

EDITORIAL

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Abnormal fatty acid profiles occur in atopic dermatitis but what do they mean?

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There are two principal families of polyunsaturated fatty acids (PUFAs), the n-6 (or ω -6) and the n-3 (or ω -3) families [1]. These are distinguished by the position of the terminal double bond within the fatty acyl chain. The simplest members of each family, linoleic acid (18:2n-6) and α -linolenic acid (18:3n-3), cannot be synthesized by mammals. As their absence from the diet results in symptoms indicative of a deficiency state, these two fatty acids are considered to be essential. Linoleic acid is found in significant quantities in many vegetable oils, including corn, sunflower and soybean oils, and in products made from such oils, such as margarines. α -Linolenic acid is found in green plant tissues, in some common vegetable oils, including soybean and rapeseed oils, and in flaxseed (also known as linseed) and flaxseed oil. Between them, linoleic and α -linolenic acids contribute over 95%, and perhaps as much as 98% of dietary PUFA intake in most western diets. The intake of linoleic acid in western countries increased greatly from about 1970, following the introduction and marketing of cooking oils and margarines. α -Linolenic acid intake probably changed little over this time. However, although typical intakes of both essential fatty acids are in excess of requirements, the changed pattern of consumption of linoleic acid has resulted in a marked increase in the ratio of n-6 to n-3 PUFAs in the diet. This ratio is currently between 5 and 20 in most western populations [2].

Although linoleic and α -linolenic acids cannot be synthesized by humans they can be metabolized to other fatty acids (Fig. 1). This is achieved by the insertion of additional double bonds into the acyl chain (i.e. unsaturation) and by elongation of the acyl chain. Thus, linoleic acid can be converted via γ -linolenic acid (18:3n-6) and di-homo- γ -linolenic acid (20:3n-6) to arachidonic acid (20:4n-6) (Fig. 1). By an analogous set of reactions catalysed by the same enzymes α -linolenic acid can be converted to eicosapentaenoic acid (EPA; 20:5n-3). Both arachidonic acid and EPA can be further metabolized, EPA

giving rise to docosapentaenoic acid (DPA; 22:5n-3) and docosahexaenoic acid (DHA; 22:6n-3) (Fig. 1). Dietary intakes of the longer chain, more unsaturated PUFAs are much, much lower than of linoleic and α -linolenic acids. Some plant oils contain γ -linolenic acid, dihomo- γ -linolenic acid and stearidonic acid (18:4n-3), but typical intakes of these fatty acids from the diet are likely to be < 10 mg/day. Arachidonic acid is found in meat and offal and intakes are estimated at 50–500 mg/day. EPA, DPA and DHA are found in fish, especially so-called 'oily' fish (tuna, salmon, mackerel, herring, sardine). One oily fish meal can provide between 1.5 and 3.5 g of these long chain n-3 PUFAs, equivalent to a daily consumption of 200–500 mg [3]. The commercial products known as fish oils also contain EPA, DPA and DHA, which typically will contribute about 30% of the fatty acids present. Thus, consumption of one typical 1 g fish oil capsule per day can provide about 300 mg of these fatty acids. In the absence of oily fish or fish oil consumption, intake of long chain n-3 PUFAs is likely to be < 100 mg/day, although foods, such as eggs, milks or breads, fortified with these fatty acids are now available in many countries.

PUFAs are important constituents of cells where they play roles assuring the correct environment for membrane protein function, maintaining membrane fluidity and regulating gene expression and cellular function [1]. In addition, some PUFAs, particularly arachidonic acid, act as substrates for synthesis of eicosanoids, which are involved in regulation of many cell and tissue responses. Arachidonic acid-derived eicosanoids are intimately involved in the regulation of inflammatory processes and immune cell functional responses [4, 5]. For example, prostaglandin E_2 (PGE₂) inhibits the production of T-helper type 1 (Th1)-type cytokines and promotes the production of Th2-type cytokines and of IgE, while leukotriene B₄ is a leucocyte chemoattractant and promotes leucocyte adhesion and degranulation. One factor limiting the synthesis of eicosanoids is the availability of the substrate, arachidonic acid, in the membranes of inflammatory cells. Because the dietary intake of linoleic

