Acta Derm Venereol (Stockh) 1990; 71: 224–228

Levels of Essential and Other Fatty Acids in Plasma and Red Cell Phospholipids from Normal Controls and Patients with Atopic Eczema

S. OLIWIECKI[1], J. L. BURTON [2], K. ELLES[3] and D. F. HORROBIN[3]

[1]The Skin Hospital, Salford, Lancashire, the [2]Department of Dermatology, Bristol Royal Infirmafry, Bristol, Great Britain, and the [3]Efamol Research Institute, Kentville, Nova Scotia, Canada

Blood samples were collected from 48 atopic eczema patients and 33 normal subjects in Bristol, and from 434 normal individuals worldwide. In the plasma phospholipids in the atopic eczema patients, the concentrations of linoleic acid and the ratio of linoleic acid to its metabolites were significantly elevated as compared with both sets of controls. In the atopic eczema patients there were major abnormalities in the red cell phospholipids with saturated and monounsaturated fatty acids being significantly elevated and the concentrations of most essential fatty acids being significantly reduced. Patients with atopic eczema thus show abnormalities related both to desaturation of essential fatty acids and to their incorporation into red cell membranes.

(Accepted October 22, 1990.)

Acta Derm Venereol (Stockh) 1991; 71: 224–228.

S. Oliwiecki, The Skin Hospital, Chapel Street, Salford, Lancashire, M60 9EP, Great Britain.

Hansen (1) in the 1930s first reported that patients with atopic eczema (AE) had low concentrations of total essential fatty acids (EFAs) in the blood. He later demonstrated that, in patients fed large amounts of linoleic acid, blood linoleic acid concentrations were normal, whereas those of arachidonic were reduced (2). It was subsequently shown that dietary linoleic acid was converted to arachidonic acid by the pathway shown in Fig. 1.

Over 40 years after the initial observations by Hansen, the issue of EFAs in AE was reopened. Adults with AE from Bristol were found to have fatty acid levels very different from those in normal Canadian controls (3,4). Linoleic acid levels were somewhat above normal, while the levels of major linoleic acid metabolites, especially arachidonic acid were below normal. The concentrations of the main dietary n–3 fatty acid alpha-linolenic acid were also at the upper range of normal while the concentrations of its metabolites were below normal. These observations raised the possibility that there might be a deficit in 6-desaturation in AE leading to normal or above normal levels of the main dietary EFAs, linoleic and alpha-linolenic acids, with below normal levels of their metabolites.

A number of investigators have repeated these measurements. Strannegard et al. (5) in children with AE found similarly abnormal EFA levels which were even further from the normal range than the adults. Linoleic acid was highly significantly elevated. Strannegard et al. also related umbilical cord blood linoleic acid concentrations to IgE as a measure of risk of developing an atopic disorder. There was a significant positive relationship between cord blood linoleic acid and IgE concentrations, indicating that a fatty acid abnormality may be present prior to the development of an overt skin disorder. EFAs are found both in adipose tissue and in human milk. Wright et al. (6,7) found that in mothers of children with AE, linoleic acid concentrations were normal or elevated in milk, while its metabolites were reduced. Similar findings were obtained in the adipose tissue of patients with atopic eczema.

Schalin-Kärrilä et al. (8) compared 25 adults with AE and 7 controls and could find no differences in plasma EFA levels. However, the controls had EFA concentrations which were different from those seen in a much larger normal Finnish population (9). When the AE patients are compared with this much larger number of Finnish controls, then again the eczema patients show above-normal linoleic acid levels and subnormal levels of its metabolites. In the USA, Bamford et al. found no difference in linoleic acid metabolite concentrations between adults with AE and normal controls. However, children with AE did have subnormal levels of arachidonic acid (10).

Thus, with some exceptions, the data point to the concept that the main dietary EFAs are above nor-

Table I. *The concentrations (mg/100 mg lipid) of fatty acids in the plasma phospholipid fraction of various groups of individuals.*

The results are shown as means ± SD. The Canadian controls, the old eczema patients and the Bristol controls have been previously reported (4,11) but are shown here for comparison purposes. Stastistical comparison of the new Bristol eczema patients with the Bristol controls and the worldwide controls were made by Student's *t*-test.

