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eCysticFibrosis Review

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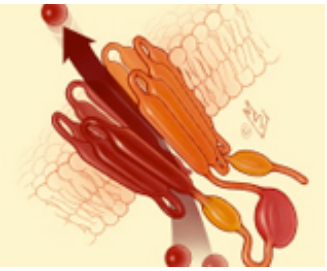

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Nutritional Challenges and Complications in Patients with Cystic Fibrosis

In this Issue...

Improvements in nutrition have been a key factor in reducing morbidity and mortality in patients with cystic fibrosis (CF). Over the past 20 years, although great progress has been made via the use of high-fat, high-calorie diets and dramatic improvements have occurred in pancreatic enzyme therapy, challenges remain in several areas, including the role of qualitative differences in macronutrients and micronutrients, and the impact of gastrointestinal (GI) disease on intake and digestion of nutrients in patients with CF. One essential step in improving nutrition—and thus survival—in patients with CF is an improved understanding of GI disease and its impact on CF nutrition.

In this issue, we (1) summarize current progress in the definition and epidemiology of 2 CF GI-related issues—small intestinal bowel overgrowth (SIBO) and distal intestinal obstruction syndrome; (2) discuss the implications of SIBO in the CF null mouse model; (3) review current research into nonpancreatic enzyme–related defects in fat absorption among patients with CF; and (4) describe a study of omega-3 polyunsaturated fatty acid supplementation in individuals with CF.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Explain the definition and describe the prevalence of small intestinal bowel overgrowth and distal intestinal obstruction syndrome among patients with cystic fibrosis (CF)
- Evaluate the role of the CF null mouse in exploring the pathophysiology of gastrointestinal disease in CF
- Describe the relative deficiency of omega-3 polyunsaturated fatty acids (PUFAs) in the tissues of patients with CF and the ability to reverse this process with supplemental omega-3 PUFAs.

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

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- Explain the definition and describe the prevalence of small intestinal bowel overgrowth and distal intestinal obstruction syndrome among patients with cystic fibrosis (CF)

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1 hour
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April 15, 2010

Expiration Date

April 14, 2012

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- Evaluate the role of the CF null mouse in exploring the pathophysiology of gastrointestinal disease in CF
- Describe the relative deficiency of omega-3 polyunsaturated fatty acids (PUFAs) in the tissues of patients with CF and the ability to reverse this process with supplemental omega-3 PUFAs.

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Guest Author's Disclosures

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COMMENTARY

In May 2005, the Cystic Fibrosis Foundation (CFF) sponsored a workshop on Gastrointestinal Outcomes and Confounders in cystic fibrosis (CF).[1] This conference addressed the impact of gastrointestinal (GI) dysfunction and disease on ingestion, digestion, and absorption of nutrients in patients with CF. The goal was to move beyond pancreatic insufficiency by examining other intraluminal factors that limit the absorption of nutrients in individuals with CF. The report noted the importance of animal models in investigating the pathophysiology of GI disease in CF. Although the animal models that

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have been developed have proven disappointing with respect to the pulmonary disease modeling of CF, they do express the phenotype of GI disease in CF with respect to distal intestinal obstruction syndrome (DIOS), small intestinal bowel overgrowth (SIBO), and failure to thrive. Factors that play a role in the effectiveness of pancreatic enzyme therapy were reviewed at the conference, including delayed gastric emptying, intestinal acidification, abnormal intraluminal solubilization, and mucosal absorption of dietary fat. The impact of SIBO on nutrient absorption was reviewed as well. Limitations with respect to the ability to measure fat absorption were examined. The report is a blueprint for research to help advance the management of nutrition and GI disease in patients with CF.

The potential impact of such advancement is clear. In 1988, the work of Corey and coworkers demonstrated that superior survival was reported in patients with CF who had superior nutritional status.[2] Infants identified with CF by neonatal screening have improved survival compared with those diagnosed based on symptoms. This improvement has been attributed to the earlier institution of good nutrition following neonatal diagnosis. [3] These and other studies identify nutrition as a therapeutic modality in patients with CF, on par with airway clearance and antimicrobial therapy.