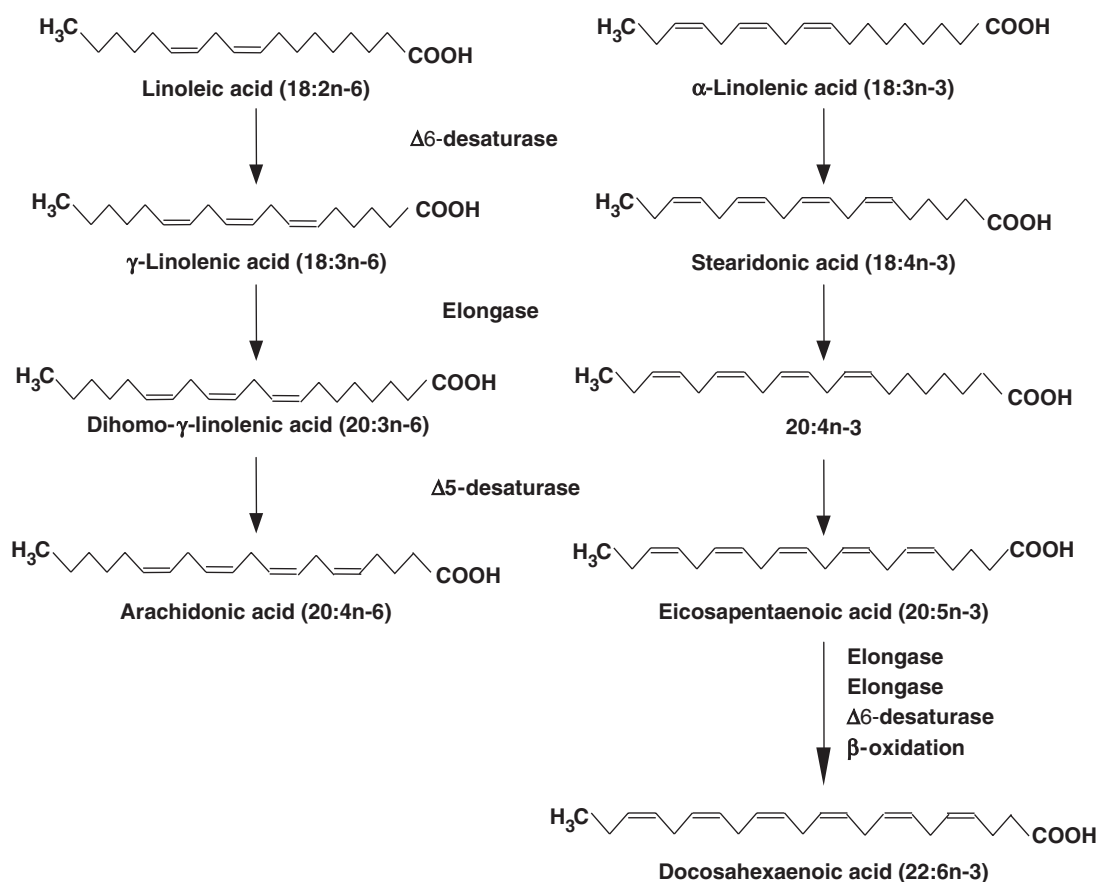


Fig 1. Pathway of conversion of linoleic and α -linolenic acids to longer chain, more unsaturated fatty acids.

acid is high relative to that of other PUFAs, it seems likely that much of the arachidonic acid present in inflammatory cell membranes has been synthesized from dietary linoleic acid. As indicated earlier, linoleic and α -linolenic acids are metabolized by the same set of enzymes (Fig. 1), effectively creating competition between the classes of fatty acids for metabolism. Because the amount of linoleic acid in the diet is greater than the amount of α -linolenic acid, metabolism of the former prevails, so promoting arachidonic acid synthesis and availability for incorporation into inflammatory cells.

There are a number of observations of significantly higher proportions of linoleic acid and significantly lower proportions of γ -linolenic, dihomo- γ -linolenic and arachidonic acids in atopic dermatitis [6]. A paper published in the current issue of *Clinical and Experimental Allergy* further examines the role of altered fatty acid profiles in atopic disease [7]. The authors examine the fatty acid compositions of buccal cheek cells, serum phospholipids and breast milk in relation to atopic dermatitis in infants aged one to six months; the compositions are compared to those of control infants and infants with non-atopic dermatitis. The rationale for using cheek cells appears to be twofold. Firstly, they represent a cell population that can be collected relatively non-invasively and secondly

they may be representative of mucosal cells further down the gastrointestinal tract. Their value as a non-invasively collected cell population that can be used as a surrogate for circulating cells would have been strengthened by a comparison with blood leucocytes or mononuclear cells. The authors found that cheek cell phospholipid linoleic acid was higher (by about 16%) in infants with atopic dermatitis than in controls or infants with non-atopic dermatitis. Furthermore γ -linolenic acid was lower (by about 50%) in serum phospholipids in infants with either atopic or non-atopic dermatitis than in controls, although levels of this fatty acid are very low (< 0.1% of total fatty acids). Clearly these observations are in accordance with earlier literature. However, no other differences in the fatty acid composition of cheek cell phospholipids were seen and no differences at all in the fatty acid composition of breast milk were identified. This may partly reflect the small number of infants studied (six, six and 19 in the atopic dermatitis, non-atopic dermatitis, and control groups, respectively), as the study may have been insufficiently powered to identify some differences among the groups.

