Essential fatty acid metabolism and its modification in atopic eczema

David F Horrobin

ABSTRACT Research from the 1930s to the 1950s established that a deficit of n-6 essential fatty acids (EFAs) leads to an inflammatory skin condition in both animals and humans. In a common inherited skin condition, atopic dermatitis (eczema), there was evidence of low blood EFA concentrations and of a therapeutic response to exceptionally high doses of linoleic acid. More recently, it has been established that there is no deficit of linoleic acid in atopic eczema. Concentrations of linoleic acid instead tend to be elevated in blood, milk, and adipose tissue of patients with atopic eczema, whereas concentrations of linoleic acid metabolites are substantially reduced. This suggests reduced conversion of linoleic acid to γ-linolenic acid (GLA). In most but not all studies, administration of GLA has been found to improve the clinically assessed skin condition, the objectively assessed skin roughness, and the elevated blood catecholamine concentrations of patients with atopic eczema. Atopic eczema may be a minor inherited abnormality of EFA metabolism. Am J Clin Nutr 2000;71(suppl):367S–72S.

KEY WORDS Atopic dermatitis, eczema, essential fatty acids, EFAs, linoleic acid, γ-linolenic acid, GLA, dihomo-γ-linolenic acid, DGLA, arachidonic acid, AA, evening primrose oil

INTRODUCTION

In 1929 and 1930 Burr and Burr (1, 2) described a new deficiency disease in rats caused by the exclusion of unsaturated fats from the diet. One outstanding feature of this disease was the development of a scaly dermatitis (1, 2). Since these original observations, it has become well established that a dietary deficiency of the n-6 essential fatty acid (EFA) linolenic acid, but not of the n-3 EFA, α-linolenic acid, leads to marked skin abnormalities (3–6). The typical lesions include dryness, scaliness, redness, weeping, and other manifestations of inflammation. There is an increase in the rate of proliferation of epidermal cells (7), a dramatic loss of the normal impermeability to water (8–10), increased metabolic activity, abnormal keratinocytes, and a great increase in the formation of sterol esters (11). The EFAs are incorporated into ceramides (12) and can be metabolized in the skin to a variety of lipoxigenase and cyclooxygenase metabolites (13–17). Skin cannot, however, convert linoleic acid through to arachidonic acid (AA) (15, 18, 19). The 2 desaturation steps that convert linoleic to γ-linolenic acid (GLA) and dihomo-γ-linolenic acid (DGLA) to AA are both missing. Conversion of GLA to DGLA, however, is rapid. The skin abnormalities that were noted primarily in rats and guinea pigs were also recorded in humans (3, 20–22). Babies fed artificial milk formula deficient in EFAs developed skin lesions similar to those seen in rats (20). Moreover, adults with severe fat malabsorption or who are being fed fat-free parenteral nutrition develop typical skin lesions that are rapidly reversed with linoleic acid supplements (3).

Hansen was a pediatrician working at the University of Minnesota and a friend of the Burrs around the time that they made their EFA discovery. Hansen noted that the skin lesions in the Burrs’ EFA-deficient rats were somewhat similar to the skin lesions in his patients with atopic dermatitis, or eczema (20–22). He speculated that atopic eczema might relate to some EFA abnormality and thus initiated the ongoing research program to investigate the relation between EFA metabolism and atopic eczema and other skin disorders.

