/l	32±9.2	2,941±1,134	<0.05
EOS, %	2.5±0	7.3±1.2	<0.05

SCORAD = Scoring atopic dermatitis; total IgE = serum total immunoglobulin E level; EOS = the number of eosinophils in percentage in comparison to all white blood cells in peripheral blood, normal values are 1–4%.

to the accumulation of saturated fatty acids (SFAs) observed during deletion or inhibition of SCD1 [26]. Little is known about the role of SCD1 during atopy in humans.

The role of FADS2 genetic expression on PUFA composition has been well established but the link to atopic disease is still controversial. This may be due to genetic differences in population subgroups. Thus, it is important to determine PUFA profiles and genetic variants in different population cohorts, in particular in groups with established atopic disease. Furthermore, the expression of both SCD1 and FADS2 in atopic patients needs to be explored.

The aim of the study was to compare the plasma composition of various triglyceride-, sterol- and phospholipid-bound PUFAs and mRNA expression of the SCD1 and FADS2 enzymes in peripheral blood mononuclear cells (PBMCs) in a cohort of healthy volunteers and AD patients.

Materials and Methods

Subjects and Sample Collection

Subjects were recruited from the Department of Dermatology, University of Debrecen, Hungary. Healthy volunteers did not have a personal or family history of atopic disease. Table 1 presents the clinical and demographic data of the healthy volunteers and patients involved in the study. Ethical approval was granted by the Ethical Committee of the University of Debrecen and followed the guidelines of the Declaration of Helsinki. Informed consent was obtained prior to the participation in the research. Blood samples were drawn by a trained phlebotomist from 20 patients with AD and from 20 healthy volunteers.

Measurement of Plasma IgE Level and SCORAD

Patients were tested for plasma total IgE by ELISA (ADALTIS Italia S.p.A., Casalecchio di Reno, Italy) according to the manufacturer's instructions. The severity of the disease was determined with the SCORAD index [27].

FADS2 Enzyme-Linked Immunosorbent Assay

FADS2 concentrations were analyzed in the Plasma of AD patients (n = 20) and healthy volunteers (n = 20) according to the manufacturers' instructions using a human FADS2 ELISA kit (Cloud-Clone Corp., Houston, Tex., USA).

Eosinophil Cell Count

The rate count of eosinophils as in whole blood was determined by Advia 120 hematology analyzer (Siemens, Deerfield, Ill., USA), as part of the routine clinical investigation of the patients and calculated as percentage. The eosinophils in the analyzer were identified based on their scatter properties and myeloperoxidase positivity.

PBMC Preparation

Blood samples were immediately transferred into a 15-ml Falcon tube after collection and centrifuged at room temperature, 2,500 rpm for 15 min. After centrifuging plasma was removed and kept at -80°C . PBMCs were isolated from anticoagulant-treated blood using Ficoll-Paque™ Plus centrifugation according to the manufacturer's instructions (GE Healthcare, Uppsala, Sweden). Shortly, the cell/plasma suspension was slowly slid down on the top of 5–10 ml Ficoll-Paque and centrifuged carefully at room temperature, 2,500 rpm for 20 min. White blood cells were removed and washed with physiological salt solution. Another centrifuging was performed at room temperature, 1,800 rpm for 10 min, the supernatant was discarded and this step was repeated twice more, with 7-min centrifuging at the given conditions. The cell pellet was suspended in 500 μl physiological salt solution and transferred into a 1.5-ml Eppendorf tube, centrifuged at room temperature, 13,000 rpm for 6 min, and the physiological salt solution was removed from the top in order to dry the pellet. The PMBC pellets were kept at -80°C until analysis.

Analysis of mRNA Expression

PBMC pellets were homogenized in Tri® reagent solution, and total RNA was isolated according to the manufacturer's guidelines (Sigma-Aldrich, Hungary). A total of 15 PBMC samples were used in both experimental groups, due to the low amount of recovered samples. The concentration and purity of RNA were measured using a NanoDrop spectrophotometer (Thermo Scientific, Hungary). For real-time quantitative PCR (QRT-PCR), total RNA was reverse transcribed into cDNA using a High Capacity Reverse Transcription kit (Life Technologies, Hungary). QRT-PCR was carried out in triplicate using predesigned MGB assays (Life Technologies) on an ABI Prism 7900 (Life Technologies). Relative mRNA levels were calculated using the comparative C_T method normalized to cyclophilin A mRNA [28]. Sequence Detector Software (version 2.1) was utilized for data analysis and relative n-fold induction was determined by the comparative threshold cycle method.