It is not clear what the abnormalities in fatty acid composition observed in atopic disease really mean. Two hypotheses have been proposed relating PUFAs to atopic disease. According to one hypothesis, the fatty acid

composition abnormalities are due to impaired activity of $\Delta 6$ -desaturase [8], the enzyme responsible for conversion of linoleic to γ -linolenic acid (Fig. 1), and that this is somehow causal in the atopic disease process (i.e. the disease results from a decreased availability of long chain n-6 PUFAs). The idea that atopic disease is related to insufficient availability of long chain n-6 PUFAs, including arachidonic acid, appears to contrast with the long-held view that the latter fatty acid supports pro-inflammatory actions. However, more recent discoveries that arachidonic acid also gives rise to anti-inflammatory and inflammation resolving mediators like lipoxin A₄ [9] may be an explanation for why a relative lack of this fatty acid may result in an atopic state. An impairment in $\Delta 6$ -desaturase activity should also affect the proportions of n-3 PUFAs as the metabolism of α -linolenic acid will be affected (Fig. 1). There are a number of observations reporting that this does appear to be the case [10–12]. As long chain n-3 PUFAs are anti-inflammatory because of their ability to interfere with arachidonic acid metabolism [13] and because they give rise to inflammation resolving mediators termed resolvins [14], a relative lack of these fatty acids may result in an atopic state. Thus, the effect of a putative impairment of $\Delta 6$ -desaturase activity in atopy may relate to decreased availability of either long chain n-6 or long chain n-3 PUFAs or both. However, the new study of Laitinen et al. [7] reports higher EPA in serum phospholipids in infants with atopic dermatitis than in controls, which does not accord either with this hypothesis or with a number of other findings reported in the literature [10–12].

The second hypothesis relating PUFAs to atopic disease is based upon the apparent co-incidence of the changing patterns of atopic disease and of consumption of linoleic acid [15, 16]. The essence of this hypothesis is that the increased consumption of linoleic acid over the last 40 years has resulted in enhanced capacity to synthesize arachidonic acid and that, through the actions of PGE₂ on T and B cells, a situation favouring skewing towards the Th2 phenotype and towards IgE production by B cells has occurred [17]. An expected marker of such a situation would be higher levels of arachidonic acid in atopy. These are clearly not observed [6]. However, it is possible that the lowered levels of arachidonic acid seen in atopy result from increased utilization by inflammatory processes rather than from impaired synthesis.

Clearly the two hypotheses relating PUFA status to atopic disease are mutually exclusive: one suggests insufficient, while the other suggests excessive, synthesis of long chain n-6 PUFAs. It seems important for research to focus upon directly testing these hypotheses. One approach may be to use stable isotopes of linoleic and α -linolenic acids to observe whether atopic individuals do have significantly altered ability to metabolize these fatty acids.

It is important to note that while this latest paper [7] adds to the growing literature demonstrating fatty acid

compositional abnormalities in atopic disease, a larger study failed to identify significant differences in fatty acid composition of breast milk between mothers with or without atopic dermatitis [18], while another study revealed only very minor differences in the fatty acid composition of blood phospholipids between atopic and non-atopic infants at birth and at 3 months of age [12]. Kankaanpää et al. [19] identified a significant difference in the proportion of only one fatty acid in atopic babies aged 3 months in serum phospholipids (lower γ -linolenic acid), cholesteryl esters (lower DHA) and triglycerides (higher linoleic acid). In a recent fairly large study no differences in fatty acid composition of colostrum or breast milk at 3 months lactation were identified between atopic and non-atopic women [20]. These findings challenge the earlier notions that atopic disease is associated, perhaps causally, with large differences in fatty acid composition. The findings of Laitinen et al. [7] effectively support this conclusion as only a limited number of differences were identified, and these were fairly small. Nevertheless even small differences in fatty acid composition of some lipid pools may be physiologically and pathophysiologically important. However, until the mechanism(s) underlying the altered fatty acid compositions that appear to occur in at least some groups of atopic individuals are better understood, it seems premature to promote interventions that will affect fatty acid composition, as these may be ineffective.

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