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REVIEW

Potential for Screening for Pancreatic Exocrine Insufficiency Using the Fecal Elastase-1 Test

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Abstract The early diagnosis of pancreatic exocrine insufficiency (PEI) is hindered because many of the functional diagnostic techniques used are expensive and require specialized facilities, which prevent their widespread availability. We have reviewed current evidence in order to compare the utility of these functional diagnostic techniques with the fecal elastase-1 (FE-1) test in the following three scenarios: screening for PEI in patients presenting with symptoms suggestive of pancreatic disease, such as abdominal pain or diarrhea; determining the presence of PEI in patients with an established diagnosis of pancreatic disease, such as chronic pancreatitis or cystic fibrosis; determining exocrine status in disorders not commonly tested for PEI, but which have a known association with this disorder. Evidence suggests the FE-1 test is reliable for the evaluation of pancreatic function in many pancreatic and non-pancreatic disorders. It is non-invasive, is less time-consuming, and is unaffected by pancreatic enzyme replacement therapy. Although it cannot be considered the gold-standard method for the functional diagnosis of PEI, the advantages of the FE-1 test make it a very appropriate test for screening patients who may be at risk of this disorder.

Keywords Fecal elastase-1 · Pancreatic exocrine insufficiency · Chronic pancreatitis · Diabetes mellitus · Malnutrition

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Introduction

Patients with pancreatic exocrine insufficiency (PEI) are sometimes misdiagnosed or left untreated because certain symptoms, such as abdominal pain, weight loss, nausea, and diarrhea, can be attributed to other diseases [e.g., functional dyspepsia, irritable bowel syndrome (IBS), or peptic ulcer] [1, 2]. PEI is caused by numerous pancreatic disorders, including chronic pancreatitis (CP), cystic fibrosis (CF), diabetes, obstruction of the pancreatic duct system by a tumor or stricture, or loss of pancreatic parenchyma following pancreatic resection [3]. PEI may also be caused by extra-pancreatic conditions, including gastric surgery, celiac disease, Zollinger–Ellison syndrome, and HIV infection [4–6]. Mild PEI is difficult to detect in patients as it may be asymptomatic [7]; however, as PEI progresses, they may present with frequent diarrhea, gas and bloating, which can cause abdominal pain, and weight loss due to impaired nutrient absorption [8]. Fat maldigestion and malabsorption are usually the determining factors that cause the most important symptoms and some clinical complications. This is because lipase activity is poorly compensated by extra-

pancreatic mechanisms and also has the poorest stability of the pancreatic enzymes in the gastrointestinal lumen [9]. Impairments in fat digestion affect the absorption of the fat-soluble vitamins A, D, E, and K, all of which, together with other PEI-related nutritional deficits, could be associated with complications such as cardiovascular disease, compromised immunity, cancerogenicity, psychological disorders, hypoprothrombinemia, bleeding disorders, night blindness, and muscle weakness [10–12]. Early detection of PEI can help prevent malabsorption-/malnutrition-associated complications by enabling expedient treatment with pancreatic enzyme replacement therapy (PERT), which numerous clinical trials have shown to be highly effective, not only in patients with CP, but also following pancreatic surgery, and in children and adults with CF [6, 13–16]. Clinically, the most common cause of PEI is CP, although symptoms of PEI may not appear until several years after disease onset [17]. In contrast, PEI is present at birth in 85% of infants with CF [18]. The high prevalence of PEI in these disorders creates a great need for a reliable, simple diagnostic tool to screen patients and determine whether they require PERT.

Diagnosis of Pancreatic Exocrine Insufficiency

Direct tests of pancreatic function, including the secretin, secretin–cholecystokinin (CCK) (secretin–pancreozymin), or secretin–cerulein stimulation tests, have the highest accuracy for evaluating pancreatic secretion, but are invasive, time-consuming, expensive, and not fully standardized [19]. Moreover, CCK and its analogs are not currently available for human use. Fecal tests, such as the 72-h fecal fat or fecal elastase-1 (FE-1) tests, and ^{13}C-breath tests have various advantages and disadvantages in the quantification of exocrine function. The 72-h fecal fat test is the gold standard for the quantification of steatorrhea, but it does not detect mild or moderate alterations of pancreatic function, which can be associated with earlier stages of pancreatic disease. Several ^{13}C-breath tests, including the ^{13}C-mixed triglyceride (MTG) test, have been developed for evaluating pancreatic exocrine function, but they are associated with greater time consumption than the FE-1 test [20]. Table 1 summarizes the advantages and disadvantages of the currently available pancreatic function tests [3, 8, 21, 22].