Fatty Acid Analysis

For the analysis of plasma fatty acid profiles, frozen plasma samples were thawed, and then the 3 internal standards (dipentadecanoylphosphatidylcholine, cholesterylpentadecanoate and tripentadecanoate) were added. Lipids were extracted by the addition of 3 ml chloroform and 1 ml methanol according to the method of Folch et al. [29]. The mixture was vortexed at 2,000 rpm for 10 min, and then the lower layer was aspirated into vials and evaporated under a nitrogen stream. Lipid extracts were reconstituted in 70 μl chloroform, and lipid classes were separated by thin layer

chromatography. The solvents for thin layer chromatography of plasma lipids were as follows: hexane:diethylether:chloroform:acetic acid (21:6:3:1, by vol.) followed by chloroform:methanol:water (65:25:4, by vol.). The bands were stained with dichlorofluorescein, removed by scraping and transesterified in 3 N HCl-methanol solution at 84°C for 45 min.

Fatty acids were analyzed by high-resolution capillary gas chromatography using a Finnigan 9001 gas chromatograph (Finnigan/Tremetrics Inc., Austin, Tex., USA) with split injection (ratio: 1:25), automatic sampler (A200SE, CTC Analytic, Switzerland) and a flame ionization detector with a DB-23 cyanopropyl column of 40 m length (J & W Scientific, Folsom, Calif., USA). The temperature program was the following: temperature of injector at 80°C for 0.1 min, temperature increase by $180^{\circ}\text{C}/\text{min}$ up to 280°C , temperature of detector at 280°C , temperature of column area at 60°C for 0.2 min, temperature increase by $40^{\circ}\text{C}/\text{min}$ up to 180°C , 5-min isotherm period, temperature increase by $1.5^{\circ}\text{C}/\text{min}$ up to 200°C , 8.5-min isotherm period, temperature increase by $40^{\circ}\text{C}/\text{min}$ up to 240°C and 13-min isotherm period. The constant linear velocity was 0.3 m/s (referred to 100°C). Peak identification was verified by comparison with authentic standards. Fatty acid results were expressed as percentages (weight by weight) of fatty acids detected with a chain length between 12 and 24 carbon atoms.

Statistics

Data are shown as mean and standard error of mean values of 3 measurements per data point. Statistical analysis was performed using the program SPSS 16.0. A p value of less than 0.05 was considered significant using the Student t test for independent samples.

Results

The fatty acid composition of plasma sterols, triglycerides and phospholipids of healthy and AD patients is shown in table 2.

SFA Composition of Sterols, Triglycerides and Phospholipids

The sum of the SFA content of sterols was significantly higher in AD patients compared to healthy subjects. Both levels of 18:0 and 20:0 were higher in the plasma of AD patients. On the other hand, for triglycerides, the sum of SFAs was significantly lower in the plasma of AD patients compared to healthy subjects with significant lower SFA 16:0 and 20:0 levels. There were no significant changes in the sum of separate SFAs in the phospholipid component in the plasma of AD patients in comparison to healthy volunteers.

MUFA Composition of Sterols, Triglycerides and Phospholipids

There were no significant differences in the sum of MUFAs in any of the lipid classes in both groups. For in-

Table 2. Fatty acid composition of plasma sterols, triglycerides and phospholipids in healthy volunteers and AD patients (n = 20)

