

Invited Commentary

Mediterranean diet and cystic fibrosis

Low serum concentrations of linoleic acid were first documented in cystic fibrosis (CF) over 40 years ago (Kuo *et al.* 1962). For many years, these were considered to be a reflection of impaired fat absorption related to the pancreatic insufficiency present in 90% of the patients. Low levels of essential fatty acids have, however, also been observed in patients without pancreatic insufficiency, indicating that the fatty acid disturbances are not solely a result of fat malabsorption (Underwood *et al.* 1972; Rogiers *et al.* 1983; Mischler *et al.* 1986). The development of more efficient pancreatic enzyme preparations that improve the fat absorption coefficient to above 90% in many patients means that a malabsorption of essential fatty acids is not likely. However, a defective pattern of *n*-3 fatty acids has been described in such patients (Lloyd-Still *et al.* 1981). This received new attention when Freedman *et al.* (1999) described a restitution of pancreatic morphology by supplementation with high doses of DHA to Cfr^{-/-} mice.

An increased release of arachidonic acid and an increased turnover of *n*-6 fatty acids have been found in many CF cell systems (Carlstedt-Duke *et al.* 1986; Levistre *et al.* 1993; Miele *et al.* 1997; Bhura-Bandali *et al.* 2000), including an overstimulation of phospholipase A₂, the rate-limiting enzyme for arachidonic acid release (Berguerand *et al.* 1997). Since arachidonic acid release is the rate-limiting step in prostanoid synthesis, this overstimulation of phospholipase A₂ results in a high production of eicosanoids (Strandvik *et al.* 1996). A high turnover would explain the low linoleic acid concentration (Fig. 1). It has been suggested that the low DHA concentration reflects a more basic defect of lipid metabolism in CF. However, linoleic acid supplementation normalises the concentration of DHA in serum (Farrell *et al.* 1985; Strandvik *et al.* 2001). It has recently also been shown that CF patients treated for 8 months with *n*-3 fatty acids showed an improvement in their linoleic acid concentration (De Vizia *et al.* 2003).

In this context, the paper in this issue by Oliveira *et al.* (2006) is of special interest. They report dietary intake and serum phospholipid fatty acids in adults with CF on a Mediterranean diet. The Spanish diet is richer in MUFA and also contains more *n*-3 fatty acids than a Western (American) diet (Simopoulos, 1999; Serra-Majem, 2003/2004). The patients in the present study were matched for age and sex with healthy controls, and a 7 d food

registration disclosed a higher energy intake and a lower intake of *n*-6 essential fatty acids in the patients, suggesting a higher *n*-3:*n*-6 ratio in the patients' diet. Despite this favourable dietary profile, similar lipid abnormalities, as found by other authors, were seen. The authors excluded malabsorption as a major factor as their patients had a stable condition and the fat absorption coefficient, considered as the gold standard for fat absorption tests, was very good. Interestingly, they found significant differences in the lipid profile associated with the pancreatic and pulmonary functions and with the severity of the genotype, corroborating the results of previous studies (Lloyd-Still *et al.* 1996; Strandvik *et al.* 2001).

The patients reported were in a relatively good clinical state compared with many reports concerning adult patients in the US and Europe. This might be related to the fact that the Mediterranean diet contained a high fat content, thus supplying patients with CF with enough calories, and the lower *n*-6:*n*-3 ratio of the fat (Serra-Majem *et al.* 2003/2004). The present study shows, however, that a Mediterranean diet is not enough as these patients also need some kind of supplementation in order to normalise their fatty acid pattern.

The causal link between the lipid abnormality and CFTR dysfunction is not clear. There might be several possible explanations. The defect might be directly related to the CFTR through an unknown function of the protein comparable to those of other ABC cassette proteins, or indirectly related to its functioning in lipid membranes. CFTR resulting from the most common gene mutation, $\Delta F508$, has been shown to have improved function at a lower temperature, suggesting that the lipid configuration around the protein might have importance for its function. Long-chain fatty acids are prone to lipid peroxidation, and an increased oxidative capacity in CF is well documented (Wood *et al.* 2001). In the paper by Oliveira *et al.* (2006), the patients were supplemented with vitamin E and none was reported to have low serum concentrations. Although increased oxidation might contribute, it is highly unlikely to be a main cause of CF-related lipid abnormalities.

Linoleic acid is an important constituent of membranes, and the last step in the synthesis of DHA is dependent on normal membrane phospholipids in mitochondria and peroxisomes. Newly identified products of both arachidonic acid

Important transformations of fatty acids

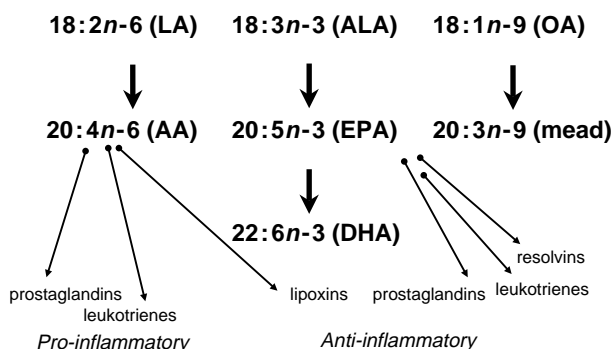


Fig. 1. Major series of fatty acids. Linoleic acid (LA) and α -linolenic acid (ALA) are the essential fatty acids, which cannot be synthesised in mammals. Major metabolites of these fatty acids are arachidonic acid (AA), EPA and docosahexaenoic acid (DHA), respectively. In essential fatty acid deficiency, oleic acid (OA) is further metabolised to eicosatrienoic acid (mead acid). Substances in smaller letters indicate the pro- and anti-inflammatory products from AA, EPA and DHA, respectively.

and DHA, lipoxins and resolvins, respectively, seem also to be involved in the pathophysiology of CF (Karp *et al.* 2005). Thus, the imbalance of lipid metabolism in CF will probably involve more metabolites than previously recognised. How to intervene in CF is still not clear (Beckles-Willson *et al.* 2002; Van Biervliet *et al.* 2005). A Mediterranean diet cannot compensate for the abnormalities, but it seems to be a solid ground for starting future interventions.

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