Pancreatic Exocrine Insufficiency (PEI) and Pancreatic Enzyme Replacement Therapy (PERT)

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Topics

- Physiology of normal digestion
- Definition Pancreatic exocrine insufficiency
- Consequences of Pancreatic exocrine insufficiency
- Diagnosing Pancreatic exocrine insufficiency
- Pancreatic enzyme replacement therapy

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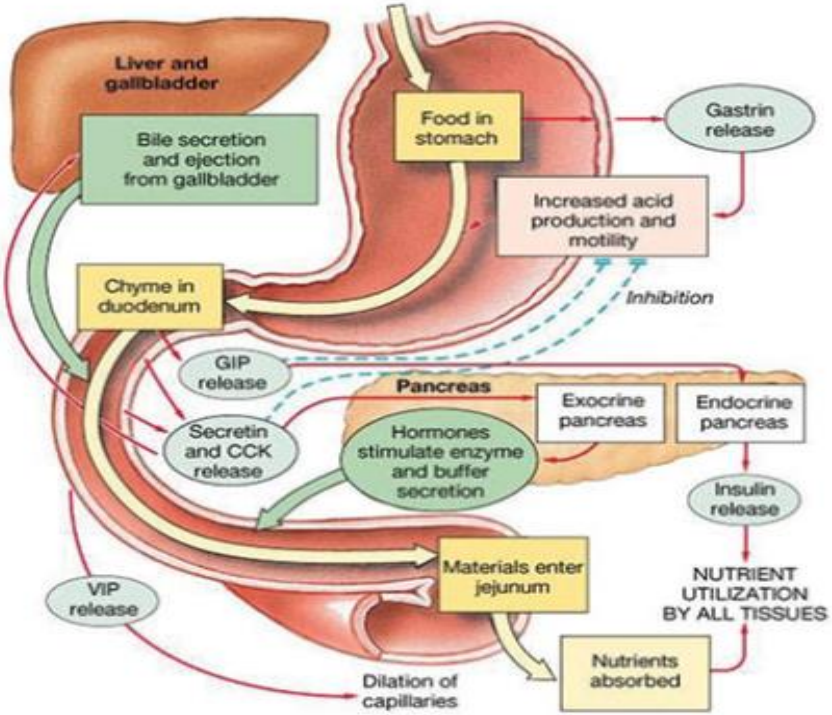
Normal Digestion

Normal Digestion



Site	Carbohydrate	Fat	Protein
Saliva	Amylase	Salivary lipase	
Gastric Secretion	Gastric Amylase	Gastric Lipase	Pepsin; Rennin; Gelatinase
Pancreatic Secretion	Amylase	Lipase; Steapsin	Trypsin; Chymotrypsin; Carboxypeptidase; Elastase
Jejunal/Ileal Secretion	Sucrase; Maltase; Isomaltase; Lactase	Intestinal Lipase	Brush Border Proteases

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Pancreatic Exocrine Insufficiency

PEI | Definition

Pancreatic enzymes are needed to help break down and absorb; carbohydrates, protein and fat

Inadequate pancreatic enzyme activity for digestion = *pancreatic exocrine insufficiency*

PEI | Causes

Primary Insufficiency (Lack of healthy pancreatic tissue)

- Pancreatic cancer (PC) / surgery
- Pancreatitis
- Cystic fibrosis

Secondary Insufficiency (Lack of pancreatic stimulation)

- GI resection (Gastric / duodenal)
- Coeliac disease / IBD
- Medications, such as octreotide

Impaired GI environment

- Low intestinal pH
- Anatomical changes after GI surgery

Some research suggesting insufficiency related to diabetes, IBS, intensive care and elderly

PEI | consequences

- Malnutrition / Sarcopenia
- Nutritional deficiencies (fat-soluble vitamins)
- Symptoms of maldigestion
- Reduced QoL & well-being
- Weight loss
- Increased risk of mortality

Patients with advanced PC treated with PERT have enhanced QoL, survival, better symptom control & tolerance to treatment

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> Pancreatology, 19 (1), 114-121 Jan 2019

Enzyme Replacement Improves Survival Among Patients With Pancreatic Cancer: Results of a Population Based Study

K J Roberts [1], C A Bannister [2], H Schrem [3]

