

Long Chain Fatty Acids and Atopic Dermatitis

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Atopic dermatitis (atopic eczema) is a common skin disorder which typically begins in the 3rd to 6th month of life and affects at least 3% of infants. The onset is often delayed until childhood but is rare in adult life. The disease tends to wax and wane. The course is unpredictable but in over 90% of the children the disease has cleared by 15 years of age. The few patients in whom the disease persists into later adult life often have pronounced epidermal changes.

In infancy the lesions tend to be erythematous, vesicular, and weeping on the face, trunk, and limbs. The child scratches whenever given the opportunity. In childhood the dermatitis becomes increasingly flexural on the limbs, leathery, dry, and excoriated. Coccal infections are common. In adults the distribution is the same as in childhood, with a marked tendency toward dryness and thickening of the flexural skin but a low-grade involvement of the trunk, face, and hands. The cardinal sign is itching and the scratching may account for most of the clinical pictures. Bacterial and viral infections such as herpes simplex often complicate the dermatitis.

Atopic dermatitis may later be associated with bronchial asthma, allergic rhinitis, conjunctivitis (hay fever), or urticaria. Other associated conditions include various types of dry scaly skin such as ichthyosis and keratosis pilaris. Keratoconus, cataract, and alopecia areata (patchy hair loss) are rarer associated features. The predisposition to these disorders is at least partly genetic and is called atopic diathesis or atopy, which is present in about 10–15% of the population.

The exact pathogenesis of atopic eczema is obscure. The presence of high levels of circulating IgE represents reagenic antibodies directed mainly against pollen, cat and dog dander, house dust mite, and certain foods. There is some evidence that infants with eczema have a low level of IgA secretion into the intestines together with a deficiency of suppressor T cells which could suggest abnormal entry of potentially antigenic ingested material causing abnormal IgE response. Dietary antigens, particularly cow's milk and eggs, may play a part in provoking dermatitis in some infants. It is advised that babies from atopic families should be breast-fed for at least 3–6 months as this may decrease the risk of eczema. Food allergens tend to be less important in older age groups and rarely provoke eczema in adults, in

whom external factors such as airborne antigens, heat, and woolen clothing cause itching and scratching. Besides the removal of causative factors and irritants, the main treatments for atopic dermatitis have focused on measures to avoid scratching. Topical corticosteroids are the mainstay of suppressive treatment followed by regular use of bland emollients. Oral antihistamines also have their place at certain times, as does UV irradiation. In recent years ingestion of long chain fatty acids has been advocated. In this review I shall discuss the rationale for such a treatment and the results obtained, as well as the difficulties in judging the results.

There are two families of essential fatty acids (see Hernell, Fig. 1., this volume). First we have the n-3 or Ω -3 family, which is so called because one double bond is three carbon atoms distant from the methyl end. α -Linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid are the fatty acids in fish oil belonging to this group. The other is the n-6 or Ω -6 family where the first double bond six carbon distant from the methyl end. The fatty acids in this series are linoleic, γ -linolenic, dihomo- γ -linolenic, and arachidonic acid. Arachidonic acid is the precursor for active inflammatory regulators such as most prostaglandins, leukotrienes, hydroxyeicosatetraenoic acid (HETE), and thromboxanes. Arachidonic acid is unstable and its content is low in most foods except cream.

Terrestrial plants contain both series. The same desaturase enzymes metabolize both families in man. Diets rich in fish oil decrease the ratio of arachidonic acid to eicosapentaenoic acid in mononuclear cells and inhibit production of interleukin-1 and tumor necrosis factor (1). The two types of fatty acids can interact by competitive inhibition and thus have vastly different metabolic effects (see ref. 2 for review).