The articles reviewed in this issue address several areas included in the agenda of Borowitz and colleagues[1]: (1) improved diagnostic criteria and epidemiology of SIBO and DIOS; (2) use of the CF null mouse model to evaluate SIBO and intestinal transit; (3) examination of intracellular enterocyte lipid metabolism; and (4) clinical and animal model studies of the interrelated areas of inflammation and lipid metabolism in CF.

Fridge and associates, discussed herein, demonstrated that SIBO is more common in CF patients than in those with other GI diseases—about 50% of the patients at our institution may be affected to some degree by this problem. Future studies will be needed to address specific risk factors for SIBO in patients with CF; however, clinicians should be alert to the situation in those who have undergone previous GI surgery. Although the article reviewed used breath hydrogen to diagnose SIBO, this may not be clinically practical. Breath hydrogen studies may be uninterpretable in patients with gastric emptying delay, which is a common problem in CF; further, the use of antibiotics may cause false negatives in breath testing. Many clinicians prescribe antibiotics to treat SIBO in the presence of such common symptoms as abdominal pain, diarrhea, bloating, and excessive bowel gas production. Resolution of symptoms following treatment is presumptive evidence of the correct diagnosis. Clearly, better diagnostic testing would improve accuracy in diagnosing SIBO; however, until then, a high index of suspicion is warranted in the CF population.

The work of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), detailed in the article by Houwen and collaborators, provides a long-needed framework for distinguishing DIOS from constipation. This work will provide a standard definition for research into the risk factors for DIOS. For clinicians, the definitions will help clarify diagnosis, although it will be important to determine prospectively if clinical outcomes match expectations based on the definitions. Clinicians should also remember that DIOS is not the only diagnosis that fits the ESPGHAN description. Other inflammatory diseases, including early inflammatory bowel disease, intestinal infection, appendicitis, and nonsteroidal anti-inflammatory agent–associated enteropathy, may mimic symptoms of DIOS. The treatment of DIOS and constipation in CF is based largely on small series reports and anecdotal experience. Although Houwen and coworkers have shown that most of these protocols work, their standard definitions will allow development of optimal diagnosis and management strategies.

De Lisle and colleagues have been exploiting the CF null mouse model to examine many aspects of SIBO and intestinal transit. In a series of papers, they have established the association of SIBO with inflammation and poor growth in the CF mouse. The article reviewed in this issue examines the interaction between intestinal transit and SIBO. Intestinal transit was unaffected by the treatment of SIBO in the mouse model. Gastric emptying was not seriously delayed, although gastroparesis is a common problem among patients with CF. De Lisle's work provides direction for investigators to examine the interrelationship of transit, SIBO, and poor growth in humans.

Borowitz and associates recommended examination of the impact of the cystic fibrosis transmembrane conductance regulator (CFTR) gene on nonpancreatic enzyme–associated fat malabsorption in CF.[1] The efficiency of the currently available enzyme supplements has revealed the importance of micelle production, intestinal mucosal

integrity, and intracellular lipid metabolism in fat malabsorption in CF. The article by Peretti and coworkers describes the use of cultured duodenal explants to show abnormalities in lipid synthesis and transport in CF enterocytes. The association of these abnormalities with essential fatty acid deficiency in CF patients, and the known impact of essential fatty acid deficiency on lipid absorption,[4] suggests that fat absorption may be another clinically significant endpoint for the evaluation of fish oil supplementation in patients with CF. De Lisle and collaborators have shown altered eicosanoid metabolism in the intestine of the CF mouse model,[5] further emphasizing the need for quantitation of intestinal inflammation as endpoints in interventions to modulate essential fatty acids in individuals with CF.

