

Should we Investigate Gastroenterology Patients for Pancreatic Exocrine Insufficiency? A Dual Centre UK Study

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ABSTRACT

Background & Aims: Pancreatic exocrine insufficiency may be under recognised in gastroenterological practice. We aimed to identify the prevalence of pancreatic insufficiency in secondary care gastroenterology clinics and determine if co-morbidity or presenting symptoms could predict diagnosis. A secondary aim was to assess response to treatment.

Methods: A dual centre retrospective analysis was conducted in secondary care gastroenterology clinics. Patients tested for pancreatic exocrine insufficiency with faecal elastase-1 (FEL-1) between 2009 and 2013 were identified in two centres. Demographics, indication and co-morbidities were recorded in addition to dose and response to pancreatic enzyme replacement therapy. Binary logistic regression was used to assess if symptoms or co-morbidities could predict pancreatic insufficiency.

Results: 1821 patients were tested, 13.1% had low FEL-1 (<200µg/g). This prevalence was sub-analysed with 5.4% having FEL-1 100-200µg/g (mild insufficiency) and 7.6% having faecal elastase readings <100µg/g. Low FEL-1 was most significantly associated with weight loss or steatorrhoea. Co-morbidity analysis showed that low levels were significantly associated with excess alcohol intake, diabetes mellitus or human immunodeficiency virus; 80.0% treated with enzyme supplements reported symptomatic benefit with no difference in response between high and low dose supplementation (p=0.761).

Conclusion: Targeting the use of FEL-1 in individuals with specific symptoms and associated conditions can lead to improved recognition of pancreatic exocrine insufficiency in a significant proportion of secondary care patients. Intervening with lifestyle advice such as smoking cessation and minimising alcohol intake could improve outcomes. In addition, up to 80% of patients with low faecal elastase respond to supplementation.

Key words: faecal elastase – pancreas – diarrhoea – pancreatic insufficiency.

Abbreviations: CFA: coefficient of fat absorption; CP: chronic pancreatitis; ELISA: enzyme-linked immune-absorbent assay; PEI: pancreatic exocrine insufficiency; FEL-1: faecal elastase-1; HIV: human immunodeficiency virus; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; PERT: pancreatic enzyme replacement therapy.

INTRODUCTION

Post mortem studies suggest that chronic pancreatitis (CP) affects 6 to 12% of the general population [1-3]. There is, however, a mismatch between these reports and the incidence of clinically reported CP. Internationally the range is reported from 4.05-13.4/100,000 [4, 5]. It has been suggested that pancreatic exocrine insufficiency (PEI) may be an

early manifestation of CP [6]. The prevalence of PEI has been reported between 11.5% and 21.7% in individuals without pre-existing gastrointestinal disease [7, 8]. Each year in the United Kingdom, around 11,000 new cases of PEI are diagnosed [9]. Current recommendations suggest screening for PEI in patients presenting with diarrhoea [10]. If faecal elastase-1 (FEL-1) is checked only when features of advanced malabsorption and pancreatic disease are present (e.g. steatorrhoea), cases of subclinical PEI and early CP could be missed. Missing the opportunity to intervene with pancreatic enzyme replacement therapy (PERT) may result in more complications of exocrine failure developing [11]. These complications include malabsorption of fat soluble vitamins, osteoporosis and carbohydrate and protein malabsorption [12].

Faecal elastase-1 is secreted by the pancreas and travels through the gut unaltered: this is distinctive in comparison with other pancreatic enzymes [13]. Faecal elastase-1 comprises around 5% of pancreatic secretion but adequately reflects secretion of more profuse pancreatic enzymes [14, 15], thus it can be employed to evaluate exocrine function. Faecal elastase-1 is highly specific and sensitive in identifying severe PEI but can be weaker in mild to moderate disease. Faecal elastase-1 has been shown to be superior to faecal chymotrypsin in diagnosis of PEI. The use of FEL-1 was validated in comparison to the gold standard secretin-caerulein test and faecal chymotrypsin in a study comprising 79 patients [14].

