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FECAL ELASTASE AND CYSTIC FIBROSIS

Identifying exocrine pancreatic function is at the core of care for patients who have CF. Pancreatic status, in other words pancreatic sufficient (PS) or pancreatic insufficient (PI), impacts GI treatment modalities. Over the years a variety of methods have been used to assess pancreatic function. More recently, the fecal elastase (FE) test has been recommended as a noninvasive method to determine pancreatic function. Several papers provide an overview of the FE test. (Daftary, 2006 and 1) This issue of The Supplement reviews the latest knowledge of FE test and CF.

FEATURED PAPERS:

Longitudinal follow-up of exocrine pancreatic function in pancreatic sufficient cystic fibrosis patients using the fecal elastase-1 test. Walkowiak J, Nousia-Arvanitakis S, Balassopoulou A, Witt M, Herzig K-H. *J Peds Gastro Nutr.* 36:474-78, 2003. **Objective:** To evaluate the usefulness of the noninvasive monoclonal FE test for the longitudinal assessment of exocrine pancreatic function in PS CF patients. **Design:** Longitudinal study. **Subjects:** 184 CF subjects; 90 female; ages 4 mo to 30 yrs (mean \pm SEM, 10.5 ± 0.6 yrs). **Results:** 32 patients were PS at start of study. Over the 5-year duration of the study 8 (25%) patients demonstrated decrease in FE level and were reclassified PI, five of these 8 patients were infants. The decline was more rapid in infants. The decrease in FE concentrations preceded the appearance of steatorrhea in all 8 patients. **Conclusions:** The FE test is a helpful screening tool for the longitudinal assessment of declining exocrine pancreatic function in PS patients with CF.

Fecal elastase-1: Utility in pancreatic function in cystic fibrosis. Daftary A, Acton J, Heubi J, Amin R. *J CF.* 5:71-6, 2006. **Purpose:** To summarize the data from studies reflecting the validity, limitations, and advantages of FE test in assessing pancreatic function in CF patients.

Comparison of monoclonal and polyclonal elisa assays for fecal elastase in patients with cystic fibrosis and pancreatic insufficiency. Borowitz D, Lin R, Baker SS. *J Peds Gastro Nutr.* 2007. **Objective:** To compare the positive predictive value of the monoclonal and the polyclonal FE tests to the coefficient of fat absorption (CFA). **Design:** PI CF patients enrolled in a large study of a new pancreatic replacement enzyme therapy (PERT). **Subjects:** 124 PI CF subjects (48 female). Mean age: 21.3 ± 8.33 yrs. **Results:** With the definition of PI set at a CFA of less than 90% and the test definition of PI using FE set at less than 100 mg/gm, the monoclonal and polyclonal assay positive predictive values equaled 97.6% and 97.4% respectively. **Conclusions:** Positive predictive value of the monoclonal and polyclonal FE tests in patients with CF, using pancreatic replacement therapy (PERT) was very good; correlation with CFA was poor. The median value for the polyclonal elastase assay was higher than for the monoclonal assay. This potentially could lead to lower sensitivity if a lower cut point is used.

SPECIAL POINTS OF INTEREST:

- **Pancreatic status, in other words pancreatic sufficient (PS) or pancreatic insufficient (PI), impacts GI treatment modalities.**
- **The FE test is a helpful screening tool for the longitudinal assessment of declining exocrine pancreatic function in PS patients with CF.**
- **Positive predictive value of the monoclonal and polyclonal FE tests in patients with CF, using pancreatic replacement therapy (PERT) was very good; correlation with CFA was poor.**

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Author: Suzanne H. Michel, MPH, RD, LDN

Editor: Donna H. Mueller, PhD, RD, FADA, LDN

REVIEW

Determination of pancreatic function in persons who have CF is essential to optimize health, improve clinical outcomes, and avoid unnecessary PERT. (Daftary, 2006) Patients who are PI need PERT; conversely, patients who are PS need to avoid unnecessary burden and expense of PERT. Determination of pancre-