Burr and Burr discovered in 1929 that rats placed on a completely fat-free diet soon developed a syndrome including scaliness of the skin and cessation of growth (3). They became normal when fats were added to the diet. The studies disclosed the essential nature of the highly unsaturated fatty acids, particularly linoleic and arachidonic acid (4). In 1933 Hansen found that patients with atopic dermatitis had low concentrations of essential fatty acids in the blood (5). By feeding the infants fat rich in unsaturated fatty acid, such as lard, raw linseed oil, or corn oil, Hansen and coworkers reported a number of clinical cures (6). In atopic patients fed large amounts of linoleic acid, blood linoleic levels were normal whereas those of arachidonic acid were reduced (7). Cornbleet showed good results from treatment with corn oil in 87 adult patients with atopic dermatitis (8). Thereafter others reported a favorable effect in about half of the subjects (9-11), while some found fair or negative results in a small number of patients (12,13). When a controlled trial showed that linolenic and linoleic acid (130 mg and 270 mg, respectively, daily) produced no effect in children with atopic dermatitis research into this mode of treatment was for a time interrupted (14).

Interest was renewed in 1981 when Lovell *et al.* reported that oral treatment of atopic dermatitis with evening primrose seed oil for 3 weeks produced a small but significant improvement (15). The following year Wright and Burton (16) published the results of a 12 week double blind, controlled, crossover study of various doses of evening primrose oil in patients with atopic dermatitis. Each capsule contained

360 mg of linoleic acid and 45 mg of γ -linolenic acid. The placebo capsules contained 500 mg of liquid paraffin. Sixty adults received either two, four, or six capsules twice daily, while 39 children (8 months to 14 years of age) received one or two capsules twice a day. In the two low dose groups in children and adults no objective improvements were noticed but patients did feel that pruritus was improved compared to placebo ($p < 0.05$). In the higher dose groups evening primrose oil was better than placebo with regard to itch, scaling, and general severity ($p < 0.01$). These responses were noted most prominently in the adult groups and less so among children. Adult patients in the high dose group noted an overall improvement in severity of about 43%. No side effects were found.

In a similar Finnish study, 25 young adult patients with atopic dermatitis randomly received either evening primrose oil or placebo for 12 weeks (17). The patients receiving evening primrose oil noted a statistically significant reduction in the severity and grade of inflammation as well as the percentage of body surface area involved. In addition they felt less dryness and itch. Patients in the placebo group also showed a significant reduction in inflammation and clinical improvement but it was less than in the group receiving evening primrose oil therapy. Evening primrose oil caused a significant rise in the amount of dihomo- γ -linolenic acid but plasma levels of thromboxane and prostaglandins were not changed. Evening primrose oil (6×0.5 g capsules) was compared to olive oil in 24 Italian children with atopic dermatitis (18). After 4 weeks the skin lesions had improved in eight of the primrose-oil-treated patients compared to one in the placebo group. Meigel *et al.* found an improvement after primrose oil in 14 of 17 patients as compared to 11 of 17 patients after olive oil or fish liver oil (19). Bamford *et al.* (20) were unable to show any favorable effect in a double blind study of 123 children and adult patients with atopic dermatitis. The doses were similar to those of Wright and Burton but the patients were less severe (11% had $>50\%$ skin involvement vs. 50% in the earlier study). In a smaller uncontrolled series of eight respectively 50 patients no convincing effects of evening primrose oil were reported (21,22). The controlled trials have recently been included in a meta-analysis by a Research Institute claiming significant benefits for evening primrose oil in atopic dermatitis (23). The findings of Bamford *et al.* were rejected in this study because the serum levels of dihomo- γ -linolenic acid also increased in their placebo-treated patients, indicating that placebo and active drugs could have been mixed. This has caused further discussion as to whether treatment with evening primrose oil is justified or not (24,25).

An intriguing rationale for treatment with evening primrose oil is the finding of raised levels of linoleic and α -linolenic acid in patients with atopic dermatitis but with reduced levels of their metabolites, suggesting that the patients have a functional defect of the desaturating enzymes, especially δ -6-desaturase (26). These findings were confirmed by Strannegård *et al.* (27) who also found that linoleic acid in umbilical cord serum was higher in babies with high serum IgE levels, who are known to be prone to the development of atopic disease. A therapeutic effect of evening primrose oil could thus be due to the fact that it bypasses the 6-desaturation step, since γ -linolenic acid provides a direct effect. Others have, however, failed to con-

firm this idea (17,28,29). Diet habits and the use of topical corticosteroids have been suggested as more plausible reasons for the reported changes in plasma phospholipid fatty acids (29).

