



THE SUPPLEMENT

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FATTY ACIDS AND CYSTIC FIBROSIS

Of the numerous fatty acids (FAs), two have been determined to be essential, in that they cannot be produced by the body and must be supplied by the diet. These two essential fatty acids (EFAs) are *alpha*-linolenic acid (ALA) and linoleic acid (LA). Arachidonic acid (AA) was thought to be essential for infants, but research indicates this may not be true. [1]

ALA is one example of FAs classified as omega-3 (w-3) FAs, while LA is an example of one of the many omega-6 (w-6) FAs. Understanding fatty acids can be a challenge because of the complex nomenclature. The reader is referred to references two and three for a more in-depth discussion of the FAs and their terminology.

The w-3 and w-6 FAs have received a great deal of attention in both the scientific and lay press. The current American diet, which is high in FAs from animal and grain sources, has a high proportion of w-6 FAs. While the recommended w-6:3 ratio is 2:1 to 3:1; the American diet ranges from 8:1 to 12:1. [2]

Omega 3 and 6 FAs play an important role in overall health. All FAs compete for the same elongases and desaturases. An increase in one group of FAs, for example w-6, may slow the transformation of w-3. Following a series of conversions through complex cascading processes, the FAs eventually influence the production of the eicosanoids, including prostaglandins, thromboxanes, and leukotrienes, which are involved in numerous vital body functions such as coagulation, vasoconstriction, and immune response. For the cascading process to be optimized, the intake of w-6 and w-3 FAs must be in the correct ratio.

In persons with CF, FA research is complicated due to the influence of dietary intake of calories, and nutrients such as fats and antioxidants. In addition, there are problems with absorption, inflammation, and the defective cystic fibrosis transmembrane conductance regulator (CFTR). For persons who have CF, it has been postulated that abnormal FA levels can exacerbate the inflammation typically seen in CF. [4,5,6]

More recent work by Freedman, [2004] and others [6] suggests that the role of FAs in CF is more complex.

FEATURED PAPERS:

Freedman SD, Blanco PG, Zaman MM, et al. Association of cystic fibrosis with abnormalities in fatty acid metabolism. N Engl J Med 350:560-9;2004.

Objective: To determine if patients with CFTR gene have similar FA defect as CF-knockout mice. **Subjects:** 38 subjects with CF (31 pancreatic insufficient (PI); 7 pancreatic sufficient (PS)); 13 obligate heterozygotes; 24 healthy controls; 11 subjects with IBD; 9 subjects with upper respiratory tract infection; and 16 subjects with asthma. **Study Design:** Cross-sectional study. **Methods:** Analysis of FAs from nasal- and rectal-biopsy specimens, nasal epithelial scrapings, and plasma. **Results:** Ratio of AA to docosahexaenoic acid (DHA) was increased in all CF subjects. **Conclusions:** Alterations in FA were similar to those in CF-knockout mice.

Van Biervliet S, Van Biervliet JP, Robberecht E, Christophe A. Docosahexaenoic acid trials in cystic fibrosis: A review of the rationale behind the clinical trials. J CF 4:27-34;2005.

Objective: To provide a review of currently available information related to DHA trials and CF. **Methods:** 90 papers

SPECIAL POINTS OF INTEREST:

- In persons with CF, FA research is complicated due to the influence of dietary intake of calories, and nutrients such as fats and antioxidants.
- For persons who have CF, it has been postulated that abnormal FA levels can exacerbate the inflammation typically seen in CF.

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FEATURED PAPERS (cont.):

discussing EFA and EFA and CF were reviewed. **Conclusions:** There is insufficient evidence to recommend routine use of w-3 FA in CF as a treatment modality.

Beckles-Wilson NNR, Elliott T, Everard MML. Omega-3 fatty acids (from fish oils) for cystic fibrosis. The Cochrane Collaboration Volume (4);2005.

Objective: Using techniques of an evidence-based review, determine if the use of w-3 FA supplementation reduces morbidity and mortality in patients who

have CF. **Methods:** Electronic and hand searches of established data bases for papers meeting search criteria. **Results:** Six studies were found which met search criteria; 2 studies met inclusion criteria. **Conclusions:** Although supplementation with w-3 FAs via fish oil capsules may provide some benefits to people with CF, there is insufficient evidence to make a strong recommendation for routine use.

