Original Article

Prevalence of Exocrine Pancreatic Insufficiency in Patients with Chronic Diarrhea

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Abstract

Background: Exocrine pancreatic insufficiency (EPI) is an underdiagnosed entity among patients with new-onset chronic diarrhea (CD). The aim of this study is to investigate the prevalence of EPI in patients with CD.

Materials and Methods: Patients with new-onset CD (≥4 weeks) from 2018 to 2021 were enrolled in this single-center prospective study. If stool fecal elastase (FE) was <200 μg/g, patients were offered a confirmatory 72-hour fecal fat test.

Results: FE testing was completed by 97 patients, of which 9 had low FE (9.3%). Average weight was significantly higher in patients with low FE (98.5 ± 29.3 kg vs 82.2 ± 22.2 kg; $P = 0.045$). There was no significant difference in gender, age, race, presence of diabetes mellitus, and history of tobacco or alcohol use between the two groups. After controlling for other factors, patients with low FE had a statistically higher weight in comparison to those with normal FE. Nine patients in the entire cohort were started on pancreatic enzymes (three based on low FE and six empirically based on high pretest probability for EPI). Six of the nine patients had complete resolution of symptoms (including two of three patients with low FE).

Conclusion: Considering the 9.3% prevalence of EPI among patients with CD, we propose screening for EPI with stool FE as part of the initial workup for these patients.

Trial Registration: Clinicaltrial.gov number NCT03407534.

Keywords: Chronic diarrhea, exocrine pancreatic insufficiency, fecal elastase, pancreatic enzyme replacement therapy, pancreatic parenchymal changes

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INTRODUCTION

Exocrine pancreatic insufficiency (EPI) is an underdiagnosed and potentially disabling disease. EPI is characterized by maldigestion and malabsorption of nutrients and vitamins. Manifestations of EPI can range from minimal abdominal discomfort to severe symptoms such as persistent abdominal pain, uncontrolled bloating, or chronic diarrhea.[1] EPI can coexist with other entities such as irritable bowel syndrome (IBS), celiac disease, or microscopic colitis and potentially exacerbate associated symptoms,[2,3] making its diagnosis challenging.

The prevalence of EPI in the United States is not well defined, and most of the published estimates being from studies conducted in other countries. A recent population-based

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study of 914 patients from Norway reported an up to 10% prevalence of EPI, as defined by fecal elastase (FE) <200 μg/g.[4] In a clinic-based study from England, the prevalence of EPI diagnosed by low FE (<200 μg/g) in 314 patients with chronic diarrhea meeting the Rome II criteria for IBS was 6.1%.[5] In Slovenia, EPI prevalence of 4.4% (also diagnosed by FE <200 μg/g) was documented among 90 patients with serological and histological evidence of celiac disease.[6] Interestingly, the pancreas appeared normal on magnetic resonance imaging (MRI) in all patients diagnosed with EPI in this study.[6] EPI (based on FE <200 μg/g) was diagnosed in 15% of asymptomatic recovered alcoholic patients in a study from Brazil of 33 former alcoholic and 43 chronic pancreatitis patients.[7] In another recent study of 280 patients with chronic diarrhea from Australia, the prevalence of EPI was 4.6%.[8]

EPI could be increasing in some Western populations due to global behavioral changes toward increased alcohol consumption and tobacco exposure, with both being recognized as risk factors for chronic pancreatitis.[9,10] Recent data from the United States and England have shown an increase in alcohol consumption across different age categories and social status. In a survey of 1,657 underage adults (ages 19 and 20) in the United States, binge drinking was reported by 24% of participants.[11] Data from the 2011 Behavioral Risk Factor Surveillance System and the 2011 National Youth Risk Behavior Survey in the United States showed that one out of every eight adult women and one out of every five high school girls had partaken in binge drinking.[12]

The prevalence of EPI in patients presenting with diarrhea in the United States has remained largely unknown. Based on the above data, we hypothesized that a large proportion (~10%) of patients with undiagnosed chronic diarrhea presenting to our gastroenterology clinics may have EPI. The aim of this study was to test this hypothesis using FE as the screening test.