EFA BIOCHEMISTRY IN ATOPIC ECZEMA

The few methods available for blood EFA analysis in the 1930s were effectively limited to measurement of the iodine number. In his first paper, Hansen (22) reported that although there was an overlap between the 2 groups, the iodine number of the serum of children with atopic eczema was ~25% lower than that of serum from normal children; this indicated that there were fewer double bonds with which iodine could combine. In a later paper he made an attempt to fractionate the various unsaturated fatty acids and came to the conclusion that there were deficits of both linoleic acid and AA (23). The former but not the latter abnormality could be corrected by giving large amounts of linoleic acid. Another group in 1935 agreed that atopic eczema patients had a tended to have low serum iodine numbers, but they found much more overlap in values with normal individuals and an average deficit of only 9% (24). In 1947, Hansen et al (25) brought together observations of the iodine numbers of serum in 380 patients with eczema and 122 normal control subjects. He noted that there was a consistent deficit in the eczema groups but that the difference was greatest in the...
youngest children and lessened progressively with age. Of patients with atopic eczema, 82% of those <2 y of age, 74% of those between 3 and 15 of age, and 55% of adults had iodine numbers below normal (25).

Hansen et al (25) theorized a possible explanation for the deficit. They could show no dietary differences between patients and control subjects and did experiments that showed that fat absorption in eczema patients was normal. They did report that the milk of mothers breast-feeding infants with eczema appeared to have lower iodine numbers than did that of mothers with healthy babies. They also thought that the eczema, or the infections associated with it, might lower the iodine value, but in the end had no real explanation (25).

Research on EFAs in atopic eczema appeared to stop for >30 y, during which time developments in gas chromatography transformed our ability to measure accurately small amounts of all the individual fatty acids present in blood. The next papers appeared in the early 1980s. Manku et al (26, 27) could not confirm that there was a deficit of linoleic acid in plasma phospholipids in adults with atopic eczema compared with normal control subjects. In fact, if anything, linoleic acid concentrations were slightly elevated. However, there was a marked deficit of the metabolites of linoleic acid: GLA, DGLA, AA, adrenic acid, and docosapentaenoic acid. Similarly, α-linolenic acid concentrations were elevated in the patients whereas the concentrations of its metabolites were reduced. Therefore, it was suggested that in atopic eczema there might be a reduced rate of activity of the enzyme Δ6-desaturase that converts linoleic acid to GLA and α-linolenic acid to stearidonic acid (26, 27). Such reduced activity might be due to a mutation in the enzyme, altered expression of the enzyme, a change in cofactors required for the enzyme, a change in hormonal regulation, or the presence of enzyme inhibitors.

A study from Sweden provided support for this concept (28). In children with atopic eczema, linoleic acid concentrations were substantially elevated, whereas concentrations of DGLA, AA, and docosahexaenoic acid were reduced highly significantly. Moreover, when these investigators looked at umbilical cord blood, they found a positive relation between the concentration of linoleic acid and the concentration of immunoglobulin E (IgE), a marker of risk for atopy. This suggested that the greater the impairment of linoleic acid metabolism, the greater was the risk of developing atopic eczema.

Further supporting studies were published. Like Hansen, Wright and Bolton (29) found that mothers breast-feeding children with eczema had higher concentrations of linoleic acid and lower concentrations of its metabolites than that of mothers with healthy children. The milk from the mothers with eczematous children had (29). Similarly, in adipose tissue, adults with atopic eczema had higher concentrations of linoleic acid and lower concentrations of linoleic acid metabolites than did control subjects (30). There have been other conflicting findings. Red blood cell EFAs have been reported to be both substantially depleted (31) and also normal or slightly elevated compared with control subjects, although in the latter case both GLA and eicosapentaenoic acid were well below normal in the eczema patients (32). Yu et al (33) found that mothers with allergies had higher concentrations of EFA metabolites in cord blood, although this was not specifically related to eczema. In a very small number of Japanese children with atopic eczema, only small deficits of both n-6 and n-3 EFAs were found in plasma phosphatidylcholine (34). However, in a much larger group of Japanese children there were significant deficits of linoleic acid, DGLA, and AA in eczematous patients compared with control children (35).

Thus, the balance of evidence is in favor of the view that in atopic eczema there is a modestly reduced rate of conversion of linoleic acid to its metabolites and possibly a reduced rate of incorporation of EFAs into phospholipids. Such an abnormality could lead to a reduced formation of prostaglandin E1 (PGE1), which in turn would lead to lower concentrations of cyclic AMP and possibly, as a consequence, to a selective hyperactivity of parts of the immune system (4, 36–39).