> Support Care Cancer, 21 (7), 1835-41 Jul 2013

Pancreatic Cancer and Supportive Care--Pancreatic Exocrine Insufficiency Negatively Impacts on Quality of Life

H M Gooden [1], K J White

> World J Gastroenterol, 25 (20), 2430-2441 2019 May 28

Contribution of Pancreatic Enzyme Replacement Therapy to Survival and Quality of Life in Patients With Pancreatic Exocrine Insufficiency

Peter Layer [1], Nataliya Kashirskaya [2], Natalya Gubergrits [3]

Pancreatology. 2017 Jan - Feb;17(1):70-75. doi: 10.1016/j.pan.2016.10.005. Epub 2016 Oct 11.

Sarcopenia is closely associated with pancreatic exocrine insufficiency in patients with pancreatic disease.

Shintakuya R[1], Uemura K[2], Murakami Y[2], Kondo N[2], Nakagawa N[2], Urabe K[2], Okano K[2], Awai K[3], Higaki T[3], Sueda T[2].

⊕ Author information

Abstract

BACKGROUND/OBJECTIVES: The loss of skeletal muscle mass (sarcopenia) is associated with the poor prognosis of pancreatic cancer. It has been reported pancreatic exocrine insufficiency (PEI) is associated with serum nutritional markers in chronic pancreatitis. However, there has been no report about the relationship between sarcopenia and PEI. The aim of this study is to determine whether body composition, including skeletal muscle (SM), subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), intramuscular adipose tissue content (IMAC), and serum nutritional markers are associated with pancreatic exocrine function in patients with pancreatic disease.

METHODS: Data were collected prospectively on 132 patients with pancreatic disease. SM, SAT, VAT and IMAC were assessed by computed tomography. Patients underwent a ^{13}C-labeled mixed triglyceride breath test to measure pancreatic exocrine function. Serum nutritional markers were measured at the same time of ^{13}C-labeled mixed triglyceride breath test. Patients were stratified by quartiles according to each body component, and for each component the lowest group was defined as the lowest quartile, treating men and women separately. The lowest group for SM was defined as sarcopenia. PEI was defined as a percentage $^{13}CO_2$ cumulative dose at 7 h below 5%.

RESULTS: Sarcopenia was associated with PEI in both men ($P < 0.001$) and women ($P = 0.012$). Serum albumin was associated with PEI in men only ($P = 0.005$). Among all patients, sarcopenia ($P = 0.001$) and serum albumin ($P = 0.058$) were associated with PEI. On multivariate analysis, only sarcopenia remained independently associated with PEI ($P < 0.001$).

CONCLUSIONS: Sarcopenia is independently associated with PEI in patients with pancreatic disease.