	Sterols			Triglycerides			Phospholipids		
	healthy volunteers	diseased patients	p value	healthy volunteers	diseased patients	p value	healthy volunteers	diseased patients	p value
Sum SFA	16.8±2.41	19.0±4.57	0.03	9.9±4.42	34.1±9.23	0.01	49.7±1.88	49.7±1.72	0.48
16:0	13.2±1.58	14.1±2.68	0.13	29.2±3.13	27.4±2.87	0.05	29.7±2.0	29.8±2.37	0.45
18:0	2.65±0.91	3.81±2.50	0.02	7.73±2.61	6.65±3.43	0.12	16.0±1.32	16.3±1.67	0.33
20:0	0.03±0.02	0.05±0.03	0.02	0.14±0.07	0.08±0.03	0.01	0.48±0.12	0.44±0.09	0.12
Sum MUFA	20.1±2.69	21.3±3.54	0.11	37.7±2.69	38.8±4.91	0.11	11.8±1.20	12.1±1.79	0.27
16:1 n-7	1.80±0.45	2.54±0.86	<0.01	2.10±0.62	2.65±0.86	0.03	0.44±0.13	0.45±0.12	0.43
18:1 n-9	17.0±2.41	17.5±2.78	0.26	33.4±2.77	33.6±4.07	0.30	7.51±0.91	7.71±1.45	0.31
Sum n-6	61.9±4.58	58.5±6.48	0.04	20.5±1.74	22.9±5.78	0.08	35.7±1.86	35.5±1.97	0.37
LA (18:2 n-6)	54.7±4.25	51.5±5.93	0.04	18.8±3.66	21.0±5.16	0.08	22.4±2.25	21.5±2.96	0.19
GLA (18:3 n-6)	0.58±0.20	0.74±0.29	0.06	0.24±0.10	0.29±0.11	0.10	0.06±0.02	0.08±0.03	0.09
DHGLA (20:3 n-6)	0.61±0.15	0.67±0.20	0.13	0.29±0.10	0.41±0.14	<0.01	2.44±0.47	3.02±0.91	0.01
AA (20:4 n-6)	5.91±1.64	5.47±1.53	0.19	1.16±0.36	1.20±0.37	0.41	9.65±2.07	9.51±1.74	0.42
Sum n-3	0.77±0.19	0.70±0.19	0.11	0.14±0.04	0.17±0.06	0.02	2.55±0.61	2.33±0.41	0.10
ALA (18:3 n-3)	0.22±0.06	0.22±0.09	0.43	0.41±0.15	0.36±0.13	0.12	0.08±0.03	0.08±0.04	0.18
EPA (20:5 n-3)	0.15±0.06	0.13±0.05	0.09	0.15±0.06	0.16±0.06	0.45	0.19±0.10	0.18±0.09	0.35
DHA (22:6 n-3)	0.23±0.07	0.20±0.07	0.07	0.19±0.10	0.18±0.07	0.45	1.78±0.49	1.59±0.28	0.07
FADS2 ratio									
GLA/LA	0.011±0.004	0.015±0.007	0.04	0.01±<0.01	0.01±0.01	0.24	0.003±0.001	0.004±0.002	0.10
DHGLA/LA	0.011±0.003	0.013±0.004	0.05	0.020±0.006	0.015±0.003	0.01	0.11±0.02	0.14±0.05	0.01
EPA/ALA	0.69±0.20	0.60±0.26	0.12	0.10±0.05	0.09±0.05	0.39	2.87±1.42	2.37±1.05	0.12
DHA/ALA	1.10±0.29	0.97±0.34	0.12	0.53±0.28	0.50±0.22	0.20	28.1±14.3	21.9±7.90	0.05
n-3/n-6 ratio									
EPA/AA	0.03±0.01	0.02±0.01	0.10	0.03±0.02	0.03±0.01	0.15	0.02±0.01	0.02±0.01	0.30
SCD1 ratios									
16:1 n-7/16:0	0.14±0.03	0.18±0.06	<0.01	0.07±0.02	0.07±0.03	0.01	0.01±<0.01	0.02±<0.01	<0.01

Values are means and standard deviations of weight percentages.

dividual MUFAs, significantly higher levels were observed for 16:1 n-7 in sterols and triglycerols in AD patients compared to healthy subjects. No differences in MUFA levels in the phospholipid component could be observed.

The SCD1 ratio, which is the MUFA/SFA ratio in this case the 16:1 n-7/16:0 ratio, was significantly decreased in all components (sterols, triglycerides and phospholipids) in the plasma of AD patients.

n-6 PUFA Composition of Sterols, Triglycerides and Phospholipids

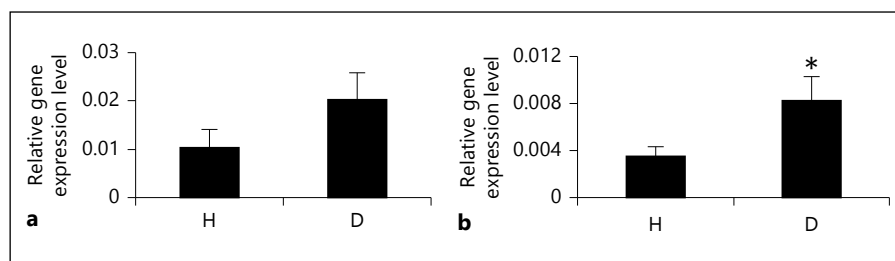
The sum of n-6 PUFAs in sterols was significantly higher in the plasma of AD patients in comparison to healthy volunteers. A slight, but not significant increase in triglycerides and phospholipids of AD patients versus healthy volunteers was also observed. LA levels in sterols were lower in the plasma of AD patients. No differences in the levels of AA in triglycerides and phospholipids

were observed. γ -Linolenic acid (GLA) and dihomog-LA (DHGLA) are of potential interest in the dietary therapy of AD. There was a trend for an increase in GLA levels in all lipid classes in the plasma of AD patients. A similar trend was also observed in DHGLA levels in sterols whereas DHGLA levels were significantly higher in triglycerides and phospholipids in the plasma of AD patients compared to healthy volunteers. AA is the precursor PUFA in the production of n-6-derived eicosanoids, and the plasma levels of AD patients showed a nonsignificant decrease in comparison to healthy volunteers in sterols and phospholipids whereas a trend for higher levels in the triglyceride component was also observed.

