

Pancreatic insufficiency in Cystic Fibrosis



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Abstract

Pancreatic insufficiency (PI) affects about 85% of the cystic fibrosis population. Although most are PI soon after birth, some will have pancreatic sufficiency (PS) for some or all of their life. Understanding the clinical presentation, diagnosis, and management of PI is crucial to the care of people with cystic fibrosis.

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1. Background

Although we think of cystic fibrosis (CF) as a disease of the lungs, it was initially recognized as a cause of failure to thrive in infants. CF was distinguished from celiac disease by Dorothy Andersen in 1938, as a form of lethal malabsorption with an abnormal pancreas on autopsy [1,2]. From the beginning, pancreatic insufficiency has been a key characteristic of CF. Cystic fibrosis is generally characterized as “pancreatic insufficient” (PI) or “pancreatic sufficient” (PS), based on whether the person has enough pancreatic function to grow and maintain health without supplemental pancreatic enzyme therapy (PERT). In general, about 85% of the CF population is PI early in life (before the age of 1 year) [3]. Pancreatic insufficiency correlates closely with the specific mutation of the CFTR genes found in the individual with CF [4]. Individuals with 2 severe CFTR mutations (classes I, II, III, and VI) tend to have early PI, often being PI at birth, while those with 2 mild CFTR mutations (classes IV and V) or with one severe and one mild mutation tend to be PS at birth [3].

Individuals with CF have evidence of pancreatic disease beginning in fetal life [5]. Autopsy studies of infants with CF demonstrated deficiency in development of pancreatic acinar

tissue compared to age-matched controls [6]; it should be noted that these autopsy studies predate both careful assessment of exocrine pancreatic sufficiency status and CF gene mutation analysis. It is thus likely but not confirmed that the tissue studied came from individuals destined to be PI. The loss of acinar tissue was progressive, with older infants deviating more from their age-matched controls. Fibrosis was common, as was variable duct dilatation. It has been thought that the injury to the pancreas is the result of secretory material collecting within the ducts, creating obstructive destruction of acinar tissue [7]. In the CF pig model, similar in utero changes were seen, with active inflammation limited to the pancreas [8]. Expression of pro-fibrotic, pro-inflammatory, and complement cascade genes are increased in CF compared to non-CF pigs [9]. In summary, in CF, substantial injury to the pancreas occurs early in life. The extent of injury is variable, as evidenced by the variable degree of exocrine insufficiency at birth [10].

The approximately 15% of individuals with CF who are PS have adequate exocrine pancreatic function to digest and absorb food and grow normally [3]. Generally, CF patients who are PS have milder pulmonary disease and longer lives than those born PI [11]. However, they do not have completely normal pancreatic function [3]. Their pancreatic function may deteriorate over time, with or without the complicating effects of pancreatitis.

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Compared to the early damage to exocrine pancreatic tissue, endocrine tissue is relatively preserved in early in life, but in many PI individuals islets cells are gradually destroyed [12]. Approximately 20% of adolescents and up to 50% of adults develop cystic fibrosis-related diabetes (CFRD), a unique form of diabetes with similarities to both type 1 and type 2 diabetes [13]. Some PS patients will also develop CFRD [14]. The pathophysiology of CFRD is complex, with early evidence of disordered glucose regulation, and evidence of diabetes generally developing after age 6 years [12]. The level of a biomarker for pancreatic sufficiency, circulating immunoreactive trypsinogen, measured in newborns, was inversely correlated with the risk of later CFRD [15]. This suggests that worse exocrine pancreatic disease in infancy predicts CFRD at an older age.

In summary, while pancreatic insufficiency was described early in the history of CF, it is recognized that not all people with CF begin life PI, and that some people with CF born PS will become PI through their lifespan. PI is the result of obstructive destruction of exocrine tissue, beginning early in life for those with 2 severe CFTR mutations. Importantly, individuals with CF born PS may become PI at any age, and without symptoms initially, emphasizing the importance of constant monitoring.