The fatty acid composition of lesional and nonlesional skin from patients with atopic dermatitis has recently been studied (30). Arachidonic acid and n-6 fatty acids of phosphatidyl choline were decreased in lesional skin whereas free arachidonic acid was increased, suggesting an increased activity of phospholipase A₂. The long chain fatty acids (22:0 + 24:0 + 25:0 + 26:0) were decreased in lesions whereas the short chain fatty acids (14:0 + 15:0 + 16:0 + 17:0 + 18:0) were markedly increased, indicating a defective maturation of long chain fatty acids (30). Of particular interest are the fatty acids that are components of acylceramides, since these might be of great importance for the water barrier function of the epidermis.

Another interesting aspect is the finding that in human breast milk from mothers of children with atopic eczema the proportion of linoleic acid was increased and that of its metabolites such as dihomogamma-linolenic acid was decreased (31). Breast milk from mothers without atopy would be expected to be best at preventing the manifestations of atopic dermatitis by providing sufficient metabolites, whereas mothers with affected children would be less able to exert this protective effect. Increased maternal consumption of polyunsaturated fatty acids with a reduction in saturated fats, during lactation, may influence the fatty acid composition of the milk. Since human milk contains more gamma-linolenic and dihomogamma-linolenic acid than cow's milk, prolonged breast-feeding could, despite this, still be of value. Dihomogamma-linolenic acid serves as precursor for prostaglandin E₁, an immunomodulating and cell-differentiating role which has been suggested to play an important part in the etiology of atopy (32). Since fatty acids are necessary for fluidity of membrane lipids, defects of their incorporation into cell membranes could also be of importance.

The effect of blackcurrant seed oil rich in gamma-linolenic acid was compared with grapeseed oil as placebo in 24 patients with atopic dermatitis (33). A certain improvement was seen in both groups but no effect could be attributed to gamma-linolenic acid. We tried in the same way to study the effect of gamma-linolenic acid in 13 patients (13–51 years of age) with atopic dermatitis. They were randomly allocated to a double blind study taking identical-looking capsules each with either 400 mg of blackcurrant oil or 400 mg of grapeseed oil (Table 1). Two hundred parts per million of d-alpha-tocopherol were added to both types of capsule. The study started in December–January and lasted for 3 months. Four capsules were taken twice daily with food. The total amount of gamma linolenic acid intake was thus similar to the evening primrose studies. Blackcurrant oil also contains only a small proportion of alpha linolenic acid (the study preparation provided 0.55 g/day). The patients all had severe atopic dermatitis with over 50% of the surface involved, and markedly raised IgE levels (300–8,000 kU/l). The severity of itching, skin condition and use of corticosteroids was evaluated before and three times during the study.

Two of the seven patients taking blackcurrant oil showed some improvement and used less corticosteroids, as did one of the six patients taking grapeseed oil. The skin condition of one patient taking blackcurrant oil slowly deteriorated and the

TABLE 1. Percent fatty acids in oils from terrestrial plants

Acid	Blackcurrant	Evening primrose	Grapeseed
Palmitic 16:0	7	7.0	8
Stearic 18:0	1.5	1.0	4
Oleic 18:1 cis 9	10	0.6	16
Elaidic 18:1 trans 9	0.5	—	—
Linoleic 18:2 cis 9, 12	48	72.7	71
γ -linolenic 18:3 cis 6,9,12	17	8.7	—
α -linolenic 18:3 cis 9,12,15	13	—	<1
Stearidonic 18:4	3	—	—

treatment was interrupted after 70 days. No certain effect could be detected in the other patients. External factors such as exposure to horses and cats, infections, and stress situations caused worsening during the treatment period, making the evaluation very difficult. In many the amount and type of corticosteroid used was uncertain. Laboratory routine data, including blood cell transaminases, were not affected. Cholesterol level remained unchanged within normal levels in all, while one patient on blackcurrant oil and two patients on grapeseed oil showed an increase in their total triglycerides after 2–3 months. Since no diet regimen was included in which saturated fatty acids consumed were controlled, the results were as a whole not possible to evaluate further.

