The Symptoms of Pancreatic Exocrine Insufficiency (PEI)

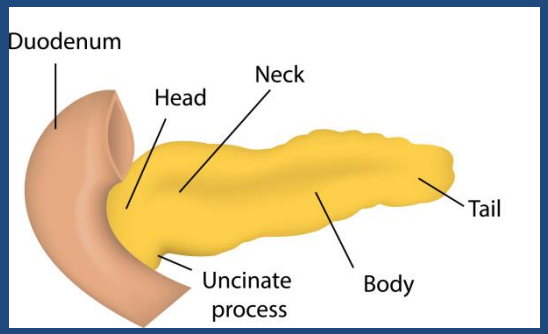
Mary Mahon, Specialist Surgical Dietitian,
Freeman Hospital,
Newcastle upon Tyne NHS Foundation Trust

Overview

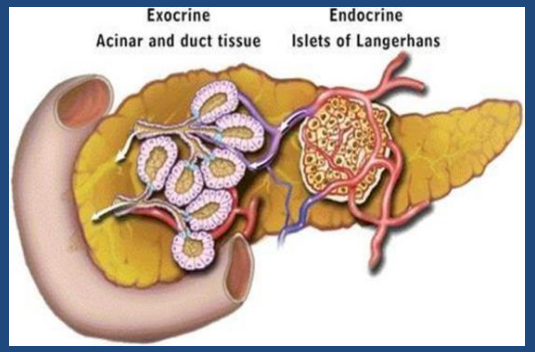
- Pancreatic function
- Exocrine function
- Pancreatic Exocrine Insufficiency
- Symptoms
- Diagnosis

The Pancreas

- Gland located in the abdomen behind the stomach
- Endocrine and (digestive) exocrine function
- Endocrine gland
  - Regulate blood sugar levels
  - Hormone secretion: insulin, glucagon, somatostatin, pancreatic polypeptide
- Exocrine gland
  - Secretes pancreatic juice into the duodenum through the pancreatic duct
  - Pancreatic juice
    - Digestive enzymes
    - Bicarbonate



Pancreatic Function

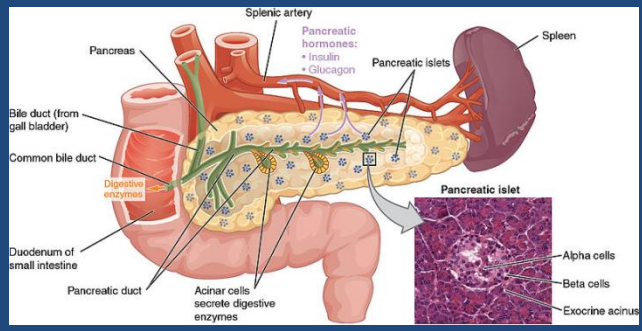


- Endocrine (Islets of Langerhans)
  - Alpha cells – glucagon
  - Beta cells - insulin
  - Delta Cells – Somatostatin

- Islet distribution similar between the head and body but >2-fold higher in the tail

- Exocrine (Acinar cells and ducts)

- Pro-Enzymes
  - Trypsinogen (1,2,3) and chymotrypsinogen (A,B)
  - Procarboxypeptidase A (1,2) and procarboxypeptidase B (1,2)
  - Prophospholipase (I,II)
  - Proelastase
  - Mesotrypsin
- Bicarbonate



Wang (2013)

Exocrine Pancreas

- Role of the pancreas in digestion
- Food is made up of many different constituents at a molecular level → macro and micronutrients
  - Macronutrients provide energy to the body: fat, protein and carbohydrate
- The pancreas has a crucial role in the digestion of all three
  - Cholecystokinin (CCK) stimulates the release of bicarbonate and pancreatic pro-enzymes which activate into **lipase, protease** and **amylase**