MATERIALS AND METHODS

Study design

This was a single-center cross-sectional study with prospective enrollment. The study was approved by the Institutional Review Board of Baylor College of Medicine, Texas, USA. Verified informed consent was obtained from each study participant prior to enrollment. This clinical trial was supported by AbbVie through an investigator-initiated grant (Clinicaltrial.gov number NCT03407534). The sponsor had no role in patient selection or data collection and did not contribute to analyzing data or drafting this manuscript.

The study objectives were to estimate the prevalence of EPI among consecutive patients presenting with new-onset chronic diarrhea (≥4 weeks) to a tertiary referral medical center and examine the predictive value of several demographics (e.g., age, race, sex, alcohol consumption, and smoking status) or clinical (e.g., presence, severity, and duration of symptoms, and history of diabetes mellitus) variables.

Study population

Patients with chronic diarrhea, defined as a frequent loose stool for ≥4 weeks in duration, presenting to the Baylor College of Medicine outpatient gastroenterology clinics, Texas, USA, between March 2018 and October 2021 were considered for this study. All patients aged 18 to 80 years presenting with chronic diarrhea were screened for eligibility, and those meeting inclusion and exclusion criteria were approached in person for verification of eligibility and informed consent.

Patients were excluded if they were known to have chronic, recurrent, acute, or autoimmune pancreatitis, pancreatic cancer, a history of pancreatectomy, Whipple surgery, gastric bypass surgery, or any Roux-en-Y gastrojejunal anastomosis. Patients with known inflammatory bowel disease, celiac disease, or microscopic colitis were also excluded. Patients who were taking over-the-counter diphenoxylate or loperamide were included in the study but had to stop these medications one week prior to FE measurement.

Study procedures

Patients who met the inclusion and exclusion criteria completed a Bristol Stool Scale, which assesses stool consistency,[13] and the Birmingham questionnaire to assess the severity of abdominal pain and bowel habit symptoms.[14] The Birmingham questionnaire consists of 14 questions on a 5-point Likert scale assessing the presence of those symptoms and their severity within the past 4 weeks of presentation.[14] Study subjects then collected 1 gram of stool in a sterile screw cap container using a spatula for FE testing. The stool sample is viable for testing for 5 days at room temperature. Patients with FE <200 μg/g were then offered a 72-hour fecal fat test to confirm EPI as per standard of care. Patients had the right to accept or decline this test per study protocol. Patients were instructed to submit only formed stool samples as per the protocol. Any liquid stool samples submitted for FE testing were excluded from processing and analysis.

The 72-hour fecal fat measurement is a 5-day test. Patients were started on a 100 g fat diet daily for two days prior

to stool collection and during the three days of stool collection (5 days total). Patients were educated regarding the fat content of commonly used food items in addition to providing a sample dietary instruction, which was offered to each study subject. A positive test for fat malabsorption is >7 grams of fat/day or >21 grams of fat in 72 hours. The study flow chart is shown in Figure 1.

We collected information on weight, body mass index, race, gender, history of diabetes mellitus, and tobacco or alcohol use by chart review. Other workup of diarrhea such as computed tomography (CT) scan, MRI or endoscopic ultrasound (EUS) were performed as per the standard of care. Lastly, we collected information on pancreatic enzyme replacement therapy (PERT).

