Early chronic pancreatitis - Are you missing it?

Darren A. Pavey MBBS FRACP

Staff Specialist, Gastroenterology
Conjoint Senior Lecturer, UNSW

Sydney Gastroenterology

NSW GOVERNMENT Health
South Western Sydney Local Health District

Pancreatic diseases and Pancreatic Exocrine Insufficiency (PEI)

What is the relevance to general practice?

Objectives:

- Pancreatic diseases
  - Chronic pancreatitis
  - Pancreatic cancer
  - Post pancreatectomy
- Pancreatic exocrine insufficiency (PEI)

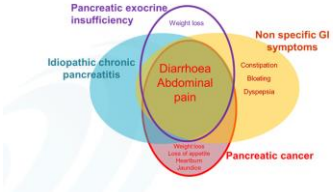
→ *often under diagnosed*
→ *With potentially severe consequences*

If my patient has the non-specific symptoms:

abdominal pain
diarrhoea
weight loss

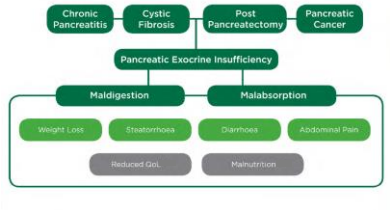
Should I be considering pancreatic disease and pancreatic exocrine insufficiency (PEI)?

Shared GI symptoms



Adapted from: Campbell J. *et al.* Gut 2014; 63:A253. Leeds J. *et al.* Clinical Gastroenterology & Hepatology 2010; 8:433–438. Keane M. *et al.* BMJ Open 2014; 4:e005730. Tozuli J. *et al.* MJA 2010; 192:661–667

Pancreatic disease and Pancreatic Exocrine Insufficiency (PEI)

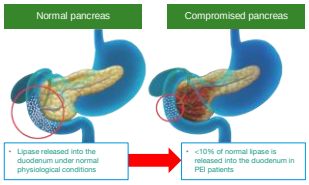


1. Dumasy Y. *et al.* Am J Gastroenterology 2004; 99(7):1350-1354. 2. Rasmussen H. *et al.* World J Gastroenterol, 2010; 16 (42): 7267-7275. 3. Domínguez-Muñoz J. *et al.* Clin Gast & Hep 2007; 5:484-488. 4. Dietitians Assoc of Aust. Australasian Clin Prac Guidelines for Nutr in Cystic Fibrosis. Sept 2006. 5. Tozuli J. *et al.* MJA 2010; 192:661-667. 6. Drewes A. *et al.* World J Gastroenterol, 2012; 18, 42: 7267-7275. 7. D'Haese J. *et al.* Pancreas 2014; 43(6):934-941.

What is

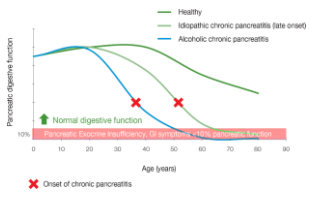
Pancreatic Exocrine Insufficiency (PEI)?

Pancreatic Exocrine Insufficiency (PEI)



Pezzilli R. et al. World J Gastroenterology. 2012; 18(48): 7938-7946

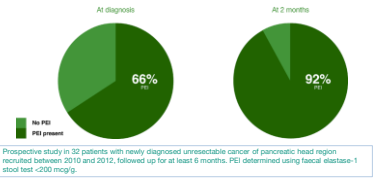
PEI and chronic pancreatitis



Adapted from: Laugier R. et al. Digestion 1991; 50:202-221, Rothenbacher D. et al. Scandinavian J Gastroenterol. 2000; 40:687-704, Vellar B. et al. International J Pancreatology. 1988; 3:487-502

PEI and pancreatic cancer

PEI prevalence in unresectable pancreatic cancer



Prospective study in 32 patients with newly diagnosed unresectable cancer of pancreatic head region recruited between 2010 and 2012, followed up for at least 6 months. PEI determined using faecal elastase-1 stool test <200 mcg/g.