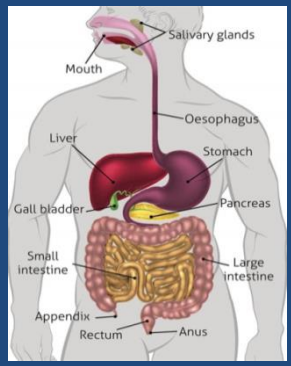
Fat → **LIPASE** → Fatty acids

Proteins → **PROTEASE** → Amino acids and peptides

Carbohydrates → **AMYLASE** → Disaccharides

Exocrine Pancreas: Digestion

- Pancreatic enzyme release occurs in response to nutritional intake
- Phases of digestion
- **Celphalic phase**
  - Mediated by the vagal nerve which is stimulated by seeing, smelling and tasting food
  - Food broken down with chewing and by mixing with amylase rich saliva
- **Gastric phase**
  - Food arrives in the stomach, mixed with stomach acid and churned into chyme
  - Gastric distension increases pancreatic enzyme secretion via the gastro-pancreatic reflex
- **Intestinal phase**
  - Chyme pumped into duodenum
  - Stimulation of exocrine pancreatic secretion by CCK
    - Enzymes and bicarbonate



Keller and Layer (2005)

PEI: The Concept

Pancreatic Exocrine Insufficiency:
Primary or secondary disturbance of exocrine pancreatic function leading to **maldigestion**

Malabsorption of nutrients

Nutritional deficiencies

PEI: The Cause

- **Primary** – reduction of exocrine secretion caused by disease
  - Obstruction of the pancreatic duct by a tumour
  - Damage of the exocrine pancreas (In particular pancreatic head)
    → HOP Ca – Not resectable
    → Prevalence of PEI 66% at diagnosis, ↑ 92% after a median FU of 2 months (Sikkens et al., 2014)

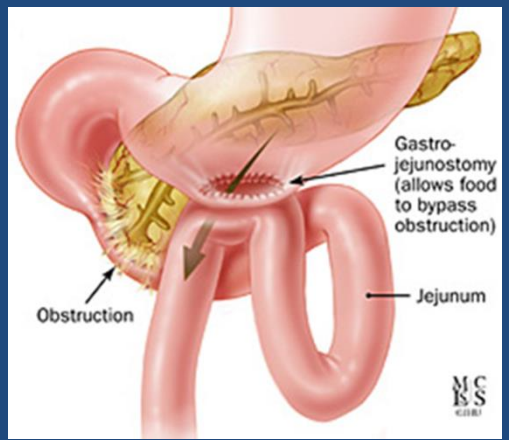
- Abnormal CCK secretion

  - Loss of pancreatic tissue following pancreatic surgery
    - Quantity and quality of the remaining pancreas

Keller and Layer (2005):Lindkvist, B (2015); Philips, M (2015)

PEI: The Cause

- **Secondary** – anatomical changes following surgery
  - Changes in intestinal pH following partial or total gastrectomy or duodenectomy
  - Asynchrony in the delivery of pancreatic juice following a bypass of the bile duct, pancreas, stomach or duodenum – enzymes and bile arrive in the intestine at different times to chyme from the stomach
    - Enhances PEI



Lindkvist, B (2015); Philips, M (2015)

PEI: The Mechanism

- If enough enzymes don't reach the duodenum, some of the nutrients in food will not be digested
  - Travel along the small intestine and into the large intestine, often triggering unpleasant symptoms
  - Gut bacteria might digest some nutrients, the rest end up expelled in the stool

- Fat malabsorption leads to most prominent symptoms

  1) Mouth, stomach and small intestine produce amylase and protease to break down proteins and carbohydrates
     - Fat digestion is more reliant on pancreatic lipase - earlier & more significant problem

  2) Fat malabsorption leads to more obvious changes in bowel function
     - Low fat diet can fail to trigger symptoms and mask problems meaning PEI may be undiagnosed
     - Weight loss, muscle wasting and other symptoms occur
     - Low fat not recommended

Keller and Layer (2005)

PEI: The Symptoms

- Abdominal discomfort
- Pain – stomach and lower back
- Bloating
- Severe meteorism
- Flatulence
- Burping
- More frequent bowel movements
- Urgency after eating/receiving an enteral feed
- Dyspepsia
- Nausea/colicky/post prandial abdominal pain
- Gastro-oesophageal reflux