The question of fish oil supplementation in CF arises during many clinical visits. Supplements are readily available and relatively inexpensive. In normal doses, they have almost no side effects. It seems easy to support both patients and parents who want to hope that a simple treatment may improve the health of someone with CF. But we should be careful about supporting an unproven therapy. Omega-3 fatty acid supplements alter membrane fatty acid profiles in CF, as demonstrated in the article reviewed by Panchaud and associates in this issue, but there is little evidence that they alter the clinical course of CF. Demonstrating an impact of omega-3 fatty acid supplements on clinically significant endpoints, including improvement in pulmonary function or improved anthropometrics, will require randomized, double-blind clinical trials in large numbers of CF patients over a number of years. Unproven use of these supplements will obstruct the necessary clinical trials, increase the expense of care through the purchase of an unproven therapy, and add to the burden of medications that the patient must ingest each day.

In the 5 years since the CFF sponsored a workshop on GI factors contributing to malabsorption in patients with CF, investigators have clearly begun to address the agenda proposed by Borowitz and coworkers.[1] Progress in the nutritional support of patients with CF is dependent on improving the utilization and the delivery of nutrients, both of which require that we understand and control the GI complications of this disease.

Commentary References

1. Borowitz D, Durie PR, Clarke LL, et al. Gastrointestinal outcomes and confounders in cystic fibrosis. *J Pediatr Gastroenterol Nutr.* 2005;41(3):273-285.
2. Corey M, McLaughlin FJ, Williams M, Levison H. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol.* 1988;41(6):583-591.
3. Lai HJ, Cheng Y, Farrell PM. The survival advantage of patients with cystic fibrosis diagnosed through neonatal screening: evidence from the United States Cystic Fibrosis Foundation registry data. *J Pediatr.* 2005;147(3 suppl):S57-S63.
4. Levy E, Garofalo C, Thibault L, et al. Intraluminal and intracellular phases of fat absorption are impaired in essential fatty acid deficiency. *Am J Physiol.* 1992;262 (2 pt 1):G319-G326.
5. De Lisle RC, Meldi L, Flynn M, Jansson K. Altered eicosanoid metabolism in the cystic fibrosis mouse small intestine. *J Pediatr Gastroenterol Nutr.* 2008;47(4): 406-416.

DEFINING DISTAL INTESTINAL OBSTRUCTION SYNDROME

Houwen RH, van der Doef HP, Sermet I, et al; ESPGHAN Cystic Fibrosis Working Group. **Defining DIOS and constipation in cystic fibrosis with a multicentre study on the incidence, characteristics, and treatment of DIOS.** *J Pediatr Gastroenterol Nutr.* 2010;50(1):38-42.

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Distal intestinal obstruction syndrome (DIOS) has long been recognized as a complication of cystic fibrosis (CF) that leads to abdominal pain, obstruction, and intussusception. The term has often been used interchangeably with constipation, creating confusion both clinically and in research. The authors, representing the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Cystic Fibrosis Working Group,

proposed consensus definitions of complete and impending DIOS and constipation in patients with CF. The group then retrospectively analyzed the records of children ≤18 years of age between 2001 and 2005 across 8 centers using the consensus definition of complete DIOS. Questionnaires were used to collect the mean number of patients with CF ≤18 years of age in each medical center from 2001 to 2005, the number of children in that same period experiencing complete DIOS, and the number of episodes of DIOS. Investigators recorded the pancreatic status of the children, whether they had meconium ileus at birth, and the specific mutations of the cystic fibrosis transmembrane regulator conductance (CFTR) gene. The treatment of DIOS in each case was described.

Complete DIOS was defined as complete intestinal obstruction with a fecal mass in the ileocecum, accompanied by abdominal pain and/or distention. *Impending* DIOS was defined as a short history of abdominal pain and/or distention, a change in the frequency or consistency of bowel movements in the last few weeks, and relief of symptoms with laxatives. Constipation in CF was defined by the group as requiring the presence of abdominal pain and/or distention, or reduced frequency of stools or increased consistency of stools, *and* that the symptoms are relieved by the use of laxatives.