Sikkens E. et al. J Clinical Gastroenterology. 2014; 48(5):e43–e46

Does pancreatic disease exist undiagnosed?

Pancreatic exocrine insufficiency (PEI)
Pancreatic cancer
Chronic Pancreatitis

Does chronic pancreatitis exist undiagnosed ?

- A study of 394 consecutive autopsies conducted in Denmark (1978)
- Histological examination of the pancreas organ
- 13% (52) have histological features consistent of chronic inflammation
- Only 0.5% (2) of these patients had a diagnosis of chronic pancreatitis

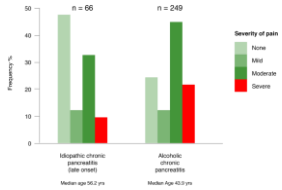
Olsen T., *Acta Path Microbiol. Scand. Sect A*, 86: 361-365,1978

Evidence for undiagnosed pancreatic disease and PEI in the general population

Study author	Patient characteristics	Country	Patient numbers	Method of investigation	Result
Olsen T. 1978[1]	Post mortem	Denmark	394 autopsies	Histology	13% pancreatic inflammation
Laugier R, *et al.* 1991[2]	Healthy persons aged 18 to 83 years	France	180 prospective	Direct secretin, CCK test	6% PEI
Rothenbacher D, *et al.* 2003[3]	General population aged 50-75 years	Germany	914 prospective	Fe-1<200mcg/g	11.5% PEI
Herzig K, *et al.* 2011[4]	Persons aged 60-92 years	Germany	106 prospective	Fe-1< 200mcg/g	21.7% PEI
Leeds J, *et al.* 2010[5]	IBS-D	United Kingdom	314 prospective	Fe-1<100mcg/g ↓ CT scan	6.1% severe PEI ↓ 21% CP
Goepp J, *et al.* 2014[6]	IBS related symptoms	USA	2258 retrospective	Fe-1 <200mcg/g	7.1% PEI
Campbell J, *et al.* 2014[7]	Diarrhoea, abdominal pain, weight loss	United Kingdom	1887 retrospective	Fe-1<200mcg/g ↓ CT, MRI, US scan	11.4% PEI ↓ 33.1% CP or PC

1. Olsen T. Acta Path Microbiol Scand. 1978; Sect. A, 86:361-365. 2. Laugier R, et al. Digestion 1991; 50:202-211.3. Rothenbacher D, et al. Scandanavian J Gastroenterol. 2003; 40:687-704. 4. Herzig K, et al. BMC Geriatrics 2011;11:4. 5. Leeds J, et al. Clinical Gastroenterology and Hepatology 2010; 8:433-438. 6. Goepp J, et al. Global Adv Health Med. 2014; 3(3):9-15. 7. Campbell J, et al. Gut 2014; 63: A353.

Why does chronic pancreatitis exist undetected?

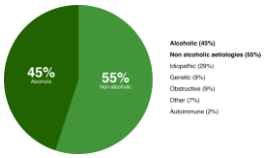


- 90% of patients with idiopathic chronic pancreatitis presents with mild, moderate or **no pain symptoms**

Retrospective analysis of patients with different types of chronic pancreatitis seen at Mayo Clinic, Rochester during 1976-1982, with prospective follow up until 1986.

Layer P, *et al.* Gastroenterology 1994; 107:1481-1487.

Aetiology of chronic pancreatitis



Alcoholic (45%)
Non alcoholic aetiologies (55%)
Idiopathic (29%)
Genetic (9%)
Obstructive (9%)
Other (7%)
Autoimmune (2%)

NAPS2: a higher than expected number of CP patients (55%) were classified with non-alcoholic aetiology

North American Pancreatitis Study 2 (NAPS2)

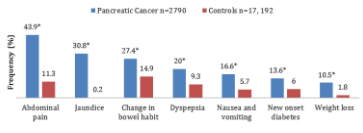
Cote G, *et al. Clin Gastro & Hepatol* 2011;9:266-273.

