

# Understanding pancreatic exocrine insufficiency and replacement therapy in pancreatic cancer

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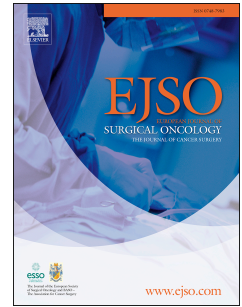
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Understanding Pancreatic Exocrine Insufficiency and replacement therapy in Pancreatic Cancer.

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**Abstract**

Pancreatic exocrine insufficiency (PEI) is highly prevalent in patients with pancreatic cancer, and has substantial implications for quality of life and survival. Post resection, PEI is associated with increased post-operative complications, longer hospital stays and higher costs. Treatment with pancreatic enzyme replacement therapy (PERT) improves quality of life and confers significant survival advantages. Despite this many patients with pancreatic cancer do not currently receive PERT. The nutritional consequences of PEI are extensive and even more relevant in the elderly owing to age related gastrointestinal tract and pancreatic changes that predispose to malnutrition.

**Keywords:** Pancreatic Exocrine Insufficiency, Pancreatic Cancer, Nutrition, Elderly

## 1. Incidence and Aetiology of PEI in Pancreatic Cancer.

Pancreatic exocrine insufficiency (PEI) may be defined as pancreatic enzyme activity insufficient to maintain digestion. (1, 2) There are multiple potential causes of PEI in pancreatic cancer; an understanding of the key anatomical, physiological, pathological and surgical principals behind these is key to being able to recognise those at risk, diagnose early and treat effectively. There are many reviews describing in detail mechanisms of PEI in pancreatic cancer. This work describes them in enough detail to allow the subsequent discussion of PEI among elderly patients with pancreatic cancer (summarised in fig 1).(3, 4)

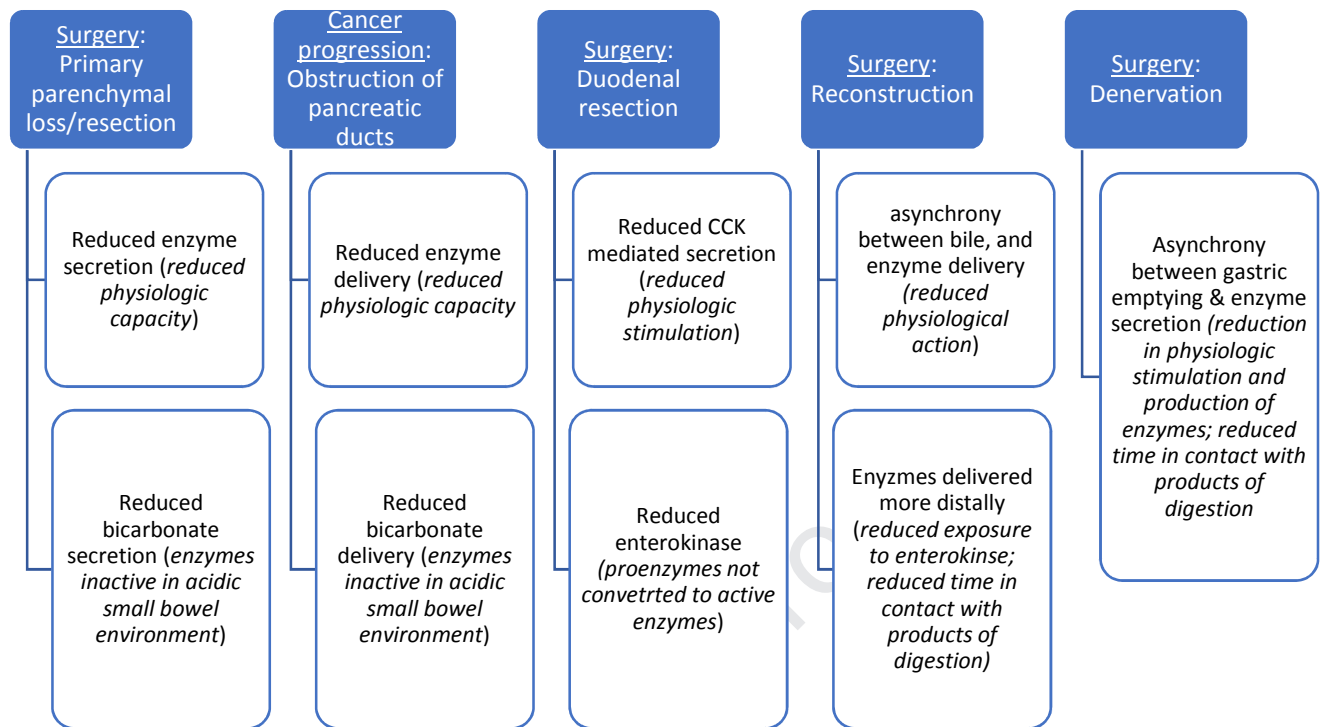
The incidence of PEI is challenging to assess, it is often underestimated as symptoms such as pain and weight loss tend to be attributed to the underlying cancer and the diagnosis is difficult to establish owing to diagnostic tools that have poor accuracy, are unpleasant, cumbersome to undertake and slow to obtain results. Furthermore, PEI is a dynamic process which tends to be progressive. A systematic review evaluating PEI in patients with pancreatic cancer before and after pancreaticoduodenectomy was performed by Tseng et al in 2016, they found the prevalence of PEI pre-operatively to be 44% and post-operatively to be 74% (range 36-100%.) (5). Further to this, the longer that patients are followed up the higher the incidence; Nordback et al chose a longer follow up time of 52 months and found that 100% of their patients post pancreaticoduodenectomy for pancreatic cancer had PEI.(6) In un-resectable cancer the incidence of PEI is reported between 66% and 92% and this has been shown to be progressive with around a 10% decline in function per month. (7)

