# Diagnosis and treatment of pancreatic exocrine insufficiency

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**Purpose of review**
Pancreatic exocrine insufficiency (PEI), defined as a secretion of pancreatic enzymes and bicarbonate insufficient to maintain a normal digestion, is a frequent but frequently underdiagnosed and undertreated condition. PEI may be secondary to different pancreatic diseases and extrapancreatic conditions. Recent data support the high clinical relevance of PEI and its treatment.

**Recent findings**
Together with symptoms of maldigestion, PEI is associated with nutritional deficiencies leading to osteoporosis, low-trauma fractures, sarcopenia and increased mortality. No single widely available test allows to diagnose PEI accurately. Diagnosis of PEI requires the evaluation of symptoms, nutritional markers and a noninvasive pancreatic function test in the appropriate clinical context. Pancreatic enzyme replacement therapy (PERT) improves digestion, symptoms, nutritional status and quality of life of patients with PEI. In addition, PERT is associated with a longer survival in patients with unresectable pancreatic cancer and after surgery for pancreatic cancer or chronic pancreatitis.

**Summary**
Awareness of PEI in different clinical conditions is required. Nutritional advice and appropriate PERT are mandatory to reduce the morbidity and mortality associated with PEI. Further studies on the clinical impact of PEI and its treatment are needed, especially in diseases other than chronic pancreatitis and cystic fibrosis.

**Keywords**
chronic pancreatitis, faecal elastase, maldigestion, malnutrition, pancreatic cancer

## INTRODUCTION

Pancreatic exocrine insufficiency (PEI), defined as the inability of the exocrine pancreatic secretion to maintain a normal food digestion, is a clinical condition that develops as a consequence of reduced secretion in pancreatic diseases, of low cholecystokinin (CCK) release in celiac disease or upper gastrointestinal surgery, or as a result of anatomical changes after surgery of the upper gastrointestinal tract. PEI can be associated with symptoms of malabsorption and nutritional deficiencies that increase morbidity and mortality. Diagnosis of PEI in clinical practice is hindered by the lack of accurate tests, and it usually requires the combination of symptoms, nutritional markers and a noninvasive pancreatic function test in the appropriate clinical context. Treatment of PEI is based on a normal, nonrestrictive healthy diet together with pancreatic enzyme replacement therapy (PERT). Dose of oral pancreatic enzymes should be individualized based on symptomatic response and objective evaluation of the nutritional status.

## CONCEPT AND PATHOGENESIS

Pancreatic function (i.e. digestion) and pancreatic secretion are not synonymous terms. In fact, digestion is frequently normal despite a variable reduction of pancreatic secretion. However, pancreatic function and secretion are concepts that have been used indistinctly in the medical literature, thus leading to some misinterpretation of diagnostic test results and treatment indications.

In patients with pancreatic diseases (chronic pancreatitis, cystic fibrosis, pancreatic cancer, after acute necrotizing pancreatitis and diabetes mellitus)

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## KEY POINTS

- PEI, defined as maldigestion, is frequent in patients with pancreatic diseases (chronic pancreatitis, cystic fibrosis, after acute necrotizing pancreatitis, pancreatic cancer) as well as a consequence of upper gastrointestinal and pancreatic surgery (pancreatoduodenectomy, gastrectomy).
- PEI is not just a cause of steatorrhea, as frequently considered, but a life-threatening condition associated with increased morbidity and mortality.
- Diagnosis of PEI relies on the evaluation of maldigestion-related symptoms, nutritional markers and a noninvasive pancreatic function test in the appropriate clinical context.
- PERT improves digestion, symptoms, nutrition and quality of life in patients with PEI.
- PERT has a significant impact on survival in patients with pancreatic cancer, both after surgery as well as in unresectable tumour.

PEI is mainly the consequence of a low pancreatic secretion of enzymes and bicarbonate because of the loss of functioning parenchyma and/or obstruction of the main pancreatic duct [1,2]. Celiac disease patients have a low postprandial CCK release, leading to a reduced stimulation of pancreatic secretion that can cause PEI [2,3]. Pancreatic and upper gastrointestinal surgery (pancreatoduodenectomy, gastrectomy, gastric bypass) is associated with a reduced CCK release and anatomical changes (asynchrony of aboral passage of nutrients and biliopancreatic secretion) that render exocrine pancreatic secretion insufficient to digest food normally [4].

## CLINICAL CONSEQUENCES

Symptoms of malabsorption in patients with PEI develop only when ingested food overcomes the digestive ability of the exocrine pancreatic secretion. Patients with PEI frequently reduce intake of fat and other hard-to-digest foods to avoid or reduce steatorrhea. In this way, symptoms of malabsorption like diarrhoea, flatulence, abdominal distention or abdominal cramps are not consistently present in patients with PEI. Weight loss is a very late event in this clinical condition.