Over the 5-year period of the study, 51 episodes of complete DIOS were recorded in 39 patients in the 8 centers (incidence: 6.2 episodes per 1000 patient-years). Episodes occurred across the full age-range of the patients. Of the 39 patients, 32 (82%) had a severe CFTR genotype, 36 (92%) were pancreatic insufficient, and 17 (44%) had a history of meconium ileus. Of the patients with complete DIOS, 53% were treated with either diatrizoate meglumine enema (Gastrografin® enema; Bracco Diagnostics Inc.) or polyethylene glycol intestinal lavage. The remaining patients were treated with enemas and/or laxatives; 2 of the 39 patients required surgery.

The absence of specific definitions of CF-related DIOS and constipation has resulted in difficulty in interpreting the literature and designing studies. The ESPGHAN has provided a framework for both the investigational and the clinical evaluation of children with CF who have these conditions. The retrospective review using the new definitions confirmed previous reports that DIOS is more common in severe, pancreatic-insufficient patients with CF. It also demonstrated the response of this entity to several different treatment modalities.

Recent reports from the CF Twin and Sibling Study have suggested that modifier genes contribute substantially to the development of meconium ileus, but not to DIOS.[1] In the same study, regression analysis demonstrated an association between meconium ileus and DIOS, but only for meconium ileus treated with surgery. Importantly, this study left the definition of DIOS up to the CF center reporting the data; repeating the analysis with the definitions developed by the ESPGHAN would ensure that the analysis included authentic episodes of DIOS.

The association between DIOS and surgical management of meconium ileus is likely due to the alteration in motility following surgery or to surgically induced bowel narrowing. It is important to confirm this observation, as it might direct therapy aimed at preventing DIOS toward children who have undergone surgical correction of meconium ileus. The current study of the epidemiology of DIOS may lack the power to analyze separately surgically treated and nonsurgically treated patients with meconium ileus, but larger and better powered studies may address this question. A recent study documented a full-thickness, lymphocyte-predominant inflammatory process in the bowel walls of 6 children with DIOS; evidence of lymphocytic myenteric ganglionitis was present in 4 of these patients.[2] The authors of this study suggest that DIOS is the result of an inflammatory process in the ileum specific to CF. Although this study would also benefit from the diagnostic criteria for DIOS described by Houwen and colleagues, it connects DIOS with the intestinal inflammation examined in, for example, the work of DeLisle, discussed below the other articles.

References

1. Blackman SM, Deering-Brose R, McWilliams R, et al. Relative contribution of genetic and non-genetic modifiers to intestinal obstruction in cystic fibrosis. *Gastroenterology.* 2006;131(4):1030-1039.
2. Smith VV, Schäppi MG, Bisset WM, et al. Lymphocytic leiomyositis and myenteric ganglionitis are intrinsic features of cystic fibrosis: studies in distal intestinal obstruction syndrome and meconium ileus. *J Pediatr Gastroenterol Nutr.* 2009;49(1):42-51.

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SMALL BOWEL BACTERIAL OVERGROWTH IN PATIENTS WITH CYSTIC FIBROSIS

Fridge JL, Conrad C, Gerson L, Castillo RO, Cox K. **Risk factors for small bowel bacterial overgrowth in cystic fibrosis.** *J Pediatr Gastroenterol Nutr.* 2007;44(2):212-218.

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Small intestinal bacterial overgrowth (SIBO) is a quantitative and qualitative change in bacterial populations in the proximal small bowel. The proximal small intestine normally has significantly fewer bacteria than does the terminal ileum (10^4 vs 10^{12} organisms/mL, respectively). Several conditions predispose individuals with cystic fibrosis (CF) to SIBO. Defects in the cystic fibrosis transmembrane regulator conductance (CFTR) gene predispose individuals to intestinal mucus dehydration. Intestinal surgery, often the result of meconium ileus in infancy, is associated with altered intestinal motility and/or blind loops. Recurrent intestinal obstruction from distal intestinal obstruction syndrome further alters motility. The authors determined if adults and children with CF demonstrate a higher prevalence of SIBO than do age-matched, non-CF patients with gastrointestinal (GI) disorders. SIBO was identified using breath hydrogen testing after an overnight fast, with a positive breath test defined as a fasting hydrogen level of ≥15 ppm or a hydrogen rise of ≥10 ppm over baseline. Subjects' medical records were reviewed, and all patients completed a quality of life questionnaire modified from the Cystic Fibrosis Questionnaire to focus on digestive issues.