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Diagnosing PEI

PEI | Diagnosis

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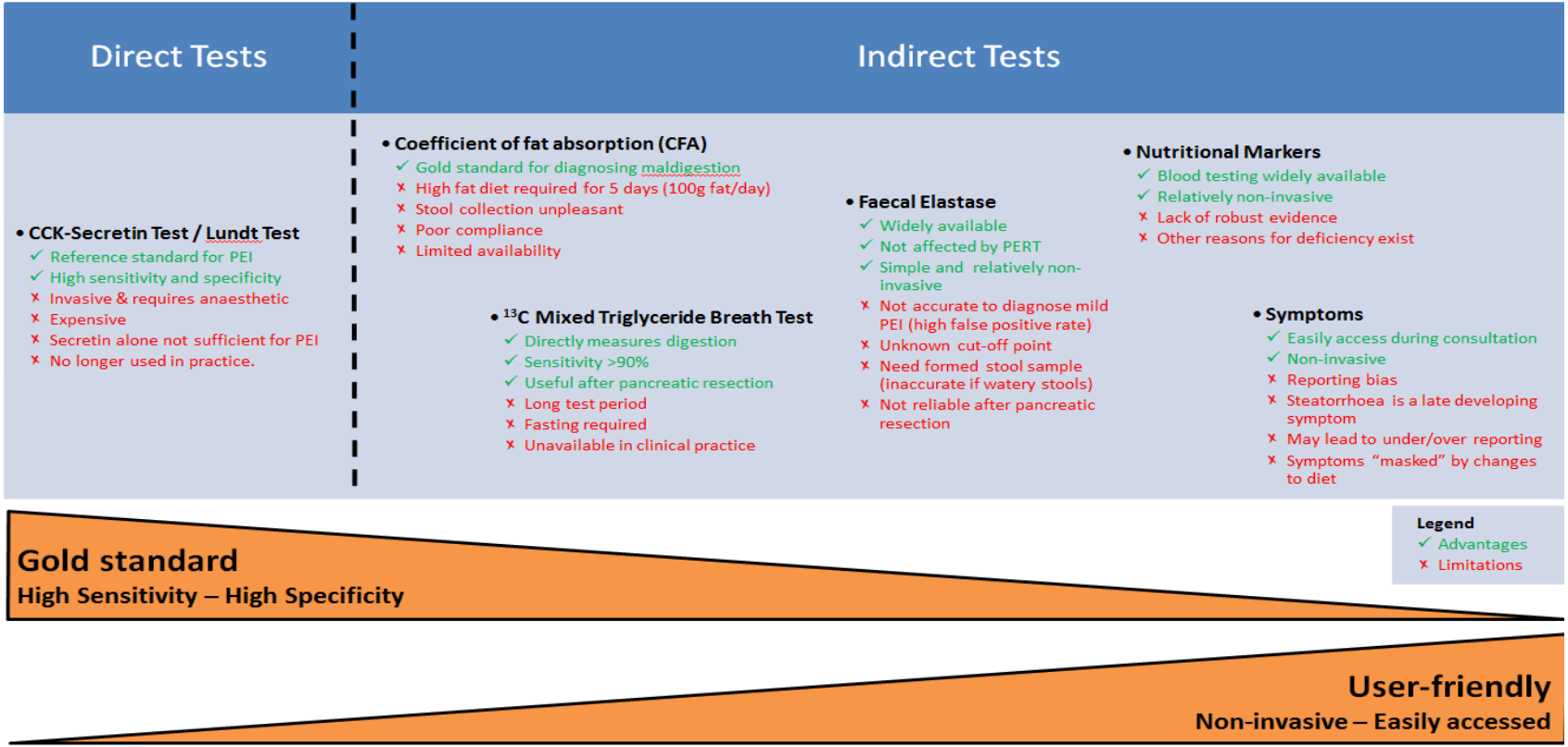

Carnie L, Lamarca A, McNamara M, Bibby N, O'Reilly D, Valle J (2020). The assessment of pancreatic exocrine function in patients with inoperable pancreatic cancer: In need of a new gold-standard. Pancreatology. 20. 10.1016/j.pan.2020.03.020.

PEI | Symptoms

- Pale/offensive smelling stools (may leave an oily appearance around the toilet bowl)
- Stools that are difficult to flush/containing undigested food
- Increased stool frequency/volume/urgency
- Loose stools/diarrhoea, especially after food
- Abdominal discomfort/bloating, especially after food
- Indigestion/flatulence
- Hypoglycaemia in patients with diabetes
- Fat-soluble vitamin deficiencies
- Weight loss despite good intake

PC | FE-1

Faecal elastase-1 is an independent predictor of survival in advanced pancreatic cancer

Stefano Partelli, Luca Frulloni, Consolato Minniti, Claudio Bassi, Giuliano Barugola, Mirko D'Onofrio, Stefano Crippa, Massimo Falconi

Patients with faecal elastase-1 ≤ 20 µg/g had a worse prognosis (median survival: 7 versus 11 months, *P* = 0.031)

- Severe PEI – 17% with clinically evident steatorrhea
- Moderate PEI- 14% with clinically evident steatorrhea

- Avoid fat or poor food intake therefore symptoms often not present

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PERT or no PERT? That is the question….

PC | NICE guidelines

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- Offer enteric-coated pacreatin with unresectable pancreatic cancer
- Consider enteric-coated pancreatin before and after pancreatic cancer resection

PC |PEI incidence

Varies in the literature:

- Inoperable pancreatic cancer: 50-100%

Bartel et al (2015).Pancreatic exocrine insufficiency in pancreatic cancer: A review of the literature, Digestive and Liver Disease, Volume 47, Issue 12, 2015, 1013-1020.)