REVIEW

There has been a long-standing interest in the role of EFA and CF. [7] Research has focused on LA and/or AA, ALA was rarely studied. In research studies of LA and/or AA, deficiency has been documented in 75 to 85% of CF subjects. [8,9] Infants with meconium ileus may be particularly vulnerable to LA deficiency. [10] Abnormalities in plasma FAs were thought due to diet and/or malabsorption. [8] Attempts to correct the abnormalities using formulas high in LA and/or calories are limited. [11,12,13] Overall, there was an increase in body weight but results related to FAs were inconclusive due to small sample sizes and limited study time. As a result of increased inflammation, CF patients may require a higher percentage of their caloric intake as EFAs. [13]

As work continued on EFAs and CF, publications appeared that alluded to a more complex role of EFAs, beyond the relationship of FA status to diet and/or malabsorption. EFA deficiency was found in newborns identified through traditional methods [14] and newborn screening. [10,15] Despite normal cord blood FA levels, infants with CF quickly developed both w-3 and w-6 EFA deficiency. [16] EFA deficiency in CF may be independent of nutritional status. Roulet [17] reported EFA deficiency in well-nourished CF patients.

Using human epithelial cells to study EFAs Bhura-Bandali [18] observed that "CF results in a defect in the utilization of LA, which is attributed in part to the defective CFTR." In CF knockout mice, increased AA but decreased DHA was found in the pancreas, lungs, and ileum. [19] DHA administration reversed the abnormality. Freedman, et al. [2004] found similar tissue findings in patients with CF, with and without PI. Strandvik noted a correlation between genotype and decreased LA and DHA. [20]

AN EVIDENCE BASED COCHRANE [2005] REVIEW FOUND THAT FISH OIL SUPPLEMENTS MAY PROVIDE SOME BENEFITS TO PERSONS WITH CF, WITH FEW SIDE EFFECTS . . .

More recently, investigators used fish oil supplements, and supplements of EPA and/or DHA to correct reduced w-3 levels. Results are mixed and Van Biervliet, et al. [2004] provides a review of these studies. There is great interest in the use of fish oil supplements with some thought that DHA dominant oils may be more effective. [21] An evidence based Cochrane [2005] review found that fish oil supplements may provide some benefits to persons with CF, with few side effects; there is insufficient evidence at this time to recommend routine use of supplements. The authors recommend a large, long-term, multicenter, randomized controlled study to determine therapeutic effect and to assess the influence of disease severity, dosage, and duration of treatment.

CLINICAL APPLICATIONS

Traditionally, those working with persons who have CF have been concerned about overall caloric intake. Fats have been encouraged due to their high caloric value. Typically, the total amount of fat was emphasized rather than the specific FAs. The most recent US CFF Pediatric Nutrition Consensus Report and the European Nutrition Consensus Statement contain discussions of EFAs. [22,23]

The DRI provides a comprehensive review of fatty acids for healthy persons. [1] As a result of the concern to increase the w-3 FAs intake, people in the United

CLINICAL APPLICATIONS (CONT.)

States are being encouraged to increase their intake of cold-water marine fish, walnuts, and oils such as flaxseed, canola, and soy. New “designer” foods, like eggs, margarine, peanut butter, and pasta, containing higher levels of w-3 FAs are appearing in stores. It is prudent to note that excessive intake of w-3 FAs may produce adverse effects, such as bleeding. [1]

For persons who have CF, there are no official recommendations for EFA intake. However, registered dietitians frequently are confronted with questions regarding EFA intake. The US CFF Consensus Report [22] and the European Consensus Report [23] discuss the importance of optimal EFA intake through dietary means that meet recommendations for the general public. Patients are encouraged to consume foods containing both ALA and LA.

Patients do ask about the use of supplements of fish oil. Although the Cochrane review found insufficient evidence to recommend routine use of supplements, there is some evidence to support their use. [24] Based on the review of literature, judicious use of fish oil supplements may cause no harm to persons with

CF, but may not result in improvement for all patients. GI discomfort was noted in some studies. [25,26] Fish oil supplements are oils therefore pancreatic enzyme replacement therapy is necessary.

Since the biologic effects of FAs depend not only on the absolute biochemical levels of a specific FA, but the ratio of w-6:w-3 FAs, [27] it may be prudent to encourage a diet that results in the recommended ratio of w-6:w-3 FAs. To spare EFAs for their non-caloric biologic roles, it is important that the diet contain sufficient calories. To prevent the oxidation of these highly unsaturated FAs, it also is recommended to provide sources of dietary antioxidants.

At this time there are no specific dietary recommendations regarding EFAs for persons who have CF. The reader is encouraged to review relevant work as it appears in the literature and apply the findings, as appropriate, to patient care.

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