A substantial time lag occurs between symptom presentation to diagnosis of pancreatic cancer

UK case control study involving 2773 patients with pancreatic ductal adenocarcinoma (PDAC)

Mean number of visits to GP = 18
Mean number of "alarm" (non specific) symptoms = 11

Symptom presentation to primary care in UK, within 2 years prior to diagnosis of pancreatic cancer



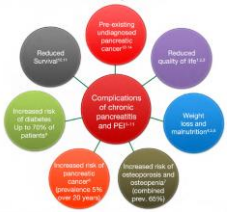
Adapted from Keane et al, BMJ, 2014
* Pancreatic cancer versus controls, P<0.001
# Symptoms with greatest frequency (>10%) shown

Keane M. *et al. BMJ Open* 2014; 4:e005730.

Consequences of undiagnosed/untreated disease

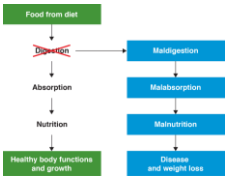
Pancreatic Exocrine Insufficiency (PEI)
Pancreatic cancer
Chronic pancreatitis

The consequences of undiagnosed pancreatic disease



1.Fitzsimmons D. *et al. Am J Gastroenterology.* 2000; 100:924-926. 2. Coates L. *et al. Curr J Gastroenterology.* 2003; 17(10):597-603. 3. D'Haese J. *et al. Pancreat.* 2014; 43(5):834-841. 4. Dumasty V. *et al. Am J Gastroenterology.* 2000; 94 (7):1830-1834. 5. Trott P. *et al. Gastroenterology Nursing.* 2001; 24(2):64-67. 6. Lindkvist B. *et al. Pancreatology.* 2012; 12:305-310. 7. Duggan S. *et al. Clinical Gastroenterology and Hepatology.* 2014; 12:239-326. 8. Lowenfels A. *et al. NEJM.* 1993; 328(20):1433-1437. 9. Ewald N & Hardt P. *World J Gastroenterology.* 2013; 19(40):7279-7283. 10. Selezan A. *et al. J. Gastrointest Liver Dis* 2006; 15:1:31-36. 11. Pinho A. *et al. Cancer Letters* 2014; 345:203-209.

Clinical consequences of PEI



Qualitative research: impact of PEI on QoL in unresectable pancreatic cancer

"Participants identified that their priority unmet supportive care need was their difficulty in managing gastrointestinal problems, diet and digestion. They expressed strong feelings of frustration and anger relating to struggling with symptoms of PEI"

"I found this very confronting, her not wanting to eat. I (crying) try to force feed her. She gets upset, it makes it worst."
Carer, male (Dad)

"I just can't get enough nutrition you know…."
Patient, female

"You've got this lack of food intake. I can't eat as much of what I used to and there are things that I can't eat."
Patient, female

Qualitative research conducted by the NSW Cancer Council, in 61 people including patients diagnosed with pancreatic cancer, carers, family members, and bereaved participants.

Gooden H. & White K. Support Care Cancer 2012.

Detecting undiagnosed/ early disease

Pancreatic exocrine insufficiency (PEI)
Pancreatic cancer
Chronic Pancreatitis

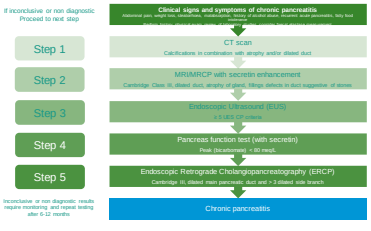
Is early detection of chronic pancreatitis and pancreatic cancer possible?

Curable (operable) *lesions* and *localised non metatastatic tumors* are detectable using technologies currently used in clinical practice

Endoscopic ultrasound (EUS) MRI Computed tomography

Lennon A et al. Cancer Research; 74 (13); 1-9, 2014

American Pancreatic Association guidelines for diagnosis of chronic pancreatitis



Adapted from Conwell D. et al. *Pancreas* 2014; 43:1143-1162.