- After cancer-related pancreatic surgery: 64-100%

Sabater et al 2016. Evidence-based Guidelines for the Management of Exocrine Pancreatic Insufficiency After Pancreatic Surgery. Ann Surg;264(6):949-958

Case study- Mr X

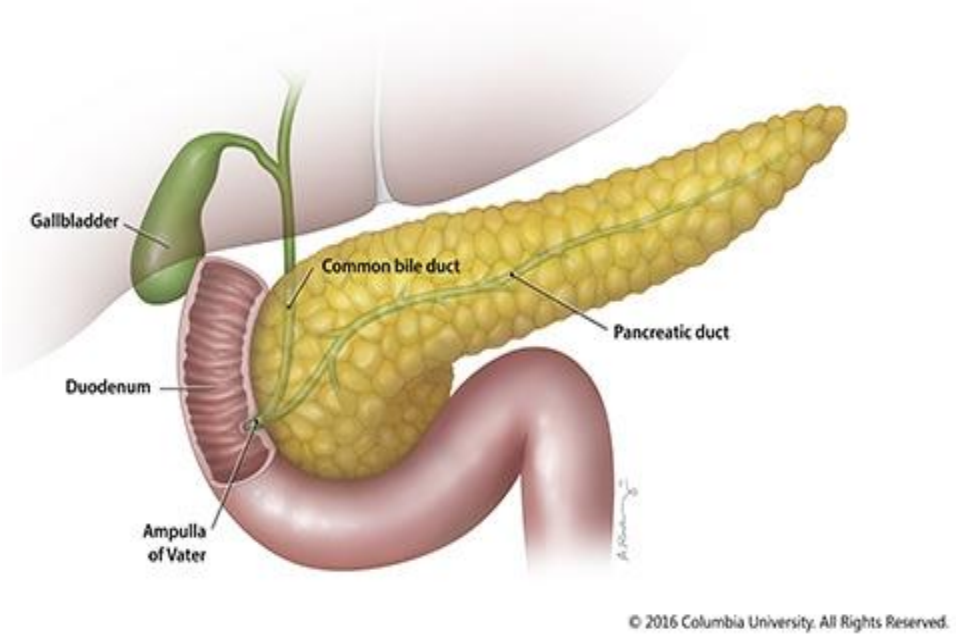
- New diagnosis head of pancreas cancer- Not jaundiced
- Weight- 96.3kg Height: 1.9m BMI: 26.7g/m² (20-25 healthy range)
- Preadmission weight of 106.1 kg indicating a 9.2% weight loss during the last few months
- Bowels opening once a day with a type 4 stool on the Bristol Stool Chart
- Other symptoms reported were frequent abdominal pain, bloating, wind, stomach gurgling, nausea which is worse after eating, smelly stools and tiredness.

PC | Who needs PERT

- If probability of PEI is high you don't need a test
- In patients with a disease/condition that could potentially cause PEI and malabsorption symptoms present - test is not needed
- Use all clinical information available including:
  - Evaluation of symptoms
  - Nutritional status
  - Clinical information (e.g. dilated pancreatic duct on CT).

Dominguez-Munoz et al. Dis Sci 2017

PC | Who needs PERT



Pancreas

- Head of pancreas- ALL
- Body- dependant on size and symptoms
- Tail- Dependant on symptoms- Lower numbers