The Fecal Elastase-1 Test

The FE-1 test measures fecal levels of elastase-1, a proteolytic enzyme produced by pancreatic acinar cells, which binds to bile salts and passes through the gut with minimal degradation. Pancreatic elastases constitute around 6% of the secretion, with fecal levels being approximately five times that of the pancreatic juice [16]. Fecal levels of elastase-1 correlate well with its pancreatic output, as well as the output of other pancreatic enzymes, such as amylase, lipase, and trypsin [17, 18]. Furthermore, elastase-1 is highly stable in feces for up to 1 week at room temperature, and for 1 month when stored at 4 °C, thus removing the requirement for specialist testing facilities or storage conditions [16]. One of the main advantages of the monoclonal FE-1 test, compared with other tests of pancreatic function, is that it does not require interruption of patient treatments with oral pancreatic enzyme supplements, because it only detects the human form of FE-1 [17]. The FE-1 test should be used with caution in patients with diarrhea, because watery stools can cause false-positive results, although this can be prevented by lyophilization of stool samples and adjustment to a standardized water content of 75% [19].

In contrast to many other pancreatic function tests, which can be expensive and require specialist testing facilities, the FE-1 test is easy to perform and samples can be obtained by either the patient or their general physician. Furthermore, it is more cost-effective test than other tests of pancreatic functions, including the secretin-stimulation test and fecal fat analysis [21]. To date, two commercially available enzyme-linked immunosorbent assays (ELISAs) have been used for the measurement of FE-1, by means of a monoclonal or polyclonal antibody. The monoclonal FE-1 assay has been confirmed to have good sensitivity and specificity for moderate and severe PEI in comparison with direct function tests, as well as with magnetic resonance cholangiopancreatography (MRCP) combined with diffusion-weighted magnetic resonance imaging (MRI) and endoscopic retrograde cholangiopancreatography (ERCP), which was long regarded as the gold standard of pancreatic imaging for CP [23–27]. More recently, a polyclonal FE-1 assay has been developed using two different polyclonal antisera to human pancreatic elastase, which recognize different antigenic epitopes [28]. It should be underlined that concentrations of FE-1 obtained with the polyclonal test tend to be higher than those obtained with the monoclonal test [29, 30]. This should be taken into account when specifying normal values with the polyclonal test. Both the monoclonal and polyclonal assays are widely used in clinical practice, with a number of studies directly comparing the two tests [28, 29, 31]; however, a direct comparison of the two tests in patients with PEI and against an appropriate reference standard has yet to be performed. Recently, a new rapid FE-1 test has been developed that allows for results to be obtained within minutes. This rapid test was compared with the classical FE-1 ELISA, with the following sensitivities and specificities in the studied groups: 92.8 and 96.6% in all subjects, 90.5 and 100% in

Table 1 Comparison of the direct and indirect pancreatic function tests currently available [3, 8, 21]

	Advantages	Disadvantages
Direct tests		
Secretin–CCK, secretin–cerulein	Gold standard for the quantification of pancreatic secretion	Invasive
Endoscopic pancreatic function test	Provides information on pancreatic enzyme and bicarbonate production	Costly
		Require specialized centers
		Lack standardization
		CCK and cerulein are no longer available in Europe
Indirect tests		
Fecal analysis		
FE-1	High sensitivity in moderate-to-severe pancreatic dysfunction	Limited sensitivity in mild pancreatic dysfunction
	Correlates well with other tests of pancreatic function	Can be affected by watery stools
	Not affected by PERT	
	Allows screening of many patients	
	Widely available	
	Easy to use	
	Single sample required	
	No diet modification needed	
	Cost-effective	
Chymotrypsin	Single sample required	Low sensitivity
	No diet modification needed	Not suitable for mild-to-moderate pancreatic dysfunction
	Cost-effective	Affected by PERT
		Chymotrypsin is inactivated during intestinal transit
		Can be affected by watery stools
72-h fecal fat quantification	Gold standard for the quantification of steatorrhea	Not suitable for mild-to-moderate pancreatic dysfunction
		Affected by PERT
		Not specific to pancreas
		Patient compliance can be poor
		Unpleasant for patients
		Cumbersome
		Limited availability
Breath test		
^{13}C-mixed triglyceride	High sensitivity in moderate-to-severe pancreatic dysfunction	Limited sensitivity in mild pancreatic dysfunction
	Correlates well with the FE-1 test and the 72-h fecal fat quantification.	Requires further validation
		Time-consuming

CCK cholecystokinin, *FE-1* fecal elastase-1, *PEI* pancreatic exocrine insufficiency, *PERT* pancreatic enzyme replacement therapy

screening non-CF samples, and 92.8 and 90.5% in CF patients [32].