A limitation of the FEL-1 assay is that stool samples should not be taken during acute diarrhoeal illnesses and should not be contaminated with urine or water from toilet basins. Dilution of the specimen can result in false positive results and over diagnosis of EPI. Manufacturers of FEL-1 assays advise repeating the stool sample in the event of diagnostic uncertainty or borderline results [16]. This potential error in diagnosis can be reduced by centrifuging or drying the sample prior to analysis [17, 18]. Overall, given its ready availability and acceptability to patients, FEL-1 is the most appropriate initial measure of exocrine pancreatic function [10].

Faecal elastase -1 can be the first step towards a diagnosis of CP; ultimately the diagnosis is made in a multimodal fashion, taking into account the clinical history, risk factors and investigation results. Investigations may include computed tomography (CT) or magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) [19].

It is important to emphasise that CP and PEI are separate diagnoses and the presence of one does not mean the other is present. Studies assessing the prevalence of PEI in CP patients report rates of PEI from 5.1% (less than 5 years CP diagnosis) [20] to 94% (over 10 years from diagnosis) [21]. Development of PEI is not always due to CP. Causes of PEI are wide ranging and mechanisms include: impairment or reduction in enzyme production (CP, pancreatic malignancy or surgery or cystic fibrosis), decreased duodenal enzyme delivery: ampullary tumour causing main pancreatic duct (MPD) obstruction, coeliac disease (reduced CCK secretion), Zollinger-Ellison syndrome (deactivation of enzymes due to reduced pH), or abnormal anatomy or motility (gastric surgery, short bowel syndrome, diabetes mellitus, Crohn's disease).

We aimed to detect the prevalence of PEI in unselected patients presenting to secondary care by testing with FEL-1 and the subsequent effect on the noted symptoms with PERT.

METHODS

A dual-centre retrospective analysis was conducted. Patients attending secondary care gastroenterology clinics between 2009 and 2013 with gastrointestinal symptoms who were offered testing for PEI with FEL-1 were identified. Patients with a pre-existing diagnosis of pancreatic malignancy or known CP and/or PEI were excluded. Patients already known to have structural pancreatic abnormalities on imaging were also excluded.

Patient demographics, indication for testing and certain co-morbidities were recorded. These included previous episodes

of acute pancreatitis, alcohol excess (defined as >21 units/week for men and >14 units/week for women where one unit is equal to 10 ml or 8 g pure alcohol), diabetes mellitus (type 1 and type 2 regardless of treatment), human immunodeficiency virus (HIV), biopsy proven coeliac disease, diarrhoea predominant irritable bowel syndrome (IBS) fulfilling Rome II criteria and inflammatory bowel disease (IBD) (ulcerative colitis or Crohn's disease). We noted the proportion of patients found to have low FEL-1 who had pancreatic imaging, the modality and results. Main pancreatic duct dilatation was defined as MPD greater than 3mm in the head or 2mm in the tail of the pancreas; this is a common convention employed by radiologists [22]. It was not possible to obtain data regarding smoking status for the patients included in the study due to lack of documentation in the clinical record.

Faecal elastase-1 was measured from stool samples using a sandwich enzyme-linked immune-absorbent assay (ELISA) containing monoclonal antibodies specific for human pancreatic FEL-1: FEL-1 measurements of <200µg/g were considered abnormal; FEL-1 values between 100µg/g and 200µg/g represented mild insufficiency, results <100µg/g were interpreted as severe insufficiency. No other methods of assessment of pancreatic function were employed.

Simple descriptive statistics were used to describe the population and assess common indicators for testing. Binary logistic regression analysis examined independent predictors of PEI using SPSS (IBM version 20). The initial dose of PERT and response to treatment was recorded. Fisher's exact test (Graph pad) was used to determine if there was a symptomatic benefit with higher doses of PERT (>120,000 units/day). The project was prospectively approved by the Research and Ethics Departments (STH 16190, South Tees 4182).

RESULTS

During the study period, 1878 patients were identified that had testing for PEI with FEL-1; 57 of these were excluded as they had pre-existing diagnoses of CP, pancreatic malignancy or PEI. Of those 57, 54.3% had low FEL-1 consistent with PEI. The remaining 1821 patients were analysed. One thousand and eleven (61.0%) patients were female, median age 51.3 (range 16-93). Two hundred thirty seven patients (13.1%) were found to have a low FEL-1 <200µg/g. Table I shows FEL-1 results split into normal (FEL-1 >200µg/g), mild insufficiency (FEL-1 100-200µg/g), moderate to severe insufficiency (FEL-1 <100µg/g). It also shows the predominant reported symptom per patient. Pre-existing co-morbidities and FEL-1 results are listed in Table II.