None of the above studies can definitely answer the question initially raised by Hansen as to whether the fatty acid changes might simply be a consequence rather than a cause of the dermatitis. However, that question can now be answered thanks to a very careful prospective study from Italy. Galli et al (40) took blood samples from the umbilical cord and at 1 and 3 mo from babies born to 57 mothers for whom one or both parents had a family history of eczema. The infants were carefully followed up for 1 y and during this time 10 babies developed atopic eczema. The concentrations of EFAs in plasma phospholipids in the umbilical cord and at 1 and 3 mo were then compared in the children who had or did not have atopic eczema at 1 y. During the first 3 mo, the children were free of skin lesions and so any differences in fatty acids could not have been caused by the eczema.

The results were striking (40). Linoleic acid concentrations were modestly but not significantly elevated in the babies who went on to develop eczema. In contrast, the concentrations of both DGLA and AA were consistently and significantly lower in those children who went on to develop eczema. Thus, the fatty acid abnormalities are present at birth and substantially predate the development of the skin lesions. This shows conclusively that the eczema does not cause the fatty acid abnormalities and suggests but does not prove that the fatty acid problems may cause the eczema. Interestingly, like Hansen (25, 41), the group in Rome found that as the children grew older, the striking fatty acid abnormalities present in the first 3 mo of life became attenuated and then disappeared.

If the EFA abnormality is causal, then measures to correct it should lead to clinical improvement in the skin condition. An important caveat, however, is that the skin lesions may be partly directly attributable to deficits of certain EFAs required for normal skin function and partly attributable to immunologic abnormalities initiated but not sustained by EFA deficiencies. In this model, an EFA abnormality in infancy would lead to skin lesions by 2 routes. The first would be the lack of EFAs acting at the level of the skin. The second would be the lack of EFAs leading to abnormal maturation and sensitization of the immune system. A hyperactive immune system would then be partly responsible for the skin lesions. Because of the memory of the immune system, such immunologic abnormalities and their effects on the skin might not be reversible by correction of the EFA deficits.

Provision of appropriate EFAs would be expected always to correct the element of skin damage directly attributable to EFA deficits. However, once sensitized, the immunologic abnormalities might not be reversible by provision of EFAs. In this model, EFA treatment would be expected to be effective if applied within the first year before significant immunologic sensitization. It could then prevent or treat both aspects of the skin
problem. At a later age, however, it may be that only the direct EFA effects on the skin are correctable by EFA treatment.

**EFFECTS OF TREATMENT WITH LINOLEIC ACID**

The only EFA sources available in practice to Hansen and his followers in the 1930s and 1940s were lard, cod liver oil, and vegetable oils like corn oil and linseed oil. All of these preparations were chosen because of their high iodine numbers. The distinction between the n−6 and n−3 EFAs was not clearly understood at the time even by Hansen. It is therefore interesting to note that the investigators who, apparently by chance, chose to use cod liver oil or linseed oil, both predominantly rich in n−3 EFAs, reported uniformly poor results (42–44). This is consistent with what we now know about the relative lack of importance of n−3 EFAs in the skin.

In contrast, those investigators who happened to choose lard or corn oil, preparations rich in primarily n−6 EFAs, reported consistently good results, with clinical improvement being related to a rise in the iodine number of the blood (25, 45–47). Interestingly, the administration of large amounts of linoleic acid failed to raise AA concentrations in the blood (23). At the time, it was not known that AA could be formed from linoleic acid in normal humans, but with hindsight this observation is consistent with modern concepts of defective conversion of linoleic acid to its metabolites in atopic eczema.

A striking feature of all of these studies in the 1930s and 1960s is the vast amount of linoleic acid that was required. Doses of corn oil ranged from 20 to 120 g, providing ∼10–60 g linoleic acid/d. Smaller amounts of the oils had no therapeutic effects.