Of 25 patients with CF, 14 (56%) met criteria for SIBO, compared with 5 of 25 non-CF GI patients (20%), which was statistically significant (P = .02). Fasting breath hydrogen levels were significantly higher in patients with CF than in those without the disease (22 ppm vs 5 ppm, respectively; P = .0001). The presence of SIBO was not correlated with quality of life. Use of low-dose azithromycin was associated with an increased risk for a positive breath hydrogen test; use of daily laxatives and inhaled ipratropium was associated with a reduced risk for a positive breath hydrogen test. The investigators concluded that there is a higher prevalence of SIBO among individuals with CF than among those without the disorder.

This study supports previous studies suggesting that SIBO is a common GI problem in patients with CF. SIBO is clinically characterized by diarrhea, malabsorption, abdominal pain, and flatulence. These conditions all contribute to malnutrition, which is itself a risk factor for decline in pulmonary function in persons with CF.

The results of this study are supported by recent studies in the CFTR null mouse.[1,2] With the use of polymerase chain reaction of bacterial 16S genomic DNA to quantitate bacteria, there was a 40-fold increase in bacteria in the CF mouse intestine compared with the wild-type mouse intestine. Bacteria were found to colonize mucus and to be associated with inflammation in the CF mouse intestine. Treatment of mice with antibiotics reduced bacterial load, decreased expression of inflammation-related genes, and improved growth in CF mice. Subsequent studies from the same group have shown reduced bacterial overgrowth in CF mice after treatment with an osmotic laxative commonly used in CF patients (polyethylene glycol in a balanced salt solution). Understanding the pathogenesis of SIBO in CF in the mouse model is key to developing strategies for the prevention and treatment of this common condition.

References

1. De Lisle RC. Altered transit and bacterial overgrowth in the cystic fibrosis mouse small intestine. *Am J Physiol Gastrointest Liver Physiol.* 2007;293(1):G104-G111.
2. De Lisle RC, Roach E, Jansson K. Effects of laxative and N-acetylcysteine on mucus accumulation, bacterial load, transit, and inflammation in the cystic fibrosis mouse small intestine. *Am J Physiol Gastrointest Liver Physiol.* 2007;293(3):G577-G584.

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IMPAIRED INTESTINAL TRANSIT IN PATIENTS WITH CYSTIC FIBROSIS

De Lisle RC. **Altered transit and bacterial overgrowth in the cystic fibrosis mouse small intestine.** *Am J Physiol Gastrointest Liver Physiol.* 2007; 293(1):G104-G111.

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Intestinal transit is reported to be slow in patients with cystic fibrosis (CF); this abnormality is thought to contribute to small intestinal bowel overgrowth (SIBO) and distal intestinal obstruction syndrome (DIOS) in these individuals. Paneth cells—a source of intraluminal antimicrobial agents—appear to be dysfunctional in the CF mouse intestine. De Lisle examined both the speed of intestinal transit in CF mice, and the interaction of transit rate with SIBO and DIOS. The importance of Paneth cell function in the development of SIBO was also studied. CF null mice were compared with congenic wild-type (WT) mice. Bacterial load was measured using quantitative polymerase chain reaction (PCR) of bacterial 16S rRNA. Paneth cell gene expression was determined by quantitative real-time reverse-transcriptase PCR. Gastric and intestinal transit was measured using a nonnutritive, nonabsorbable tracer—rhodamine-dextran— administered to the mice 20 minutes before death. Contents of the stomach and segments of the intestine were evacuated, and rhodamine fluorescence was determined. Gastric emptying was defined as the percent of tracer remaining in the stomach at 20 minutes. For each of 10 intestinal segments, the fraction of fluorescence per segment was determined. Previous work by this author demonstrated SIBO in CF mice; antibiotic treatment resulted in reduced bacterial load and improved growth in these mice.[1] For this study, transit was examined in both untreated and antibiotic-treated mice.

