**Linoleic acid supplement in cystic fibrosis: friend or foe?**

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Several clinical observations suggest that changes in fatty acid concentrations are associated with the pathogenesis of chronic lung disease. As an example, cystic fibrosis (CF) subjects have lower concentrations of essential fatty acids in their plasma lipids compared with normal control subjects (6, 7). Although pathogenesis of CF lung disease is not a direct consequence of changes in fatty acids, the course of the disease may be influenced by these changes and other related changes in eicosanoid production. Asthma and chronic obstructive pulmonary disease (COPD) subjects have also been reported to have lower ratios of ω-3 to ω-6 fatty acids in plasma lipids compared with normal control subjects (14). In addition to the general importance of fat as an energy source, essential fatty acids are important for cellular homeostasis. The two essential fatty acids supplied as dietary supplement, α-linolenic acid (ALA) and linoleic acid (LA), belong to the ω-3 and ω-6 families of polyunsaturated fatty acids (PUFAs), respectively. The PUFAs are metabolized into longer chain fatty acids that have important biological functions. Arachidonic acid (AA) is synthesized from LA, whereas eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids are from ALA (Fig. 1). Even though a precise mechanism for low LA levels in CF is unknown, the increased metabolism of the ω-6 fatty acid pathway is shown to be a potential mechanism (1, 3).

The *Pseudomonas aeruginosa* bacterial infection has been shown to have a critical role in pathogenesis of both CF and COPD (12, 13), however, it is unclear why these patients are highly sensitive to the *P. aeruginosa* infections. In the case of a monogenic lung disease, CF, the absence of cystic fibrosis transmembrane conductance regulator (CFTR) protein from the plasma membrane has been shown to result in an inherent hyperinflammatory lung phenotype causing chronic obstructive lung disease in both humans and *Cfr*−/− mice (11, 16). Defective fatty acid metabolism is considered to be a potential mechanism for altered immune response in CF. A recent study shows that lower LA levels in CF are due to its increased metabolism to AA via Δ-6 desaturase (1). The human bronchial alveolar lavage fluids (BALF) of CF subjects show elevated levels of both AA (8) and PGE2 (15). We recently demonstrated that AA-PGE2-mediated IL-8 chemokine secretion in CF (18) is a mechanism for neutrophil chemotaxis and pathogenesis of chronic inflammatory lung disease (Fig. 1). In this issue of *AJP-Lung*, Zaman and colleagues (20) demonstrate that LA supplements induce PGE2-IL-8-mediated inflammation in CF due to increased levels of AA. However, higher LA supplement may induce cAMP-CFTR activity (Fig. 1) in non-CF subjects and a small group of CF subjects, like G551D with partially functional CFTR on the cell surface, but will have no significant benefit in ΔF508-CF subjects.

![Fig. 1. Schematic of polyunsaturated fatty acid (PUFA) metabolism in cystic fibrosis. CFTR, cystic fibrosis transmembrane conductance regulator.](http://apjplung.physiology.org/)

These authors have used both in vitro and in vivo models to test the clinical significance of the recommendation that CF patients should consume a high-fat diet containing >6% LA. The data are of high clinical relevance because CF patients display a fatty acid imbalance with low LA and variable changes in AA. In contrast to previous observations, data from the study suggest that LA supplement in CF for controlling inflammation may augment the progression of the lung disease by increasing AA, PGE2, and IL-8 levels. Moreover, 100 mg of LA induces neutrophil chemotaxis in *Cfr*−/− compared with *Cfr*+/− lungs. As a proof of concept, PUFAs or dietary supplements have not shown very promising results in controlling inflammation in CF thus far. However, dietary LA seems to have some advantage for the growth of CF infants (17). We propose that sequential deciphering of fatty acid imbalance and lipid raft-mediated inflammatory signaling (4, 5) in CF may lead to the identification of better and more specific therapeutic target(s) to improve the overall CF pathophysiology and lung function.

As an alternative to high-dose LA supplements, it is anticipated that ω-3 PUFA-containing dietary bioactive agents (like DHA ethyl ester) will downmodulate inflammatory and immune responses in CF and other chronic inflammatory diseases by targeting sphingolipid metabolism and ceramide accumulation. The most novel finding, possibly relevant to increased inflammation in CF, is that the expression of defective CFTR affects sphingolipid metabolism and ceramide mass (9, 10). It is becoming clear that the inability to express wild-type CFTR increases ceramide accumulation. Moreover, data obtained in different CF murine models suggest that normalization of ceramide levels prevent the secretion of select inflammatory markers and the susceptibility to infection (Refs. 4, 16; unpublished observations).

More than 10 studies assessed the feasibility and clinical benefit of receiving ω-3 fatty acid supplements in CF. As recently reviewed, 6 out of the 10 studies revealed no signif-
icant improvement in lung and liver function, whereas 2 studies reported improvement in lung function measured by increased forced expiratory volume in 1 s (FEV$_1$), forced vital capacity (FVC), and Shwachman scores or FEV$_1$ alone (19). In contrast, a 60-day treatment of a congenic murine model of CF with DHA showed no obvious improvements in the morphology of lungs, pancreas, or intestine, however, a reduced periporal inflammation was observed. Current studies demonstrate that ω-3 supplementation can increase DHA and EPA levels, however, ω-3 fatty acids have yet to present a stable or significant therapeutic benefit. Although current studies have not resolved whether normalization of fatty acid profiles is clinically relevant (2), recent data demonstrate that ω-3 fatty acid, DHA, can normalize increased metabolism of LA, providing a rationale for supplementation. Future studies investigating the mechanisms of fatty acid and sphingolipid metabolism in CF hold a promise to identify novel strategies to control chronic inflammatory response in CF.

To summarize, the current data (20) suggest that the risk-benefit of increasing LA supplements for CF patients needs careful evaluation by preclinical and clinical studies. Although appropriate LA doses show a significant benefit for infant weight gain and head growth, higher doses may be detrimental. Moreover, increasing LA supplements in adolescence or adulthood may not be critical for growth benefits compared with the risks associated with propagation or exacerbation of the chronic CF lung disease. The data from this study raise a caution for current recommendations to increase LA intake in CF subjects due to the deficiency of systemic LA levels. The findings of this study also raise a concern on the use of high-dose LA for subjects suffering from other chronic airway inflammatory diseases like COPD and asthma.

**REFERENCES**