Statistical methods

Descriptive statistics were computed for all variables, including means, standard deviations, and percentiles for continuous variables, and frequencies and percentages for categorical factors. The prevalence of EPI was calculated as the proportion (and 95% confidence intervals) of patients with FE <200 μg/g among those who had an interpretable FE test result. Analysis of variance (ANOVA) and independent sample *t*-test were used to compare continuous variables between patients with and without EPI, while Pearson's Chi-square and Fischer's exact tests were applied for comparing categorical variables. Linear regression models were fitted to account for potential confounding variables on the effect of weight on the final outcome. A P value < 0.05 was considered statistically significant. All data analysis was performed using SPSS version 28 (IBM, Armonk, NY, USA).

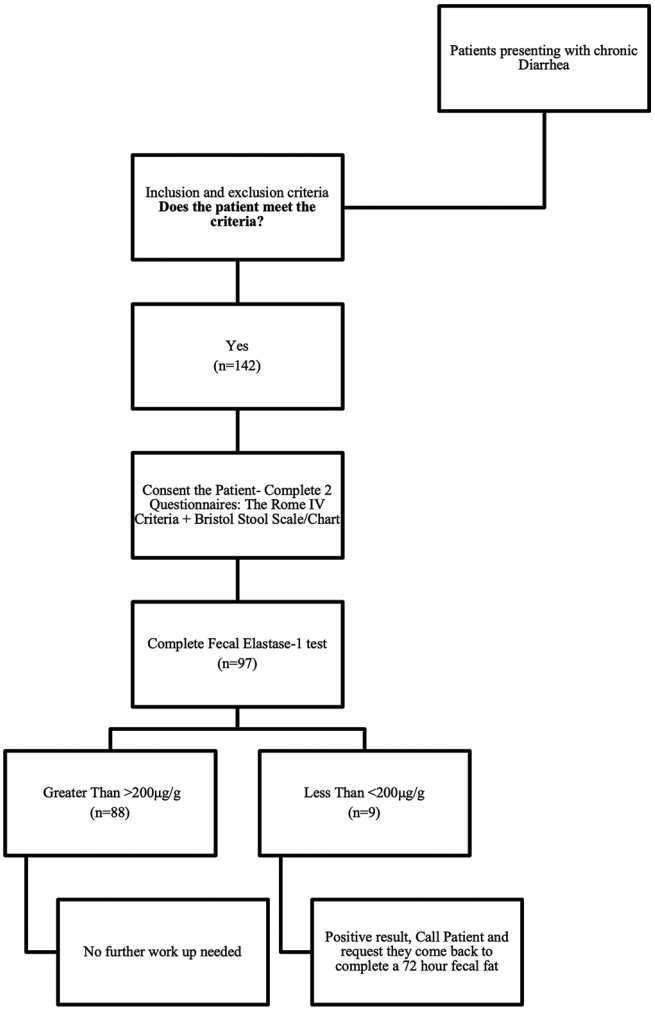

Figure 1: Flowchart of study participants

RESULTS

Patient characteristics

Ninety-seven patients with chronic diarrhea who met the initial study inclusion criteria and completed the stool collection were enrolled in the study. The average age of participants was 53.4 ± 16.3 years old. Most (n = 61; 62.9%) participants were female. The racial/ethnic distribution was white in 78.4% (n = 76) and black in 15.5% (n = 15). The average weight was 83.7 ± 23.2 kg. A total of 17.5% of patients had a history of smoking, 42.3% reported alcohol consumption, and 34% had a history of diabetes. Table 1 summarizes baseline characteristics in patients with low and normal FE.

Fecal elastase testing

Of the ninety-seven patients who completed FE testing, 9 (9.3%) had a FE <200 μg/g. Of these, five patients had FE levels ≤100 μg/g.

There was no statistically significant gender difference between patients with and without low FE (P = 0.646). Two patients with low FE had a history of diabetes, alcohol intake, and tobacco use. Only three patients completed stool collection for 72-hour fecal fat evaluation, all of which were within normal limits. Despite multiple attempts, confirmatory 72-hour fecal fat testing was not performed in six patients.