It should be noted that the designation "FE-1" used for the commercial assays is technically a misnomer since elastase-1 is neither expressed nor excreted by the human pancreas [33, 34]. The current HUGO gene nomenclature distinguishes between five isoforms officially designated as "chymotrypsin-like elastases," namely CELA1, CELA2A, CELA2B, CELA3A, and CELA3B. The commercial "FE-1" assays, in fact, detect CELA2 and CELA3 isoforms [35], the different biological functions of which remain largely unknown. Despite these cell biological uncertainties, the assays are well established as diagnostic tools for PEI.

The widespread availability of the FE-1 test, together with its reliability, ease of use, and cost-effectiveness, makes it a good choice as the first-line test of pancreatic

function. The potential utility of the FE-1 test in scenarios relevant to the daily clinical practice of the treating physician is explored here, specifically:

- screening for PEI in patients presenting with symptoms suggestive of pancreatic disease, such as abdominal pain or diarrhea
- determining the presence of PEI in patients with an established diagnosis of pancreatic disease, such as CP or CF
- determining exocrine status in disorders not commonly tested for PEI, but which have a known association with this complication.

Methodology

To identify relevant publications reporting the use of the FE-1 test in diagnosing PEI, a PubMed literature search was conducted (between May 31, 2006, and May 31, 2016) using the following key words: "((pancreatic exocrine insufficiency[Title/Abstract]) AND (fecal[Title/Abstract] OR faecal[Title/Abstract]) AND elastase)". In addition, reference lists from the selected articles were used to obtain further articles not included in the electronic database. An additional search was performed using the keyword "pancreatic exocrine insufficiency[Title]" to help identify different disorders in which the FE-1 test might be useful for screening patients for PEI. The results of these literature searches form the basis of this narrative review.

Results

Patients Presenting with Symptoms of Suspected Pancreatic Disease

Pancreatic diseases are mainly diagnosed based on morphological findings; however, patients may not undergo an appropriate imaging procedure and thus diagnosis of pancreatic disease is frequently overlooked [2, 36]. For example, CP, the most common cause of PEI, develops over years, usually with an early phase lasting approximately 5 years, characterized by acute episodes of pancreatitis, pain, hospitalizations, and surgical interventions [37]. The middle phase of CP, lasting around 5–10 years, is generally distinguished by a reduction in the acute manifestations and by the progression of morphological changes and PEI. In the late phase, around 10–12 years after disease onset, complications associated with the development of PEI and diabetes become much more apparent [37]. Nevertheless, this typical clinical presentation is not always present, and a relevant proportion of patients with CP present with symptoms mimicking dyspepsia or IBS [2, 36]. In addition, diabetes mellitus may be the only clinical manifestation of the disease in some patients [38].

Diagnosis and Standard of Care in Patients Presenting with Symptoms of Pancreatic Disease

Endoscopic ultrasound (EUS) and MRCP, combined with diffusion-weighted MRI, are the two most accurate imaging methods for detecting changes in pancreatic ductal and parenchymal morphology [37]. The development of multidetector computerized tomography (CT) has improved the accuracy of CT in diagnosing CP and pancreatic neoplasms; however, the improved accuracy is only in cases where there is focal enlargement of the pancreas, which occurs in approximately 30% of CP cases, and these disorders have several overlapping morphologic features that limit its application [39]. Indeed, diagnosing CP by imaging techniques can miss cases in which morphological changes are not very prominent [37]; however, declining pancreatic exocrine secretion may precede detectable morphological changes [40].

For many years, the gold-standard methods of examining pancreatic function have been the secretin-stimulation tests, which include the secretin-only, secretin–CCK, and secretin–cerulein tests. Currently, the secretin-only test is the only direct test of pancreatic function. These tests involve the fluoroscopic placement of a nasojejunal tube for duodenal aspiration or the endoscopic collection of duodenal juice, in order to measure volume, pH, and bicarbonate concentration, following stimulation with secretin [19, 41]. When the secretin-stimulation test is performed in combination with CCK or cerulein, pancreatic enzyme output can also be measured from the duodenal aspiration [19, 41]. The endoscopic pancreatic function test, based on the quantification of the bicarbonate concentration peak in duodenal juice after secretin stimulation, is highly standardized and, currently, the most frequently used direct test [41]. All of the direct function tests are time-consuming, expensive, and not always available in every clinical setting [19]. Despite these methodological issues, and prior to it becoming unavailable, the secretin–CCK test was generally considered the gold standard for the functional diagnosis of CP for many years.

