Original research

What is the significance of a faecal elastase-1 level between 200 and 500µg/g?

Alok Mathew,[1] Darren Fernandes ,[2,3] H Jervoise N Andreyev [2,4]

[1]Royal Derby Hospital, Derby, UK
[2]Department of Gastroenterology, United Lincolnshire Hospitals NHS Trust, Lincoln, UK
[3]School of Health and Social Care, Community and Health Research Unit, University of Lincoln, Lincoln, UK
[4]The Biomedical Research Centre, Nottingham Digestive Diseases Centre, School of Medicine, University of Nottingham, Nottingham, UK

Correspondence to
Dr Darren Fernandes, Gastroenterology, United Lincolnshire Hospitals NHS Trust, Lincoln, UK; dcrfernandes@gmail.com

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ABSTRACT

Background Pancreatic exocrine insufficiency is a cause of malabsorption. It is generally diagnosed if faecal elastase-1 (FE-1) levels are below 200 µg/g. Pancreatic function is assumed to be normal when faecal elastase levels are >500 µg/g. The significance of faecal elastase levels above 200 µg/g but less than 500 µg/g is unclear.

Methods This retrospective study reports the response to treatment in patients who had an FE-1 level between 200 and 500 µg/g.

Results Of these 82 patients, 28 were offered pancreatic enzyme replacement therapy (PERT). A clinical response, defined as an improvement in their initial symptoms after commencing PERT, was seen in 20 patients (71%), 7 with potentially predisposing conditions and 13 with functional diarrhoea. PERT particularly abolished or improved diarrhoea, steatorrhoea and flatulence.

Conclusion Clinicians should, therefore, be aware that a trial of PERT given to patients with FE-1 levels between 200 and 500 µg/g may lead to improvement in gastrointestinal symptoms.

INTRODUCTION

The pancreas plays an essential role in the digestion, absorption and metabolism of carbohydrates, fats and proteins.[1] Pancreatic exocrine insufficiency (PEI) is a condition whereby reduced pancreatic enzyme activity (mainly pancreatic lipase) in the intestinal lumen leads to impaired digestion.[1] Impaired digestion potentially results in nutrient malabsorption and malnutrition, as well as disturbed regulation of gastrointestinal (GI) motor and secretory functions.[2] PEI may present with symptoms such as bloating, abdominal discomfort, steatorrhoea (clay-coloured, loose, greasy, foul smelling stool), diarrhoea, excess flatulence and

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The diagnosis of pancreatic exocrine insufficiency (PEI) is often delayed in patients without an obvious predisposing cause. National Institute for Health and Care Excellence guidance recommends that this should not be considered in patients with functional diarrhoea or IBS-like symptoms. Recent UK guidance on the management of PEI is very comprehensive but does not address what to do with patients with a pancreatic faecal elastase level which lies between 200 and 500 ug/g.

WHAT THIS STUDY ADDS

⇒ We show that three-quarters of patients with a faecal elastase level between 200 and 500 ug/g trialled with pancreatic enzyme replacement therapy (PERT) appear to have a beneficial response, the majority of whom had no obvious predisposing cause. It is also of note that the majority of patients who had a faecal elastase-1 (FE-1) in the range of 200–500 ug/g but were not offered PERT by their managing clinician, continued to remain symptomatic despite other interventions. Therefore, clinicians should be aware that a trial of PERT in these cases can lead to a rapid improvement in symptoms.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests that there may not be distinct cut-off level for FE-1 levels to represent PEI and that instead, this is a graded and gradual decline. Future randomised controlled trials should, therefore, seek to gather more information about the use of PERT in patients with an FE-1 level between 200 and 500 ug/g to see if this response is clinically significant.

Table 1 Conditions/therapies associated with pancreatic exocrine insufficiency

Type of issue	Specific conditions	Prevalence
Intrinsic pancreatic disease	Chronic pancreatitis neoplasia	94% within 10 years of onset of chronic pancreatitis.[18] 66%–94% of patients with unresectable pancreatic cancer.[19 20]
Reduced CCK secretion	Coeliac disease	4%–80% in untreated coeliac disease (measured by FE-1).[21–26] 12% in patients with chronic diarrhoea on a gluten-free diet (based on pancreatic testing or trial of PERT) 18% (based on steatorrhoea and trial of PERT).[27 28]
Congenital disease	Pancreaticum divisum cystic fibrosis	48% based on faecal fat excretion.[29] 85% before the age of 1 year.[14]
Inflammatory bowel disease	Crohn's disease	14%–30%.[11 30]
	Ulcerative colitis	Up to 22% using FE.[11] Up to 50% using a secretin-cerulein test and 74% using para-aminobenzoic acid test.[31 32]
Bile acid malabsorption	May coexist[27]	No data but should be considered.[13]
Small intestinal bacterial overgrowth	May coexist[27]	Consider antibiotic therapy in those not responding to/not tolerating PERT.[33]
HIV disease	Due to disease[34 35] or secondary to antiretroviral medication particularly Didanosine[31 36]	Up to 54% with improvements in faecal fat loss following institution of PERT.[37 38]
Diabetes mellitus	Type 1 diabetes Type 2 diabetes	Up to 6% in type 1 diabetics with diarrhoea[39] and 26–44% otherwise.[40–43] 12%–20%[40–43]. Inadequate data whether there is any symptom improvement with PERT in those without diarrhoea.[44]
Oncological therapies	Tyrosine kinase inhibitors Checkpoint inhibitors Somatostatin analogues	7% in those treated with sorafenib.[45] 1% after nivolumab[46 47] and reported after pembrolizumab.[48 49] Chronic use can affect up to 38%.[50]