PEI: The Symptoms - Steatorrhea

- Steatorrhea
  - Bulky
  - Oily
  - Pale orange/yellow or chalky
  - Foul-smelling
  - Loose or runny
  - Undigested food in stools
  - Float
  - Difficult to flush
  - Stain the toilet bowl

PEI: The Symptoms - Steatorrhea

- Steattorrhea → > 90% of exocrine function is lost (Di Magno et al. 1973)
  - Late symptom of malabsorption, fat malabsorption may occur earlier without abdominal symptoms
- Don't just rely on patient reported steatorrhea – not reliable
  - Midha et al. (2008) pt reported - 5% v lab proven - 36% (31%)
  - Sudeep et al. (2011) pt reported - 31% v lab proven – 69% (37%)
- Steatorrhoea will only be apparent in patients consuming adequate dietary fat
  - patients restrict their fat intake in an attempt to help reduce symptoms
  - Response to inappropriate advice promoting fat restriction
    - Not advised as it can mask PEI and exacerbate malnutrition

PEI: The Symptoms – Biochemical

- Hypoglycaemia in diabetes
- Fat soluble vitamin (A,D,E,K) deficiency
  - Bone problems, bruising and poor wound healing, higher rates of infections, visual problems, neurological symptoms, muscle weakness and fatigue
- Other abnormally low nutritional markers
  - Prealbumin, retinol-binding protein, magnesium, selenium, zinc, copper and iron

Lindkvist, B (2012)

PEI: The Symptoms – Anthropometric & Functional

- Unexplained weight loss
- Failure to gain weight despite good dietary intake
  - Malabsorption
  - Barriers to intake

- Sarcopenia and loss of muscle function
  - Significant association with PEI
  - 65% of pancreatic cancer patients
  - Associated with decreased survival
  - Higher toxicity in patients receiving chemotherapy

Chan et al. (2019); Griffin et al. (2019)

PEI: Diagnosis

- It is difficult to test the function of the pancreas because it is buried deep in the abdomen

- Methods of diagnosis
  - **Coefficient of fat absorption (CFA)** – measures the % of fat an individual absorbs
  - **13C- mixed triglyceride breath test** (MTG) - measures the amount of lipase secreted by the pancreas
  - Faecal elastase - measures the levels of pancreatic enzymes in the stool
  - **Clinical assessment** - professional judgement

Dominguez-Munoz, J.E (2010)

Faecal Elastase (PE-1)

- Most commonly used method in the UK
- Faecal PE-1 is highly stable and not degraded during passage through the gastrointestinal tract
  - Levels are a good reflection of the pancreatic output of enzymes
  - Elastase secretion may be reduced earlier and to a greater extent than the other digestive enzymes
  - Not affected by transit time
  - Not affected by pancreatic enzyme replacement therapy (PERT); therefore, it is a true reflection of pancreatic exocrine function
- Limited accuracy according to research but good practice to request if PEI is suspected
  - Profuse watery stool samples may result in a falsely low PE-1 due to dilution
  - Fails to detect mild insufficiency
  - Depends on practicalities in your centre

Dominguez-Munoz, J.E (2010); Singh V.K.(2017)

Faecal Elastase (PE-1)

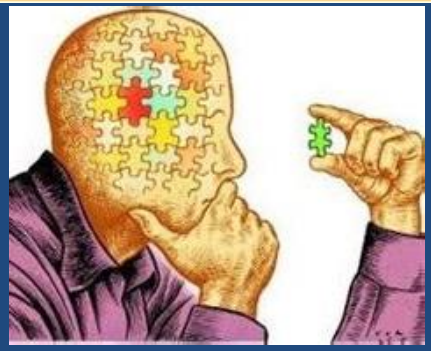
- **Normal function → PE-1 >500ug**
- **Suboptimal function** → may be a reduction in secretions but this does not necessarily indicate PEI
  - treat symptoms if reported

PEI/Pancreatic Function	Faecal Elastase
Normal	>500ug
Suboptimal	200-500ug
Mild - Moderate	100-200ug
Severe	<100ug