2. Clinical presentation and differential diagnosis

The classic symptoms and signs of exocrine pancreatic insufficiency include weight loss, gas, bloating, dyspepsia and loose foul-smelling oily stools that can be difficult to flush (steatorrhea). It should be noted that these signs and symptoms do not help to differentiate pancreatic from non-pancreatic causes of malabsorption (Table 1). Exocrine pancreatic insufficiency may develop without symptoms, or may be characterized by failure to thrive in the infant and child or unexplained weight loss in the adult.

Differential diagnosis for PI is quite broad. It is important to consider CF when symptoms of PI are present. Newborn screening has reduced sensitivity to the possibility of CF as a cause of failure to thrive or weight loss, but there are reports of missed diagnosis of CF in CF newborn screening [16,17]. Older children and adults may have been born before the institution of newborn screen for CF in the state of their birth; older individuals with PS CF may develop PI over time, sometimes without knowing they have CF. Thus, despite the use of newborn screen for CF in most developed countries, a sweat chloride should be an early step in the differential diagnosis of pancreatic insufficiency or malabsorption. Other diseases that may

mimic PI CF include other causes of pancreatic insufficiency, other causes of intestinal malabsorption, and some behavioral problems (see Table 2). A general guide to the evaluation of malabsorption is available [18]. The initial evaluation should include a careful history and physical exam, which will guide the selection of laboratory, imaging studies, and procedures.

3. Diagnostic workup

3.1. Tests for pancreatic insufficiency

Two problems complicate the diagnosis of exocrine pancreatic insufficiency. First, there is no gold standard for the diagnosis or degree of severity of pancreatic exocrine insufficiency. Second, available tests are positive only when the exocrine pancreatic function is severely impaired [19]. There are multiple indirect and direct tests of pancreatic exocrine function. The indirect tests include laboratory evaluations of blood and stool as well as breath tests. Because of methodological problems, blood and breath tests are not in common use and will not be discussed. The direct tests involve the collection of secretagogue-stimulated pancreatic fluid in the duodenum through a Dreiling tube or an

Table 1
Non-pancreatic causes of malabsorption.

Celiac disease
Crohn's disease
Zollinger-Ellison syndrome
Small intestinal bacterial overgrowth
Gastroparesis
Gastric bypass surgery
Short bowel syndrome

Table 2
Differential diagnosis of pancreatic insufficiency.

Age	Class	Disease
Infant	Pancreatic insufficiency	Schwachman-Diamond
		Pearson's Pancreas-Marrow
		Johanson-Blizzard Syndrome
Child	Pancreatic insufficiency	Pancreatectomy
		Schwachman-Diamond
		Pearson's Pancreas-Marrow
Adult	Pancreatic insufficiency	Pancreatectomy
		Schwachman-Diamond
		Chronic pancreatitis
Infant	Intestinal malabsorption	Short bowel
		Congenital malabsorption syndromes ^a
		Infection
Child	Intestinal malabsorption	Cholestasis
		Infection
		Short bowel
Adult	Intestinal malabsorption	Celiac disease
		Cholestasis
		Crohn's disease
Infant	Behavioral	Infection
		Celiac disease
		Cholestasis
Child	Behavioral	Gastric bypass surgery
		Crohn's disease
		Zollinger-Ellison Syndrome
Adult	Behavioral	Short bowel
		Neglect/abuse
		Munchausen by proxy
Child	Behavioral	Neglect/abuse
		Munchausen by proxy
		Anorexia (use of purges)
Adult	Behavioral	Anorexia (use of purges)

^a Including abetalipoproteinemia, hypobetalipoproteinemia, intestinal lymphangectasia.

endoscope. Imaging to demonstrate pancreatic flow is also in current use.

3.1.1. Indirect tests

The gold standard for diagnosing steatorrhea is a 72 h fecal fat estimation using the van de Kamer method [20]. A positive test is defined as >7 g of fat over a 24 h period. This is only indicative of the presence and not the cause of fat malabsorption. It remains, however, the most common test performed for research, especially to assess the effectiveness of pancreatic enzyme replacement therapy [21]. As this test involves consuming a high fat diet (100 g fat diet each day for adults) for 5 days with the collection of all stool output over the last 3 days, it is not commonly performed due to its inconvenient and cumbersome nature. The test measures steatorrhea, which only occurs once pancreatic lipase output has fallen to <5–10% of normal [22]. It does not measure other elements of pancreatic exocrine function and cannot identify mild or moderate insufficiency. It should be noted that infants have a normal coefficient of fat absorption of $\geq 85\%$, compared to adult normal valued of $\geq 93\%$ [23]; thus when this test is used in infants a different standard must be applied. Qualitative fecal fat (“spot fecal fat”) is not recommended due to its lack of specificity since a high fat intake in a normal patient can lead to a false positive result and diets rich in calcium can lead to increased fecal fat excretion [24]. The acid steatocrit has similar limitations and was shown to be less accurate than fecal fat excretion studies [25].