Factors predictive of low fecal elastase in our cohort

Patients with low FE were of statistically higher weight in comparison to those with normal FE (P = 0.045). There was no statistically significant difference in age, gender, tobacco use, alcohol consumption, or diagnosis of diabetes amongst patients with low or normal FE. In further regression analysis, controlling for the confounding effects of gender, history of diabetes mellitus, tobacco use, and alcohol consumption, patients with low FE had a statistically higher weight in

comparison to those with normal FE. Although patients with low FE had higher Birmingham severity scores in comparison to those with normal FE (27.45 ± 8.41 vs 26.98 ± 9.88), this relationship was not statistically significant ($P = 0.656$).

Comparison of radiological findings in patients with low and normal FE

Six of nine patients with low FE had concurrent imaging with EUS ($n = 3$) or other radiological modalities such as CT scan ($n = 2$) or MRI ($n = 1$). EUS revealed chronic pancreatitis in two patients and pancreatic parenchymal changes in one patient. Three patients had a normal pancreas on CT scan or MRI. A summary of radiological or echoendoscopical findings in those with low FE can be found in Table 2.

Concurrent EUS, CT scan, or MRI was available in 51 of 88 patients with normal FE. The summary of abnormal radiological findings includes atrophic pancreas on CT scan or MRI ($n = 4$), fatty pancreas on MRI ($n = 1$), and parenchymal changes on EUS (fatty pancreas = 2, hyperechoic strands and lobularity = 3, and mild chronic pancreatitis = 2).

Table 1: Patient characteristics with low and normal fecal elastase

Variables	Low FE (*n*=9), *n* (%)	Normal FE (*n*=88), *n* (%)	*P*
Female gender	5 (55.6)	56 (63.6)	0.723
Race (White)	8 (88.9)	68 (77.3)	1.00
Tobacco smoking			
Yes	2 (22.2)	15 (17)	0.655
No	7 (77.8)	73 (83)	
Alcohol drinking			
Yes	2 (22.2)	39 (44.3)	0.293
No	7 (77.8)	48 (54.5)	
History of diabetes			
Yes	2 (22.2)	31 (35.2)	0.741
No	7 (77.8)	57 (64.8)	
Age (years)	53.67±13.55	52.39±16.56	0.171
Weight (kg)	98.48±29.33	82.22±22.16	0.045
BMI	30.63±5.65	28.07±6.54	0.262
Symptom severity index	27.44±8.41	26.97±9.88	0.656

BMI – Body mass index; FE – Fecal elastase

Enzyme replacement therapy

Nine patients were started on pancreatic enzyme supplements based on a high likelihood of EPI, as per the discretion of the provider while further workup was in progress; three had low FE. Symptoms improved in 2/3 with low FE and 3/5 with normal FE. The three patients with normal FE and symptom improvement on enzyme replacement therapy were noted to have had pancreatic changes on follow-up imaging: atrophy on MRI ($n = 1$), chronic pancreatitis on EUS ($n = 1$), and parenchymal changes with fatty pancreas on EUS ($n = 1$). Summary of patients who were started on pancreatic enzymes can be found in Table 3.

DISCUSSION

The result of this study is remarkable for 9.3% prevalence of EPI among patients with new-onset chronic diarrhea. There were no significant differences in demographic or clinical features between the groups with low and normal FE, highlighting the role of systematic testing in this group of patients. EPI is most commonly seen in patients with chronic pancreatitis, pancreatic cancer, and cystic fibrosis, all of which were excluded in this study. However, EPI could also be associated with conditions such as IBS or diabetes mellitus, which could lead to bacterial overgrowth or bacterial elastase degradation.[15] In the literature, concordance occurrence of EPI and diarrhea dominant-IBS has been reported in up to 6.1% of the population.[5] Limited testing and follow up among patients with low FE suggest the presence of subtle pancreatic changes on imaging and symptomatic response to enzyme replacement therapy.