CF mice in this study developed SIBO as early as 8 days of age—before Paneth cells are active in the mouse. The intestinal bacterial burden in CF mice was greatest in the proximal intestine, suggesting that the accumulation of mucus (associated with intestinal obstruction resembling DIOS) found in the terminal ileum is not a factor in the development of SIBO. Gastric emptying in CF mice was 80% of that in WT mice—a minimal delay. Intestinal transit differed greatly between WT and CF mice. WT mice demonstrated fluorescence in 2 peaks—at 25% and at about 65% down the length of the small intestine. CF mice had a distribution of fluorescence in the first third of the intestine, with little beyond that point. Broad-spectrum antibiotics had no effect on either gastric emptying or intestinal transit in the CF mouse, despite improvement in weight in the treated mice.

De Lisle demonstrates that SIBO occurs in the CF mouse and that slow intestinal transit may contribute to its development. Although the author concluded that Paneth cell dysfunction does not contribute to the development of SIBO in infant CF mice, the life-long occurrence of SIBO in individuals with CF might be impacted by the absence of antimicrobial factors from Paneth cells. Studies of the ontogeny of SIBO could be an important focus of future CF research.

Both SIBO and slow intestinal transit are increasingly being recognized as crucial clinical issues in CF care, because they contribute to the difficulty that CF patients encounter in growing and maintaining weight. The discomfort produced by SIBO and slow intestinal transit may impair intake in CF patients and reduce quality of life. SIBO is associated with diarrhea and malabsorption. Slow intestinal transit has also been described in CF, [2] and may affect appetite and growth. The disorder in transit may also be a factor in the development of duodenogastric bilirubin reflux, recently reported in a small group of CF patients. The authors of this study speculate that this could cause some of the abdominal pain that occurs frequently in individuals with CF.[3]

References

1. Norkina O, Burnett TG, De Lisle RC. Bacterial overgrowth in the cystic fibrosis transmembrane conductance regulator null mouse small intestine. *Infect Immun.* 2004 Oct;72(10):6040-6049.

2. Mascarenhas MR, Mondick JT, Barrett JS, Zhuang H, Edwards K, Schall JI. Comparison of gastric emptying and small bowel transit in subjects with CF and healthy controls. *Pediatr Pulmonol Suppl.* 2006;29:377 (Abstract).
3. Hallberg K, Fandriks L, Strandvik B. Duodenogastric bile reflux is common in cystic fibrosis. *J Pediatr Gastroenterol Nutr.* 2004 Mar;38(3):312-316.

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NONPANCREATIC MECHANISMS OF LIPID MALABSORPTION IN PATIENTS WITH CYSTIC FIBROSIS

Peretti N, Roy CC, Drouin E, et al. **Abnormal intracellular lipid processing contributes to fat malabsorption in cystic fibrosis patients.** *Am J Physiol Gastrointest Liver Physiol.* 2006;290(4):G609-G615.

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Exogenous pancreatic enzyme supplementation alone has not normalized the absorption of fat in patients with cystic fibrosis (CF). Many individuals with the disease experience residual steatorrhea, leading to weight loss and poor growth despite high-quality enzyme therapy. It has been suggested that intraluminal or intracellular cystic fibrosis transmembrane conductance regulator (CFTR) gene–mediated defects, rather than lipolytic defects, might be the cause of this fat malabsorption.[1] Peretti and colleagues examined lipid transport in duodenal biopsies from 6 patients with CF and compared them with biopsies from 6 age-matched, healthy controls. Biopsies were examined by histopathology and by assay of disaccharidase activities, to ensure that they were intact. Lipid synthesis and secretion by the biopsy tissue were determined by following incorporation of [^{14}C]palmitic acid into different lipid classes. Apolipoprotein (apo) biogenesis was measured as incorporation of [^{3}H]leucine into apoB and apoA-I. Microsomal triglyceride transfer protein activity was assayed by evaluating the transfer of radiolabeled triglyceride from donor to acceptor small unilamellar vesicles.