Imaging

Two hundred two out of 238 (84.9%) patients with low FEL-1 had abdominal imaging with 69 (34.2%) of these patients having pancreatic abnormalities. Imaging modalities employed included CT (63.7%), US abdomen (29.2%) and MRI (7.1%). Sixty patients had changes consistent with CP (20 calcification, 35 atrophy, 3 duct dilatation, 7 general cystic change and 4 pseudocysts), 6 cases showed evidence of a recent or on-going episode of acute pancreatitis and 2 cases were found to have pancreatic malignancy.

Table I. Prevalence of low fecal elastase-1 (FEL-1) by symptom.

	Prevalence of predominant symptom		FEL-1 >200µg/g			FEL-1 100-200µg/g			FEL-1 <100µg/g		
	n (%)	n	OR (95% CI)	p	n	OR (95% CI)	p	n	OR (95% CI)	p	
Diarrhoea	1229 (67.49)	1069/1229	16.70 (3.21-86.82)	0.83	68/1229	0.35 (0.042-2.96)	0.07	92/1229	0.06 (0.01-0.26)	0.73	
Abdominal pain	356 (19.55)	318/356	20.92 (3.92-111.58)	0.99	14/356	0.25 (0.03-2.18)	0.03	24/356	0.05 (0.01-0.26)	0.59	
Weight loss	110 (6.04)	85/110	8.50 (1.55-46.50)	0.38	12/110	0.73 (0.08-6.63)	0.39	13/110	0.10 (0.02-0.50)	0.05	
Bloating	62 (3.41)	56/62	23.33 (3.69-147.41)	0.91	3/62	0.31 (0.02-3.41)	0.11	3/62	0.04 (0.01-0.25)	0.38	
Other	48 (2.64)	45/48	37.50 (5.01-280.91)	0.73	1/48	0.12 (0.01-2.31)	0.07	2/48	0.03 (0.001-0.03)	0.19	
Nausea	9 (0.49)	9/9	-	1.0	0/9	-	1.0	0/9	-	1.0	
Steatorrhoea	7 (0.38)	2/7	Reference	0.01	1/7	Reference		4/7	Reference	<0.001	
Total	1821	1584			99			138			

The main symptom reported by patients is shown. P values were calculated with binary logistic regression analysis and denote significance of each symptom as a predictor finding low FEL-1. The lowest prevalence variable (steatorrhoea) was used as the reference variable for calculating odds ratios for the risk of low FEL-1.

Not all patients with low FEL-1 had evidence of imaging when records were reviewed. There was no difference in age when comparing the two groups that were imaged and those that were not (57.9 years vs 54.5 years, $p=0.24$). Some patients may have gone on to have imaging later in their clinical course, which may partly explain why 15.1% of patients did not have imaging. Some patients may have had cross sectional imaging at their local hospitals, the results of which were not always available for data collection during this study.

Pancreatic enzyme replacement therapy

One hundred forty-seven out of 238 (61.8%) patients with FEL-1 <200µg/g were identified as being treated with PERT from review of the medical records. Total daily doses varied from 30,000 to 420,000 units of lipase per day (median dose 120,000 units). One hundred seventeen (79.6%) of the 147 patients treated reported benefit in symptoms. Due to the information available in the clinical records it was not possible to quantify the exact benefit conferred by PERT. For the purposes of this study,