Other researchers have studied the effect of dietary supplementation with n-3 fatty acids (eicosapentaenoic) for 12 weeks in atopic dermatitis (34). They gave 10 g of fish oil *versus* placebo (olive oil) in a double blind study of 31 patients. Severity score showed no significant between the active and the placebo groups before and after the trial. Patients' assessment scores with fish oil were superior to placebo with regard to itch ($p < 0.05$), scale ($p < 0.05$), and total symptoms score ($p < 0.02$). No significant difference was found between the groups with regard to topical steroid use during the trial.

CONCLUSION

A moderately beneficial effect of γ -linolenic acid and eicosapentaenoic acid in patients with atopic dermatitis has been documented in some studies, and this cannot be disregarded. That others have failed to show an effect of γ -linolenic acid can be due to the fact that eczema patients' skin is sensitive to so many other factors in our environment which could easily have obscured a slight improvement caused by the fatty acids. We do not know if there is a special subgroup of atopic dermatitis where such a treatment is of particular importance. Larger doses of purer products and control of fatty acid intake in the daily diet in very well-controlled studies with an inert placebo are needed. Interrelated effects of long chain fatty acids suggest that a "balanced" intake of the n-6 and n-3 series could be important. The effects

obtained currently with long chain fatty acids seem for a clinician to be in most cases quite small when compared to the improvement seen following a 2 week hospital admission or a vacation in different surroundings.

To have any chance of inhibiting the decrease in suppressor cells and the increase in IgE in atopic children it would be necessary to treat infants before the age of 3 months when such changes are seen. This means that we should consider treating the mothers during pregnancy and/or lactation. Controlled studies have to be done in the future before any recommendations can be made.

REFERENCES

1. Endres S, Ghorbani R, Kelley VE, *et al.* The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *N Engl J Med* 1989; 320: 265-71.
2. Garg ML, Thomson ABR, Clandinin MT. Interactions of saturated, n-6 and n-3 polyunsaturated fatty acids to modulate arachidonic acid metabolism. *J Lipid Res* 1990; 31: 271-7.
3. Burr GO, Burr MM. A new deficiency disease produced by rigid exclusion of fat from diet. *J Biol Chem* 1929; 82: 345-67.
4. Burr GO, Burr MM, Miller ES. On the fatty acids essential in nutrition. *J Biol Chem* 1932; 97: 1-6.
5. Hansen AE. Serum lipid changes and therapeutic effects of various oils in infantile eczema. *Proc Soc Exp Biol Med* 1933; 31: 160-1.
6. Hansen AE, Knott EM, Wiese HF, Shaperman E, McQuarrie I. Eczema and essential fatty acids. *Am J Dis Child* 1947; 73: 1-18.
7. Brown WR, Hansen AE. Arachidonic and linoleic acid of serum in normal and eczematous human subjects. *Proc Soc Exp Biol Med* 1937; 30: 113-6.
8. Cornbleet T. Use of maize oil (unsaturated fatty acids) in the treatment of eczema: preliminary report. *Arch Dermatol Syph* 1935; 31: 224-34.
9. Finnerud CW, Kester RL, Wiese HF. Ingestion of lard in the treatment of eczema and allied dermatoses. *Arch Dermatol Syph* 1941; 44: 849-53.
10. Ginsberg JE, Bernstein C. Effects of oils containing unsaturated fatty acids on patients with dermatitis. *Arch Dermatol Syph* 1937; 36: 1033-35.
11. Azerad E, Grupper C. Le traitement de l'eczéma par les acides gras non saturés. *Semin Hospital Paris* 1949; 25: 684-9.
12. Epstein NN, Glick D. Unsaturated fatty acids in eczema: observations on acne vulgaris, psoriasis and xantoma palpebrarum. *Arch Dermatol Syph* 1937; 35: 427-32.
13. Taub SJ, Zakon SJ. The use of unsaturated fatty acids in the treatment of eczema (atopic dermatitis, neurodermatitis). *JAMA* 1935; 105: 1675.
14. Petit JHS. Use of unsaturated fatty acids in the treatment of eczema of childhood. *BMJ* 1954; i: 79-81.
15. Lovell CR, Burton JL, Horrobin DF. Treatment of atopic eczema with evening primrose oil. *Lancet* 1981; i: 278.
16. Wright S, Burton JL. Oral evening-primrose-seed oil improves atopic eczema. *Lancet* 1982; ii: 1120-2.
17. Schalin-Karrila M, Mattila L, Jansen CT, Uotila P. 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.
18. Bordoni A, Biagi PL, Masi M, *et al.* Evening primrose oil (Efamol) in the treatment of children with atopic eczema. *Drugs Exp Clin Res* 1987; 14: 291-7.
19. Meigel W, Dettke T, Meigel E-M, Lenze U. Additive orale Therapie der atopischen Dermatitis mit ungesättigten Fettsäuren. *Z Hautkr* 1987; 62[Suppl 1]: 100-3.
20. Bamford JTM, Gibson RW, Reiner CM. Atopic eczema unresponsive to evening primrose oil (linoleic and α -linolenic acids). *J Am Acad Dermatol* 1985; 13: 959-65.