Again, with hindsight, we can now see that this was good evidence that atopic eczema is not a simple deficiency of EFAs. Depending on age and weight, the skin lesions of dietary EFA deficiency in humans can readily be corrected by daily linoleic acid doses in the 0.5–3.0-g range. Something strange is happening when much higher doses are required to correct the skin lesions. This is therefore consistent with the view that the rate of conversion of linoleic acid to its metabolites is reduced and thus that very high linoleic acid doses are required to correct the concentrations of the downstream metabolites.

Despite the high doses of oils required, the use of fats was perhaps the predominant treatment of atopic eczema during the 1940s. The era came to an end as a result of 2 factors: the introduction of topical steroids with their often dramatic, if short-term, effects in suppressing skin inflammation, and the publication in 1954 of a seriously flawed clinical trial by Pettit (48) that appears to have been triggered by publicity about the value of EFAs in treating eczema. The trial seems to have been a deliberate attempt to prove that the use of EFAs was ineffective and was not constructed as a reasonable trial of Hansen’s concepts. Twenty-seven children were entered into the study. Twelve were given the then routine topical treatment with boric acid and tar. Fifteen were given an ointment containing 1.7% linoleic acid and a daily capsule containing 0.27 g linoleic acid. The method of randomization was not stated, but the children were assessed by a clinician who did not know which children were receiving which treatment. The children receiving the EFA regimen instead of standard therapy did considerably worse than those receiving standard treatment. This study was then followed by one in which all the children received topical treatment but 20 of 36 received 1 EFA capsule/d in addition. There were no differences between the groups and hence no additional therapeutic effect of the EFA supplement.

It is difficult to think of a trial more carefully designed not to replicate the EFA treatments that had been successful. Most of the previous reports had indicated a requirement of ≥10 g linoleic acid/d. Given the knowledge at the time, the homeopathic dose of 0.27 g could not have been expected to have any effect. Yet, because the study was purportedly controlled, it destroyed for a generation any serious interest in using EFAs in treatment.

**EFFECTS OF TREATMENT WITH GLA: BIOCHEMICAL AND OBJECTIVE EFFECTS**

If, in atopic eczema, there is a reduced rate of conversion of linoleic acid to GLA, then it makes sense to use GLA rather than linoleic acid in treatment. Starting in the early 1980s, there have now been substantial numbers of studies in which GLA was administered in the form of evening primrose oil (EPO), which contains ∼72% linoleic acid and 9% GLA. Administration of 2, 4, and 6 g EPO/d in the form of a specially selected variety (Efamol; Efamol Ltd, Guildford, United Kingdom) produced a significant dose-related rise in plasma phospholipid DGLA in adult patients with atopic eczema and a less consistent rise in AA (26). In Japanese children with atopic eczema, administration of GLA corrected the previously abnormal plasma phospholipid EFA profile (35). EPO, given as 2, 4, and 6 g/d produced dose-related increases in DGLA and AA in both blood neutrophils and in epidermal phosphatidylycerine and phosphatidylethanolamine (49). The rise in DGLA could contribute to an antiinflammatory and proliferation-controlling effect in the skin by 2 routes. First, DGLA can be converted to PGE1, which can stimulate cyclic AMP and inhibit phospholipase. Second, DGLA can be metabolized to 15-hydroxy-DGLA, which is an inhibitor of lipoxigenases and hence of leukotriene formation (11, 50–53). There is some evidence that soluble interleukin 2 receptor concentrations may be elevated in atopic eczema. It is therefore of interest that EPO was able to suppress interleukin 2 receptor concentrations in eczema patients (F Humphreys, JA Symonds, GW Duff, JAA Hunter, unpublished observations, 1997).

There are several abnormalities in atopic eczema that can be objectively and quantitatively assessed. These include the elevated blood catecholamine concentrations and the roughness of apparently normal areas of skin.

