Pancreatic Exocrine Insufficiency in Chronic Diarrhea

Marcellus Simadibrata K, Daldiyono Hardjodisastro, A Aziz Rani

Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine
University of Indonesia/Cipto Mangunkusumo General National Hospital

ABSTRACT

Background: *One of the causes of chronic diarrhea is pancreatic exocrine insufficiency. Chronic diarrhea cases are commonly encountered in Indonesia.*

Materials & Methods: *All patients with chronic diarrhea at hospitals in Jakarta were included in this study and dyspeptic patients were used as control subjects. The study and control subjects must submit their stool for fecal pancreatic elastase-1 examination at a private laboratory in Jakarta. Mild/moderate pancreatic exocrine insufficiency was defined if the concentration was between 100 - 200 µg E1/g stool. Severe pancreatic exocrine insufficiency was defined if the concentration was below 100 µg E1/g stool. The data was analyzed using Fisher or Kruskal-Wallis tests.*

Results: *There were 32 chronic diarrhea patients with a male to female ratio of 19/13 (59.38%/40.62%). The most frequent age range was 50-59 years old (39.5%). The characteristics (sex, age and race) of chronic diarrhea patients were matched with the characteristics of dyspeptic patients as control subjects ($p > 0.05$). The fecal elastase-1 results in chronic diarrhea displayed greater pancreatic exocrine insufficiency (< 200 µg E1/g stool) than in dyspepsia (control) (≥ 200 µg E1/g stool, $p < 0.001$). The mean fecal elastase-1 result in chronic diarrhea and in dyspepsia were 316.29 ± 195.44 vs. 475.93 ± 65.33 µg E1/g stool ($p < 0.001$). Six patients (18.74%) were established as having severe pancreatic exocrine insufficiency. Seven patients (21.88%) were found with mild/moderate pancreatic exocrine insufficiency.*

Conclusion: *Pancreatic exocrine insufficiency was found frequently in chronic diarrhea.*

Keywords: *Pancreatic exocrine insufficiency, chronic diarrhea, fecal pancreatic elastase-1*

INTRODUCTION

Chronic diarrhea cases are commonly encountered in Indonesia.[1] One of the causes of chronic diarrhea is pancreatic exocrine insufficiency. Pancreatic insufficiency occurs if the pancreas is unable to secrete chemicals and digestive enzymes for normal digestion. If the pancreatic insufficiency is severe, malabsorption occurs, causing reduced absorption of essential nutrients and the development of watery stool containing unabsorbed fat (steatorrhea). Mild pancreatic insufficiency is often difficult to diagnose. There are two kinds of pancreatic exocrine insufficiency, which are primary and secondary pancreatic exocrine insufficiency. Primary pancreatic insufficiency is caused by pancreatic abnormalities, such as cystic fibrosis, chronic pancreatitis, pancreatic resection surgery, pancreatic tumor, and diabetes mellitus. Secondary pancreatic insufficiency is caused by bowel disease, such as celiac disease, tropical sprue, Crohn's disease, and autoimmune diseases such as systemic lupus erythematosus.[2-5]

One of the efforts to detect pancreatic exocrine insufficiency is the fecal pancreatic elastase-1 test.[6-13] This examination is one of the pancreatic function tests that does not use a tube and does not require a lot of time.[6] SZIEGOLEIT[14,15] is the founder of human pancreatic elastase-1, which is classified as an acid elastase, as an endoprotease and new sterol-binding protein that is found in human pancreatic secretion and stool. Human pancreatic elastase-1 does not degraded during bowel transit. Fecal elastase-1 levels are 5 to 6 times that of pancreatic fluid, and fecal elastase remains stable for 1 week in room temperature. Thus, fecal elastase-1 concentrations reflect pancreatic exocrine function.[15,16] The sensitivity of pancreatic elastase-1 test

in mild pancreatic insufficiency ranges around 0 to 63%, 77 - 100% in moderate pancreatic insufficiency, and 100% in severe pancreatic insufficiency.[7,17,18,19] The specificity of elastase-1 in stool is 93%.