n-3 PUFA Composition of Sterols, Triglycerides and Phospholipids

The sum of n-3 PUFAs was significantly lower in plasma triglycerides of atopic patients compared to healthy volunteers while it was lower but not significant in sterols

Fig. 1. Relative gene expression levels of the two fatty acid-metabolizing enzymes SCD1 (**a**) and FADS2 (**b**) from human PBMCs (n = 15) by QRT-PCR analysis. H = Healthy volunteers; D = diseased patients; * p < 0.05.



and phospholipids. There was no difference between groups in ALA levels in sterols and phospholipids, while in triglycerides a slight, but non-significant lower level could be observed in the AD patients. EPA (20:5 n-3) and DHA (22:6 n-3) levels were nonsignificantly lower in sterols and phospholipids in AD patients. EPA levels in triglycerides of AD patients were higher compared to healthy subjects but these did not reach significance while DHA levels were similar between both groups.

Ratios between Various PUFAs

n-3/n-6 PUFA Ratios. A trend towards lower levels of n-3 PUFA EPA/n-6 PUFA AA ratios in AD patients versus healthy subjects in all lipid classes were observed; however, these did not reach significance. In contrast, the n-3 PUFA GLA/n-6 PUFA LA ratio was significantly higher in the sterols of atopic patients compared to healthy subjects. This ratio was also slightly higher in phospholipids of AD patients. The level of triglycerides was similar between both groups.

n-3/n-3 PUFA and n-6/n-6 PUFA Ratios Depending on FADS2 Metabolism. The n-6 PUFA DHGLA versus n-6 PUFA LA ratios were significantly higher in all lipid classes in the plasma of AD patients compared to healthy subjects. There was a trend towards lower EPA/ALA ratios in all lipid classes of AD patients but these were not significant. Furthermore DHA/ALA ratios in sterols and triglycerides in AD patients were also lower without reaching significance and a significant lower DHA/ALA ratio was observed in phospholipids of AD patients.

Expression of FADS2 and SCD1 in the PBMCs of AD Patients

The mRNA expression of the FADS2 enzyme in PBMCs was significantly higher in AD patients in comparison to healthy volunteers. Furthermore, SCD1, a key enzyme in fatty acid metabolism, responsible for the production of the MUFA oleic acid from the SFA stearic acid was higher in AD patients than healthy volunteers, but this was not significant (fig. 1).

Serum Protein Concentration of FADS2

The protein concentration of FADS2 in the serum of AD patients (5.9 ± 3.2 ng/ml) was similar to that of healthy volunteers (5.8 ± 3.3 ng/ml).

Discussion

Fatty acids are known to be important nutrients (fig. 2) mainly bound to other lipids in the diet as well as in the human organism [1]. They are important precursors of various bioactive derivatives, the eicosanoids and docosanoids being pro- and anti-inflammatory derivatives [30]. The role of FADS2 polymorphisms on PUFA concentrations has been well established but the link to atopic disease remains unclear, therefore we determined the concentration of fatty acids like SFAs, MUFAs and PUFAs bound to sterols, triglycerides and phospholipids in healthy subjects and AD patients. Additionally the FADS2 ratios and SCD1 ratios, respectively the n-3/n-6 ratios, were measured.

SFA levels were in general higher in AD patients together with higher individual MUFA levels. This was confirmed by higher ratios of MUFA/SFA in AD patients especially for 16:1 n-7/16:0 which suggest increased formation of SCD1-derived metabolites in AD patients, while higher mRNA expression of SCD1 in PBMCs from human AD patients was not observed. The $\Delta 9$ -desaturase SCD1 enzyme is known to mainly metabolize the SFAs 16:0 and 18:0 to 16:1 and 18:1 in various organs including the skin and several cells of the immune system [24, 31, 32]; however, the exact function of SCD1 during atopy and allergic sensitization remains unknown [22, 33].