	Canadian controls	Bristol controls	World controls	AE, Bristol, old	AE, Bristol, new
n-6 EFAs					
18:2	21.5±2.8	26.8±3.4	25.7±4.1	24.5±3.4	30.8±4.3[ab]
18:3	0.2±0.1	Tr	Tr	Tr	Tr
20:3	3.1±1.6	2.9±0.5	2.6±0.6	2.6±0.5	2.8±0.8
20:4	11.4±1.7	11.1±0.6	10.8±2.2	6.8±1.1	10.7±1.8
22:4	0.7±0.3	0.3±0.1	0.3±0.2	0.4±0.2	0.3±0.2
22:5	1.1±0.7	0.3±0.2	0.2±0.2	0.1±0.1	0.2±0.4
18:2/metabolites	1.30	1.84	1.85	2.47	2.20[ab]
n-3 EFAs					
18:3	0.3±0.5	0.2±0.2	0.2±0.3	0.4±0.2	0.3±0.2
20:5	1.0±0.4	1.6±0.8	1.4±1.1	0.8±0.6	1.4±0.6
22:5	0.9±0.3	1.1±0.3	1.0±0.9	0.7±0.2	0.8±0.4
22:6	3.5±0.9	4.3±1.0	4.5±1.7	2.4±0.6	3.5±1.9
Others					
16:0	25.8±1.7	26.7±2.3	26.8±2.3	30.1±1.9	26.8±2.0
18:0	11.6±1.3	9.1±2.0	10.0±2.9	13.5±1.8	8.8±2.5
18:1	13.5±2.2	12.1±1.3	13.7±3.2	14.1±1.3	11.1±1.4
n	50	33	434	41	48

[a] significantly different from Bristol controls at $p < 0.05$ or les. [b] significantly different from worldwide controls at $p < 0.05$ or less.

mal or in the upper part of the normal range in patients with AE, while their metabolites are below normal. This raises the possibility that 6-desaturation may in some way be impaired.

It is nearly a decade since interest in Hansen's work was renewed. During this time, in response to information about coronary heart disease risk, the intake of linoleic acid has increased with no comparable increase – and possibly even a reduction – in saturated fats. High linoleic acid intakes might influence the concentrations of linoleic acid metabolites. We therefore felt it appropriate to repeat the earlier studies, comparing EFA concentrations in a new series of AE patients from Bristol with those in samples from Bristol controls (11) and also from a much larger number of worldwide controls and those from the original Bristol sample of eczema patients. In addition we looked at the fatty acid levels in phospholipids from red cell membranes.

PATIENTS AND METHODS

Blood samples were taken from 48 patients with AE, attending the Dermatology Clinic at the Bristol Royal Infirmary. All patients had been referred by their general practitioners as having eczema of such a severity as to require specialist attention. All had the clinical features of typical atopic dermatitis, accompanied by a personal or family history of atopic disorders. Blood samples were also taken from 33 individuals in Bristol who, as far as could be ascertained, were in normal health, who were not taking recreational or therapeutic drugs and who had no personal or family history of atopy (11). Finally blood samples were taken from 434 normal individuals in 13 different European populations (four in the USA, three in Britain, two in Canada and one each in Denmark, Ireland, Norway and Finland). Plasma samples were available from all individuals and red blood cell samples from 26 of the new AE patients, from 32 of the Bristol controls and from 279 of the normal individuals collected elsewhere.

All the samples were sent frozen by air from their place of collection to the Efamol Research Institute in Kentville, Nova Scotia, Canada. There they were analysed for their fatty acid composition as previously described (12). In brief, total lipids were extracted and the phospholipid class was separated by thin-layer chromatography. The phospholipid band was then scraped off the plates, trans-methylated and the resulting fatty acid methyl esters analysed by gas chromatography. The results of the Bristol controls have been reported in another context (11) but are described here for the first time in relation to atopic eczema.

Table II. *The concentrations (mg/100 mg lipid) of fatty acids in the red cell phospholipid fraction of various groups of individuals.*

The results are shown as mean ± SD. The groups are as in Table I. Statistical comparisons of the new Bristol eczema patients and the Bristol and worldwide controls were made by Student's *t*-test.

	Bristol controls	World controls	AE, Bristol, new
n-6 EFAs			
18:2	15.2±3.2	14.7±3.0	12.9±3.2[ab]
20:3	1.7±0.5	1.6±0.5	1.3±0.7[a]
20:4	17.9±4.2	15.4±4.0	10.5±4.9[ab]
22:4	2.2±0.8	2.2±1.0	1.5±1.1
22:5	0.8±0.8	0.6±0.9	0.6±0.6
n-3 EFAs			
18:3	0.2±0.5	0.1±0.2	0.2±0.2
20:5	1.4±0.5	1.2±0.9	0.6±0.5[ab]
22:5	2.6±0.8	2.3±0.8	1.1±1.0[ab]
22:6	6.3±1.5	6.2±2.3	2.0±1.8[ab]
Others			
16:0	22.0±4.0	22.9±3.8	31.4±6.9[ab]
18:0	11.1±2.5	12.8±2.9	13.9±3.1[a]
18:1	15.0±2.2	15.8±2.3	19.7±2.8[ab]
Unsaturation index	193.3	178.4	119.5
	n=32	n=279	n=26

[a] significantly different from Bristol controls at $p < 0.05$ or less. [b] significantly different from worldwide controls at $p < 0.05$ or less. The unsaturation index was calculated by multiplying the concentration of each fatty acid by the number of double bonds it contains and adding up the result.