Other direct pancreatic exocrine examination such as the secretin-cholecystokinine test or caerulein secretin, even though considered gold standards, are not available in Indonesia, are not practical, time-consuming, invasive, and expensive.[12] Other indirect tests such as the dilaurate fluorescence test, NBT-PABA, or bentiromide, fecal chymotrypsin, have only limited sensitivity for mild/moderate pancreatic insufficiency, and are influenced by several drugs, diarrhea, pH, as well as gastrointestinal surgery, thereby reducing their specificity.[12] Based on the above, this study uses the fecal pancreatic elastase-1 test to assess pancreatic exocrine function.

MATERIALS AND METHODS

All patients with chronic diarrhea at our hospital and other private hospitals in Jakarta and dyspeptic patients were used as control subjects were included in this study. Chronic diarrhea was diagnosed if the passage of stool were more than 200 g per day or if passage of soft and watery stool was more than 3 times per day with or without blood or mucous in the stool and it lasted more than 15 days. The study and control subjects must submit a stool sample for fecal pancreatic elastase-1 examination at a private laboratory in Jakarta. Fecal pancreatic elastase-1 concentration was measured using ELISA (Schebo^{R}, Tech, Germany). All patients with chronic diarrhea underwent history taking, physical examination, ultrasound examination, esophagogastroduodenoscopy, colonoscopy, and laboratory examinations including stool sample, routine blood examination, blood sugar, liver function, thyroid function, serum amylase-lipase, etc. All patients with dyspepsia underwent history taking, physical examination, ultrasound examination, upper abdominal CT-scan (if necessary), esophagogastroduodenoscopy, colonoscopy, and laboratory evaluation.

The exclusion criteria were lack of cooperation, heart failure, severe pulmonary obstruction, renal failure, and peptic ulcer in the group with dyspepsia. Mild/moderate pancreatic exocrine insufficiency was defined if the concentration was between 100-200 µg E1/g stool. Severe pancreatic exocrine insufficiency was defined if the concentration was below 100 µg E1/g stool. Normal pancreatic exocrine function was defined if the concentration was the same or above 200 µg E1/g stool.[12] The data was analyzed using Fisher or Kruskal-Wallis tests.

RESULTS

There were 32 chronic diarrhea patients with a male to female ratio of 19/13 (59.38%/40.62%) and 32 dyspeptic patients as control subjects. The most frequent age range was 50-59 years old (37.5%). The characteristics (sex, age and race) of chronic diarrhea patients were matched with the characteristics of dyspeptic patients as control subjects ($p > 0.05$). The fecal pancreatic elastase-1 results in chronic diarrhea displayed greater pancreatic exocrine insufficiency (< 200 µg E1/g stool) than in dyspepsia as control subject (≥ 200 µg E1/g stool). The difference in fecal pancreatic elastase-1 results was significant ($p < 0.001$). The mean fecal pancreatic elastase-1 result in chronic diarrhea and in dyspepsia were 316.29 ± 195.44 vs. 475.93 ± 65.33 µg E1/g stool ($p < 0.001$). Thirteen (40.62%) patients had pancreatic exocrine insufficiency. Six patients (18.74%) were categorized as having severe pancreatic exocrine insufficiency. Seven patients (21.88%) were found with mild/moderate pancreatic exocrine insufficiency.

Table 1. Characteristics of Patients with Chronic Diarrhea and Dyspeptic Syndrome

Characteristic	Chronic Diarrhea (n=32)	Dyspeptic Syndrome (n=32)	p
Age (years old)			
10 - 19	0	3	0.09
20 - 29	1	1	
30 - 39	4	11	
40 - 49	6	4	
50 - 59	12	7	
60 - 69	6	5	
70 - 79	3	0	
80 - 89	0	1	
Sex			
Male	19	20	0.79
Female	13	12	
Ethnic group			
Javanese	3	7	0.57
Chinese	16	21	
Sundanese	2	0	
Padangnese	2	1	
Bataknese	1	1	
Other	2	2	
Results of fecal elastase-1 (µg E1/g stool)			
< 200	13	0	< 0.001
≥ 200	19	32	