Fecal elastase-1 (FE-1) is the most commonly used test to screen for pancreatic exocrine insufficiency. The monoclonal ELISA assay is considered to be more accurate than the polyclonal test for FE-1 [26]. The sensitivity and specificity of FE-1 for diagnosing PI improves when a cut-off concentration of <128 $\mu\text{g/g}$ stool is utilized [27], with a recent study reporting that 84 $\mu\text{g/g}$ stool has even higher diagnostic accuracy with a sensitivity of 87.5%, specificity of 81.6%, PPV 66.7%, NPV 93.9%, and AUC of 0.861 when compared to 72 h fecal fat estimation [28]. Others note that a level >100 $\mu\text{g/g}$ stool has a 99% predictive value for the subject not being PI [29]. FE-1 is recommended for the assessment of PI in CF patients as well as for annual monitoring of PS CF patients for conversion to PI [30]. The advantages of FE-1 determination are that the test is simple, inexpensive, results are not affected by the use of PERT and stool specimens can be assayed as late as 5 days from the time of collection. There can be false positive results if the test is performed on a watery stool specimen; therefore, all FE-1 testing should be performed on a formed or semi-formed stool specimen. Individuals with severe malnutrition may also have false positive FE-1 [31], although in the case of a patient with CF the PI is the likely cause of the malnutrition. In non-CF patients, testing should be repeated after nutritional repletion.

3.1.2. Direct tests

The direct tests involve the collection of cholecystokinin and/or secretin stimulated pancreatic fluid from the duodenum at specified time points for the assessment of pancreatic enzyme and bicarbonate concentrations, respectively. The direct test was originally performed using Dreiling tubes that contained three ports - a gastric port to aspirate all gastric secretions, an

infusion port for a non-absorbable marker and an aspiration port to collect duodenal fluid. Given similar results of secretin stimulated pancreatic function testing in crossover trials using Dreiling tubes and sample collection by endoscopy in healthy subjects [32] and patients with chronic pancreatitis [33], endoscopy has largely replaced the use of Dreiling tubes. A modified version of the endoscopic secretin pancreatic function test, where pancreatic fluid was collected at 30 and 45 min instead of 60 min, was able to accurately differentiate between PI-CF ($n = 13$) and PS-CF ($n = 18$) patients as well as normal controls ($n = 25$) [34]. The major drawbacks to the direct endoscopic function tests are that they are expensive, require an invasive procedure with sedation, lack standard protocols with clear reference values, and the brief pancreatic fluid aspiration periods can result in abnormal bicarbonate concentrations in normal individuals. These tests are rarely used in CF, however a protocol for their performance is available [35].

3.1.3. Imaging

Although radiologic and endoscopic imaging is highly accurate for diagnosing the morphologic changes of chronic pancreatitis, their utility for diagnosing PI is questionable. Studies that have evaluated radiographic and endoscopic imaging have used other indirect and direct tests of PI as their standard. A recent study evaluated secretin stimulated magnetic resonance imaging (s-MRI) for the diagnosis of PI in CF. They found that the secreted pancreatic fluid volume at 13 min had the highest diagnostic accuracy for PI with an AUC of 0.93. In this study, s-MRI distinguished healthy controls from PI CF well, but did not distinguish PS and PI CF well [36]. Another study that evaluated secretin-ultrasonography showed that the degree of duodenal filling was an accurate predictor of PI, especially in CF compared to chronic pancreatitis patients [37]. There are several disadvantages to using these studies for diagnosing PI including inter-observer variability, high cost of secretin, and the lack of controlled studies.