21. Skogh M. Atopic eczema unresponsive to evening primrose oil (linoleic and γ -linolenic acids). *J Am Acad Dermatol* 1986; 15: 114-5.
22. Rasmussen J. Management of atopic dermatitis. *Allergy* 1989; 44[Suppl 9]: 108-13.
23. 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.
24. Sharpe GR, Farr PM. Evening primrose oil and eczema. *Lancet* 1990; 335: 667-8.
25. Horrobin DF, Stewart C. Evening primrose oil in atopic eczema. *Lancet* 1990; 335: 664-5.
26. Manku MS, Horrobin DF, Morse NL, Wright S, Burton JL. Essential fatty acids in the plasma phospholipids of patients with atopic eczema. *Br J Dermatol* 1984; 110: 643-8.
27. Strannegård IL, Svennerholm L, Strannegård Ö. 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: 422-3.
28. Nissen HP, Wehrmann W, Kroll U, Kreyser HW. Veränderungen im Plasma-Lipid-Muster bei Patienten mit Neurodermitis-Beeinflussung durch Applikation umgesättigter Fettsäuren. *Fette Wissenschaftl Tech* (Fat Sci Technol) 1988; 90: 268-71.
29. Schäfer L, Kragballe K, Jepsen LV, Iversen L. Reduced neutrophil LTB₄ release in atopic dermatitis patients despite normal fatty acid composition. *J Invest Dermatol* 1991; 96: 16-19.
30. Schäfer L, Kragballe K. Abnormalities in epidermal lipid metabolism in patients with atopic dermatitis. *J Invest Dermatol* 1991; 96: 10-15.
31. Wright S, Bolton C. Breast milk fatty acids in mothers of children with atopic eczema. *Br J Nutr* 1989; 62: 693-7.
32. Melnik BC, Plewig G. Is the origin of atopy linked to deficient conversion of α -6-fatty acids to prostaglandin E₁? *J Am Acad Dermatol* 1989; 21: 557-63.
33. Rilliet A, Queille C, Saurat J-H. Effects of gamma-linolenic acid in atopic dermatitis. *Dermatologica* 1988; 177: 257.
34. Bjorneboe A, Soyland E, Bjorneboe G-EA, Rajka G, Drevon CA. Effect of dietary supplementation with eicosapentaenoic acid in the treatment of atopic dermatitis. *Br J Dermatol* 1987; 117: 463-9.