Table 2. The Correlation between Results of Fecal Pancreatic Elastase -1 and Patient Characteristics

Characteristic	Mean Fecal Pancreatic Elastase-1 Level μg E1/g stool)	p
Type of disease		
Chronic diarrhea	316.29 ± 195.44	< 0.001
Dyspeptic syndrome	475.93 ± 65.33	
Sex		
Male	386.73 ± 166.01	0.58
Female	410.74 ± 166.85	
Age (years old)		
10 - 19	400.57 ± 172.22	0.53
20 - 29	500.00 ± 0.00	
30 - 39	467.08 ± 100.58	
40 - 49	379.52 ± 195.89	
50 - 59	370.74 ± 178.55	
60 - 69	342.02 ± 173.63	
70 - 79	347.17 ± 264.72	
80 - 89	500.00 ± 0.00	

Table 3. Illness Found in Chronic Diarrhea

Illness in Chronic Diarrhea	Frequency (n=32)	Percentage (%)
Gluten enteropathy	3	9.37
HIV	1	3.13
Irritable Bowel Syndrome	3	9.37
Infective colitis	13	40.63
Colonic cancer	1	3.13
Liver cirrhosis/chronic hepatitis	2	6.24
Diabetes mellitus	3	9.37
Ulcerative colitis	1	3.13
Thyrotoxicosis	1	3.13
Chronic pancreatitis	1	3.13
Pancreatic cancer	1	3.13
Unknown	2	6.24

Note: There could be one or more abnormalities in one case

Table 4. Pancreatic Exocrine Insufficiency among Patients with Chronic Diarrhea

Illness in Chronic Diarrhea	Mild/moderate Pancreatic Insufficiency or Fecal Pancreatic Elastase-1 100-200 l g E1/g stool (n=7)	Severe Pancreatic Insufficiency or Fecal Pancreatic Elastase-1 < 100 l g E1/g stool (n=6)
Chronic pancreatitis	0	1
Pancreatic cancer	0	1
Diabetes mellitus	1	0
Gluten enteropathy	1	0
Thyrotoxicosis + infective colitis	1	0
HIV + infective colitis	1	0
Infective colitis	1	1
Colonic cancer	0	1
Irritable bowel syndrome	2	0
Unknown	0	2

Two out of 3 patients (66.67%) with pancreatic abnormality had severe pancreatic exocrine insufficiency (fecal pancreatic elastase-1 of less than 100 µg E1/g stool). There were 1 out of 3 (33.33%) cases of mild/moderate pancreatic exocrine insufficiency among patients with pancreatic abnormality. Two out of 8 patients (25%) with bowel (extra-pancreatic) abnormality had severe pancreatic exocrine insufficiency, while 6 out of 8 cases (75%) with bowel (extra-pancreatic) abnormality had mild/moderate pancreatic exocrine insufficiency. There were 2 cases with severe pancreatic exocrine insufficiency whose the cause of chronic diarrhea was unknown, but this is most probably caused by pancreatic abnormality, as bowel and gastric examinations exhibited normal findings (see table 4).

DISCUSSION

In the group of chronic diarrhea, there was a fecal pancreatic elastase-1 result of < 200 µg E1/g stool, which is greater than among dyspeptic patients (13 cases compared to 0). This is in line with references that state that pancreatic exocrine insufficiency can be caused by pancreatic disease or intestinal disease and not due to gastric or esophageal abnormality. Chronic diarrhea can of course be caused by pancreatic or intestinal disease or abnormality.[2-5] The characteristics of the chronic diarrhea group and that with dyspepsia have been arranged from the inclusion to be the same and not significantly different, in order to reduce bias in the examination of fecal pancreatic elastase-1.

From this study, we found that in patients with chronic diarrhea due to pancreatic abnormality, the degree of pancreatic insufficiency is more severe compared to in patients with chronic diarrhea due to bowel abnormality (66.67% vs. 25%). Among patients with pancreatic abnormality, more had fecal pancreatic elastase-1 levels of less than 100 µgE1/g stool. This is in line with references that state that the concentration of fecal elastase among patients with chronic pancreatitis is significantly lower than among patients with non-pancreatic gastrointestinal disease.[12, 19] In this study, in cases with chronic pancreatitis and pancreatic cancer, more severe pancreatic exocrine insufficiency was found. During severe pancreatic exocrine insufficiency, there are usually symptoms of malabsorption and chronic fatty diarrhea (steatorrhea).