PEI must be considered to be a digestive problem and not simply a secretory problem. Although reduced enzymatic secretion may factor in PEI, there are many other, more

convoluted ways in which the end action of pancreatic enzymes may not be realised (See Figure 1). The fundamental principle is that the enough enzymes must get be able to mix with food in a co-ordinated fashion and at an appropriate pH for enzymatic function.

A primary parenchymal problem can occur in both resectable and unresectable disease where tissue is either replaced by tumour or resected in attempted cure. Obstruction of the pancreatic ducts by tumour can prevent both pancreatic enzymes and bicarbonate secretions from reaching the small bowel, not only reducing the enzyme volume but also preventing correction of the luminal pH to a level within which pancreatic enzymes can function. For those undergoing pancreaticoduodenectomy, there is a significant impact on the anatomy and physiology involved in maintaining normal digestion. Removing the duodenum reduces the cholecystokinin mediated phase of pancreatic enzyme secretion (intestinal phase). During resection, there occurs division of autonomic nerves supplying the pancreas altering the normal physiological control mechanisms. (3) Following reconstruction, pancreatic secretions are no longer delivered into the duodenum but more distally where the environment is more acidic (denaturing enzymes) and lower in enterokinase (reducing enzyme activation). In addition, asynchrony between the delivery of pancreatic secretions, bile and food may occur with the creation of a pancreatico-jejunojejunostomy and hepaticojejunostomy on a roux loop.(7, 8) All of the above can culminate in an insufficient volume of enzymes being delivered to an environment that may be too acidic for them to work, too low in enterokinase for further activation and at a time that may not co-ordinate with gastric emptying and bile delivery. (See Figure 1 for a summary)

Figure 1 Contributing factors to PEI in pancreatic cancer



In addition to PEI there are other contributing factors to weight loss and malnutrition in pancreatic cancer. Chronic, subclinical inflammation can be present (as in many solid tumours), C-reactive protein has been shown to correlate to both prognosis and cachexia in pancreatic cancer. (9, 10) Tumour derived islet amyloid polypeptide (IAPP) which is specific to pancreatic cancer contributes to weight loss. (11) In the later stages of cancer increased energy requirements of the tumour's metabolism also causes wasting (The Warburg effect). (12, 13)

## 2. The effect of aging on PEI

There are numerous described effects of aging on the pancreas, many of which can contribute to reduced pancreatic enzyme secretion but which, for the majority do not result

in a clinically relevant insufficiency *in isolation*. Age related changes can be considered neoplastic or non-neoplastic. Neoplastic changes such as PanIN (pancreatic intra-epithelial neoplasia), IPMN (Intraductal papillary mucinous neoplasms) and PDAC (Pancreatic ductal adenocarcinoma) all increase significantly with advancing age and epidemiological studies have observed age as the most important risk factor for pancreatic cancer with the median age at diagnosis of pancreatic cancer being 72.(14) Common non-neoplastic changes that are seen with increasing age are: reduction in pancreatic volume, fatty replacement, increasing fibrosis, lobulocentric pancreatic atrophy, acinar ectasia (or dilation), Pancreatic duct ectasia and islet cell changes. (15, 16)