3.2. Application in the patient

All individuals diagnosed with CF, regardless of age, should have testing for pancreatic insufficiency performed as soon as possible [23,38]. While the CF Foundation recommends testing with either a 72 h fecal fat analysis or FE-1, in practice the majority of testing is done using FE-1. Infants with two copies of severe CFTR mutations are generally pancreatic insufficient (FE-1 <200 $\mu\text{g/g}$ stool) before 4 months of age [10]. Some authors have found small numbers of subjects with fluctuating FE-1 in the first year of life [39], but generally a low initial FE-1 portends pancreatic insufficiency and the need for PERT. Children with low FE-1 and a genotype compatible with PI should not have the test repeated multiple times looking for a normal result to eliminate the need for PERT. Infants with a normal FE-1 at their first test should be retested at one year of age, and yearly thereafter, or when symptoms of PI develop, as individuals who are PS at diagnosis may well develop PI with time [30,40]. For the infant with 2 severe CFTR mutations who tests PS, very close monitoring of growth and consideration of

more frequent testing in the first year may prevent significant failure to thrive. In one study of infants, of 13 who were PS at age <3 months, 3 became PI over the first year of life [39]. Similarly, of 32 people with CF who were PS and followed for 5 years, 8 ended the 5 year study PI (5 infants and 3 adults) [41]. Notably, decreased FE-1 concentration in the stool preceded development of steatorrhea in all patients.

Individuals with clinical evidence of pancreatic insufficiency at the time of testing, or who are known to have 2 severe disease causing CFTR mutations can be started on pancreatic enzyme therapy (PERT) ahead of results [23]. This is particularly crucial for infants, who may develop nutritional deficits during the diagnostic period if not on PERT. If the individual screens negative for PI using the FE-1 test the PERT can be stopped. The patient's genetic analysis is not the basis for provision of PERT.

All PI individuals should have testing of levels of fat-soluble vitamins (A, E, D, and K) at diagnosis and then, at a minimum, every year. Deficiencies of each of the fat soluble vitamins have been found in people with cystic fibrosis and adverse clinical consequences have occurred [42,43]. Low vitamin A is associated with night blindness, xerophthalmia, abnormalities of perinatal development, deficient tissue repair, and immune deficiencies [44]. Ideally, laboratory testing for vitamin A would include both plasma retinol (to assess deficiency) and retinyl esters (to assess toxicity). In practice, many labs measure only retinol. Vitamin D deficiency impairs bone health, regulation of cell proliferation and differentiation, the immune system, and cardiac and neurologic functions [45]. Testing for vitamin D sufficiency in people with CF is generally done by quantitating circulating levels of 25-hydroxyvitamin D; testing for 1,25-hydroxyvitamin D should not be necessary in individuals with normal kidney function [46]. The most common supplemental form of vitamin D is vitamin D₂, or ergocalciferol, a plant derived or artificially synthesized form of the vitamin. In contrast, vitamin D synthesized in the skin is vitamin D₃. In some labs, testing for "total vitamin D" or "vitamin D deficiency" has limited detection of vitamin D₂, underestimating total vitamin D in an individual supplemented with vitamin D₂. This can lead to prescription of excessive doses of vitamin D. Most labs have an assay that separately measures both D₂ and D₃. Clinicians should be careful to choose the appropriate test. Vitamin E is crucial for normal neurologic development; deficiency has been associated with spinocerebellar ataxia, pigmented retinopathy, and skeletal myopathy [47]. Vitamin E should be assayed as α -tocopherol, ideally measured in the fasting state with simultaneous measurement of total lipid (cholesterol plus triglycerides). The ratio of α -tocopherol (in mg) to total lipid (in g) is a more accurate reflection of vitamin E tissue stores than the α -tocopherol alone. Vitamin K is critical in coagulation, as well skeletal health. Vitamin K measurements reflect recent intake of this vitamin and are not useful [48]. We do not recommend assaying vitamin K levels. PIKVA-II (proteins induced by vitamin K absence or antagonism) is a long-lived form of vitamin K that may be of value in assessing adequacy of this vitamin, but few labs perform this test. PT/INR is generally used to assess adequate vitamin K levels, with the known limitation that this is an insensitive method. Testing for vitamin B12 deficiency should not be necessary unless

the individual has prolonged untreated PI [49]. Supplementation should be directed by the test results (see below).

