

Fat Balance in Cystic Fibrosis: Is It only a Simple Matter of Maldigestion and Malabsorption?

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Cystic fibrosis (CF), the most common severe genetic disease in Caucasian populations, causes a generalized disorder of the secretory epithelia of all exocrine glands. The basic defect of altered salt and water transport leads to secondary alterations of the pancreas and the gastrointestinal, hepatobiliary and respiratory tracts. Fifteen years after the identification of the gene locus for CF [1], the hope for a complete pathogenetic understanding and effective treatment of the disease has not yet been realized. Up to now, more than 1,200 mutations have been identified in the *CF transmembrane conductance regulator* gene (*CFTR*) and no clear relation between all the different phenotypes and mutations has been unequivocally demonstrated [2]. From the clinical standpoint, CF is the only hereditary disease in which pancreatic involvement can be expressed by both exocrine insufficiency (without pancreatic inflammatory disease) and pancreatitis [3]. Exocrine pancreatic insufficiency occurs in the vast majority of patients and, at least in Western Europe, seems to be associated with the $\Delta F508$ mutation [4].

The "older" CF gets, the more clearly intraluminal fat maldigestion increases as decreased secretion of lipase and colipase become more severe. Thus, body fat balance in CF is considered mainly related to the maldigestion and malabsorption of nutrients; as a consequence, determination of fecal elastase, 72-h fecal fat determination, and ^{13}C

mixed triglyceride breath tests were used as diagnostic tools, and pancreatic enzyme replacement therapy is aimed at restoring digestion. During the past 30 years, several studies report alterations of the body's essential fatty acids in patients with CF and these abnormalities have been presumed to be secondary to fat malabsorption and not a primary abnormality due to *CFTR* mutations [5]. A decrease in the plasma levels of linoleic acid and docosahexaenoic acid with a compensatory increase in the levels of eicosatrienoic acid causes a deficiency of essential fatty acids and an alteration of their pattern and turnover in CF [6]. Recently, Freedman *et al.* [7] reported important data demonstrating that abnormalities in the metabolism of arachidonic acid (the most important metabolic product of linoleic acid) and docosahexaenoic acid may be a primary event in CF as the *CFTR* gene plays a direct role in cellular fatty acid metabolism. The authors analyze fatty acids from nasal and rectal biopsy specimens, nasal epithelial scrapings and plasma from 38 patients with CF, 13 obligate heterozygotes, 24 healthy controls, 11 patients with inflammatory bowel disease and 25 subjects with respiratory diseases. In patients with CF, an increased ratio of arachidonic to docosahexaenoic acid in the nasal and rectal epithelium (tissues that express *CFTR*) was discovered. Values were significantly increased both in CF patients with and those without exocrine pancreatic insufficiency as compared to values in healthy

control subjects. The authors suggest that the low docosahexaenoic acid levels may be important in the excessive host inflammatory response in CF, as the metabolites of this fatty acid are potent anti-inflammatory mediators which are normally generated during the resolution of the inflammation. According to this speculation, abnormalities of fatty acid levels in patients with CF may explain, at least in part, the inflammatory state associated with this disease and could lead to an important role for specific dietary supplementation.

A balanced fat metabolism represents an important target in the life of patients with CF; recent knowledge indicates that tracing it back to a maldigestion/malabsorption issue is oversimplistic.

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Keywords Cystic Fibrosis; Cystic Fibrosis Transmembrane Conductance Regulator; Malabsorption Syndromes; Malnutrition; Pancreatic Insufficiency

Abbreviations CF: cystic fibrosis

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