Another important fatty acid desaturase, the $\Delta 6$ -desaturase FADS2, is known to play an important role in the metabolism of n-3 and n-6 PUFAs [34]. FADS2 metabolizes the n-6 PUFA LA to GLA and further to AA but also the n-3 PUFA ALA to stearidonic acid (18:4 n-3) and eicosatetraenoic acid (20:4 n-3) and further to EPA and DHA [8]. FADS2 dysfunctional polymorphisms were

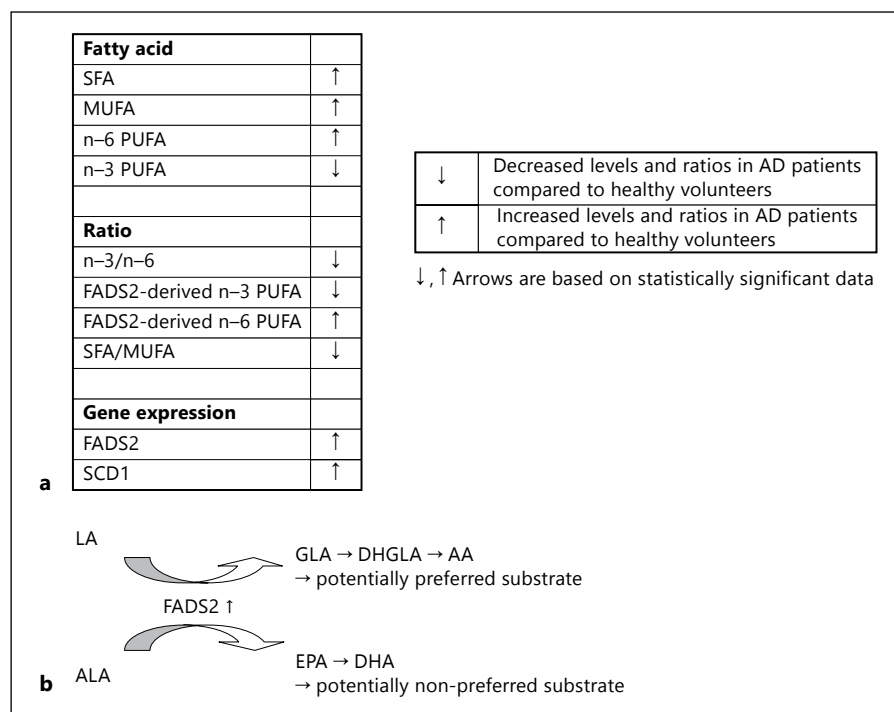


Fig. 2. a Summary findings based on significant values obtained from our analytical data. **b** Schematic outline of FADS2 metabolism.

usually found to be associated with an atopic phenotype [35]. In our study an increased expression of FADS2 mRNA expression was found in the PBMCs of AD patients. A significant higher concentration of FADS2 in serum of AD patients was not confirmed, maybe because FADS2 is mainly a cell-based enzyme [36] and its tissue and cell specific regulation in humans cannot be examined conclusively. FADS2 is related to an increased production of AA-derived pro-inflammatory eicosanoids [37]. We observed higher ratios of n-6 PUFA-derived FADS2 metabolites and lower n-3 PUFA-derived FADS2 metabolites which partly confirmed the findings of Zouboulis et al. [37]. The n-6 PUFA-derived FADS2 metabolites are the precursors of highly bioactive pro-inflammatory eicosanoids like prostaglandins, leukotrienes and thromboxanes while n-3 PUFA-derived FADS2 metabolites are mainly precursors of potent pro-resolving eicosanoids and docosanoids like resolvins, protectins and maresins [30]. This phenomenon might be one important reason why the chronic inflammatory status in various atopic diseases does not improve and is kept stable.

In conclusion, we found that specific plasma fatty acid and especially PUFA concentrations correlate with PBMC expression of the fatty acid-metabolizing enzyme FADS2. An increased expression of FADS2 in PBMCs and at the same time an increase in the FADS2 n-6 PUFA AA and decreased FADS2 n-3 PUFA EPA or DHA was observed;

however, protein concentrations of FADS in serum were not increased in atopic patients. This phenomenon may be an important factor for the chronic nature of this skin disorder and our findings suggest that during chronic atopic dermatitis less pro-resolving metabolites mainly originating from n-3 PUFAs and more pro-inflammatory metabolites mainly from n-6 PUFAs were produced which may contribute to maintain the inflammatory status in chronic atopic dermatitis. We speculate that this novel knowledge may be of importance to find a systemic approach for the prevention and therapy of chronic AD.

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Disclosure Statement

The authors declare no conflict of interest.

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