How is PEI detected?

Direct test:

- Secretin-caerulein tubular test

Indirect tests:

- 3 day faecal fat test
- **Faecal elastase-1 stool test**
- 13C mixed triglyceride breath test

Faecal Elastase-1 Stool Test

- Faecal elastase-1 test is becoming more common in clinical practice[1]
- In 2010, it was reported to be the most popular test used to evaluate PEI[2]
- Requires a single formed stool sample[2]
- Measures the elastase concentration in the stool[1,2]
- Specificity: approximately 93%[3]

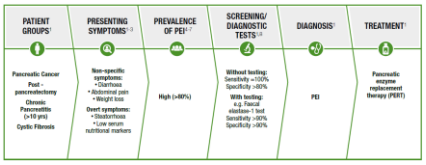
>200 µg/g stool: normal value[2]

<200 µg/g stool: mild PEI[1]

<100 µg/g stool: severe PEI[1]

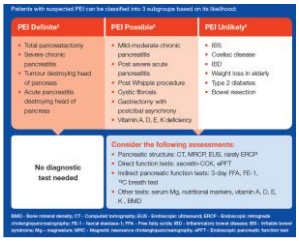
1. Tocol J. *et al.* MJA 2010; 3. Sikkens E. *et al. Best Pract Res Clinical Gastroenterol.* 2010; (24):337-347. 3. Losser C. *et al. Gut* 1996; 39: 580-586.

PEI Diagnostic pathway



1. Tocol J. *et al.* MJA 2010; 192:461–467. 2. Thomas P. *et al. Gut* 2002; 52(Suppl V):v1–v15. 3. Lindkvist B. *et al. Pancreatology* 2012; 12: 305-310. 4. Dietitians Assoc of Australia. Australasian Clin. Prac. Guidelines for Nutr in Cystic Fibrosis. Sept 2006. 5. Sikkens E. *et al. J Clin Gastroenterology* 2014; 48: e40-e46. 6. Sikkens E. *et al. BJS* 2014; 101: 109-113. 7. Dunsay Y. *et al. Am J Gastroenterology* 2004; 99(7):1350-1354. 8. Losser C. *et al. Gut* 1996; 39: 580-586.

PEI Diagnostic pathway



Treatment of PEI

Pancreatic Enzyme Replacement Therapy (PERT)

PERT treatment goals[1]

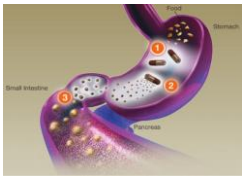
- eliminate maldigestion
- eliminate malabsorption
- maintain adequate nutrition

1. Tocol. et al. MJA 2010; 192: 461-467

Recommendations to investigate for pancreatic disease and PEI in patients presenting with chronic diarrhoea symptoms

International guidelines for management of PEI in pancreatic cancer patients

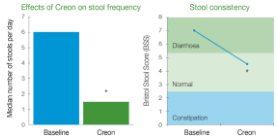
Delivery of pancreatic enzymes using a modern oral formulation



1. The capsule containing pancreatic enzymes enters the stomach along with the food.
1. The outer capsule dissolves rapidly to release enteric coated mini-microspheres which mix with the chyme
2. The mini-microspheres with particle size (0.7-1.6 mm) passes through the pylorus together with the chyme.

The active digestive enzymes are released in the duodenum to digest nutrients.

Effects of PERT on GI symptoms (PEI in Chronic Pancreatitis)



* p<0.002 vs IBS-D patients with normal Fe- I levels
Open label study, n=19, t=12 weeks, all patients with PEI: FE-1 <100 µg/g stool.
Dose: Creon 30,000 units three times daily.