Table II. Prevalence of low fecal elastase-1 (FEL-1) by co-morbidity

	Prevalence of comorbidity		FEL-1 >200µg/g			FEL-1 100-200µg/g			FEL-1 <100µg/g		
	n (%)	n	OR (95% CI)	p	n	OR (95% CI)	p	n	OR (95% CI)	p	
Alcohol	104 (5.71)	66/104	2.12 (0.81-5.58)	<0.001	9/104	0.16 (0.06-0.55)	0.17	29/104	1.55 (0.48-5.02)	<0.001	
Diabetes mellitus	124 (6.81)	82/124	2.39 (0.92-6.21)	<0.001	24/124	0.46 (0.16-1.24)	<0.001	18/124	4.68 (1.12-14.43)	0.007	
Irritable bowel syndrome	332 (18.23)	319/332	29.99 (10.59-84.96)	<0.001	8/332	0.05 (0.01-0.15)	0.08	5/332	4.06 (1.34-12.28)	0.001	
Coeliac disease	183 (10.05)	161/183	8.94 (3.33-24.00)	0.68	9/183	0.09 (0.03-0.30)	0.92	13/183	4.31 (1.41-13.14)	0.632	
Inflammatory bowel disease	127 (6.97)	96/127	5.01 (1.91-13.14)	<0.001	14/127	0.23 (0.08-0.67)	0.005	17/127	0.61 (0.18-2.07)	0.006	
Acute pancreatitis	42 (2.31)	28/42	2.44 (0.82-7.27)	0.01	3/42	0.14 (0.03-0.640)	0.91	11/42	1.42 (0.39-5.18)	0.004	
HIV	20 (1.10)	9/20	Reference	<0.001	7/20	Reference	<0.001	4/20	Reference	0.108	
Total patients	1821										

All co-morbidities were recorded i.e. patients may have had more than one co-morbidity listed. P values were calculated with binary logistic regression analysis and show significance of presence of co-morbidities in predicting presence of low FEL-1. The lowest prevalence variable (HIV) was used as the reference variable for calculating odds ratios for the risk of low FEL-1.

benefit was defined as a documented improvement in symptoms. This included reduced frequency of diarrhoea, reduction in abdominal pain or gain in weight. Nutritional markers were not assessed as part of the study design.

A standard PERT dosing regime was not applied to patients in the study and the doses prescribed reflect practice of individual clinicians. From review of case records available at the time of data collection it was only possible to positively identify 147/238 patients who had been treated with PERT. It is possible that a proportion of the 238 patients with low FEL-1 were felt to have shown a false positive result and were not treated by their clinician. It is also feasible that patients were offered treatment with PERT but that this decision was not documented in the clinical correspondence.

Where enough data was available there was no difference in symptomatic relief when comparing patients receiving less than 120,000 units per day (21/64) and those receiving 120,000 units or more per day (43/64, $p=0.761$)

DISCUSSION

Faecal elastase-1 was used to test pancreatic function given its availability and ease of use for patients. There are many ways to assess pancreatic function, but no test is one hundred percent specific or sensitive. The accepted gold standard for diagnosis of PEI is the secretin-caerulein test [14]. This test is, however, time consuming for patients and does not have widespread clinical application. It is rarely performed in general clinical practice.

Direct tests involving hormonal stimulation of the pancreas boast the greatest specificity and sensitivity, but are invasive and time and labour intensive [6]. Patients must undergo gastric and duodenal intubation whilst either secretin or cholecystokinin is injected intravenously. Resulting pancreatic secretions are then aspirated and analysed. Due to resource limitations and acceptability to patients, these tests are not widely available or performed. Indirect tests measuring pancreatic enzymes in the stool are more widely used due to their relative simplicity and acceptability [9]. In the UK, the current standard of care for screening for PEI is FEL-1. It is the most widely used indirect test of pancreatic function and is superior to other tests such as faecal chymotrypsin [13, 14]. The British Society of Gastroenterology (BSG) guidelines for investigation of chronic diarrhoea advocate routine FEL-1 measurement as a first line assessment of pancreatic function [10].

Faecal elastase-1 levels $<100\mu\text{g/g}$ are considered to represent severe PEI and levels $100\text{--}200\mu\text{g/g}$ are said to be consistent with mild to moderate PEI; however, these reference ranges do not have a strong evidence base. One study comparing the coefficient of fat absorption (CFA) with FEL-1 reported that PEI could only be diagnosed reliably when FEL-1 fell below $15\mu\text{g/g}$ in patients with CP [23]. Other studies report that FEL-1 boasts sensitivities of 100% in severe PEI (cut off $<100\mu\text{g/g}$), 89–100% in moderate disease and 33–65% in mild cases of PEI [14, 24, 25]. Individuals presenting with acute diarrhoeal illnesses (e.g. infective diarrhoea or IBD) can be incorrectly diagnosed with PEI. Manufacturers of FEL-1 assays advise repeating the test when dilute or watery specimens are provided to confirm the diagnosis of PEI. In the event of diagnostic uncertainty, the sample should be repeated.