The mean of fecal pancreatic elastase-1 result in patients with chronic diarrhea is significantly lower compared to patients with dyspepsia (316.29 ± 196.44 µg E1/g stool vs. 475.93 ± 65.33 µg E1/g stool). This finding is in line with other findings that found that the chronic pancreatitis is significantly lower than that of normal subjects or patients with non-pancreatic intestinal disease.[12,19]

It is evident that fecal pancreatic elastase-1 is not related to sex and age. This finding is in line with other references.[7,9,10,20]

Chronic diarrhea may be caused by abnormalities or other diseases like gluten enteropathy, infective colitis, chronic pancreatitis, etc., but these abnormalities/ diseases may not be the sole cause of chronic diarrhea. In one case of chronic diarrhea there could be more than one cause. This result is in line with previous studies.[1] According to a reference, diabetes mellitus could be accompanied by pancreatic insufficiency,[8] but in this study only one diabetic had pancreatic exocrine insufficiency.

Among patients with intestinal disease, there is a possibility to have secondary pancreatic insufficiency.[12,19,21] This is in line with the findings from this study, where secondary pancreatic insufficiency is found in patients with colonic cancer and infective colitis. The correlation between intestinal abnormality and pancreatic exocrine dysfunction is unclear.[21]

In this study, there was a problem in diagnosing primary pancreatic abnormality such as cystic fibrosis, etc, due to the lack of laboratory facilities in Indonesia and limitations in the cost of this study. In this study, there were 2 (two) cases where no clear cause of chronic diarrhea was found, but they have severe pancreatic insufficiency (< 100 µg E1/g stool). This abnormality indicates pancreatic disease, even though this was not proven or detected using the available diagnostic facilities. Thus, fecal pancreatic elastase-1 examination can assist physicians in detecting and treating the cause of chronic diarrhea.[20, 21, 22]

CONCLUSION

Pancreatic exocrine insufficiency was found frequently in chronic diarrhea.

ACKNOWLEDGEMENT

We acknowledge Prodia laboratory and their technicians for providing the reagents and assisting the examination of fecal pancreatic elastase-1.

REFERENCES

1. Simadibrata M. Chronic diarrhea in Indonesian people. Thesis Doctor. University of Amsterdam 2002
2. Pancreatic Insufficiency. http://www.fredmeyer.com/HNConcern/Pancreatic Insufficiency.htm: 1-5
3. Mery CM. Exocrine pancreatic insufficiency in tropical sprue. High Beam Research-Alternative Medicine Review 2001:1-2
4. Pancreatic elastase, fecal and serum. http://www.palpath.com/pancreas.htm:1