DISCUSSION

Dr. Cunnane: I wonder if there is a problem of linoleic acid utilization or oxidation in atopy. Kristian Bjerve (1), who has looked at patients on long-term total parenteral nutrition in whom safflower oil was the source of essential fatty acids, has seen a dramatic improvement in the dermal lesions after giving very small amounts of α -linolenic acid. I suggest that if this is a genuine effect it may partly be due to the fact that α -linolenic acid is readily oxidized and that linoleic acid may be channeled toward an oxidation route in people with insufficient α -linolenic acid, thereby causing a deficiency systemically which can be avoided or corrected by α -linolenic acid supplements. Thus in patients who respond to evening primrose oil the effect may simply be through providing additional linoleic acid.

Dr. Koletzko: In Germany it has been proposed recently that γ -linolenic acid should be used by pregnant and lactating women to prevent atopy in their babies. This seems irresponsible to me in the present state of knowledge. I appreciate that long chain fatty acids may well have a therapeutic effect on the disease, which is obviously related to immunologic mechanisms. However, I have my doubts as to whether the basic cause of the problem is really a defect of δ -6-desaturase, as you have stated, and I should appreciate a further comment on this.

Dr. Juhlin: I understand your doubts on the existence of a deficit in the δ -desaturases in atopic dermatitis since no direct measurements of the enzyme have been made. The evidence is only indirect and is based on the finding of low arachidonic acid levels despite raised levels of linoleic acid. Another explanation for the deficiency of arachidonic acid could be that its turnover in plasma is faster than in healthy subjects.

Dr. Small: Is breast milk abnormal in women who are atopic?

Dr. Juhlin: A deficiency in milk γ -linolenic acid has been shown.

Dr. Guesry: A study published in 1986 (2) showed that milk of atopic mothers had very low levels of specific antibetalactoglobulin IgA compared with control mothers, so I don't think it is likely that such milk is protective against allergy in the baby. In another study (3) two groups of lactating mothers with atopic children were compared. In one group the mothers had a diet low in allergens, in the other group the mothers were on a normal diet. There was a striking reduction in the severity of atopic eczema in the low allergen group, showing that transmission of allergens was more important than IgA or long chain polyunsaturated fatty acids.

Dr. Galli: Is there any evidence of altered eicosanoid production in atopic eczema?

Dr. Juhlin: The arachidonic acid derived inflammatory mediators are raised in affected skin of patients with atopic dermatitis, which might also indicate increased consumption of arachidonic acid. The whole cascade of prostaglandins increases in the skin in almost any inflammatory lesion.

Dr. Merrill: Skin is rich in acylglucoceramides and acylceramides which have a highly unsaturated fatty acid composition. These fatty acids are now available as creams for cosmetic purposes. It might be worth trying these formulations as a route for administering unsaturated fatty acids, since they more closely mimic the form in which such fatty acids are found in the skin.

Dr. Juhlin: The O-acylceramides are located intercellularly in the skin surface and it would be of great interest to influence them. Studies of γ -linolenic acid-rich oils have been disappointing in atopic dermatitis, but other formulations such as you suggest might certainly be worth exploring.

REFERENCES

1. Bjerve KS, Mostad IL, Thoresen L. Alpha-linolenic acid deficiency in patients on long-term gastric-tube feeding: estimation of linolenic acid and long-chain unsaturated n-3 fatty acid requirement in man. *Am J Clin Nutr* 1987; 45: 66-77.
2. Machtinger S, Moss R. Cow's milk allergy in breast fed infants. The role of antigen and maternal secretory IgA antibody. *J Allergy Clin Immunol* 1986; 77: 341-7.
3. Chandra RK, Puri S, Surarya C, *et al.* Influence of maternal food antigen avoidance during pregnancy and lactation on prevalence of atopic eczema in infants. *Clin Allergy* 1986; 16: 565-9.