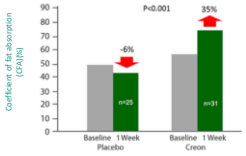
Patients on pancreatic enzyme therapy (Creon) showed a clinically significant response:

- Stool frequency reduced from 6 to 1.5 per day (p<0.002)
- Stool consistency changed from "diarrhoea" to "normal" (p<0.002)

Observational study involving 19 patients identified with PEI using the faecal elastase-1 stool test. Patients were treated with Creon 30,000 units lipase with meals for 12 weeks. Patient symptoms were recorded using Bristol stool scale and the number of stools per day.

Effect of PERT on fat malabsorption in patients with pancreatic exocrine insufficiency post pancreatic surgery

A randomised, double blind, placebo controlled study over 7 days

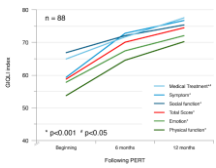


58 patients with pancreatic exocrine insufficiency after pancreatic resection due to malignancy or chronic pancreatitis.

PERT significantly improves fat absorption by 35% after one week.

Seiler C. et al, Aliment Pharm & Ther, 2013

Effects of PERT on the quality of life (QoL) of patients with chronic pancreatitis

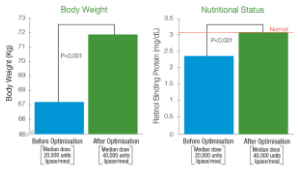


ERT significantly improved QoL of patients in terms of :

- Physical function
- Social function
- Emotion
- Medical treatment
- GI Symptoms
  - diarrhoea/steatorrhoea
  - abdominal pain
  - nausea
  - vomiting
  - weight loss

Observational prospective, multicentre study which assessed symptom and quality of life over one year in patients with newly diagnosed PEI associated with chronic pancreatitis without prior pancreatic enzyme treatment. Quality of life was assessed using gastrointestinal quality of life index (GIQLI)

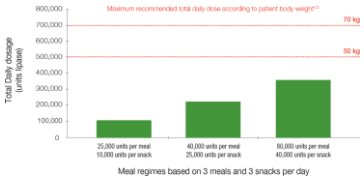
Effects of PERT on body weight and nutritional status



Observational study over 12 months, n=23

Observational uncontrolled study involving 20 patients with pancreatic exocrine insufficiency associated chronic pancreatitis. At baseline, these patients were treated with pancreatic enzyme replacement therapy with the dosage titrated to avoid the symptoms of weight loss and diarrhoea. The dosage was increased and titrated to achieve normal fat absorption as determined by 13C mixed triglyceride breath test. This treatment was continued for one year.

PERT adult dose range



Maximum dose recommended by:
1. Cystic Fibrosis (CF) Consensus Conference – Creon Product Information.
2. Australasian Guidelines for Management of Pancreatic Exocrine Insufficiency (Toouli. et al. AJA 2010; 192(8): 461–467).

Management of PEI using PERT

PERT:

- Initially – 25,000 to 40,000 units lipase with each meal
- Encourage patients to eat 6 smaller meals per day rather than 3 large meals
- If required, increase dose up 80,000 lipase units with each meal

Other considerations:

- Patient compliance
- Many patients have acidic intestinal pH which decrease enzyme release from preparations which have pH sensitive enteric coating
  - Acid suppressing agents may be required in some patients
- Lack of weight gain due to inadequate fat intake
  - Fat restriction not required with PERT

1. Creon Product Information. 2. Toouli J. et al. AJA 2010; 192: 461–467.

Summary

- Pancreatic diseases and PEI have similar GI symptoms
- PEI is associated with exocrine (and endocrine pancreatic) diseases including chronic pancreatitis and pancreatic cancers

- PERT is the main treatment option for PEI
- PERT provides symptomatic benefit and improved QoL for those patients with pancreatic insufficiency

- Clinicians should be aware of the problem of under diagnosing these conditions
  - and have a low threshold for checking FEL-1 and assessing pancreatic insufficiency of patients

1. Creon Product Information. 2. Toouli J. et al. AJA 2010; 192: 461–467.