Patients with low FEL-1 did not routinely have repeat measurements. It is possible that a proportion of the 13.1% with low FEL-1 represented false positives; however, this subgroup is likely to be small. Clinicians should not be deterred from checking FEL-1 and considering PEI as a diagnosis but should exercise caution in labelling patients as exocrine insufficient on the basis of one abnormal FEL-1 result. Where a high pre-test suspicion of PEI exists, e.g. in a patient with symptoms strongly suggestive of CP, clinical evidence of malnutrition and risk factors such as smoking or heavy alcohol intake, a single FEL-1 measurement may be deemed adequate to make a diagnosis of PEI. It would be rare to make a diagnosis of PEI based on FEL-1 alone, as the presence of PEI should prompt imaging of the pancreas to exclude pancreatic malignancy as an underlying cause. Ultimately, a clinician's professional judgement will come into play when making the diagnosis in the absence of readily available direct tests.

This large series demonstrates that low FEL-1 levels are commonly identified in secondary care gastroenterology patients referred for investigation of various symptoms. History of weight loss or steatorrhoea significantly predicts for PEI. Due to the retrospective nature of the study quantification of faecal fat was not performed. The presence of steatorrhoea as described by a patient and interpreted by a clinician may not represent true steatorrhoea. Ideally the CFA should have been calculated, defined as $(\text{mean fat intake} - \text{mean stool fat}) / \text{mean fat intake}$ [26].

Our study benefits from a large cohort referred to two secondary care gastroenterology centres with a variety of symptoms. Similar rates of PEI were detected in this study by case finding compared to existing studies (13.1% $<200\mu\text{g/g}$, 5.4% $100\text{--}200\mu\text{g/g}$, 7.6% $<100\mu\text{g/g}$) [7, 8]. This supports the hypothesis that PEI is common in gastroenterology practice and clinicians should have a low threshold for checking FEL-1 in patients presenting with symptoms other than diarrhoea. It could be argued that the proportion of patients with low FEL-1 in this cohort is high compared to the general population as patients attending gastroenterology clinics have already undergone selection through referral to secondary care. Gastroenterologists may also have a heightened awareness of utility of FEL-1. On the other hand, the cohort being assessed presented with a variety of complaints and those with existing pancreatic diagnoses were excluded from the study.

It would have been helpful to report smoking status of patients included in this study. However, due to the quality of record keeping assessed in data acquisition, it is not possible to provide this information. A study of 540 patients with CP reported "cigarette smoking was an independent, dose-dependent risk factor for CP" [4]. Dose dependent relationships have also been demonstrated between smoking and risk of CP (OR 1.65 >100 cigarettes per lifetime, OR 1.8 current smokers, OR 1.87 >1 pack per day) [27]. The benefits of identifying smokers would mean that smoking cessation interventions could be made to reduce the chance of patients without CP developing it in the future. Designing a similar study as this with prospective data collection would allow for the assessment of smoking status and assessment of risk carried by smoking for developing PEI. The primary aim of this study was to quantify the presence of PEI not CP and

therefore we feel that not including data on smoking status was an acceptable limitation.

Although we were unable to supply data detailing the proportion of patients attending gastroenterology clinics screened for PEI during the recruitment period, finding a positive result in 13.1% of patients indicates that it is a useful test and should be performed routinely. Increasing awareness of the detection rates in our secondary care population should increase awareness of the scale of the condition and help clinicians identify PEI earlier.

Symptoms

The frequency of predominant presenting symptoms seen was in line with those seen in general gastroenterology clinics [28]. The prevalence of chronic diarrhoea has been estimated at 4-5% of the general Western population [29, 30], so it is unsurprising that the majority of patients studied reported diarrhoea as the predominant symptom (67.03%).

Weight loss and steatorrhoea independently showed significantly high association with detection of FEL-1 <100µg/g ($p=0.05$ and $p<0.001$, respectively). Steatorrhoea and fat malabsorption are well-recognised and specific symptoms of pancreatic insufficiency [31]. Weight loss is commonly seen in the general gastroenterology setting and is not specific to PEI. Clinicians may have a lower threshold for screening with FEL-1 in this group. We would encourage testing for PEI in individuals presenting with weight loss even where diarrhoea is not present.