- **Mild PEI** → reduced secretion of one or more enzymes with normal bicarbonate concentration in duodenal juice and normal faecal fat excretion
- **Moderate PEI** → reduced enzyme output and bicarbonate concentration but normal faecal fat excretion
- **Severe PEI** → reduced enzyme output and bicarbonate concentration plus steatorrhea

LÖhr et al. (2017)

Clinical Judgement



- In practice, PE-1 not always ideal
  - Vulnerable to time constraints
  - Suitability of the sample

- Often depend on clinical judgment to diagnose PEI
  - Thorough history taking helps capture any GI symptoms
  - Nutritional status assessed through diet histories/recall , weight histories and micronutrient monitoring
  - Anthropometric and functional status can be evaluated and monitored through handgrip strength and functional tests such as timed up and go
  - A combination of assessment methods is likely to provide the most comprehensive assessment of PEI

Dominguez-Munoz, J.E (2010); Philips, M (2015)

Clinical consequences of PEI

- If left untreated/undiagnosed
  - → Malnutrition
  - → Higher infection risk
  - → Fat soluble vitamin deficiency
  - → Higher fracture risk
  - → Higher risk of cardiovascular events
  - → Poor glycaemic control
  - → Poor QOL
  - → Higher mortality

Summary

- The secretion of digestive enzymes can be affected in PEI, and extremely reduced exocrine pancreatic secretion has been significantly correlated with poor survival
- Even if patients do not have PEI at the time of diagnosis, most will develop it during the course of their disease
- Clinical judgement of symptoms is the best form of diagnosis in practice

References

Chan, M.Y and Chok, K.S.H. (2019) Sarcopenia in pancreatic cancer – effects on surgical outcomes and chemotherapy. **World Journal of Gastrointestinal Oncology,** 11(7), pp. 527-537.

DiMagno EP, Go VL, Summerskill WH (1973). Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. **The New England Journal of Medicine**, 288, pp. 813–5.

Dominguez-Munoz, J.E (2010). Diagnosis of chronic pancreatitis: functional testing. **Best Practice & Research Clinical Gastroenterology**, 24, pp.233-241.

Griffin, O.M. (2019). Characterising the impact of body composition change during neoadjuvant chemotherapy for pancreatic cancer. **Pancreatology,** 19, pp. 850-857.

Keller J, Layer P. (2005). Human pancreatic exocrine response to nutrients in health and disease. **Gut,** 54(6) pp. 1-28.

Lindkvist, B et al. (2012). Serum nutritional markers for prediction of pancreatic exocrine insufficiency in chronic pancreatitis. **Pancreatology,** 12, pp. 305-310.

Lindkvist, B et al. (2015). Clinical, anthropometric and laboratory nutritional markers of pancreatic exocrine insufficiency: Prevalence and diagnostic use. **Pancreatology,** http://dx.doi.org/10.1016/j.pan.2015.07.001

Lohr, J.M. (2017) United European Gastroenterology evidence based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU) **United European Gastroenterology Journal,** 5(2), pp. 153–199.

Midha, S. Singh, N. Sachdev, V. Tandon, R.K. Joshi, Y.K. and Garg, P.K. (2008) Cause and effect relationship of malnutrition with idiopathic chronic pancreatitis: prospective case-control study. **Journal of Gastroenterology and Hepatology**, 23 (9) pp.1378-1383.

Philips, M (2015). Pancreatic exocrine insufficiency following pancreatic resection. **Pancreatology**, 15, pp. 449-455.

Sikkens EC, Cahen DL, de Wit J, et al (2014). A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. **Journal of Clinical Gastroenterology**, 48, pp. 43–6.

Singh V.K. (2017). Less common etiologies of exocrine pancreatic insufficiency. **World Journal of Gastroenterology**, 23(39), pp. 7059-7076.

Sudeep, K. Chacko, A. Thomas, N. Selvakumar, R. George, B. Paul, T.V. and Seshadri, M.S. (2011) Predictors of osteodystrophy in patients with chronic nonalcoholic pancreatitis with or without diabetes. **Endocrine Practice**, 17 (6) pp. 897-905.