4. Routine management

The management of pancreatic insufficiency in individuals with CF is a lifelong therapy. It is crucial that treatment include age-appropriate education through the lifespan, emphasizing the importance of good nutrition in prolonging survival in CF and the effective use of PERT. The majority of this work falls to the dietitian specialized in CF care. Partnering with the CF dietitian early in the management of a patient with CF, and acting as a member of the CF team, will reduce error, inconsistent recommendations, and improve consistency of care of these complex patients.

4.1. PERT

Provision of appropriate PERT is crucial to normal growth and development in children and maintenance of weight in adults. The majority of patients will use enteric-coated porcine-derived enzymes packaged into gelatin capsules. While the gelatin capsule dissolves in the stomach, the enteric coating around the enzymes dissolves at a pH of 5–5.5 [50]. Studies of the intestinal pH in CF have shown that this pH is reached more distally in the intestine in CF than in normal individuals, suggesting that pancreatic enzymes are likely available more distally in CF than in normal individuals [51,52]. Enzymes without enteric coating are susceptible to destruction by gastric acid; this is not true for enteric-coated enzymes and modern PERT does not require acid suppression for survival of the enzymes into the intestine [53] (for other reasons for providing acid suppression to individuals with CF, see below).

PERT capsules are available in a number of different strengths, allowing provision of the appropriate dose to all ages of patients. The number after the enzyme name denotes the number of lipase units/capsule in 1000's. The strength of the capsule should be chosen to minimize the number of capsules a patient must take with meals while allowing an appropriate enzyme dose. Patients and families should be limited to a single strength of enzyme capsule to avoid confusion. They should also be instructed in the safe use of enzymes, including the risk of ingesting excessive doses of enzymes: enzymes should be viewed as medications. Enzymes must not be exposed to heat (for example, storage in a glove compartment in a car in summer), as this may reduce their effectiveness. Enzymes should be taken during or just after a meal [54]. Schools often insist that children take their enzymes in the nurse's office, then proceed to the cafeteria. It is unlikely that active enzyme remains by the time the child eats their meal. This can lead to poor weight gain; physicians should impress upon the schools the risk to the child in this restriction.

Some individuals may express cultural or religious objections to the use of porcine-derived pancreatic enzymes. It is important to make patients aware that the "enzymes" sold in many health food stores or as alternative therapies do not have the capacity to digest food and are not appropriate substitutes

for pharmaceutical PERT. At present, there is no PERT derived from kosher or halal animals; no FDA-approved PERT is vegan. When there are concerns, encouraging consultation with clergy is advised early in the clinical course. In general, Jewish and Muslim clergy have approved the use of porcine-derived enzymes as a life-saving therapy.

Dosing of PERT can be based on body weight, fat content of meals, or pancreatic lipase output. Specific recommendations for infants, older children, and adults are noted below. In particular, the CFF Infant Guidelines provide important information for the use of enzymes in this age group, including methods to administer enzymes to infants [40]. The CF Dietitian is well-versed in the provision of appropriate enzyme doses and should be consulted. For body weight based dosing, the CF Foundation recommends 500–2500 units of lipase/kg per meal and half of this with snacks for individuals beyond infancy. For dosing by fat content of meals, 500–4000 units of lipase per gram of fat ingested per day is considered to more closely mimic pancreatic enzyme secretion in response to a meal. However, the quantity of fat in meals can be difficult for patients to calculate. Dosing by pancreatic lipase output is only applicable to adults. Studies have shown that the mean postprandial lipase output of 2000–4000 units/min is maintained for 4 h after a meal. Thus, a total of 480,000–960,000 units of lipase are secreted during a meal [55]. In order to prevent fat malabsorption, lipase output has to exceed 5–10% of normal levels; therefore, 50,000–100,000 units of lipase are required per meal. This last method is not generally used in the management of CF.