Clinical Experience of the Fecal Elastase-1 Test Compared with those of the Secretin-Stimulation Tests

The diagnostic value of the FE-1 test for evaluating pancreatic function in patients with suspected/confirmed pancreatic disease has been compared with those of the secretin–CCK and secretin–cerulein tests in a number of clinical studies (Table 2) [23, 42–47]. From these studies,

Table 2 Comparison of the FE-1 test with the direct pancreatic function tests, the secretin–CCK or secretin–cerulein tests [23, 39–44]

Study (*n*)	Patient population	Sensitivity and specificity versus secretin-stimulation tests
Lankisch et al. [44]	Patients with suspected PEI	Sensitivity
($n = 64$)	ULN for FE-1: 200 μg/g stool	Mild: 67%
		Moderate: 100%
		Severe: 100%
		Overall: 93%
		Specificity
		Overall: 94%
Leodolter et al. [47]	Patients with chronic pancreatitis diagnosed via imaging procedures	Sensitivity
($n = 40$)	ULN for FE-1: 200 μg/g stool	Mild: 25%
		Moderate: 35%
		Severe: 85%
		Overall: 48%
		Specificity
		Overall: 100%
Löser et al. [23]	Patients with mild ($n = 8$), moderate ($n = 14$), or severe ($n = 22$) PEI	Sensitivity
($n = 129$)	Patients with GI disease of non-pancreatic origin ($n = 35$)	Mild: 63%
	Healthy controls ($n = 50$)	Moderate: 100%
	ULN for FE-1: 200 μg/g stool	Severe: 100%
		Overall: 93%
		Specificity
		Overall: 93%
Lüth et al. [42]	Patients with clinical symptoms of malassimilation	Sensitivity
($n = 127$)	ULN for FE-1: 200 μg/g stool	Mild: 65%
		Moderate: 89%
		Severe: 100%
		Specificity
		Overall: 55%
Soldan et al. [43]	Patients with cystic fibrosis ($n = 16$)	Sensitivity[a]
($n = 39$)	Healthy controls ($n = 23$)	Severe: 100%
	ULN for FE-1: 200 μg/g stool	Specificity[b]
		Overall: 96%
Stein et al. [45]	Patients with suspected malabsorption syndromes	Sensitivity
($n = 164$)	(history of diarrhea, weight loss)	Overall: 93%
	Patients with previously established causes of malabsorption or maldigestion	Specificity
	Patients with functional abdominal pain, but with entirely normal markers of GI functions served as controls	Overall: 94%
	ULN for FE-1: 175 μg/g stool	
Walkowiak et al. [46]	Patients with cystic fibrosis	Sensitivity
($n = 28$)	ULN for FE-1: 200 μg/g stool	Mild: 25%
		Moderate: 100%
		Severe: 100%
		Overall: 89.3%
		Specificity
		Overall: 96.4%

CCK cholecystokinin, *FE-1* fecal elastase-1, *GI* gastrointestinal, *PEI* pancreatic exocrine insufficiency, *ULN* upper limit of normal

[a] No patients had mild or moderate PEI

[b] Based on one healthy control having FE-1 < 200 μg/g stool

the average sensitivity of the FE-1 test for mild impairment of pancreatic function was approximately 65% of those of the secretin–CCK or secretin–cerulein tests, with the sensitivities for moderate-to-severe impairment being around 100% [23, 42, 44]. Loser and colleagues [23] published one of the first reports on the sensitivity and specificity of the FE-1 test for evaluating pancreatic function in patients with pancreatic disease or gastrointestinal disease of non-pancreatic origin. By using a cut-off of ≤200 μg/g stool, FE-1 sensitivity was 63% for patients with mild impairment of pancreatic function and 100% for both moderate and severe impairment, with a specificity of 93% of the secretin–CCK test [23]. In the same year, Stein and colleagues [45] examined the use of the FE-1 test for the diagnosis of impaired pancreatic secretion in 164 patients presenting with symptoms of malabsorption syndromes (history of diarrhea, weight loss), or with previously established causes of malabsorption or maldigestion (PEI due to CP or CF, IBS, celiac disease). They found that FE-1 levels correlated well with the duodenal output of elastase, amylase, lipase, and trypsin, and that the overall sensitivity and specificity of the FE-1 test in patients with impaired pancreatic function were 93 and 94%, respectively, indicating that it is a good test for screening patients with symptoms of maldigestion or malabsorption to detect pancreatic disease [45].