IN CF, IT HAS LONG BEEN KNOWN THAT EATING, AND IN PARTICULAR MEALTIMES, CAN BE SOURCES OF STRESS TO THE FAMILY. (BLUEBOND-LANGNER)

atic status based solely on gastrointestinal history not only can lead to misdiagnosis of PI, but also can miss the diagnosis of medical conditions with symptoms similar to fat malabsorption, such as bacterial overgrowth or celiac disease. Additionally, Walkowiak (Walkowiak, 2003) found that the decline in FE preceded signs and symptoms of fat malabsorption. Using the monoclonal FE test Borowitz, et al (2) evaluated pancreatic function in 1215 PI CF children and 67 (5.5%) were determined to meet criteria for discontinuation of PERT. In a population of 85 CF patients identified as PI, Cohen, et al (3) identified 10 (12%) to be PS when evaluated using the monoclonal FE test.

Pancreatic function testing can be divided into two types, direct and indirect. Direct pancreatic function tests involve the collection of duodenal fluid to measure enzymes produced by the pancreas. Direct pancreatic function tests have the highest specificity and sensitivity. The secretin-cholecystokinin test is considered the "gold standard" of direct pancreatic function testing. (4) Direct measurement of pancreatic function through pancreatic stimulation studies can be invasive (requiring duodenal intubation and intravenous injection of pancreatic stimulant), time consuming, uncomfortable, expensive, and are often not standardized. (Daftary, 2006 and 1) Sequential testing to determine changes in pancreatic function is arduous and stressful, especially for patients with advanced lung disease. (1) Therefore, direct studies rarely are performed clinically.

Indirect pancreatic function tests are less invasive and less expensive. They often include the analysis of undigested food or measurement of pancreatic enzyme in stool. Examples of indirect tests are: fecal fat excretion; pancreolauryl test without stimulation; steatocrit, breath tests; and FE test. A comprehensive review of indirect pancreatic function tests in children is provided

by Walkowiak, et al. (4) Many indirect tests have limited specificity and sensitivity, particularly with patients with mild to moderate exocrine pancreatic insufficiency. (4)

The fecal fat test is an indirect test that has been used extensively within the CF population to determine pancreatic function. It is a 72-hour study requiring the consumption of a diet containing a specific amount of fat, careful recording of food intake, and collection of all stool during the three-day period. It is labor intensive for the patient and/or parent and fraught with potential error. The results are reported as a CFA and reflect the amount of fat absorbed. If the test results indicate malabsorption, the cause of the malabsorption is not defined and could be the result of a medical condition other than CF.

An indirect pancreatic function test that is relatively new to CF is the FE test. Pancreatic elastase is a human and pancreas specific enzyme and is one of over 20 digestive enzymes excreted by the pancreas. It is involved in the hydrolysis of peptide bonds. Elastase has the physical chemical property of being stable as it passes through the GI tract; and it is not broken down by intraluminal proteases. Elastase concentration increases as stool passes through the colon and water is withdrawn, thereby making it easy to measure in the stool. (1) There is significant correlation between fecal and duodenal elastase concentration and duodenal lipase, amylase, and trypsin; thus, FE levels reflect the levels of other pancreatic enzymes. (Daftary, 2006) Compared to other methods of determining exocrine pancreatic function, the FE test may be the least invasive while providing reliable, quickly available results. Additionally, it is relatively inexpensive, requires a small amount of stool sample which can be stored at room temperature for short periods of time, (Daftary, 2006) although freezing may reduce odor. Results of the FE test are reported in $\mu\text{g/g}$. Most young, healthy, non-CF adults have FE over 200 $\mu\text{g/g}$. A FE result of less than 15 $\mu\text{g/g}$ is reflective of severe PI. In one large study of patients with CF, the mean value of the monoclonal FE test was 3.9 mg/g for PI patients (range = 0 – 189) and was 491 mg/g for PS patients (range 208 – 867). (2)

Although the monoclonal test gives somewhat lower results than the polyclonal test, regardless of which test is used, patients with CF who have FE less than 200 mg/g should be treated with PERT. Of note, the FE test will identify both primary PI, as is seen in CF, and secondary PI as is seen in cases of severe mucosal damage such as celiac disease. If the cells in the

REVIEW (CONT.)