There are no clear guidelines for provision of PERT during enteral tube feeding [56]. PERT capsules should not be crushed or dissolved for insertion into enteral feeds. Some authors have shown that provision of half the required dose of PERT at the beginning of feeding and the second half at the end of feeding is effective in promoting weight gain [57,58]. While some centers crush non-enteric coated enzyme into tube feedings, there is no evidence that this is effective. Recently a cartridge with immobilized pancreatic lipase has been approved by the Food and Drug Administration for use in adults with PI. Thus far there is limited data on its use, however it appears to be safe and effective at improving fat digestion in enteral feedings [59]. Of note, as the cartridge contains only lipase, it is suitable for feedings to provide supplemental calories, but may not be suitable for patients who receive the majority of all their nutrients via enteral feedings.

Studies have shown that the intestinal tract in CF is relatively acidic, likely both from the lack of pancreatic bicarbonate and the abnormal bicarbonate secretion from intestinal cells [60]. This has led to speculation that bile acids, crucial for mixed micelle formation, may precipitate in the CF intestine [61]. Acid suppression, usually with proton pump inhibitor, has been suggested to improve bile salt availability and thus, absorption [62–67]. There is no clear evidence supporting the use of proton pump inhibitors in this context. When individuals with CF are not thriving, a trial of acid suppression may be appropriate. Given the known potential complications of long-term acid suppression, the trial should be limited with clear endpoints (weight gain, for example).

4.2. Dosing of fat soluble vitamins

Fat soluble vitamin supplementation should begin in PI patients at the same time as initiation of PERT. Levels of A, E, D, and PT/INR should be performed annually and 3–6 months after a change in vitamin therapy [30]. Practically speaking, people with CF are usually supplemented with fixed ratio supplements containing water-miscible forms of the fat soluble vitamins. The content of CF-specific multivitamins is available on line [68].

However, some individuals develop deficiency of a single fat soluble vitamin, and must have additional supplementation of it. A discussion of individual vitamins and preferred forms for supplementation in CF was recently reviewed [30]. Maintaining bone health in CF has proven especially difficult; Cystic Fibrosis Foundation guidelines are available [46].

4.3. Endocrine insufficiency

Familiarity with CFRD, its diagnosis and management is important to accurate assessment and treatment of gastrointestinal disease in CF. While the care of the individual with CFRD should be done by an endocrinologist with experience in this unique form of diabetes, review of the Cystic Fibrosis Foundation guidelines for CFRD and a review of the current thinking on this disease is important [13,69,70].

4.3.1. Novel therapies

Technology may improve our ability to prevent or treat exocrine pancreatic insufficiency in CF. Children ages 2–5 years with CFTR gating mutations were shown to have an improvement in FE-1 during a trial of ivacaftor [71]. This may suggest that, as modulators are tested in younger populations, that some preservation or recovery of exocrine pancreatic function may be seen.

Alternatives to porcine-derived PERT are being studied. Liprotamase is a biotechnology-derived combination of crystalline lipase, crystalline protease, and amorphous amylase. It has been evaluated in phase I, II, and an open-labeled phase III study [72]. The phase III study demonstrated that the product was safe, well-tolerated, and associated with age-appropriate weight gain or maintenance in PI CF subjects. Concern has been expressed because liprotamase does not include many other pancreatic enzymes present at low concentrations in porcine extracts; this enzyme is not approved by the FDA, but studies continue.

A recent randomized crossover trial of a novel liquid microbial lipase (NM-BL) formulation showed efficacy for the treatment of PI in CF patients [73]. This was an early phase trial; therefore, a larger phase III study will be required before this is available for patients. The advantage of this formulation is that it could be used in younger patients and/or those requiring enteral nutrition through feeding tubes.

Pancreatic transplantation can restore exocrine function, but at the cost of life-time immunosuppression. In CF, some patients requiring liver transplantation have had concomitant pancreas transplant [74] and it has been recommended that this be

considered more often [75]. Isolated pancreas transplant for CF-related diabetes is not recommended.

5. Complications and their management

The most common concern associated with PERT is poor growth and/or loss of weight despite provision of adequate PERT dose. The most common cause is poor patient adherence to PERT or mishandling of PERT. Patients and their families should be closely questioned regarding this. For adults, PERT may not be covered adequately by insurance. The CF Foundation has programs designed to assist in the purchase of PERT [76], as do some pharmaceutical companies.