Cholangiocarcinoma

- Distal- dependant on size and symptoms
- Hilar- Unlikely

Ampulla/ Duodenal

- Dependant on size, location and symptoms

Types of surgery & risk of PEI

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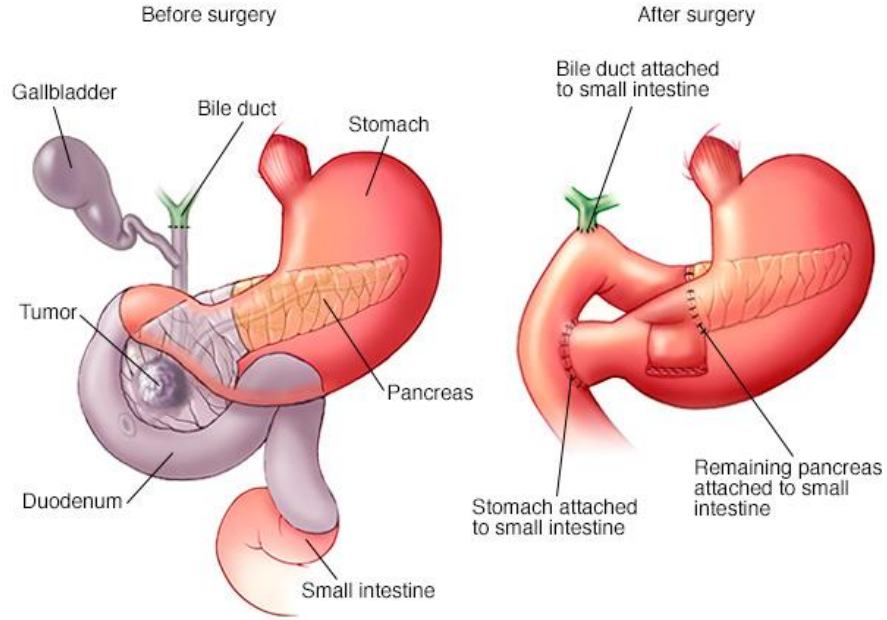
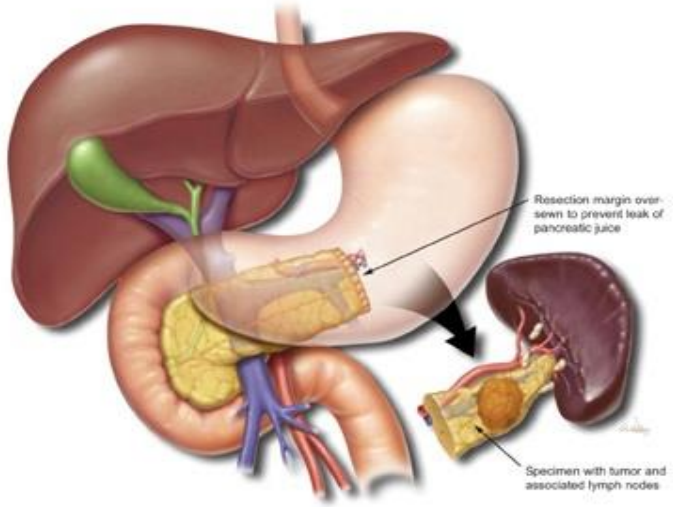
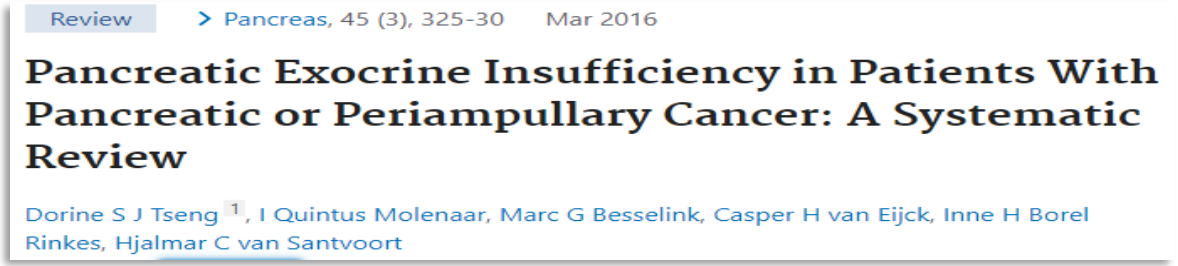




Case study- surgery

- Distal pancreatectomy
- Weight loss post op 84kg to 67kg in 2 months
- Faecal elastase = 423
- Bowels opening every 2 days with Movicol. Occasional stomach gurgling, urgency and smelly stools
- Eating 3 small meals a day, few snacks and x1 Scandishake a day. Portions 50% of normal



Review > Pancreas, 45 (3), 325-30 Mar 2016

Pancreatic Exocrine Insufficiency in Patients With Pancreatic or Periampullary Cancer: A Systematic Review

Dorine S J Tseng [1], I Quintus Molenaar, Marc G Besselink, Casper H van Eijck, Inne H Borel Rinkes, Hjalmar C van Santvoort

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n = 693 patients
Diagnosis of PEI depending on the type of surgery

- Pancreaticoduodenectomy:
  - Before 44% (range, 42%–47%)
  - After 74% (range, 36%–100%)

- Distal pancreatectomy:

- Before 20% (range, 16%–67%)
- After 67% to 80%

- Total pancreatectomy:
  - Before PEI 63%

Pancreas exocrine replacement therapy is associated with increased survival following pancreatoduodenectomy for periampullary malignancy