RESULTS

The results of the analyses of plasma phospholipids are shown in Table I. This compares the original Bristol AE patients and Canadian controls studied 8 years ago, the new Bristol AE patients, the new Bristol controls, and the much larger series of worldwide controls.

As compared with the previous Bristol AE sample, the new sample shows significantly higher levels of linoleic acid, arachidonic acid and eicosapentaenoic acid and significantly lower levels of the saturated fatty acid, stearic acid (18:0) and the mono-unsaturate, oleic acid (18:1). These changes are what might be expected if patients had started consuming a diet richer in polyunsaturated fat and with a reduced saturated fat element.

The only fatty acid in the new AE sample that was significantly different from all the control samples was linoleic acid, was markedly higher in the AE patients. Arachidonic acid and docosahexaenoic acid tended to be lower in the AE patients than in both sets of new controls, but not significantly so. The ratio of linoleic acid to its metabolites was significantly greater in the AE patients than in both sets of controls.

The analyses of red cell phospholipids in the new AE patients and in the Bristol and worldwide controls are shown in Table II. Red cell fatty acids were not analysed in the earlier set of AE patients. The differences between the patients and both sets of controls are very large for some of the fatty acids. The two main saturated fatty acids, palmitic and stearic (16:0 and 18:0), and the mono-unsaturate, oleic (18:1n–9), are all highly significantly elevated ($p < 0.001$ or less) in the AE patients as compared with both sets of controls. Linoleic acid (18:2n–6), in contrast to the position in plasma is significantly lower in the AE patients. Levels of dihomogammalinolenic acid (DGLA, 20:3n–6), adrenic acid (22:4n–6) and especially arachidonic acid (20:4n–6), eicosapentaenoic acid (EPA, 20:5n–3), docosapentaenoic acid (DPA, 22:5n–3) and docosahexaenoic acid (22:6n–3) are all significantly reduced in the AE patients as compared with both sets of controls. Thus the AE patients show a general elevation in saturates and mono-unsaturates and a general reduction in essential fatty acids, changes which would be expected to be associated with increases in membrane microviscosity and reduced cellular flexibility.

DISCUSSION

With regard to plasma phospholipids, the new set of atopic eczema patients were less different from both sets of normal controls than the original set. The changes between the new and the previous set of AE patients are consistent with increased consumption of polyunsaturated fatty acids and a reduced consumption of saturated fats. Linoleic acid levels, and the ratio of linoleic acid to its metabolites were significantly higher in the AE patients than in either set of controls. This abnormality in the ratio of linoleic acid to its metabolites is consistent with previous observations in plasma, milk and adipose tissue (3–7).

The explanation for the increased ratio of linoleic acid to its metabolites is uncertain. One possibility is

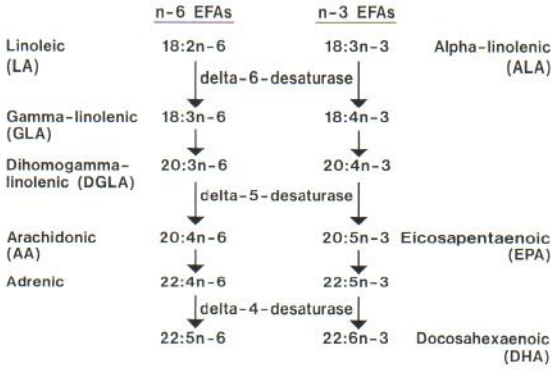

Fig. 1.

that in atopy there might be reduced 6-desaturation activity as previously suggested (3, 4, 12, 13). If this were so, then by-passing the 6-desaturation step and providing gamma-linolenic acid (GLA, Fig. 1) directly, should have a therapeutic effect. GLA in the form of evening primrose oil (Epogam) does indeed have clinical therapeutic actions in atopic eczema (14). It has also been shown to produce smoothing of the typical rough skin of AE patients as measured by the objective technique of profilometry (15, 16).