Co-morbidities

Pancreatic exocrine insufficiency testing is recommended in patients with both type 1 and type 2 diabetes presenting with diarrhoea [32]. The prevalence of PEI (FEL-1 <100µg/g) in patients with diabetes ranges from 12-44% [32-34]. The results of this study are in line with previously published studies in diabetics (14.5%).

Of 20 patients with HIV, 55% had low FEL-1 levels. Eighteen of the patients presented with diarrhoea as the predominant feature. Small studies exist quantifying the prevalence of PEI in HIV positive patients and estimate rates between 36 and 50% [35, 36]. Although only a small number of patients in this study were HIV positive we would recommend screening for PEI in HIV given the high prevalence demonstrated.

The role of alcohol in the pathogenesis of CP is long recognised. However, there is relatively little clinical data estimating the prevalence of PEI in patients with excess alcohol intake. A study assessing FEL-1 levels in patients with alcohol-related liver disease found a prevalence of PEI of 7% [37]. We found that 36.5% and 27.9% of patients with history of high alcohol intake had FEL-1 levels <200µg/g and <100µg/g, respectively. This supports screening for PEI in patients with history of excessive alcohol intake presenting to gastroenterology with a variety of gastrointestinal symptoms.

We found a low prevalence of PEI in coeliac disease, however, there have been benefits shown in testing for PEI in coeliac patients whose symptoms do not resolve on a gluten free diet [38].

Imaging

A third of our patients with low FEL-1 had pancreatic abnormalities consistent with CP on cross-sectional imaging.

The risk of pancreatic cancer is known to increase with the duration of CP [39], therefore follow up imaging in CP is recommended [40]. Two cases of pancreatic cancer were identified in our cohort, thus supporting routine pancreatic imaging when PEI is diagnosed.

The results reported reflect day-to-day observed clinical practice. The majority of patients in the study presented with diarrhoeal symptoms, which would not usually be assessed with cross sectional imaging according to the BSG guidelines [10]. It is therefore not possible to comment on the radiological assessment of pancreatic structure in patients with normal FEL-1. It is, however, possible that some patients with normal FEL-1 could have undiagnosed CP in the absence of PEI.

Pancreatic enzyme replacement therapy

There was a significant response in most patients with a low FEL-1 with PERT. It was, however, difficult to determine the exact nature of the response given the retrospective nature of the study. The results may be subject to bias at levels of patient reporting, clinician documentation and interpretation and also at the level of data collection by the investigators. It is also possible that some patients experienced a placebo effect from PERT and their low FEL-1 results were indeed false positive results. Further pancreatic assessment with investigations such as endoscopic ultrasound or secretin stimulated MRI would have helped identify any patients with false positive FEL-1 results and eliminate this detection bias.

In the non-responding group of 30 (20%) patients there was no difference in patients taking initial high (greater than 120,000 units per day) or low dose PERT ($p=0.761$). It is feasible that some of the patients in the cohort may have had a false positive FEL-1 result which could account for the incomplete response rates seen in patients treated with PERT. There was wide variability in the doses of PERT prescribed. Enzyme therapy is used to mimic normal exocrine pancreatic function by administering enzymes at meal times to assist weight gain and maintain normal nutritional status [37]. Many factors govern the optimal dose of PERT including age, degree of PEI and fat content of food. It has been suggested that in healthy individuals, around 30,000 units of lipase per meal are required to maintain physiological digestion and absorption [41]. There is varying opinion in the literature regarding optimum doses of PERT in PEI. Estimates have been placed in the region of 25,000 – 50,000 units lipase per meal [42-44]. Some patients included in this study received sub-therapeutic doses of PERT (10,000 units per meal). This highlights an important point that clinicians may have poor understanding of enzyme doses required to maintain physiological digestion. The introduction of a PERT prescribing protocol would be helpful to ensure patients with PEI are treated with adequate enzyme replacement.

Nutritional markers were not assessed in this study. It is recognised that certain markers such as magnesium, haemoglobin, albumin and retinol binding protein can be used to predict presence of PEI [31] and deficiencies of fat soluble vitamins can be present in up to 63% of patients with CP sometimes presenting prior to onset of exocrine insufficiency [45]. The risk of osteoporosis and decreased bone mineral density is also well described in PEI [46]. Nutritional

consequences of PEI are not reported in this cohort, although further investigation could be pursued in this area and would provide valuable data to augment the existing evidence base.