Keith J. Roberts[1], Harald Schrem[2], James Hodson[3], Roberta Angelico[1], Bobby V.M. Dasari[1], Chris A. Coldham[1], Ravi Marudanayagam[1], Robert P. Sutcliffe[1], Paolo Muiesan[1], John Isaac[1] & Darius F. Mirza[1]

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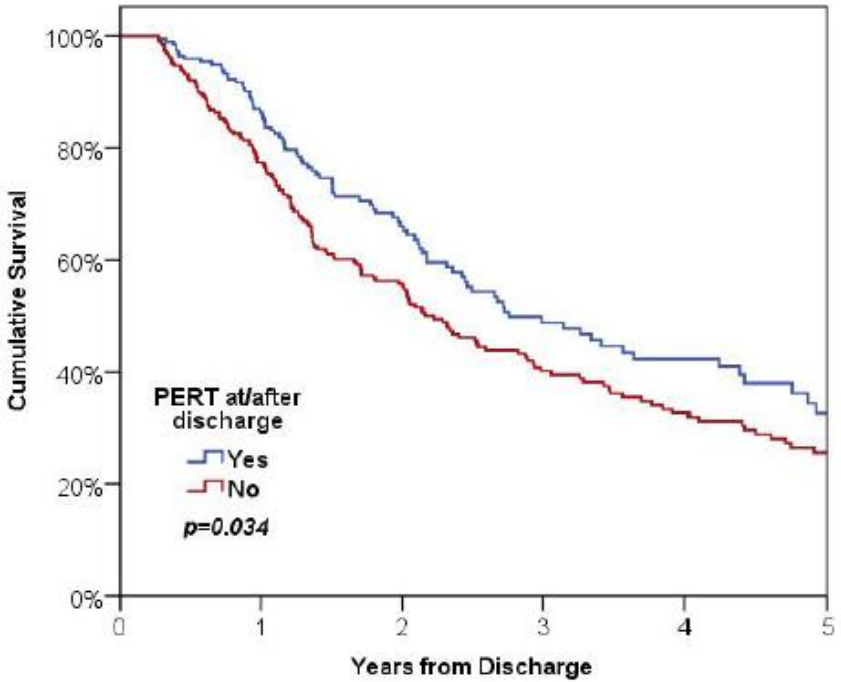

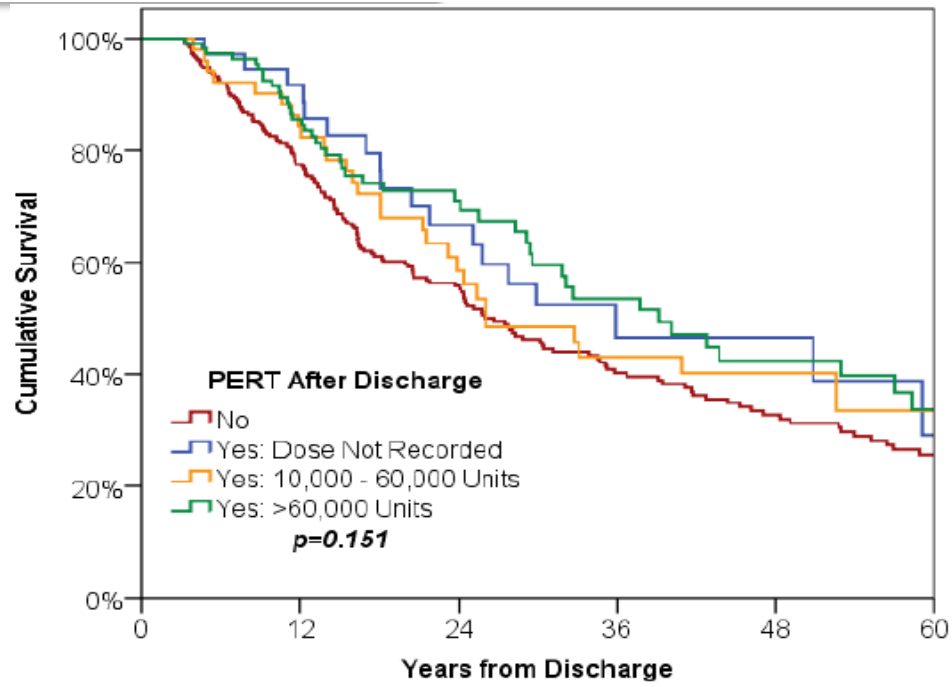

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PERT

Pancreatic enzyme replacement therapy (PERT)