Many studies have reported on changes in pancreatic exocrine secretion with advancing age. These have largely been done using secretory stimulants followed by duodenal aspiration. Fikry et al were the first to demonstrate a reduction in pancreatic enzyme secretion with increased age and the majority of subsequent studies have correlated a decrease in pancreatic secretion with increasing age.(17-22) However, a few studies, including a large study by Gullo et al have failed to support these results.(23) There are many potential reasons behind these discordant results, one of which being the variable methods of stimulation and collection. More recently, Bulow et al conducted a study of secretory function in 970 patients using secretin enhanced MRCP and found a 30% reduction in pancreatic secretion (after stimulation) in those over the age of 80. This is supported by a study by Torigoe et al using cine-dynamic MRCP showing an age-related decline in pancreatic juice secretion.(24, 25) Table one is an overview of the literature reporting on the secretory function of the pancreas in older age. There is much less information available on clinically relevant pancreatic exocrine insufficiency with increasing

age and those that have reported this largely show that the functional reserve of the exocrine pancreas is such that these age-related changes are not usually significant. However, one can infer that with increased age will come decreased reserve and thus older patients with pancreatic cancer (resectable or un-resectable) must be considered at increased risk of developing PEI.

**Table 1:** Studies evaluating the change in the secretory function of the pancreas with increasing age.

Author	Findings	No.	Year	Diagnostics
<b>Rosenberg et al (26)</b>	No difference in pancreatic juice volumes or bicarbonate output between patients older and younger than age 50	103	1966	Secretin test
<b>Fikry et al (19)</b>	Reduction in pancreatic enzyme output in age group 60-72	23	1968	Secretin test
<b>Bartos and Groh (27)</b>	Bicarbonate and amylase secretion decreased after second stimulation age 61-73	20	1969	Secretin + CCK stimulation
<b>Mossner et al (18)</b>	Secretion rate significantly lower in the old than in the young after first and second stimulation	18	1982	Secretin pancreozym test
<b>Tiscornia et al (17)</b>	Women over 45: secretory patterns showed decline of flow and bicarbonate output.	76	1986	Secretin test
<b>Gullo et al (23)</b>	failed to show any decreases in output in group aged 61 to 78 compared to younger group.	60	1986	Fluorescein dilaurate test
<b>Vellas et al (20)</b>	Reduced enzyme OP up to 40% in elderly	28	1988	Duodenal aspirates
<b>Ishibashi et al (21)</b>	enzyme secretion gradually decreased with age. fluid volume and bicarbonate relatively rapid decline from the late 50s	65	1991	Secretin test
<b>Laugier et al (22)</b>	linear decrease in the volume, bicarbonate output, and lipase concentration of pancreatic juice in response to stimulation with secretin and CCK with advancing age	180	1991	Secretin test
<b>Torigoe et al (24)</b>	Secretory flow decreasing with age	53	2014	MRCP cine-dynamic
<b>Bulow et al (25)</b>	30% secretion reduction (after stimulation) in those over 80 yrsn	970	2014	MRCP secretin stimulation



### 3. Consequences of PEI

#### **Symptoms and quality of life**

The presentation of PEI is often missed as many of the symptoms, especially in early disease are subtle such as weight loss, diarrhoea, flatulence and abdominal distension and tend to be attributed to the underlying malignant process.(28) Furthermore, in order to manifest symptoms of PEI, the digestive capacity of the pancreas must be overwhelmed and patients may unconsciously adjust their eating habits to prevent unpleasant symptoms. It is commonly thought that the cardinal sign of PEI is steathorrhoea, this only occurs with severe PEI and may not be recognisable if that patient is avoiding fat intake. (2, 29)

Johnson et al developed a PEI specific Patient Reported Outcome tool based on an extensive literature review and their own expert led patient interviews. In addition to evaluating symptom concepts they also described their wide-ranging impact on; daily activities, emotional wellbeing, diet, social functioning, work and sleep.(30) They went further to divide each symptom category or 'Concept' (Pain, Bloating, stool symptoms, nausea and vomiting, eating related symptoms and tiredness) into 'Sub-concepts' and evaluated the frequency of each (See Table 2).(28) Unfortunately this tool has not been validated specifically for use in pancreatic cancer.