In addition, a meta-analysis of eight studies published by Siegmund and colleagues in 2004, comparing non-invasive and invasive pancreatic function tests, reported that the FE-1 test has sensitivities of 54% for mild, 75% for moderate, and 95% for severe PEI, with an overall specificity of 79% [48]. These figures can be interpreted such that the FE-1 can return a false-positive result in about 20% of cases, especially when mild-to-moderate PEI is present. This is one of the reasons why a lower threshold for a positive test (i.e., pathological low FE-1) has been proposed by subsequent studies [49].

Diagnosis of Pancreatic Exocrine Insufficiency in Patients with Established Pancreatic Disease

Prevalence of Pancreatic Exocrine Insufficiency in Pancreatic Disorders

Many patients develop PEI secondary to their underlying condition [22]. CP, the most common cause of PEI, has a prevalence of 13.5–49.3 in 100,000 in the general population; the prevalence of PEI in these patients has been proposed to occur in 35–50% of patients 10–15 years after onset [37, 50]. As already noted, PEI is present at birth in 85% of infants with CF, a disease in which it is caused by blocking of the exocrine gland with viscous secretions [51]. PEI can develop in patients with pancreatic or periampullary cancer due to loss of pancreatic parenchyma or obstruction of the pancreatic duct [52]. Indeed, a recent systematic review identified PEI as being present in approximately half of all patients undergoing resection for pancreatic or periampullary cancer [52]. Recent studies have also indicated that PEI is much more common in acute pancreatitis (~21–29%) than previously thought, and that treatment with PERT can help to improve outcomes (reduced weight loss and flatulence, improved quality of life) [53, 54]. Alcohol use and smoking are major factors in the development of acute pancreatitis and, together with the presence and extension of pancreatic necrosis, have been shown to correlate with the development of PEI [55]. PEI has been shown to be prevalent in approximately 87% of patients with autoimmune pancreatitis (AIP) [56]. Difficulty in diagnosing AIP means that many undiagnosed patients are left untreated, resulting in fibrosis and pancreatic acinar and islet cell loss and leading to decreased endocrine and pancreatic function [57]. The high rate of PEI in these different patient populations suggests that pancreatic functional testing should be routinely performed to help identify those in need of PERT.

Diagnosis of Pancreatic Exocrine Insufficiency in Patients with Established Pancreatic Disease

Calculation of the coefficient of fat absorption (CFA) following the 72-h fecal fat test is regularly noted as the gold standard for diagnosing steatorrhea [19]; however, this test has many limitations and does not discriminate between hepatobiliary, intestinal, and pancreatic causes of fat malabsorption [51]. CFA calculation requires patient compliance to a strict diet, usually containing 100 g fat/day for at least 5 days, and they must collect and refrigerate all of their stools for the last 72 h. It is unpleasant, is time-consuming, has limited availability, and patients on PERT must discontinue treatment during the test period [19]. These limitations make fecal fat testing difficult to perform in an outpatient setting, thus limiting the number of patients in which it can be applied. Despite these limitations, the US Food and Drug Administration and the European Medicines Agency require the use of CFA quantification for the diagnosis of PEI and the evaluation of PERT efficacy in clinical trials. Although FE-1 testing is not a requirement in clinical trials, it has been investigated as a diagnostic tool for PEI in a large number of studies, and some countries' guidelines suggest that it be used to establish a diagnosis of PEI prior to commencing treatment with PERT [58, 59]. However, an exception to this would be PEI due to surgical diversion of the intestine, where FE-1 can have false-negative results and PERT may be indicated even when FE-1 results are normal.

Clinical Experience of the Fecal Elastase-1 Test Compared with the 72-h Fecal Fat Test in Detecting Pancreatic Exocrine Insufficiency in Patients with Pancreatic Disorders

A small number of studies have compared the use of the FE-1 test with the 72-h fecal fat test in diagnosing PEI. Some studies in children with CF have indicated that the FE-1 test should be the first one performed [51, 60]. Cohen and colleagues [60] performed the FE-1 and 72-h fecal fat tests in patients with CF and found that children with FE-1 $\leq$ 15 μg/g stool had significantly lower ($p = 0.009$) CFA than those with residual pancreatic activity (FE-1 > 15 μg/g stool), leading the authors to suggest that FE-1 be used to test pancreatic status in all children with CF. Some studies have also shown good correlation of the FE-1 test with fecal fat testing in this patient population [25], while others have indicated that fecal fat excretion should always be performed in patients with CF for evaluation of pancreatic function [61].