There is no gold standard for the diagnosis of IBS, and the majority of patients with negative initial workup for other etiologies causing a change in bowel habits are presumed to have IBS as the etiology of their symptoms. It is possible that patients with undiagnosed EPI could be categorized as having IBS before the correct diagnosis is established, which could lead to a delay in potential life-changing treatment intervention. Based on our cohort and similar to

Table 2: Radiological findings, 72-h fecal fat, and pancreatic enzyme supplements in the nine patients with low fecal elastase

Pancreatic imaging	72-h fecal fat		Pancreatic enzyme supplement
	Not performed	Normal	
CT scan - normal pancreas		1	Improvement
CT scan - normal pancreas	1		Did not start
EUS- hyperechoic strands not meeting criteria for chronic pancreatitis	1		Did not start
MRI - normal pancreas	1		Did not start
EUS - moderate to severe chronic pancreatitis		1	No improvement
EUS - early changes of chronic pancreatitis		1	Improvement
No abdominal imaging, patient lost to follow up			Did not start

CT – Computed tomography; EUS – Endoscopic ultrasound; MRI – Magnetic resonance imaging

Table 3: Summary of radiological findings in nine patients who were started on pancreatic enzymes supplements while workup was in progress

Baseline fecal elastase	Clinical status after initiation of pancreatic enzyme	Imaging findings	Imaging findings
Low	*Improvement on pancreatic enzyme*	Patient A: CT scan showed normal appearing pancreas	Patient B: EUS showed early changes of chronic pancreatitis
	No improvement on pancreatic enzyme		Patient C: EUS showed moderate to severe chronic pancreatitis
Normal	*Improvement on pancreatic enzyme*	Patient D: MRI showed atrophic pancreas Patient F: EUS showed early stages of chronic pancreatitis	Patient E: EUS showed hyperechoic strands and fatty infiltration, not meeting criteria for chronic pancreatitis
	No improvement on pancreatic enzyme	Patient G: EUS showed hyperechoic strands not meeting criteria for chornic pancreatitis	Patient H: No abdominal imaging
Unkown (lab error)	*Improvement on pancreatic enzyme*		Patient I: MRI showed normal pancreas

CT – Computed tomography; EUS – Endoscopic ultrasound; MRI – Magnetic resonance imaging

the previously published European studies, EPI and celiac disease have similar prevalence in patients with chronic diarrhea. Despite this similarity in prevalence, the most recent American Gastroenterological Association guideline in 2019 recommends against routine testing for EPI in patients with unexplained chronic diarrhea.[16] However, many experts have been advocating for the incorporation of FE testing to rule out EPI in the initiwal workup of patients with chronic diarrhea.[17,18] This also is of utmost importance, especially in high-risk patients, especially those with diabetes mellitus or chronic alcohol users.[19]

The observed prevalence in our study (9.3%) is in line with previously reported EPI prevalence in European and Southern American countries, which have ranged between 4.4% and 15%.[4-7]

Spot FE testing is an easily accessible test to screen for EPI among patients with chronic diarrhea with high sensitivity and specificity. Although the sensitivity of FE is moderate in patients with mild chronic pancreatitis, the higher sensitivity in patients with advanced chronic pancreatitis, combined with the ease of use, makes it a good initial screening tool for EPI.[20] The time frame between the occurrence of parenchymal changes as the result of acute or chronic pancreatitis with a diagnosis of EPI is unclear. In a recent prospective, multicenter, longitudinal cohort study by Phillips *et al*., 34.1% of the 85 patients with acute pancreatitis developed EPI within a 12-month follow-up period.[21]

In our study, three patients with low FE had normal 72-hour fecal fat testing. Interestingly, two of these three patients achieved EPI symptom resolution on PERT. Although the historically 72-hour fecal fat collection is the gold standard test for diagnosis of EPI, most recently, Korostensky *et al*. demonstrated limited validity of this test in the current era due to lack of patient compliance with the high-fat diet and dietary diary, manual errors in the titration steps, as well as high false positivity in the setting of loose stool consistency.[22] It is also possible that the EPI diagnosed in this study, which excluded patients with overt pancreatic disease, reflects a milder variety of pancreatic insufficiency that would not produce abnormal 72-hour fecal fat amounts.