Various brands:

- Creon 10,000, 25000
- Nutrizyme 22 capsules
- Pancrex V powder
- Pancrease HL capsules

Starting dose:
50-72,000 units lipase with meals
20-50,000 units with snacks and milky drinks
(Bruno *et al.* 1998, Whitcomb *et al.*2010, Domínguez-Muñoz 2011)

Take with a proton pump inhibitor (PPI)
- Omeprazole 20mg BD

Source: Porcine
Approval gained for members of Jewish and Muslim community to take
Consider vegetarians- consent needed, no alternative!!

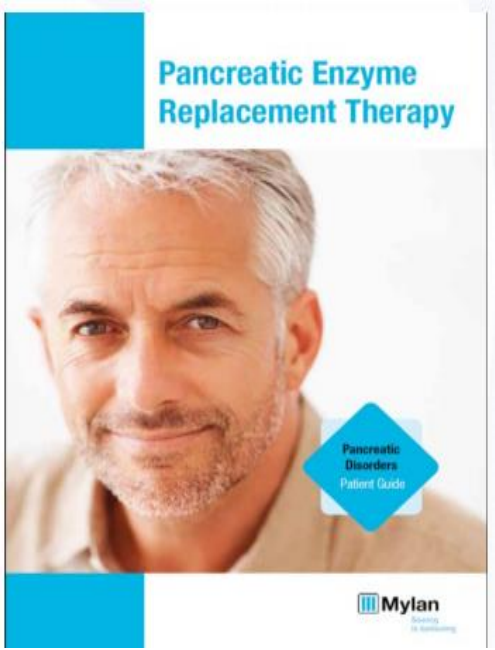
PERT | Prescribing

Observations:

- Starting dose varies across Manchester
- Education about PERT varies
  - Patients don't know what PERT is
  - Patients don't know how to take PERT

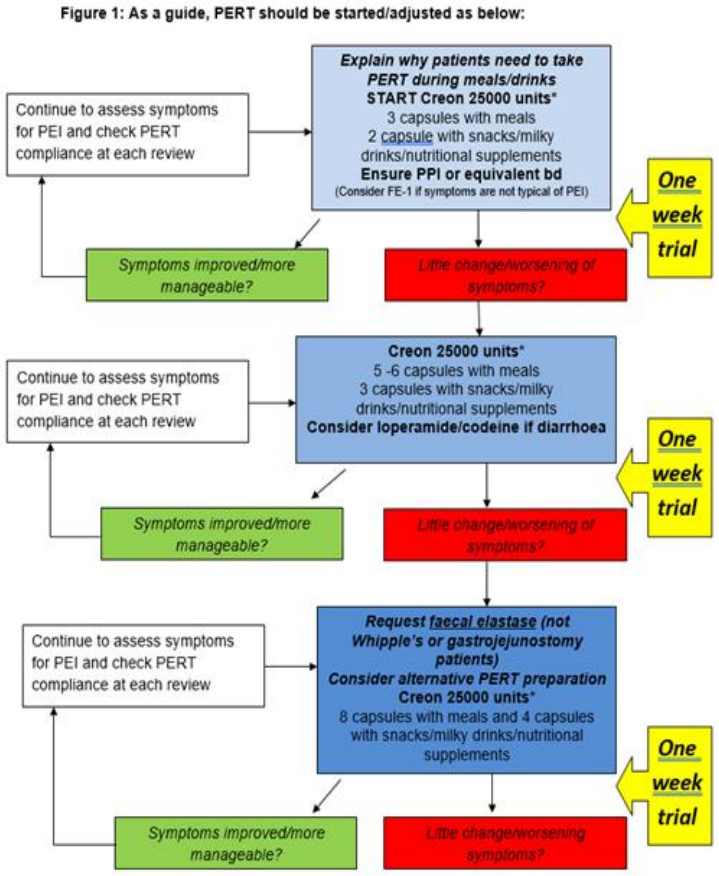
Recommendations:

- Need to standardise starting dose
- Need to provide education about PERT at prescription
- Need to monitor ongoing PERT compliance