The literature on PEI suggests that clinically significant PEI occurs when greater than 90% of pancreatic acinar function is lost [47] and that PEI develops a median of 12 years after diagnosis of CP [48]. Patients with CP do not, therefore, have PEI by definition but are certainly at risk of developing it in the future. A debate also exists regarding the optimal reference ranges of FEL-1. Anecdotally, PEI has been described as a binary phenomenon, but when taking into account the gradual destruction of the pancreatic tissue it is logical to hypothesise that a spectrum of disease severity exists. Extrapolation of this idea leads to the suggestion that symptoms must develop over a period of time, perhaps insidiously at first, then becoming more severe. As demonstrated by Sikkens et al., nutritional deficiencies can develop in CP prior to the onset of clinical PEI [49]. It is, therefore, crucial to identify PEI as early as possible when the symptoms may be diverse and indistinct and avoid misdiagnosing functional bowel disorders. Early intervention also presents opportunity to intervene with lifestyle advice such as smoking cessation and consuming alcohol within recommended limits to improve future outcomes.

CONCLUSION

We recommend a low threshold for screening for PEI with FEL-1 in patients presenting to secondary care. Those with abnormal FEL-1 levels should undergo specific pancreatic assessment. The work up should include cross sectional pancreatic imaging, assessment of risk factors, nutritional markers and complications of PEI such as osteoporosis. Patients should be followed up with a monitoring of response to treatment and titration of PERT.

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Authors' contributions: J.A.C. helped design the study, collect, analyse and interpret data and draft the article. K.A.F., D.J., S.L., H.T., A.R. and M.K. collected and assisted interpreting data and reviewed the final manuscript. D.S.S. conceived and designed the study and reviewed the manuscript. A.D.H. assisted with data interpretation, analysis and reviewed the final manuscript.

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Este oare necesar să fie investigați pacienții digestivi pentru insuficiența pancreatică exocrină? Un studiu efectuat în două centre din UK

ABSTRACT / REZUMAT

Premize și Scop: Insuficiența pancreatică exocrină (PEI) este probabil subestimată în practica gastroenterologică. Scopul studiului a fost acela de a evalua prevalența PEI în clinicile cu profil de gastroenterologie și de a stabili dacă comorbiditatea sau simptomul prezentat pot indica diagnosticul. Un alt scop a fost acela de a aprecia răspunsul la tratament.

Metodă: A fost efectuată o analiză retrospectivă în două clinici de gastroenterologie de nivel secundar. Au fost identificați pacienții având PEI diagnosticată prin testul elastază-1 fecală (FEL-1) în perioada 2009-2013. Caracteristicile lor demografice, indicația pentru evaluare și comorbiditățile au fost înregistrate, de asemenea doza administrată și răspunsul la terapia de substituție enzimatică. S-a utilizat regresia logistică binară pentru a stabili dacă simptomele sau comorbiditățile pot indica prezența insuficienței pancreatice.

Rezultate: Dintre cei 1821 pacienți testați, 13,1% au avut nivel scăzut al FEL-1 ($<200\mu\text{g/g}$): 5,4% au avut FEL-1 100-200 $\mu\text{g/g}$ (insuficiență ușoară), iar 7,6% sub 100 $\mu\text{g/g}$. Nivelul redus al FEL-1 s-a asociat semnificativ cu scăderea din greutate și steatoreea. Analiza comorbidităților a arătat că nivelul scăzut de FEL-1 s-a asociat semnificativ cu consumul în exces de alcool, diabetul zaharat sau prezența infecției cu HIV. Dintre cei tratați cu supliment enzimatic, 80% au raportat ameliorare, fără a exista o diferență semnificativă statistic între doza redusă și cea mare de enzime administrate ($p=0.761$).

Concluzie: Evaluarea FEL-1 la pacienții cu simptome specifice și condiții asociate poate conduce la o recunoaștere mai bună a insuficienței pancreatice la pacienții din asistența secundară. Pentru aceștia, recomandările de modificare a modului de viață, respectiv de sistare a fumatului și reducere a consumului de alcool, pot ameliora evoluția. În plus, aproximativ 80% dintre pacienții cu FEL-1 scăzut răspund favorabil la suplimentarea enzimatică.