The formation and release of lipids in CF duodenal biopsies was modestly decreased compared with that in normal duodenal biopsies. Incorporation of [^{14}C]palmitic acid into triglycerides, phospholipids, and cholesteryl ester was decreased from control levels by 22%, 31%, and 30%, respectively. Output of triglycerides, phospholipids, and cholesteryl ester into the medium was more significantly impaired, being decreased from control levels by 40%, 38%, and 42%, respectively. These findings demonstrate that although synthesis of lipids is impaired in CF duodenal biopsies, secretion of these lipids is more seriously impaired. The production of apoB-48 and apoA-I was decreased in CF tissue (to 60% and 70% of controls, respectively). There was no difference between CF and normal individuals with respect to microsomal triglyceride transfer protein activity (measured as %transfer). Fatty acid composition of plasma from CF and control patients was measured, with CF patients' plasma showing essential fatty acid deficiency, along with a significant decrease in polyunsaturated fatty acids and an increase in the proportion of saturated fatty acids. The authors concluded that their work demonstrates the reduced capacity of the CF patients' intestines to esterify lipids, produce apolipoproteins, and assemble lipoproteins. They speculated that these abnormalities may be CFTR-related.

Peretti and associates have demonstrated a substantial impairment in the enterocyte intracellular phase of fat absorption in patients with CF. Most importantly, cultured duodenal explants from CF patients were less able to synthesize lipids, were defective in lipoprotein secretion, and had decreased production of apolipoproteins compared with control explants. Although the authors were not able to determine specific pathways responsible for these defects, they did show that the effects are not the result of diminished microsomal triglyceride transfer protein activity. They suggested that essential fatty acid deficiency may contribute to the dysfunction of enterocyte lipid metabolism, similar to the impairment of intraluminal and intracellular fat absorption pathways by essential fatty acid deficiency in rats.[2]

Nonpancreatic enzyme–dependent factors are becoming increasingly important in understanding and, eventually, treating CF lipid malabsorption. High-quality pancreatic enzyme supplements and well-studied supplementation protocols have dramatically improved the digestion of lipids in pancreatic-insufficient CF patients. Even so, studies indicate that malabsorption of long-chain monomeric fats and phospholipids continues to be a concern in patients with CF.[3] Possible mechanisms for this malabsorption include abnormal bile salt kinetics in CF, with poor mixed micelle formation or abnormal terminal ileal function from meconium ileus surgery in infancy or epithelial inflammatory injury. To this list, the current authors add abnormal intracellular metabolism in the enterocytes, resulting in abnormal plasma lipid transport and fat malabsorption. The role of essential fatty acid deficiency in these lipid metabolic abnormalities is particularly intriguing, given the attention to studies of essential fatty acid supplementation in patients with CF.

References

1. Borowitz D, Durie PR, Clarke LL, et al. Gastrointestinal outcomes and confounders in cystic fibrosis. *J Pediatr Gastroenterol Nutr.* 2005;41(3):273-285.
2. Levy E, Garofalo C, Thibault L, et al. Intraluminal and intracellular phases of fat absorption are impaired in essential fatty acid deficiency. *Am J Physiol.* 1992;262(2 pt 1):G319-G326.
3. Kalivianakis M, Minich DM, Bijleveld CM, et al. Fat malabsorption in cystic fibrosis patients receiving enzyme replacement therapy is due to impaired intestinal uptake of long-chain fatty acids. *Am J Clin Nutr.* 1999;69(1):127-134.

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SUPPLEMENTATION OF OMEGA-3 POLYUNSATURATED FATTY ACIDS IN PATIENTS WITH CYSTIC FIBROSIS

Panchaud A, Sauty A, Kernen Y, et al. **Biological effects of a dietary omega-3 polyunsaturated fatty acids supplementation in cystic fibrosis patients: a randomized, crossover placebo-controlled trial.** *Clin Nutr.* 2006;25(3):418-427.