**Table 2.** Adapted from Johnson et al. Concepts and sub-concepts identified in the development of a PRO tool for PEI. **(28)**

Concept	Sub-concept	Frequency
<b>Pain</b>	Abdominal	84%
	Non-abdominal	16%
<b>Bloating symptoms</b>	Stomach noises	82%
	Flatulence	33%
	Trapped wind	15%
<b>Bowel movement/Stool related symptoms</b>	Constipation	48%
	Increased frequency	18%
	Urgency	33%
	Diarrhoea	75%
	Fatty stool	49%
	Change in stool colour	48%
<b>Nausea/Vomiting</b>	Nausea alone	44%
	Vomiting alone	21%
	Nausea and vomiting	21%
<b>Eating related symptoms</b>	Weight loss	67%
	Loss of appetite	33%
<b>Tiredness</b>		41%

### Nutritional consequences

The principal consequence of PEI is malnutrition. For those with pancreatic cancer over 80% have lost weight at diagnosis and over a third have lost at least 10% of their body weight. (31) The ensuing nutritional deficiencies are broad-ranging and include proteins (albumin, pre-albumin, retinol binding protein, transferrin, lipoproteins and apo-lipoproteins), fat-soluble vitamins (A, D, E and K), calcium, magnesium, zinc, thiamine and folic acid. (32, 33) It

is important to consider that vitamins A, D and E are already reduced in the elderly and decline with increasing age.(34) These deficiencies can have significant clinical implications with PEI having been shown to increase the risk of sarcopenia, cardiovascular events and osteoporosis (and associated fractures).(35-37) Sarcopenia has been linked to increased perioperative mortality and reduced survival among patients with pancreatic cancer. (38-40) Following pancreatic resection PEI has been shown to increase costs, post-operative complications and length of hospital stay. (41-44)

With the clear nutritional implications of PEI it is imperative to diagnose and treat it as early as possible with the goal of maintaining a normal digestion. Ongoing care requires regular specialist dietetic support to enable continued clinical, dietary, biochemical and anthropometric assessments with appropriate intervention. (45, 46)

The nutritional consequences of PEI are extensive and even more relevant in the elderly owing to age related pancreatic changes and gastrointestinal tract changes that predispose to malnutrition. It is well recognized that the elderly are at high risk of malnutrition and that this is frequently underdiagnosed, contributing factors include: poor appetite, social and psychological factors, delayed gastric emptying, neurodegeneration of the enteric nervous system, altered gastric and colonic motility and the previously discussed pancreatic changes.(47, 48)

#### 4. Diagnosis of PEI

Early diagnosis (and subsequent treatment) of PEI is key to improving quality of life and survival. The subject of PEI diagnostics is extremely broad so this section is limited to an overview of currently available tests relevant to the diagnosis of PEI in those with pancreatic cancer. Diagnosis of PEI is either direct (looking at the secretory output of the pancreas) or indirect (looking at the digestive effect of pancreatic secretions).

The gold standard measurement for fat maldigestion is faecal fat quantification (or coefficient of fat analysis (CFA)), comparing stool excreted fat to orally ingested fat and requiring strict adherence to a high fat diet and 72-hour collection of faeces. Not only is this test difficult to control outside of a research environment but it is unpleasant and time consuming for both patients and laboratory staff. (49) It is also purely a measure of fat digestion, not pancreas specific and it is not useful for mild PEI. (50) For measuring pancreatic secretion, the most accurate method is using an oro-duodenal tube to collect pancreatic secretions after stimulation. There is wide variation in the method of pancreatic stimulation, the diagnostic criteria and timings. The majority measure bicarbonate output after secretin stimulation rather than enzyme measurement. Owing to the need for endoscopic equipment and the invasive nature of the test this is not carried out routinely and is largely limited to complex cases referred to specialist centres.

The most widely used direct test is FE-1, which assesses a spot stool sample for a pancreatic produced enzyme that is minimally affected by GI degradation and has a reported sensitivity of 73-100% for severe PEI. Unfortunately, although being relatively easy to perform, FE-1 is of limited use owing to poor sensitivity in mild PEI (between 0 and 63%) and unreliability in watery stool or following pancreatic resection. (51-53)

More recently, there has been increasing interest in the  $^{13}\text{C}$  Mixed triglyceride test ( $^{13}\text{C}$ -MTG) breath test, which has shown promising results with Dominguez-Munoz et al producing a standardisable test format and reporting a sensitivity of 93% and a specificity of 92%. It is a good reflection not just of pancreatic secretion of lipase but of the overall digestive effect. Unfortunately, this is not widely available owing to need for  $^{13}\text{C}$  labelled substrate and a testing timeframe requirement of 6 hours.(54)

There is not yet available a perfect diagnostic test for PEI in pancreatic cancer, thus in everyday practice the diagnosis must be approached on a basis of clinical suspicion and may be supported by a diagnostic test (dependent on geography but most likely to be FE-1) and nutritional assessments.