CCK, cholecystokinin; FE-1, faecal elastase-1; PERT, pancreatic enzyme replacement therapy.

weight loss and may be difficult to distinguish from many other GI conditions.[3] Symptoms of PEI are thought to develop when secretion of lipase and other pancreatic enzymes are reduced to <10% of normal values. However, symptomatic PEI may depend not only on pancreatic enzyme levels but also on underlying conditions (table 1); intrinsic pancreatic disease, as a result of reduced cholecystokinin (CCK) secretion or as a result of congenital conditions or secondary to other conditions[4 5] and potentially is better measured by a graded response in faecal elastase-1 (FE-1) levels rather than a precise cut-off.[6]

The most accurate tests for diagnosing pancreatic insufficiency are either unpleasant (prolonged faecal fat collection and quantification) or cumbersome (radiolabelled studies or endoscopically obtained pancreatic secretion analysis) and in clinical practice have been largely superseded by measurement of pancreatic FE-1 testing. FE-1 is an enzyme produced and released by the pancreas and remains intact during intestinal transit.[7] Vagal innervation to the pancreas stimulates FE-1 secretion in response to the sense, smell and taste of food and as a result of stomach wall distension. Acidic chyme entering the duodenum also leads to CCK release which stimulates secretion of pancreatic enzymes. As it is not degraded, stool concentration of FE-1 is a measure of the exocrine function of the pancreas. It is highly sensitive and specific for detecting advanced PEI but may be less reliable in milder cases, in patients following pancreatic resection or in patients with looser stools.[3 7–9] Increased water content in stools may have a dilutional effect on FE-1 concentration, thereby giving falsely low results. However, this limitation can be addressed by lyophilisation of the stool sample or centrifugation to reduce the water content.[10] In addition, a diurnal variation in FE-1 levels may affect interpretation of results.[11]

Patients who are diagnosed with PEI and treated with pancreatic enzyme replacement therapy (PERT) have increased survival and improvement in quality of life (QoL).[12] However, recent UK guidelines do not discuss the management of patients with potential PEI but who have FE-1 levels above the frequently quoted cut-off level of 200 µg/g,.[12 13] Therefore, the aim of this study was to assess the significance of an FE-1 level between 200 and 500 µg/g.

METHODS

This was a retrospective study which was approved by the United Lincolnshire Hospitals Trust audit committee (L0448) and deemed not to require the consent of the patient.

In our hospital laboratory, FE-1 concentration is determined using an ELISA. The polyclonal antibodies used are specific to human FE-1 and not affected by PERT.[14] A list of all patients who had an FE-1 sample measured at United Lincolnshire Hospitals NHS Trust were identified by the pathology laboratory. Those with results of <200 µg/g or >500 µg/g were excluded.

Table 2 Patient characteristics of those with an FE-1 result between 200 and 500 µg/g

	Male	Female	Total
Number	28	50	78
Age in years (median and range)	68 (30–90)	60 (27–86)	63 (27–90)
Abdominal symptoms			
Bloating	8	16	24
Diarrhoea	21	34	55
Flatulence	5	10	15
Pain	5	17	22
Steatorrhoea	2	6	8
Other GI conditions			
Coeliac disease	1	1	2
IBD	8	0	8
Pancreatic surgery	0	1	1
History of colorectal cancer	2	3	5
Other	6	9	15
No other GI condition	11	36	47
Numbers with FE level:			
200–300	6	13	19
300–400	12	16	28
400–500	10	21	31
Numbers offered PERT	10	18	28

FE-1, faecal elastase-1; GI, gastrointestinal; IBD, inflammatory bowel disease; PERT, pancreatic enzyme replacement therapy.