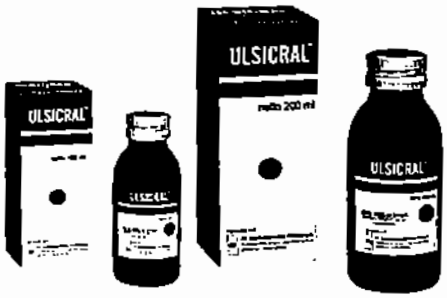
5. Rathmann W, Wareham N, Icks A, Haastert B, Giani G. Pancreatic exocrine insufficiency in type 1 and type 2 diabetes. Pediatr Pulmonol 2000;29:172-6
6. Stein J, Jung M, Sziegoleit A, Zeuzem S, Wolfgang F, Caspary, et al. Immunoreactive elastase-1: Clinical evaluation of a new non invasive test of pancreatic function. Clinical Chemistry 1996;42(2):222-6
7. Gullo L, Ventrucci M, Tomassetti P, Migliori M, Pezzilli R. Fecal elastase-1 determination in chronic pancreatitis. Dig Dis Sci 1999;44(1):210-3
8. Hardt PD, Kloer HU. Diabetes mellitus and exocrine pancreatic disease. In: Johnson CD, Imrie CW. Pancreatic disease: Towards the year 2000. Schebo Tech. 2000.p.33-9
9. Dominguez-Munoz JE, Hieronymus C, Sauerbruch T, Malfertheiner P. Fecal elastase test: evaluation of a new non invasive pancreatic function test. Am J Gastroenterol 1995;90:1834-7
10. Gullo L, Graziano L, Babbini S, Battistini A, Lazzari R, Pezzilli R. Faecal elastase-1 in children with cystic fibrosis. Eur J Pediatr 1997;136:770-2
11. Philips IJ, Rowe DJ, Connett G, Dewar P. Faecal elastase-1: a marker of exocrine pancreatic insufficiency in cystic fibrosis. Abstract from the focus ACB National Meeting 1998
12. Loser C, Mollgaard A, Folsch UR. Faecal elastase-1: a novel, highly sensitive, and specific tubeless pancreatic function test. Gut 1996;39(4):580-6
13. Stein J, Jung M, Zeuzem S, Lembcke B, Caspary WF. Fecal elastase-1 in pancreatic insufficiency: correlation with the secretin-pancreozymin test. Abstracts II world congresses of gastroenterology. 10th Congress of Gastroenterology, 8th Congress of Digestive Endoscopy, 5th Congress of Colo-proctology. Los Angeles, Califomia USA. October 2-7 1994: poster presentations 870P
14. Sziegoleit A. A novel proteinase from human pancreas. Biochem J 1984;219-735
15. Sziegoleit A, Linder D. Studies on the sterol binding capacity of human pancreatic elastase. Gastroenterology 1991;100:768
16. Muench R, Ammann R. Fecal immunoreactive lipase: a new tubeless pancreatic function test. Scand J Gastroenterol 1992;27:289
17. Gullo L. Faecal elastase-1 in chronis pancreatitis. Letters to the editor. Gut 1999;444:290
18. Thomas PD, Forbes A, Green J, Howdle P, Long R, Playford R, et al. Guidelines for the investigation of chronic diarrhea, 2nd ed. Gut 2003;52:v1
19. Lankisch PG, Schmidt I, Konig H, Lehnick D, Knollmann R, Lohr M, Liebe S. Faecal elastase-1: not helpful in diagnosing chronic pancreatitis associated with mild to moderate exocrine pancreatic insufficiency. Gut 1998;42:551-4
20. Glasbrenner B, Schon A, Klatt S, Beckh K, Adler G. Clinical evaluation of the faecal elastase test in the diagnosis and staging of chronic pancreatitis. Eur J Gastroenterol Hepatol 1996;8: 1117-20
21. Schappi MG, Smith VV, Cubitt D, Milla PJ, Lindley KJ. Faecal elastase-1 concentration is a marker of duodenal enteropathy. Arch Dis Childhood 2002;86:50-3
22. Caronna S, Di Maggio S, Gallo M, Angell A, Gaia E. Fecal elastase-1 predicts degree of insufficiency in chronic pancreatic diseases. XXIX Meeting EPC European Pancreatic Club Digestion. London UK. Dig 1997;58:S2

Penatalaksanaan Terpadu GERD

DOMETA®
Domperidone tablet & sirup

TERBUKTI EFEKTIF
MEMPERCEPAT
PENGOSONGAN LAMBUNG
TANPA EFEK SAMPING
EKSTRAPIRAMIDAL

ULSICRAL® 100 ml 200 ml
Sukralfat Suspensi



MELINDUNGI DAN
MENYEMBUHKAN
ULKUS PEPTIK
(CYTOPROTECTIVE)

ZEPRAL®
Omeprazole 20 mg

PENGONTROL ASAM
LAMBUNG YANG
EFEKTIF

PT. IKAPHARMINDO PUTRAMAS
Pharmaceutical Laboratories

Jl. Pulogadung Raya No. 29 Kawasan Industri Pulogadung Jakarta 13920
Tlp. : (62-21) 4614766 / 4600086 (hunting) e-mail : secretary@ikapharmindo.com www.ikapharmindo.com