A small number of studies have examined the accuracy of the FE-1 test for detecting PEI in patients with CP, using the 72-h fecal fat test as a reference method. Symersky and colleagues [62] evaluated the accuracy of FE-1 in the diagnosis of pancreatic (secondary to CP) and extra-pancreatic steatorrhea. They found that FE-1 is frequently low in patients with CP and steatorrhea in comparison with those with extra-pancreatic conditions. However, an FE-1 < 200 μg/g was not accurate in differentiating between CP patients with or without steatorrhea. More recently, Benini and colleagues [49] compared the performance of the FE-1 test with the fecal fat in patients with chronic pancreatic disorders. They found that steatorrhea of ≥7 g fat excretion/day was present when FE-1 levels were severely reduced (FE-1 $\leq$ 15 μg/g stool). Nevertheless, no patient in their study had FE-1 concentration between 15 and 150 μg/g, and thus the most appropriate cut-off point for PEI in this population cannot be established based on their data [49].

The accuracy of the FE-1 test, compared with the 72-h fecal fat test, for PEI in patients after pancreatic surgery has also been evaluated in a few studies. Benini and colleagues [49] found that steatorrhea of ≥7 g fat excretion/day may be present in patients following pancreatic resection when FE-1 levels are only slightly reduced. This was in agreement with another study, which found that the FE-1 test had poor specificity in detecting PEI in a number of patients following resection for pancreatic malignancy [63]. However, the authors did suggest a different optimal cut-off for FE-1 of 128 μg/g stool to diagnose PEI (defined by a CFA < 93%) in these patients. Nevertheless, since impaired pancreatic secretion is just one of the factors leading to PEI in patients after pancreatic surgery, where physiological abnormalities (low CCK release, asynchrony between the gastric emptying of nutrients and the pancreatic secretion) secondary to the surgical anatomical changes also play a major role, the FE-1 test cannot be used to examine PEI in this condition.

Clinical Experience of the Fecal Elastase-1 Test Compared with that of the ^{13}C-Mixed Triglyceride Test

^{13}C-MTG breath test measures intraduodenal lipase activity by determining the percentage dose recovered of ^{13}C over a period of 4–10 h following ingestion of a meal containing the ^{13}C-labeled fat. The ^{13}C-labeled fat is digested by pancreatic lipase, following which it is absorbed, oxidized, and can be detected in exhaled breath as an indirect measure of lipolysis within the small intestine [20]. In a study examining the usefulness of the ^{13}C-MTG breath test compared with the FE-1 test in patients with CP or following pancreatic surgery, both tests correlated with one another; however, the accuracy rate for clinical symptoms, including clinical steatorrhea, for the FE-1 test (62%) was lower than that for the breath test (88%) [64]. It should be noted that the number of patients undergoing pancreatic surgery ($n = 95$) was much higher than those with CP ($n = 10$) [64]. Thus, the ^{13}C-MTG breath test may be more appropriate for the diagnosis of PEI secondary to CP and pancreatic surgery, but the FE-1 test is more widely available and easier to perform, making it more applicable in patients with PEI caused by non-surgical mechanisms.

Using the Fecal Elastase-1 Test to Determine Exocrine Status in Patients with Disorders Not Commonly Tested for Pancreatic Exocrine Insufficiency

Diabetes Mellitus

A major advantage of the FE-1 test is that it allows for screening of much larger patient populations in diseases where pancreatic functional testing is not routinely performed, such as diabetes mellitus [65, 66]. PEI was first suspected of being associated with diabetes more than 70 years ago, but the extent of this association was not revealed until recent years [67]. Indeed, in a large-scale study of patients with diabetes, it was found that 51.1% of individuals with type 1 and 35.4% of those with type 2 diabetes had reduced FE-1 levels [66]. Overall, 17.8% of all patients with diabetes had mild impairment of pancreatic secretion, while 22.9% had more severely impaired pancreatic function. Following this observation, similar findings have been reported in more than 15 studies, although there remains some debate as to whether this is a true observation in type 1 and type 2 diabetes or if type 3c

diabetes is much more common than previously believed [68, 69]. The findings of these studies and the correlation of FE-1 levels with diabetes duration have led some to suggest that pancreatic function should be routinely evaluated by FE-1 testing in these patients [68]. Nevertheless, the prevalence of PEI, as well as the impact of PERT, in patients with diabetes deserves further investigation.

HIV/AIDS

For many years, it has been known that HIV/AIDS is associated with the development of acute pancreatitis in ~40–45% of patients [4, 53, 70]. Studies have also shown a correlation between drug-induced pancreatic toxicity and certain antiretroviral drugs [71]. A recent study using the FE-1 test to diagnose PEI in patients with HIV reported improvement of symptoms in 77% of cases with PERT [4]. The authors suggested that FE-1 testing be performed as a routine work-up for patients with HIV infection presenting with chronic diarrhea to determine if they have PEI and could benefit from PERT [4]. More studies are required to confirm this observation before a general recommendation can be drawn.

