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ORIGINAL ARTICLE

Pancreatic exocrine insufficiency: Comparing fecal elastase 1 with 72-h stool for fecal fat estimation

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Abstract
Introduction Identification of pancreatic exocrine insufficiency (PEI) is important in the management of chronic pancreatitis. The 72-h stool for fecal fat estimation (FFE) has long been considered a gold standard indirect test for the diagnosis of PEI. However, the test is cumbersome for both patients and laboratory personnel alike. In this study, we aimed to assess fecal elastase 1 (FE1) as an alternate to FFE for the diagnosis of PEI.
Methods In all, 87 consecutive patients diagnosed with chronic pancreatitis were included in this study. FFE and FE1 estimation was done for all the patients. For FE1, two cutoffs (<100 and <200 μg) were selected to define pancreatic exocrine insufficiency. The sensitivity, specificity, and positive and negative predictive values for the two cutoffs were estimated. Kappa statistics was used to assess degree of agreement between both tests.
Results All patients completed the study and were included in the analysis. The sensitivity, specificity, and positive and negative predictive value and PABAK (prevalence and bias adjusted kappa) for FE1 <100 μg was 84.9, 47.6, 83.6, 50, and 0.52, respectively. For FE1 <200 μg, it was 90.9, 9.5, 75.95, 25, and 0.43, respectively.
Conclusion FE1 is a sensitive test; however, it does not have a good agreement with FFE. FE1 may be used as screening test for PEI in patients with chronic pancreatitis.

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Keywords Chronic pancreatitis · Elastase · Exocrine insufficiency · Stool fat

Introduction

Acinar and ductal cells constitute exocrine pancreas and they together account for approximately 90 % of pancreatic tissue. Damage to pancreas in the form of chronic pancreatitis, cystic fibrosis, or pancreatic surgery can lead to pancreatic exocrine insufficiency (PEI) [1] resulting in maldigestion and subsequently nutritional deficiency. Therefore, identification of PEI is critical in management of patients with pancreatic disorders [2].

There are direct and indirect methods for estimation of PEI. Direct measurements require duodenal intubation and aspiration of pancreatic secretion after administration of secretagogues. The direct methods of identification of PEI though very sensitive and specific are invasive, time-consuming, and expensive [2]. The indirect tests on the other hand are relatively simple to perform and measure either the pancreatic enzyme or the by-products of enzyme activity.

The 72-h stool for fecal fat estimation (FFE) is considered a "gold standard" indirect test for the estimation of PEI [3–5]. However, the test is cumbersome for patients as well as for laboratory personnel. The study requires the patient to be on a high fat diet (100 g per day) and collect all stools produced in the last 72 h of the study period. For laboratory personnel, the test entails handling of large volumes of stool. Estimation of fecal elastase 1 (FE1) in stool on the other hand is a relatively simpler test. Elastase 1, a serine endopeptidase produced by the pancreas is composed of 240 amino acids and its molecular weight is 26 kD. Elastase 1 remains bound to bile acids during its passage through the intestine and is concentrated further in the large intestine. It is stable at a wide range of

pH and temperature and is resistant to proteolytic cleavage. It can be measured on a spot sample of stool by sandwich enzyme-linked immunosorbent assay [6]. The simplicity of the test makes it a reasonable alternative to FFE. Although established in its use as a test for pancreatic insufficiency, there is limited data comparing FE1 to FFE [5, 7].

The present study was done with an aim to evaluate FE1 as an alternative to FFE to diagnose PEI in patients with chronic pancreatitis.

Methods

This study was conducted in the Department of Gastroenterology, Christian Medical College, Vellore, India, and approved by the Institutional Ethics committee. The study was funded by a fluid research grant received from Institutional Review Board at Christian Medical College, Vellore, India. Consecutive patients, more than 18 years of age, and diagnosed with chronic pancreatitis were included in this study. The diagnosis of chronic pancreatitis was based on history and abdominal imaging (CT scan/MRI/EUS) consistent with the diagnosis of chronic pancreatitis. Pregnant women, patients with diarrhea, malignancy, and a recent history (within last 4 weeks) of exacerbation of chronic pancreatitis were excluded from the study.

All patients underwent FFE and FE1 assay. The samples for both the tests were collected separately. For FFE, patients were given 50 g of butter along with a predefined meal for 5 days thus ensuring at least 100 g of fat intake per day for 5 days. If the patients were taking pancreatic enzyme supplementation, then the enzymes were stopped for 2 weeks prior to the test to allow washout [8]. After the first 2 days of fat loading, stool was collected for the next 72 h. FFE was done using van de Kamer method [9]. PEI was diagnosed if the stool fat was >18 g in a 72-h stool collection [9–11].

FE1 estimation was done using Pancreatic Elastase ELISA kit from BioServ Diagnostics (BioServ Analytics and Medical Devices Ltd., Rostock, Germany). The assay is a solid phase enzyme immunoassay based on double sandwich technique which uses two polyclonal antibodies that recognize different epitopes on human pancreatic elastase sequences. The test was conducted as per kit manufacturer's instructions. A single spot sample of stool was used for the test. For FE1, two different cutoffs (<100 and <200 μg) based on published literature were selected to define PEI [12, 13].

Statistical methods

Previous studies had reported that FE1 has a sensitivity of 96 % for identification of PEI [14]. We estimated that for a precision of 5 % and 95 % confidence interval, we would need to recruit 59 subjects. Assuming a 20 % drop out rate, we planned to recruit at least 75 patients with chronic pancreatitis in this study.

Baseline data were presented as mean ± standard deviation, median and range for continuous variables, and as proportions for categorical variables. Sensitivity and specificity of FE1 were calculated using FFE as the reference. Kappa statistics was used to assess the degree of agreement between the two tests.