Elevated epinephrine and norepinephrine concentrations in eczema patients were significantly reduced by 4 wk of treatment with EPO but not by control treatment (54). Two groups have assessed skin roughness in atopic eczema, one by assessing the roughness of a skin cast using an electronic stylus (profilometry) (55), and the other by using light-reflectance as a measure of roughness (56). Both techniques have shown a significant objective reduction in roughness after oral treatment with EPO. Thus, administration of GLA has demonstrable effects on plasma, neutrophil, and skin fatty acid profiles in patients with atopic eczema and is also able to normalize skin roughness and plasma catecholamines.

**EFFECTS OF TREATMENT WITH GLA: CLINICAL EFFECTS**

The first clinical study of GLA was a pilot investigation of treatment for 3 wk that showed a modest beneficial effect (57).
A much larger randomized controlled study of 3 dosages (2, 4, and 6 g EPO/d as Efamol; Efamol Ltd) in adults and of 2 dosages (1 and 2 g/d) in children was then performed (58). This showed highly significant, dose-related, beneficial effects of treatment. This triggered a substantial series of investigations (6).

Schalini-Karrila et al (59) found a significant benefit of EPO in a randomized study. An important feature of the study was that patients could use as much steroid as they wished during the study and the amounts were carefully measured. The placebo-treated patients used more than 3 times as much steroid as the EPO-treated ones, a significant and important difference in view of concerns about steroid side effects, especially in young children. Bordoni et al (60) and Biagi et al (61, 62) obtained exceptionally good results in a placebo-controlled trial in 2–4-y-old children and went on to show that these results could be sustained over a long period of time. Other positive results in placebo-controlled studies were obtained with topical EPO (63), with oral EPO in hyperactivity associated with atopic eczema (64), in adults with atopic dermatitis (65), and in women with premenstrual exacerbations of eczema (66).

Two substantial studies with negative results have been reported. Bamford et al (67) observed no effect of EPO in 123 patients. However, analysis of the blood samples taken at the beginning and end of the study showed that in both the GLA and placebo groups there were elevations of DGLA in plasma phospholipids (69). This may indicate that some patients received the wrong treatment, thus invalidating the comparisons between the groups. The second study (68), like that of Pettit (48), had some strange features. Two scoring systems were used in the trial, one devised by the authors and the other a recognized and validated system. For some reason, the published paper contained only the results of the authors’ system; it did not include the results obtained with the previously validated scoring system, which actually showed a significant beneficial effect of EPO (69–71).

Moreover, when treatment was stopped, the improvements noted in the placebo group were rapidly reversed, whereas those in the EPO group persisted, leading to a substantial increase in the difference between the treated and placebo groups in the washout period. Again, the authors of the published paper failed to point this out (69–71).

All the randomized, placebo-controlled trials conducted up to that time were included in a meta-analysis (72). This meta-analysis showed a highly significant difference between treatment and placebo groups, particularly with regard to the symptom of itching. The significant effects remained even when the first large study with negative results was included in the analysis. The second study that reported negative results (described above) had not been completed at the time of the meta-analysis; however, when it was included in the database, the significance of the difference between treatment and placebo groups actually increased (73).

Virtually all patients with atopic eczema are being treated with topical steroids of varying potency. Ethical committees have generally refused to allow such treatments to be stopped to perform placebo-controlled studies of GLA. As a result, because most study subjects have also been using steroids, the trials of GLA have been trials of whether it or placebo can produce improvements in eczema over and above those that can be produced by topical steroids alone. This is a severe test, especially because there are good theoretical reasons why steroids may interfere with the effects of GLA. There is reasonable evidence that some of the antidermatitis actions of DGLA require its conversion to PGE1 and to 15-hydroxy-DGLA. By blocking the mobilization of precursor fatty acids, steroids may interfere with this mechanism. To my knowledge, 22 randomized, controlled trials of GLA in atopic eczema have now been conducted. A few have been in patients receiving only emollients or mild steroids, most have been in patients who were receiving steroids of mild to moderate potency, and others, including the second study with negative results, have been in patients receiving potent steroids. Any effect of GLA would therefore have to be over and above that achieved by such steroids. Interestingly, when the studies are ranked according to the potency of the steroids being received by the patients, the apparent efficiency of GLA is greater in patients receiving emollients only than in those receiving mild steroids, which is greater than that in those receiving moderately potent or potent steroids.