The abnormalities in the AE patients in red cell phospholipid fatty acids were much more servere than those seen in the plasma. There was a general reduction in the concentrations of almost all the polyunsaturates and a general increase in concentrations of saturates and mono-unsaturates. As a result the unsaturation index of the membrane phospholipids (Table II) was dramatically reduced in the AE patients as compared with both sets of controls. The unsaturation index of membrane phospholipids is very closely negatively correlated with the microviscosity of the membrane ($r = 0.98$, 17). Thus although microviscosity was not studied in this study, it is to be expected that the microviscosity of the red cell membrane will be substantially increased in patients with AE. This will make red cells less fluid and less able to flow easily through capillaries, including those of the skin.

The red cell abnormalities suggest that something more is at fault in AE than a simple deficit of 6-desaturation. The reductions in red cell EFA levels were much more profound than the reductions in the corresponding plasma phospholipids. In particular, whereas linoleic acid levels were elevated in the plasma, they were below normal in the red cell membranes, suggesting defective incorporation of EFAs into the membrane. As yet, very little is known about factors regulating membrane incorporation of fatty acids.

These results extend the previous observations and again indicate that fatty acid metabolism is abnormal in atopic eczema. More work is required to define the precise nature of that abnormality.

REFERENCES

1. Hansen AE. Serum lipids in eczema and other pathological conditions. Am J Dis Child 1937; 53: 933–946.
2. Brown WR, Hansen AE. Arachidonic acid and linoleic acid of serum in normal and eczematous human subjects. Proc Soc Exp Biol Med 1937; 30: 113–116.
3. Manku MS, Horrobin DF, Morse N, et al. Reduced levels of prostaglandin precursors in the blood of atopic patients: defective delta-6-desaturase function as a biochemical basis for atopy. Prostaglandins Leukot Med 1982; 9: 615–628.
4. Manku MS, Horrobin DF, Morse NL, et al. Essential fatty acids in the plasma phospholipids of patients with atopic eczema. Br J Dermatol 1984; 110: 643–648.
5. Strannegard I-L, Svennerholm L, Strannegard O. Essential fatty acids in serum lecithin of children with atopic dermatitis and in umbilical cord serum of infants with high or low IgE levels. Int Arch Allergy Appl Immunol 1987; 82: 422–423.
6. Wright S, Bolton C. Breast milk fatty acids in mothers of children with atopic aczema. Br J Nutr 1989; 62: 693–697.
7. Wright S, Sanders TAB. Adipose tissue fatty acid composition in patients with atopic eczema [in press].
8. Schalin-Kärrilä M, Mattilä L, Jansen CT, et al. Evening primrose oil in the treatment of atopic eczema: effect on clinical status, plasma phospholipid fatty acids and circulating blood prostaglandins. Br J Dermatol 1987; 117: 11–19.
9. Nikkari T, Salo M, Maatela J, Aromaa A. Serum fatty acids in Finnish men. Atherosclerosis 1983; 49: 139–148.
10. Bamford JTM, Gibson RW, Renier CM. Atopic eczema unresponsive to evening primrose oil (linoleic and gamma-linolenic acids). J Am Acad Dermatol 1985; 3: 959–965.
11. Harrison RJ, Klouda PT, Easty DL, Manku M, Stewart JCM. Association between keratoconus and atopy. Br J Ophthalmol 1989; 73: 816–822.
12. Manku MS, Horrobin DF, Huang Y-S, Morse N. Fatty acids in plasma and red cell membranes in normal humans. Lipids 1983; 18: 906–908.
13. Melnik BC, Plewig G. Is the origin of atopy linked to dificient conversion of w-6 fatty acids to prostaglandin E1? J Am Acad Dermatol 1989; 21: 557–563.
14. Morse PF, Horrobin DF, Manku MS, et al. Meta-analysis of placebo-controlled studies of the efficacy of Epogam in the treatment of atopic eczema. Relationship between plasma essential fatty acid changes and clinical response. Br J Dermatol 1989; 121: 75–90.
15. Marshall RJ, Evans RW. Measurement of the effects of essential fatty acids on human skin smoothness. In:

Omega-6 Essential Fatty Acids: Pathophysiology and Roles in Clinical Medicine. New York; Alan R Liss, 1990; 81–98.
16. Nissen HP, Wehrmann W, Kroll U, Kreyser HW. Influence of polyunsaturated fatty acids on the plasma phospholipids of atopic patients. Fat Sci Tech 1988; 7: 268–271.
17. Biagi PL, Bordoni A, Celadon M, Hrelia S, Horrobin DF. Gamma-linolenic acid dietary supplementation can reverse the aging influence on rat liver microsome delta-6-desaturase activity [subm. for publ.].