Notes and medical records of those remaining were retrospectively reviewed. For those seen as outpatients, clinical symptoms were recorded before PERT was trialled and subsequent clinic letters were reviewed and used to assess response to treatment. A response to PERT was defined for this study if the patient reported that their presenting symptoms had responded to treatment, if PERT improved their QoL and if they continued to take PERT following an initial trial.

RESULTS

Eighty-two patients who were tested between April 2019 and March 2021 were were found to have an FE-1 level of 200–500 µg/g, of whom 78 were seen in a clinic. Patient characteristics are detailed in table 2. Symptoms that prompted FE-1 testing were diarrhoea, steatorrhoea, bloating, flatulence and abdominal pain.

FE-1 testing for 68 patients was carried out specifically to exclude PEI as a diagnosis due to the presenting symptoms, in 5 patients to assess for a change in levels following treatment with an antibiotic, in 2 patients for symptoms of steatorrhoea, in 2 patients it was tested alongside a faecal calprotectin, with the reason for this being unclear, and in one patient for diarrhoeal episodes but not specifically to exclude PEI .

Six patients were told explicitly that the FE-1 level of between 200–500 µg/g was a normal result and Creon was not trialled. A further 44 were not given a trial of PERT, but no reason was stated for this in the notes. Of the 28 (36%) patients given a trial of Creon,

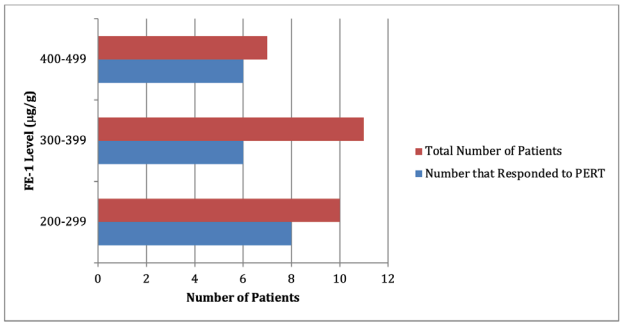

Figure 1 The number of patients with FE-1 of between 200–500 µg/g that responded to a trial of PERT.

20 (71%) reported a beneficial response to treatment (figure 1). Adjuvant treatment was also used in some of these patients with eight prescribed multivitamins and 3 offered proton pump inhibitors. Although other forms of PERT are available, within our cohort, only Creon was prescribed. The dosing regime varied, with the majority being trialled on two capsules (50 000 units) with meals and one capsule (25 000 units) with snacks. Others were offered a total daily dose between 150 000–200 000 units daily. 3 patients did not tolerate Creon, developing nausea and vomiting.

From the 20 patients who responded to PERT, thereby suggesting a diagnosis of PEI, only 7 (35%) had risk factors associated with the condition, 4 had diabetes mellitus, 1 had coeliac disease, 1 had Crohn's disease, 1 had undergone pancreatic surgery. The remaining 21 (65%) had symptoms labelled as irritable bowel syndrome (IBS) or functional diarrhoea.

Our data suggest the main symptoms that responded to PERT were diarrhoea, steatorrhoea, bloating and abdominal pain. All 20 patients who showed improvement stated that their diarrhoea was either no longer present or improved considerably following commencement of PERT (table 3).

Of those not given a trial of PERT (figure 2), over 50% of those remained symptomatic. However, 30% reported that their symptoms resolved. In this retrospective study, the data were not available to comment definitively on the reasons for the resolution of symptoms.

Table 3 Showing the response of symptoms for patients when given a trial of PERT

Symptoms	Improvement	No change	Worse	Not stated
Bloating	1	0	0	3
Diarrhoea	20	0	0	0
Flatulence	2	0	0	3
Pain	2	0	0	1
Steatorrhoea	2	0	0	1

PERT, pancreatic enzyme replacement therapy.

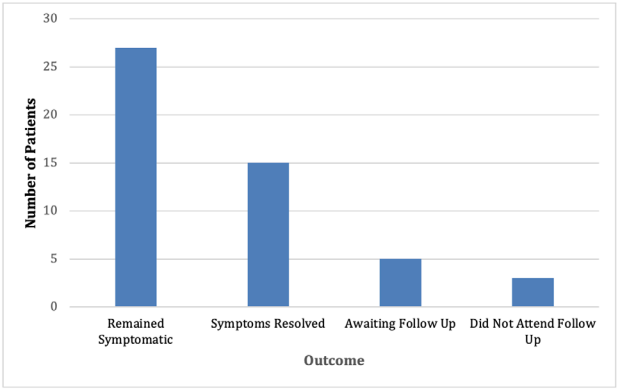

Figure 2 Illustrates the outcomes of patients who were not trialled on PERT.

DISCUSSION

Our results show that three-quarters of patients with an FE-1 level of between 200 and 500 µg/g trialled with PERT report a significant clinical response to treatment.