Irritable Bowel Syndrome

In a study examining the prevalence of PEI in diarrhea-predominant IBS and the effects of PERT on this disorder, a low FE-1 result was detected in 6.1% of patients. PERT produced significant improvements in stool frequency ($p < 0.001$), stool consistency ($p < 0.001$), and abdominal pain ($p = 0.003$) in patients with FE-1 levels <100 µg/g stool [36]. This study does not suggest that PERT should be considered as a therapeutic option for IBS, but that PEI, most probably secondary to undiagnosed CP, may be frequently misdiagnosed as IBS. In this scenario, FE-1 testing may help to exclude PEI as a cause of diarrhea-predominant, IBS-like symptoms.

Celiac Disease

Patients with celiac disease have abnormally low postprandial stimulation of pancreatic secretion secondary to low CCK release [72]. Interestingly, this low CCK release has been demonstrated not only in patients with duodenal mucosal atrophy, but also in those with intraepithelial lymphocytes as the single histological manifestation of celiac disease [72]. In this context, low FE-1 levels (<200 µg/g stool) have proven to be common (>30%) in patients with celiac disease and chronic diarrhea who adhere to a gluten-free diet [5]. In 90% of these patients, treatment with PERT resulted in a significant reduction of stool frequency ($p \leq 0.001$). Many of the patients who respond well to PERT can have their treatment reduced, or even stopped completely, following recovery of CCK release and thus of pancreatic function. The FE-1 test could be useful for monitoring PEI in these patients, as it can detect recovery of endogenous FE-1 levels without interference of PERT.

Discussion

This narrative review aimed to examine the potential utility of the FE-1 test in identifying patients with PEI and to highlight the different patient populations that might benefit from screening with this method. Our review of the literature revealed that, owing to underdiagnosis of PEI in

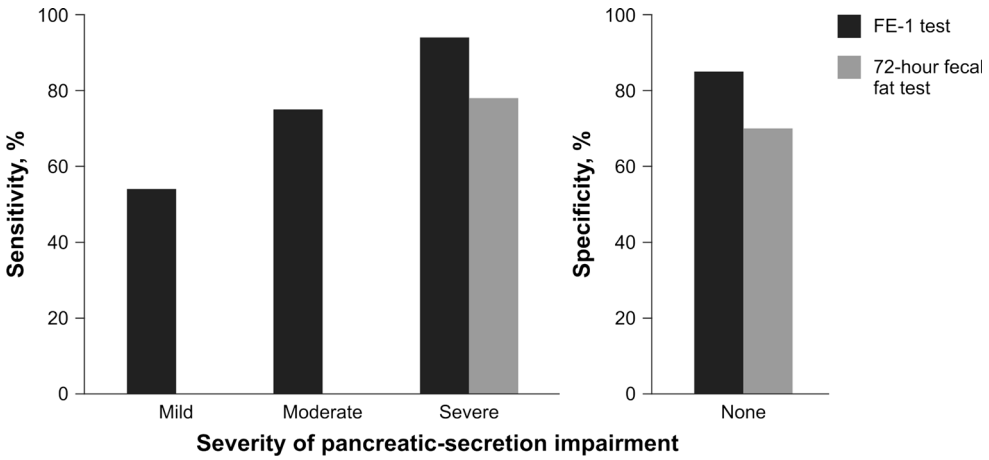

Fig. 1 Comparison of the sensitivities and specificities of the FE-1 and 72-h fecal fat tests in diagnosing impaired pancreatic secretion. Sensitivities and specificities were normalized against the "gold standard" pancreatic functions tests, the secretin and secretin–CCK tests. Sensitivity indicates the ability of the test to correctly identify patients with impaired pancreatic secretion, whereas specificity indicates the ability of the test to correctly identify patients without the disease [48, 58]. CCK, cholecystokinin; FE-1, fecal elastase-1

many pancreatic and non-pancreatic disorders, there is a significant need for a simple, reliable test to screen patients for this complication, such as the FE-1 test. Populations who could benefit from FE-1 testing include: patients presenting with symptoms suggestive of pancreatic disease, such as abdominal pain or diarrhea; patients with an established diagnosis of pancreatic disease, such as CP or CF; and patients with disorders not commonly tested for PEI, but which have a known association with this complication, such as HIV/AIDS, IBS-like symptoms, and celiac disease. The identification of more patients with PEI in these different populations could help reduce the risk of malabsorption-/malnutrition-associated complications by the initiation of PERT.