Together with a poor quality of life, the main consequence of PEI is malnutrition [5]. Deficiencies of fat-soluble vitamins, different proteins like prealbumin, retinol-binding protein, apolipoproteins, high-density lipoproteins and transferrin and micronutrients like magnesium and zinc are frequently present in patients with PEI [6]. PEI and the associated nutritional deficiencies have been shown to increase the risk of osteoporosis and low-trauma fractures [7], sarcopenia [8▪▪] and cardiovascular events [9▪]. In addition, PEI is an independent factor associated with a high mortality in patients with chronic pancreatitis [10▪▪].

Shintakuya *et al.* [8▪▪] reported an independent and significant association between PEI and sarcopenia in a series of 132 patients with different pancreatic diseases. On the contrary, PEI was not associated with less subcutaneous and visceral fat in the same study. This finding is clinically important as the presence of overweight does not allow to exclude PEI in patients with pancreatic diseases.

In a recent retrospective analysis of a prospectively collected cohort of 430 patients with chronic pancreatitis, PEI [odds ratio (OR) 3.42, 95% confidence interval (CI) 1.53-7.66], toxic cause of the disease (alcohol and/or smoking) and liver cirrhosis were independently associated with an increased mortality [10▪▪]. Interestingly, mortality of patients with chronic pancreatitis and PEI, but not that of patients without PEI, was markedly increased compared with the mortality of the general population.

PEI is a consistent finding in patients with pancreatic cancer, mainly if the tumour is located in the head of the pancreas. Studies reported over the last years have shown that PEI is a major cause of weight loss and cachexia in these patients, as well as a factor associated with short survival [11,12]. In addition, PEI has a significant impact on the quality of life of patients with pancreatic cancer [13].

PEI develops in the vast majority of patients after pancreatic surgery, and is associated with postoperative complications, longer hospital stays and higher costs [14].

## DIAGNOSIS

Pretest probability of PEI is very high in patients with chronic calcifying pancreatitis [15,16▪], after acute pancreatitis with extensive pancreatic necrosis [17▪], in pancreatic cancer located in the head of the pancreas [18▪] and after surgical procedures such as pancreatoduodenectomy [14,19▪]. PEI occurs quasisystematically after pancreatoduodenectomy irrespective of the reconstruction scheme (pancreatogastrostomy or pancreatojejunostomy) [20▪▪].

Together with the evaluation of maldigestion-related symptoms and nutritional status, a noninvasive pancreatic function test should be performed for the diagnosis of PEI [21▪▪]. There is some misunderstanding among physicians about the information provided by different pancreatic function tests,

leading to different criteria to define PEI and to indicate PERT. It is important to recognize that the ability of the secreted pancreatic enzymes to digest food varies importantly according to factors like aboral transit of nutrients and biliopancreatic secretion, which is altered after upper gastrointestinal and pancreatic surgery, and luminal pH. Pancreatic function (i.e. digestion of nutrients) and pancreatic secretion are not, therefore, synonymous terms, and tests evaluating pancreatic secretion do not allow to evaluate pancreatic function.

Pancreatic function can be evaluated by the coefficient of fat absorption (CFA) and the $^{13}$C-mixed triglyceride breath test ($^{13}$C-MTG-BT). CFA is generally accepted as the gold standard and currently is the only test accepted by the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the indication and monitoring of PERT in clinical trials. However, CFA is neither specific of PEI nor easily applicable to clinical practice because of limited patients' compliance and unpleasant handling of faecal samples in the lab [1].

The $^{13}$C-MTG-BT has been optimized and validated as an alternative to CFA for PEI in patients with chronic pancreatitis [22]. The test is based on the quantification of the recovery rate of $^{13}CO_2$ over 6 h after a meal containing 250 mg of $^{13}$C-MTG. Breath test is simple, noninvasive and accurate for the diagnosis of PEI and the evaluation of the efficacy of PERT in clinical practice, but it is not yet widely available.

Pancreatic secretion can be evaluated by the endoscopic pancreatic function test (ePFT) and faecal elastase-1 test. The ePFT has been developed as an alternative to the classical secretin-pancreozymin test [23]. It is based on the quantification of the bicarbonate concentration in samples of duodenal juice collected over 45–60 min after intravenous secretin injection (normal >80 mEq/l). This test is highly sensitive to detect small changes in pancreatic secretion and it is mainly indicated to support the diagnosis of chronic pancreatitis in patients with indeterminate morphological findings of the disease on imaging techniques.