Although it is widely believed patients with PEI will only display symptoms when pancreatic function has dropped to <10%[13] it has been suggested that these patients may instead demonstrate a graded response to reduced exocrine function and so might benefit from having a trial of treatment at higher levels of faecal elastase than those which identify severe loss of function.[6] Our findings support this suggestion.

The prompt diagnosis and treatment of PEI has significant benefits to patients. There is substantial evidence that PERT allows patients with PEI to improve body weight by preventing malnutrition, a known risk factor for decreased survival.[15] Furthermore, treatment also reduces the occurrence of GI symptoms and abdominal pain commonly associated with PEI, thereby improving patients' QoL.[16 17] Patients are most likely to benefit if they are properly educated on how to take PERT correctly (figure 3).

Our results show that while coexisting GI conditions may be present many patients have no clear cause for PEI. In our experience, a trial of 10 days of PERT is adequate in most patients to be clear whether PERT is beneficial.

There were limitations associated with our study. First, this is a retrospective notes review and the patient cohort was heterogeneous. As data were also not recorded specifically for this study, specific questions or information may not have been noted. A variety of clinicians with differing ways of interpreting what the patient tells them and possibly differing priorities saw these patients. Our sample size is also small and based in the rural area of Lincolnshire and our results might not be generalisable to the overall population. No formal and potentially more robust patient-reported outcome measure (PROMs) was used to assess objectively patients' symptoms before and after treatment and it is impossible to say unequivocally that a placebo response was not responsible for improvement in some patients. Indeed, we saw that in patients not treated with PERT a minority reported spontaneous resolution of their symptoms. Finally, patient follow-up was often limited so we cannot comment whether reported improvements were sustained.

CONCLUSION

We have shown in our retrospective study an association between FE-1 levels between 200 and 500 µg/g and an improvement in GI symptoms following initiation of PERT. It is for this reason that clinicians should remain open to the possibility that PEI may occur in a graded manner and that there are a group of patients

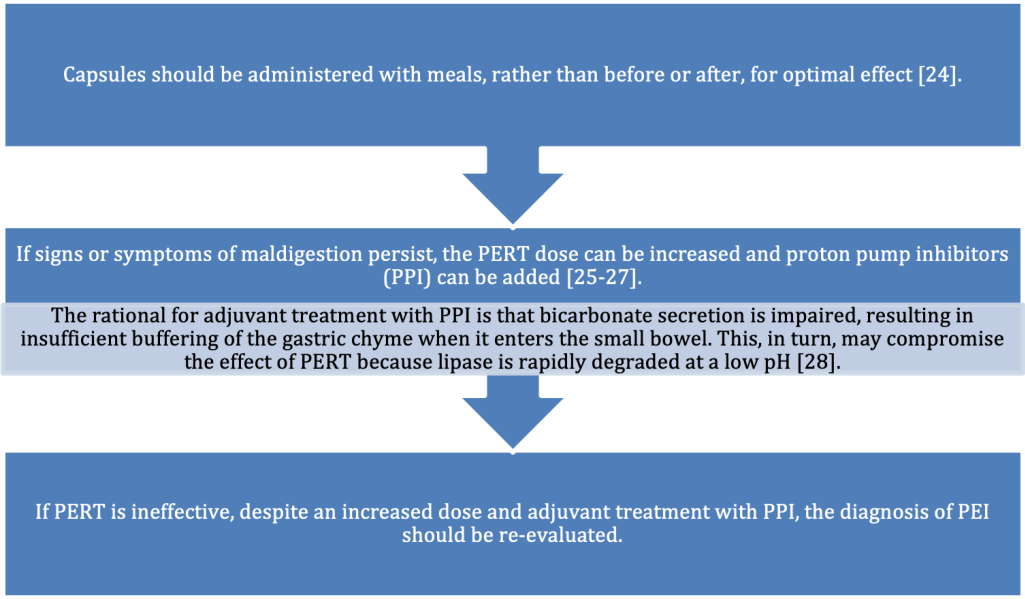

Figure 3 Explaining how PERT should be administered.

who may benefit from treatment. In addition, for those who do not fully respond to PERT, other GI diagnoses should also be sought. It is therefore hoped that this retrospective data can be used in helping with the formation of new, prospectively collected cohort studies which would assess the use of PERT in patients with FE-1 levels between 200 and 500 µg/g and that responses are measured during a standardised follow-up period using validated PROMs to reach a definitive conclusion.

Contributors DF and HJNA came up with the concept for the study. AM and DF performed data collection and analysis. DF, AM and HJNA were all involved in writing and reviewing the final manuscript. DF is the guarantor of the study.

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ORCID iDs
Darren Fernandes http://orcid.org/0000-0002-8697-920X
H Jervoise N Andreyev http://orcid.org/0000-0002-7165-6352

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