The data are being submitted for publication but are summarized in Table 1. It is clear that powerful steroids interfere with the ability to show an effect of GLA.

Although randomized, controlled trials are the only way to prove whether a treatment works, assessment of the value of a treatment in routine clinical practice is likely to require extensive open studies. Several of these have been performed with GLA (73, 74). They showed that GLA is effective in routine use and that, in addition to improving eczema, it can substantially reduce the use of drugs with potential side effects, such as antibiotics, oral steroids, and potent topical steroids (73–78). In one particularly interesting study, 2–4 times the usual adult dose of EPO was given to children with very severe atopic eczema who had been hospitalized repeatedly for their illness (78). These very high doses, reminiscent of the high doses of oils used in the 1930s, had dramatic effects, often producing complete skin clearing in these very difficult cases (78). It may be that the doses of GLA used to date have been suboptimal; studies to investigate the effect of higher doses are now under way.

To date, there have been far fewer studies on n–3 EFAs in atopic eczema. Modest beneficial effects have been reported

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
</table>
| Effects of treatment with γ-linolenic acid (GLA) in 22 randomized, placebo-controlled trials divided according to whether patients were receiving as background treatment emollients and hydrocortisone only or steroids more potent than hydrocortisone

<table>
<thead>
<tr>
<th>Study outcome</th>
<th>Patient groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Potent steroids</td>
</tr>
<tr>
<td>No effect</td>
<td>33 [3]</td>
</tr>
</tbody>
</table>

1 Number of studies represented in brackets.
In the largest study (145 patients), the effects of 6 g/d of either corn oil or concentrated fish oil were compared. Both groups improved substantially and significantly although there were no differences between them (82).

**DISCUSSION**

Although there are undoubtedly dissenting voices, the majority of investigators who have studied the biochemistry of atopic eczema have come to the conclusion that EFA metabolism is abnormal. The evidence is consistent with a reduced rate of conversion of the dietary EFAs to their metabolites and possibly with reduced incorporation of EFAs into membrane phospholipids.

The results of clinical studies have also been mixed, but the balance of evidence indicates that very high doses of linoleic acid or modest doses of GLA acid produce clinical improvement, particularly in itching. Results from Wutrich (78), who used very high doses of EPO, suggest that further exploration of the dose-response relation may be rewarding.

Atopic eczema may be a genetically determined variant of EFA metabolism, a consequence of which is increased reactivity of the immune system. In the past, this may have been beneficial particularly in itching. Results from Wutrich (78), who used very high doses of EPO, suggest that further exploration of the dose-response relation may be rewarding.

Although there are undoubtedly dissenting voices, the majority of investigators who have studied the biochemistry of atopic eczema have come to the conclusion that EFA metabolism is abnormal. The evidence is consistent with a reduced rate of conversion of the dietary EFAs to their metabolites and possibly with reduced incorporation of EFAs into membrane phospholipids.

The results of clinical studies have also been mixed, but the balance of evidence indicates that very high doses of linoleic acid or modest doses of GLA acid produce clinical improvement, particularly in itching. Results from Wutrich (78), who used very high doses of EPO, suggest that further exploration of the dose-response relation may be rewarding.

Atopic eczema may be a genetically determined variant of EFA metabolism, a consequence of which is increased reactivity of the immune system. In the past, this may have been beneficial particularly in itching. Results from Wutrich (78), who used very high doses of EPO, suggest that further exploration of the dose-response relation may be rewarding.

**REFERENCES**