Pancreatic elastase is a pancreatic-specific enzyme that it is not degraded during the intestinal transit. In this way, faecal elastase concentration significantly correlates with pancreatic secretion of the enzyme [24]. The faecal elastase-1 test is simple, feasible and widely available, and is therefore, very frequently used for PEI diagnosis. Accuracy of faecal elastase-1 for PEI, as compared with CFA as gold standard, is limited [25▪]. Very low faecal elastase-1 values are most probably associated with PEI, whereas high values allow to exclude it. Faecal elastase-1 should be considered together with an appropriate evaluation of symptoms, signs and nutritional status, as it has been recently proposed [26▪] (Fig. 1). The relevance of the clinical context in interpreting faecal elastase-1 results has been recently underlined [27▪].

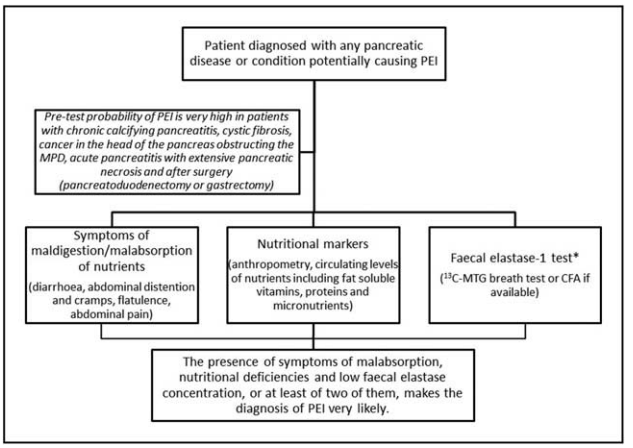


**FIGURE 1.** Algorithm for the diagnosis of pancreatic exocrine insufficiency in clinical practice. *The accuracy of the faecal elastase test for PEI is lower after surgery compared with nonoperated patients. PEI, pancreatic exocrine insufficiency; MTG, mixed triglyceride; CFA, coefficient of fat absorption.

Other methods, like the quantification of the pancreatic secretion volume during magnetic resonance cholangiopancreatography after intravenous secretin (s-MRCP), are not accurate enough for the diagnosis of PEI in clinical practice [21▪▪].

## TREATMENT

Treatment of PEI is based on dietary advice and PERT. Inhibition of gastric acid secretion is occasionally needed to improve the efficacy of PERT. The aim of therapy is to relieve maldigestion-related symptoms and to ensure a normal nutritional status lifelong. PERT is indicated in all patients with PEI (maldigestion) because of the presence of symptoms and/or nutritional deficiencies.

### Nutritional therapy

Malnutrition is frequent in patients with PEI of any cause. Body weight, BMI and weight loss should be documented in these patients together with anthropometric measurements of mid-arm circumference, triceps skin-fold and hand-grip strength. Screening for a deficiency of proteins, fat-soluble vitamins, zinc and magnesium should be also performed [21▪▪].

Improved nutritional status can be achieved with individualized dietary counselling [21▪▪]. As a general rule, diet should be as normal as possible,

and fat restriction and very high-fibre diets should be avoided. A low-fat diet is associated with reduced pancreatic secretion, intraluminal instability of pancreatic lipase and lower efficacy of oral pancreatic enzymes, whereas dietary fibre inactivates pancreatic lipase. Small, frequent, high-energy meals are generally recommended, as they are easier to digest than large meals in patients with a reduced pancreatic secretion. Oral nutritional supplements are usually not required, with the exception of patients who cannot meet their nutritional requirements despite dietary intervention (e.g. patients with pancreatic cancer) [21▪▪].

## Pancreatic enzyme replacement therapy

Together with the dietary advice, PERT is the cornerstone of PEI therapy. PERT should mimic pancreatic physiology as much as possible. With this aim, enteric-coated microspheres or mini-microspheres of less than 2 mm in size are generally preferred [21▪▪]. Enteric coating avoids acid-mediated inactivation of pancreatic enzymes in the stomach, whereas the small pellet size ensures a parallel gastric emptying of the enzymes with the nutrients. Micro-tablets or mini-tablets of 2.2–2.5 mm in size may be also effective, although scientific evidence is more limited. A clinical trial comparing microspheres and mini-microspheres for PEI in cystic fibrosis reported similar efficacy [28], but comparative studies in other diseases or after surgery are lacking. Enzyme pellets should disperse and mix with the food in the stomach to improve efficacy. With this aim, oral pancreatic enzymes should be distributed along with meals and snacks [29].

In patients with chronic pancreatitis and PEI, PERT has been shown to improve fat and protein digestion, to relieve maldigestion-related symptoms, to normalize nutrition and to improve quality of life [30▪]. In addition, PERT has been shown to increase survival after surgery for chronic pancreatitis in a retrospective study [31]. In patients operated on for periampullary tumours including pancreatic cancer, PERT has been retrospectively shown to increase survival as well, mainly in patients with dilated main pancreatic duct [32▪▪]. Finally, a recent retrospective study has underlined the significant impact of PERT on survival in patients with unresectable pancreatic cancer, either locally advanced or metastatic, mainly in those with significant weight loss [33▪▪].