If convinced that PERT is being used correctly, a thorough investigation for other causes of failure to thrive or weight loss is important. Some individuals with CF cannot orally consume the calories necessary for appropriate growth or weight maintenance, and may require supplemental feedings via an enteral feeding tube to maintain their health. The decision to place an enteral feeding tube should be preceded by an investigation of other causes of poor weight gain or maintenance [18,56].

Direct complications of PERT are limited. Some providers and patients have suggested that PERT can cause constipation, but studies have not supported this [77]. In the early 1990's, a life-threatening entity termed fibrosing colonopathy affected a small number of CF patients [78–80]. Individuals with this condition developed abdominal pain, diarrhea, and evidence of intestinal obstruction. Investigation showed a severely damaged colon with loss of haustral markings, severe fibrosis, and loss of motility. This illness was associated with very high doses of pancreatic enzymes. Limiting PERT doses to <10,000 lipase units/kg/day ended the epidemic of fibrosing colonopathy [81].

6. Potential clinical trial endpoints

There are several potential pancreatic endpoints that could be utilized for a trial of new CF therapies but all of these have limitations. Fecal elastase has been used in studies of modulators to assess changes in pancreatic function [71]. As stated above, the current measures of exocrine pancreatic function require severe insufficiency to be informative. Subtle changes in function cannot be detected with current technology. The coefficient of fat absorption (CFA) has been the regulatory “gold standard” for trials assessing the efficacy of PERT. However, given the limitations discussed above, another measure to assess the efficacy of PERT is needed. The malabsorption blood test has been suggested as a possible method to detect differences in fat absorption in people with CF with or without enzymes. In this currently experimental test, pentadecanoic acid (a free fatty acid) and triheptadecanoic acid (a triglyceride requiring lipase for absorption) are given simultaneously. The difference between the serum concentration of the two fats reflects pancreatic-based digestion [82,83].

For PS-CF patients with acute pancreatitis, the frequency of additional episodes of acute pancreatitis could be a trial endpoint. However, a trial utilizing this endpoint would require many patients and take several years as the frequency of acute

pancreatitis varies by CFTR genotype [84], and possibly, environmental exposures (e.g. alcohol, smoking) that are known to reduce CFTR function [85–88]. It is also not clear whether reducing the frequency of additional episodes of acute pancreatitis in PS-CF will reduce the risk of conversion to PI and/or the development of chronic pancreatitis.

7. Future directions

While the use of CFTR modulators is focused on improving pulmonary function, their impact on pancreatic function may play a critical role in improving well-being and survival in people with cystic fibrosis. Understanding which therapies have the most impact on the pancreas, and the necessary timing to maximize this effect will be important. Optimizing PERT would be advantageous. Improved release of PERT in the intestine, the capacity to determine optimal dosing, and strategies to improve patient adherence are crucial.

8. Clinical practice points

- Approximately 85% of the CF population is PI early in life (before the age of 1 year).
- Some people with CF born PS will become PI through their lifespan.
- All individuals diagnosed with CF, regardless of age, should have testing for pancreatic insufficiency performed as soon as possible. In practice the majority of testing is done using FE-1.
- Individuals with clinical evidence of pancreatic insufficiency at the time of testing, or who are known to have 2 severe disease causing CFTR mutations can be started on pancreatic enzyme therapy (PERT) ahead of results. Provision of appropriate PERT is crucial to normal growth and development in children and maintenance of weight in adults
- All PI individuals should have testing of levels of fat-soluble vitamins (A, E, D, and K) at diagnosis and then, at a minimum, every year.
- Urgent evaluation of the patient with poor growth and/or loss of weight despite provision of adequate PERT is critical.

9. Summary

In summary, pancreatic insufficiency affects a substantial portion of the cystic fibrosis population. Applying best practices with respect to diagnosis and management can improve nutrition in people with cystic fibrosis. The 10–15% of people with CF born pancreatic sufficient will need monitoring for possible future loss of pancreatic function and consideration of pancreatitis as a diagnosis for abdominal pain.

Conflict of interest

AbbVie, Inc (SJS, consultant), Cystic Fibrosis Foundation (SJS, consultant); AbbVie, Novo Nordisk, Akcea, Ariel Precision Medicine (VS, consultant), Nordmark (VK, advisory board participant).

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