To date, the correlation between EPI and the presence of pancreatic parenchymal changes in radiological modalities has remained unclear. In a previous retrospective study of 40 patients (non-overlapping with this study's cohort) with low FE at our institution, 82.5% of patients with EPI, defined as FE <200 μg/g, had new EUS findings of chronic pancreatitis, fatty pancreas, and pancreatic solid or cystic masses.[23] A recent study also demonstrated a higher prevalence of EPI and chronic pancreatitis in patients with diffuse echogenicity on EUS compared to the control group (47% vs. 6%, $P < 0.001$; and 42% vs. 17%, $P = 0.002$, respectively).[24] An interesting finding in our study is symptom resolution in the three patients who had normal FE but were started on PERT based on their pretest likelihood for EPI based on pancreatic parenchymal changes, suggestive of fatty pancreas and chronic pancreatitis or pancreatic atrophy on EUS or MRI.

In our study, patients with low FE had a higher weight in comparison to those with normal FE values. Obesity could lead to a wide range of comorbidities, such as fatty liver disease and chronic pancreatitis.[25,26] The result of our study highlights the importance of testing for EPI, especially in obese patients with unexplained chronic diarrhea.

Strengths and limitations

The strength of our study includes its prospective enrollment and testing in consecutive patients presenting

with diarrhea. In addition, our study is among the first studies to estimate the prevalence of EPI among patients with chronic diarrhea of unclear etiology and without obvious pancreatic disease in the United States. However, there are also limitations to this study. Only 68.3% of patients completed FE testing, which highlights difficulties in performing any stool-based examination. Another limitation of this study is the lack of patient follow-up after low FE testing for confirmatory fecal fat testing. We were not able to confirm the diagnosis of EPI with 72-hour fecal fat quantification testing in most subjects with low FE; patients were unwilling to proceed with further testing due to the complexity of 72-hour fecal fat collection, restricted dietary requirement, or were unable to follow-up due to a lack of interest or personal inquiries.

CONCLUSION

Given the high prevalence of EPI in up to 9.3% of patients with new-onset chronic diarrhea, we propose testing for FE as part of the initial workup for patients presenting with new-onset chronic diarrhea. Testing for EPI is particularly important in patients with risk factors for EPI, such as a history of tobacco and alcohol consumption or obesity. Larger, prospective studies are needed to ascertain the best practice to diagnose EPI with fecal stool-based testing to achieve efficient and cost-effective clinical endpoints.

Ethical considerations

The study was approved by the Institutional Review Board of Baylor College of Medicine (H-37932, 7/27/2021), Texas, USA. All study participants provided written consent before inclusion in the study. The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: T.K., S.A., M.M., N.B., H.E., and M.O.; Methodology: T.K. and M.O.; Data analysis: T.K. and M.O.; Writing–original draft preparation: T.K. and M.O.; Writing – review and editing: T.K., S.A., M.M., N.B., H.E., and M.O.; Supervision: H.E. and M.O.

All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

- Tara Keihanian: Tara Keihanian is consultant for ConMed, Boston Scientific, Microtech, and Neptun Medical
- Suneal Agarwal: No conflict of interest to disclose
- Nabil Mansour: No conflict of interest to disclose
- Michael Mercado: No conflict of interest to disclose
- Hashem B. El-Serag: No conflict of interest to disclose
- Mohamed O. Othman: Mohamed O. Othman is a consultant for Olympus, Boston Scientific Corporation, Abbvie, ConMed, Lumendi and Apollo. Mohamed O. Othman received research grants from Lucid Diagnostics, AbbVie, and ConMed.

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