Recommendations for FE-1 Testing in Different Patient Populations

Patients presenting to their general physician with symptoms of pancreatic disease, especially in countries with long referral times for specialist facilities, should be routinely screened for PEI. Identification of pancreatic dysfunction at this earlier stage would help to ensure that these patients receive further tests, such as pancreatic imaging, as a priority. Based on the available data, and when compared to the secretin-stimulation tests, the FE-1 test has the greater potential to detect PEI as a cause of abdominal symptoms, owing to its wider availability and ease of use, as well as it being less stressful for the patient [45]. Although no study has specifically evaluated the benefit of FE-1 as a screening test prior to ordering more expensive and invasive tests, it has repeatedly shown good sensitivity and specificity in patients with PEI, and is frequently used in clinical practice worldwide [23, 45].

The high rate of undiagnosed PEI in patients with chronic pancreatic diseases, including CP, CF, and pancreatic cancer, justifies the need for routine pancreatic functional testing in these populations to help identify those in need of PERT [1, 37, 50]. Compared with the 72-h fecal fat test and the ^{13}C-breath test, the FE-1 test is more suitable for screening patients for PEI because it is less time-consuming, is less unpleasant for the patient, and can detect altered pancreatic function of all severities (although limited for mild PEI [65%] compared with moderate-to-severe impairment [$\sim$100%]), while the 72-h fecal fat test cannot (Fig. 1) [23, 42, 44, 58]. As most of the common pancreatic diseases have an associated risk of developing PEI, which itself can worsen with disease progression, we believe that the FE-1 test should be performed in these at-risk patient populations at regular intervals to help identify those who could benefit from PERT.

It should be noted that recent guidelines published by the European Society for Clinical Nutrition and Metabolism (ESPEN), the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), and the European Cystic Fibrosis Society (ECFS) recommend that the FE-1 test be performed at yearly intervals in pancreatic sufficient patients with CF to determine their need for PERT [73].

FE-1 Cut-off limits

The lower the FE-1 levels, the higher the probability that the patient suffers from PEI and requires PERT. Physicians should be aware that an exact cut-off of FE-1 levels for PEI in different clinical scenarios cannot be established, and that FE-1 levels should be considered together with an appropriate evaluation of symptoms, signs, and nutritional status [74]. For example, in patients with chronic diarrhea, low FE-1 results support the need to investigate whether this symptom is caused by pancreatic disease and PEI. Additionally, in patients with CP (or any other pancreatic disease) and malnutrition or symptoms of maldigestion (e.g., history of diarrhea, weight loss), low FE-1 results support PEI as the underlying cause (in contrast to other factors, such as alcoholism or dietary issues). It should be stressed that by identifying more patients who could benefit from PERT, we can help prevent the many complications associated with malabsorption and malnutrition [10, 11].

Conclusion

The FE-1 test is reliable for the evaluation of pancreatic function in many pancreatic and non-pancreatic disorders, as it is non-invasive, is less time-consuming than the direct and indirect tests typically seen as the gold standard for diagnosis, and is unaffected by PERT. Screening of patients presenting with symptoms suggestive of pancreatic disease, such as abdominal pain or diarrhea, patients with an established diagnosis of pancreatic disease, such as CP, CF, or pancreatic cancer, and patients with disorders not commonly tested for PEI, but which have a known association with this complication (e.g., HIV/AIDS, IBS-like symptoms, celiac disease), could help identify and treat more individuals with this complication, thus potentially reducing the burden of malnutrition-/malabsorption-associated complications. Although the FE-1 test cannot be considered the gold-standard method for the functional diagnosis of PEI owing to its limited sensitivity in mild pancreatic dysfunction and limited specificity in watery stools, its advantages make it a very appropriate test for screening patients who may be at risk of this disorder.

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Compliance with ethical standards

Conflicts of interest Prof. Domínguez-Muñoz has participated in consulting and speaking activities for Abbott Laboratories Ltd., Mylan N.V., and Allergan plc. Prof. Hardt has participated in consulting and speaking activities for Abbott Laboratories Ltd., AbbVie Ltd., and Shire plc. Prof. Lerch has participated in consulting and speaking activities for AbbVie Ltd., Abbott Laboratories Ltd., Dr. Falk Pharma GmbH, AstraZeneca plc., Nordmark Arzneimittel GmbH & Co. KG, Centogene AG, and KMG. Prof. Löhr has participated in consulting and speaking activities for Abbott Laboratories Ltd., and consultancy activities for Nordmark Arzneimittel GmbH & Co. KG.

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