Oral enzymes should be given at a dose able to avoid symptoms and to normalize the nutritional status of patients with PEI. A starting dose of 40 000–50 000 Ph.U. (Eur.Ph.U. or USP) with main meals, and half that dose with snacks is generally recommended for patients with a benign disease (e.g. chronic pancreatitis) and a normal aboral gastrointestinal transit [21▪▪] (Fig. 2). This dose can be, however, insufficient in patients with pancreatic cancer, because of increased nutritional requirements, and in those after gastrointestinal and pancreatic surgery, because of difficulties of normalizing digestion in anatomically altered aboral gastrointestinal transit. A dose of 75 000 Ph.U. per meal has been shown to increase significant fat digestion (CFA increased from 56.9% at baseline to 76.6% on PERT) and protein digestion (CNA increased from 55.3 to 73.0%) in patients after pancreatic surgery compared with placebo, but the mean CFA (%) in patients on PERT ($76.6 \pm 17.2$) was still far below normal (>93%) [34]. If fat and protein digestion can be further improved by increasing PERT dose requires further investigations.

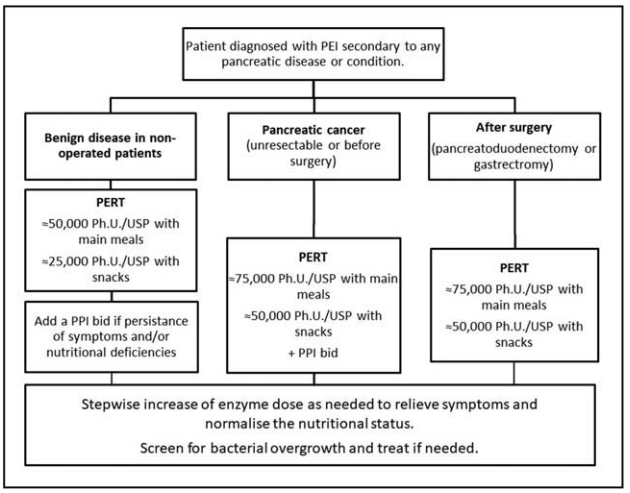


**FIGURE 2.** Proposed algorithm for the treatment of pancreatic exocrine insufficiency in different clinical conditions.

In compliant patients with unsatisfactory clinical response, the enzyme dose should be increased (doubled or tripled) or a proton pump inhibitor (PPI) should be added [21▪▪]. If these strategies fail, another cause for maldigestion should be sought (e.g. bacterial overgrowth) (Fig. 2). In fact, bacterial overgrowth is frequently associated with PEI [35▪▪]. Intestinal pH is frequently acidic in patients with PEI because of a low pancreatic bicarbonate secretion. Activity of pancreatic enzymes, both endogenous and orally given, is highly dependent on intraluminal pH. In addition, enteric coating requires a pH greater than 5.5 to dissolve. Because of that, some patients benefit from the addition of a proton pump inhibitor (e.g. omeprazole 20 mg twice daily) to PERT [36]. This is especially important in patients with pancreatic cancer, as pancreatic bicarbonate secretion is practically abolished because of obstruction of the main pancreatic duct in these patients.

## CONCLUSION

PEI is a frequent and life-threatening complication of pancreatic diseases and extrapancreatic conditions. PEI may cause symptoms of malabsorption (e.g. diarrhoea, flatulence, abdominal cramps, weight loss) and a deficient nutritional status that is associated with increased morbidity (osteoporosis and low-trauma fractures, sarcopenia, cardiovascular events) and mortality. Diagnosis of PEI in different clinical conditions is obviously influenced by the pretest probability of the disease, that is very high in patients with chronic calcifying pancreatitis, acute necrotizing pancreatitis, pancreatic cancer and after pancreatic surgery. The evaluation of maldigestion-related symptoms, nutritional status and a noninvasive pancreatic function test (e.g. faecal elastase-1) allows diagnosing PEI with a high accuracy in the appropriate clinical context. Treatment of PEI should avoid symptoms and nutritional deficiencies. An individualized dietary advice together with the appropriate PERT are the cornerstones of PEI therapy. PERT not only improves digestion, symptoms, nutrition and quality of life, but also survival in patients with PEI. The impact of PEI and PERT in conditions other than diseases of the exocrine pancreas (e.g. gastrectomy, gastric bypass, type 1 and 2 diabetes mellitus) deserves further investigations.

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