Table 1 Baseline variables of patients included in the study. Fecal fat estimation—72-h stool for fecal fat estimation

Variable	(*n* = 87)
Mean age (SD) (years)	38 (12)
Male *n* (%)	69 (79.3)
Etiology	
Idiopathic *n* (%)	72 (82.8)
Alcohol *n* (%)	13 (14.9)
Cystic fibrosis *n* (%)	1 (1.1)
Familial *n* (%)	1 (1.1)
Pain *n* (%)	74 (85.1)
Intermittent pain *n* (%)	64 (86.5)
Continuous pain *n* (%)	10 (13.5)
Disease duration	
≤5 years *n* (%)	58 (66.7)
>5–10 years *n* (%)	25 (28.7)
>10 years *n* (%)	04 (4.6)
Blood sugar	
Diabetes mellitus *n* (%)	38 (43.7)
Prediabetes mellitus *n* (%)	22 (25.3)
History of steatorrhea *n* (%)	62 (71.3)
FFE >18 g/72 h *n* (%)	66 (75.9)

Results

A total of 87 patients with chronic pancreatitis were included in this study. The patients were predominantly male (79.3 %) and the mean age was 38 (SD 12) years. The baseline characteristics are provided in Table 1.

Table 2 Sensitivity, specificity, positive predictive value, and negative predictive value

Cutoffs	FFE >18 g/72 h FE1 <100 μg Value (95 % CI)	F >18 g/72 h FE1 <200 μg Value (95 % CI)
Sensitivity	84.9 (73.9–92.5)	90.9 (81.3–96.6)
Specificity	47.6 (25.7–70.2)	9.5 (1.2–30.4)
Positive predictive value	83.6 (72.5–91)	75.95 (65.02–84.9)
Negative predictive value	50 (27.2–72.8)	25 (3.2–65.1)
PABAK	0.52 (0.30–0.72)	0.4 (0.21–0.62)

PABAK prevalence adjusted bias adjusted Kappa, *FFE* 72-h stool for fecal fat, *FE* fecal elastase 1

Most patients had history of intermittent abdominal pain. While most patients had imaging changes consistent with chronic pancreatitis on CT/MRI, in 13 patients, the changes were detected using endoscopic ultrasound. Calcification was noted in 68 (78 %) patients. A history of steatorrhea was present in 71 % of patients.

FFE and FE1 analysis was done in all patients. Median FFE value was 25.5 g (range 7.3–85.5) and median FE1 value was 25 μg (range 2–580). The sensitivity, specificity, and positive and negative predictive value and Kappa for FE1 using cutoffs <100 and <200 μg are shown in Table 2.

Discussion

PEI usually develops as a consequence of chronic pancreatitis but has been identified in other scenarios as well. In this study, 71.3 % of patients complained of steatorrhea. The FFE showed that a higher percentage of patients had PEI, suggesting occurrence of subclinical PEI, a fact corroborated by our earlier study in patients with chronic pancreatitis [11]. This underscores the need of testing for PEI, amongst patients with chronic pancreatitis.

In the present study, we included patients diagnosed with chronic pancreatitis and attempted to assess ability of FE1 to diagnose PEI. For FE1, authors have used differing cutoffs to define presence of exocrine insufficiency. For FE1 using a cutoff of <100 μg, the sensitivity was 84.5 % and the specificity was 47.6 %. Using a higher cutoff of <200 μg for FE1, the sensitivity increased marginally; however, the specificity declined markedly. Only a few studies have evaluated the utility of FE1 using FFE as the gold standard. Lankisch et al. in their study used secretin pancreozymin test and fecal fat estimation to define PEI. Amongst patients with steatorrhea, an abnormal FE1 (<200 μg) was noted in 82 % of patients. In patients without steatorrhea, abnormal FE1 was seen in 37 %, indicating a good sensitivity for the test but a poor specificity [12]. Symersky et al. in their study found a very low sensitivity of FE in identifying steatorrhea amongst patients with chronic pancreatitis [15]. On the other hand, Benini et al. reported a high sensitivity (98.0 and 91.8 for cutoff of <200 and <100 μg, respectively) of FE1 when they compared it with fecal fat. However, they did report a much higher specificity for FE (69.7 and 94.8 for cutoff of <200 and <100 μg, respectively) than what we obtained in our study [13]. The variations in the reported sensitivity and specificity of FE1 amongst studies could be related to different gold standards and differing cutoffs used to define PEI.

A major limitation of the study was a high prevalence of exocrine insufficiency in the study population. This introduced a spectrum bias, limiting our interpretation of the positive and negative predictive values. To assess the degree of agreement between the two tests, kappa statistics was calculated. As the prevalence of PEI was high in our study population, PABAK (prevalence and bias adjusted kappa) was calculated. Using PABAK, there appeared to be a moderate agreement between the two tests when cutoff to define PEI for FE1 is taken as <100 μg and a fair agreement when cutoff is <200 μg.

The results of this study indicates that although FE1 is the sensitive test to diagnose PEI, it has low specificity and lacks correlation with the results of FFE suggesting that FE1 cannot be used in isolation. The test may however be useful as screening test for PEI in patients with chronic pancreatitis. Further studies are warranted to evaluate new options for detecting PEI in patients with chronic pancreatitis.

Compliance with ethical standards

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Conflict of interest SDC, RTK, AR, AJJ, EGS, AKD, DD, BKC, PS, and KAB declare that they have no conflict of interest.

Ethical approval The study was conducted in accordance with the ethical standards of the Institutional ethics committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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