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Patients with cystic fibrosis (CF) have an abnormal fatty acid profile, with excess arachidonic acid (AA) and low docosahexaenoic acid (DHA) in tissues and plasma. As this fatty acid profile is associated with increased tissue inflammation, Panchaud and coworkers sought to demonstrate that supplementation of CF patients with an omega-3 polyunsaturated fatty acid (PUFA) mixture could alter the lipid composition of CF tissue. In this double-blind, randomized, crossover, placebo-controlled trial, an oral liquid supplement ("omega-3 PUFA supplement") containing stearidonic acid, gamma-linolenic acid, eicosapentaenoic acid (EPA), and DHA was used. A total of 17 patients with CF were randomly assigned to receive either an omega-3 PUFA mixture before placebo or placebo before the omega-3 PUFA mixture. The dose of the supplement was weight-based; each treatment period lasted 6 months. The effectiveness of supplementation was measured by assaying the PUFA content of neutrophil membranes. The biologic effect of altering fatty acid content of neutrophil membranes was measured by determination of the leukotriene B4/leukotriene B5 (LTB4/LTB5) ratio after in vitro activation of neutrophils and assaying interleukin-8 (IL-8) metabolism.

The 17 patients studied were 18 ± 9 years of age, and 10 were male. Forced expiratory volume in 1 second (FEV1) was 30% to 60% of predicted in 10 of the 17 patients. There was a significant increase in neutrophil membrane EPA levels (0.5 ± 0.2 at baseline, 0.7 ± 0.6 with placebo, and 1.6 ± 0.6 with the PUFA mixture; $P < .01$) and a decrease in AA/EPA ratio (30.9 ± 18.2 at baseline, 31.1 ± 23.2 with placebo, and 7.5 ± 3.0 with the PUFA mixture; $P < .01$). Stimulated neutrophil release of leukotrienes was altered by PUFA mixture supplementation, from an LTB4/LTB5 ratio of 78 ± 38 at baseline to 72 ± 24 after placebo and 24 ± 7 after the PUFA mixture ($P < .001$, compared to the ratio after placebo). No changes in peripheral neutrophil responses to IL-8 were observed. Additionally, no changes in pulmonary function or anthropometric parameters were reported. Subjects tolerated the PUFA mixture well.

Patients with CF exhibit fatty acid composition that differs from what is normal. Freedman and collaborators demonstrated increased AA/DHA ratios in nasal and rectal mucosa of CF patients compared with controls.[1] Fatty acid abnormalities in individuals with CF are unlikely to be related to inadequate long-chain fat intake or malabsorption of fatty acids. Low linoleic acid in tissue lipids appears to result from cystic fibrosis transmembrane regulator conductance (CFTR) gene–related defective phospholipid synthesis and increased production of AA from linoleic acid. It is less clear why DHA levels are decreased in CF tissues. Several investigators have questioned whether supplementation of specific fatty acids can successfully increase their tissue levels in patients with CF.[2]

This study demonstrates that supplementation of omega-3 PUFAs in patients with CF results in incorporation of these PUFAs into neutrophil membranes, and that this alteration has biologic consequences—that is, alteration of the character of leukotrienes released from in vitro activated neutrophils. As LTB5 is a weaker neutrophil chemoattractant than LTB4, this suggests that supplementation of CF patients with omega-3 PUFAs might reduce inflammation. Particular strengths of this study were the randomization of subjects to the omega-3 PUFA supplement or placebo and the long period of supplementation. As long-chain omega-3 fatty acids are associated with anti-inflammatory effects in many diseases, there is speculation that supplementation of these fatty acids might improve clinical status in CF via a reduction in inflammation. The authors note that a long-term supplementation trial in a large population of CF subjects is warranted, in order to determine if the biologic effects observed with omega-3 PUFA supplementation have a clinically significant effect on patients with CF.

References

1. Freedman SD, Blanco PG, Zaman MM, et al. Association of cystic fibrosis with abnormalities in fatty acid metabolism. *N Engl J Med.* 2004;350(6):560-569.
2. Cawood AL, Carroll MP, Wootton SA, Calder PC. Is there a case for n-3 fatty acid supplementation in cystic fibrosis? *Curr Opin Clin Nutr Metab Care.* 2005;8(2):153-159.

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