GI mucosa that release hormonal signals to the pancreas are sloughed, pancreatic enzymes will not be released. In the PI CF patient the problem is irreversible. Secondary PI is reversible if the mucosa heals.

Initial work with FE used the monoclonal assay methodology. An enzyme-linked immunosorbent assay (ELISA) for human FE determination using **monoclonal** antibodies has been available commercially. (6) An ELISA with four different **polyclonal** antibodies also is commercially available. (Borowitz, 2007) In peer-reviewed journals, concern has been expressed that the polyclonal FE test may not be as valid as the monoclonal FE test. The monoclonal FE test is specific to human elastase, and the use of PERT does not influence results. (7) In nonCF patients, studies comparing the monoclonal test to the polyclonal test indicated that the latter may detect some substances different from those measured by the monoclonal test thereby overestimating the elastase present in human stool. (8) Moreover, of concern to clinicians treating CF patients is the statement in the polyclonal test kit

package insert that recommends, when using the polyclonal FE test, PERT be interrupted for up to three days prior to collection of the stool specimen in order to avoid cross-reaction with porcine protein.

To address these concerns, Borowitz et al. (Borowitz, 2007) evaluated both the monoclonal and polyclonal FE test with CF patients on PERT and compared the results to CFA. In CF patients on PERT the positive predictive values of either the monoclonal or polyclonal test were similar whether the cutpoint for PI was set at 100 or 200 mg/g. The values for the polyclonal test were higher than for the monoclonal test and there were more patients with values between 100 mg/g and 200 mg/g when the polyclonal test was used. It is unlikely that any CF-PI patients will be missed if all those with FE of less than 200 mg/g are treated with PERT. Unfortunately, FE correlated poorly with CFA and so, when information regarding the degree of fat malabsorption is indicated, the FE test cannot replace the 72-hour fecal fat test.

CLINICAL APPLICATIONS

The FE test is specific to pancreatic insufficiency and has a high specificity and sensitivity in identifying moderate to severe PI in people who have CF. The FE test continues to be refined for clinical usefulness. It can be used to assess pancreatic function in infants by two weeks of age, independent of gestational age (Daftery, 2006), thusly identifying PI infants possibly prior to overt symptoms of fat malabsorption. This is an important advantage as newborn screening becomes more available at CF Centers nationally. Infants identified as PS may convert to PI in the first two years of life. (10) In a group of PS patients studied by Walkowiak et al., (Walkowiak, 2003) five infants converted to PI within the first year of life. This led the researcher to recommend a more frequent and cautious assessment of pancreatic function in PS CF infants, with the FE test being done on a regular basis in the first year of life even if the infant is asymptomatic. Additionally, older PS CF patients with at least one severe or unknown mutation should be assessed for progression of pancreatic function. (Walkowiak, 2003)

As with any test, it is imperative that standardized procedures for the FE test be followed. Based on Borowitz's study (Borowitz, 2007) both the monoclonal or polyclonal tests appear to provide informative results while the patient remains on PERT, yet some clinical laboratories ask that patients discontinue

PERT use for three days prior to stool collection. Watery stool or stool from an ostomy should not be used for the FE test. The RD is encouraged to contact the CF Center's clinical laboratory for Center-specific directions as to the use of PERT, amount of stool sample required, and methodology for sample storage.

When reviewing FE research studies the reader must be aware of the type of assay used and the medical diagnosis, if any, of the study sample. Current research studies are evaluating a number of innovative indirect pancreatic function tests. When reviewing research describing pancreatic function tests it is important to know the research design and the study sample since PI as seen in CF and the use of PERT may influence results.

In summary, the FE test is a useful addition in the overall management of people who have CF. In addition to using this test, the RD needs to continue to assess: caloric intake; food and nutrient consumption; GI function; blood levels of fat-soluble vitamins and other nutrients; growth and development and PERT adequacy.

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EURAND PHARMACEUTICALS, INC.

790 Township Line Road
Suite 250
Yardley, PA 19067

Phone: 267-759-9400
E-mail: newsletterinfo@eurand.com

Visit our Web Site
www.eurand.com

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