Of note, it is important to consider regular screening for Type 3c diabetes and micronutrient deficiencies (described in section 3). Loss of pancreatic parenchyma can lead to pancreatogenic (Type 3) diabetes where (unlike Type 2 diabetes) peripheral insulin sensitivity is maintained or enhanced. (55) Other conditions to consider, are alternate or con-current diagnoses of small bowel bacterial overgrowth and bile salt malabsorption. The reconstructive element of pancreaticoduodenectomy predisposes to both and the incidence of small bowel bacterial overgrowth is much higher in the elderly.(56)

##### 5. Treatment of PEI with Pancreatic Enzyme Replacement Therapy (PERT)

Treatment of PEI using exogenous enzymes is an essential component of the care of pancreatic cancer patients and is now recommended by the National Institute of Clinical Excellence (NICE) for all patients in the United Kingdom. The advantages of PERT are clear, it is well established that PERT improves fat and protein absorption and reduces steathorrhoea and early studies showed weight maintenance in those with pancreatic cancer receiving PERT in comparison to those not receiving PERT. Thus not only can PERT correct malabsorption and malnutrition it improves symptoms and quality of life. However, more recently the advantages of PERT have been shown to be much more significant among with patients with resectable or unresectable disease. A large study published in 2018 by Dominguez-Munoz et al suggested that PERT conferred a survival advantage to those with unresectable pancreatic cancer receiving PERT. Patients in the PERT cohort received more chemotherapy so it is possible that the survival advantage was secondary to improved patients functioning and ability to receive palliative chemotherapy rather than as a direct effect of PERT. However, that study was closely followed by a population based propensity matched cohort study by Roberts et al reporting that PERT was independently associated with greater survival in those with cancer regardless of chemotherapy.(57)The treatment effect of PERT being similar in size to that of surgery or chemotherapy. Among resectable periampullary cancer an observational study of 469 patients undergoing pancreaticoduodenectomy reported the use of PERT was associated with improved survival in multivariate and propensity matched models. (58)

However, the treatment effect of PERT among elderly patients has not been subject to review and once more the benefits of PERT are assumed based upon benefits observed across entire patient populations regardless of age.

As discussed above, it is not simply replacing enzymes but ensuring the right amount of enzyme gets to the right place for absorption, at the correct pH and at the same time as chyme. Therefore, consideration must be given to dosing, enteric coating, timing of administration, granule size and adjuncts such as PPIs. Enteric coated mini-microspheres are preferred in order to overcome the barriers of gastric pH and delayed gastric emptying. (1)

As the majority of pancreatic cancer patients with PEI also have reduced bicarbonate concentrations (owing to duct obstruction in unresectable disease and altered physiology in resection) it is especially important to consider the addition of a proton pump inhibitor to ensure an appropriate pH environment for enzyme activity. (59) Dosing is based around 10% of function being required for adequate (not normal) digestion, a 'normal' pancreas produces 900,000 units and therefore at least 90,000 units are required to meet adequate digestion. There is likely to be some residual enzyme secretion and a recommended starting dose for pancreatic cancer is 50,000-75,000 units of lipase with meals and 25,000-50,000 units of lipase with snacks or supplements.(46, 60) This dose may need to be significantly increased especially following pancreatic resection, dependent on response. Regular dietetic review is important to assess response, compliance, and give dietary counseling. Diet should be as normal as possible, avoiding either low fat or high fibre regimens and sticking to small, frequent, high energy meals that are easier to digest. Nutritional supplements may be required in those unable to meet their dietary requirements. (1)

Timing is aimed at ensuring that the enzyme preparation reaches the duodenum at the same time as chyme, a randomised, three-way cross over study performed by Domingomunoz et al advised that PERT should be given just after or distributed along the meal rather than before but concluded that enteric coated mini-microspheres are highly effective in improving fat maldigestion regardless of the administration schedule.(61)

Despite the clear advantages, therapy with PERT is often not routine. Some 60-80% of patients with PEI do not currently receive PERT. An as yet unpublished 2018 prospective national audit of pancreatic cancer, RICOCHET, reports that the majority of patients with pancreatic cancer and PEI in the UK do not receive PERT; this is consistent with data from other European countries and Australia, showing that only around 20% of patients with overt symptoms of PEI received PERT. (62-64)

#### Key Learning Points

- PEI is prevalent in resectable and unresectable pancreatic cancer and is often undertreated; it is also progressive.
- PEI symptoms are frequently mistakenly attributed to the underlying disease.
- There is a strong evidence base for the use of PERT to improve nutritional parameters, quality of life and duration of survival.
- Involvement of a dietician and continued nutritional and anthropometric assessments are essential to ensure nutritional optimisation.
- Although not well explored, the reduction in pancreatic reserve in the elderly is likely to leave them at higher risk of PEI in pancreatic cancer and thus it is paramount that PEI must be considered early in this patient group and their nutritional status appropriately monitored.

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