PERT | Christie audit

- Algorithm created
- Local agreement for HPB CNS & dietitians to adjust PERT
- Currently awaiting publication and agreement at HPB cancer pathway board
- Starting dose 75,000 meals and 50,000 snacks and ONS
- Weekly review and increase if ongoing symptoms



PERT | Tips

- Take with all meals, snacks, milky drinks & nutritional supplements
- Take ½ with first mouthful & ½ throughout meal
- If a delay between meal courses/ slowly drinking supplements- extra enzymes needed
- Swallow capsules whole with a cold drink
  - If need to open; mix into yoghurt or acidic fruit puree
- Do not store in a warm place (trouser pocket/window sill)
- If having a fatty / larger meal – take more than normal. Titrate doses if ongoing symptoms
- If tolerance issues try alternative brand

Randomised clinical trial: a 1-week, double-blind, placebo-controlled study of pancreatin 25 000 Ph. Eur. minimicrospheres (Creon 25000 MMS) for pancreatic exocrine insufficiency after pancreatic surgery, with a 1-year open-label extension

C. M. Seiler*, J. Izbicki†, L. Varga-Szabó‡, L. Czakó§, J. Fiók¶, C. Sperti**, M. M. Lerch††, R. Pezzilli‡‡, G. Vasileva§§, Á. Pap¶¶, M. Varga*** & H. Friess†††

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	Baseline (n = 58)	End (n = 48)	P-value*
CFA, %	53.6 ± 20.6	78.4 ± 20.7	<0.001
CNA, %	52.8 ± 24.4	74.6 ± 14.0	<0.001
Stool fat, g/day	46.7 ± 26.0	19.1 ± 13.6	<0.001
Stool nitrogen, g/day	6.7 ± 3.5	3.2 ± 1.8	<0.001
Fat intake, g/day†	101.2 ± 32.3	94.4 ± 30.9	n.d.
Nitrogen intake, g/day†	14.8 ± 5.7	13.6 ± 5.8	n.d.
Stool weight, g/day	467 ± 231	235 ± 121	<0.001
Number of stools per day	2.4 ± 1.6	1.5 ± 0.8‡	<0.001
Body weight, kg	68.2 ± 15.8	70.5 ± 16.3§	<0.05
Body mass index, kg/m^2	23.6 ± 5.2	24.5 ± 5.4§	<0.05

CFA, coefficient of fat absorption; CNA, coefficient of nitrogen absorption; n.d., not determined; OLE, open-label extension; s.d., standard deviation.

* P-value is for study end vs. baseline.

† n = 50 at end of OLE.

‡ n = 52 at end of OLE.

§ n = 51 at end of OLE.

Table 4 | CFA, CNA, stool characteristics, body weight, and body mass index at baseline and end of the OLE, unadjusted mean ± s.d. (OLE full analysis sample)

75,000 units meals and 50,000 snacks

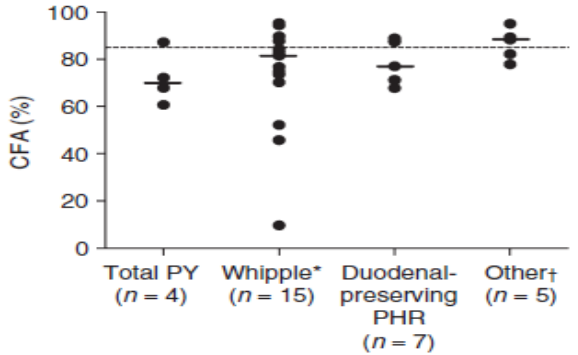


Figure 5 | CFA values at the end of double-blind treatment according to type of surgery in patients receiving pancreatin during the double-blind period (n = 31; CFA data missing at end of double-blind phase in one patient). Dashed line indicates desired CFA threshold of 85%. Solid line indicates median value in each category. *Whipple procedure or equivalent, e.g. pylorus-preserving pancreaticoduodenectomy. †Pancreatic resection with splenectomy (n = 1), distal resection (n = 1), partial pancreatectomy due to arterial aneurysm resection (n = 1), longitudinal resection (n = 1), pancreatic head resection with cholecystectomy (n = 1). CFA, coefficient of fat absorption; PHR, pancreatic head resection; PY, pancreatectomy.

Case study-Mr X

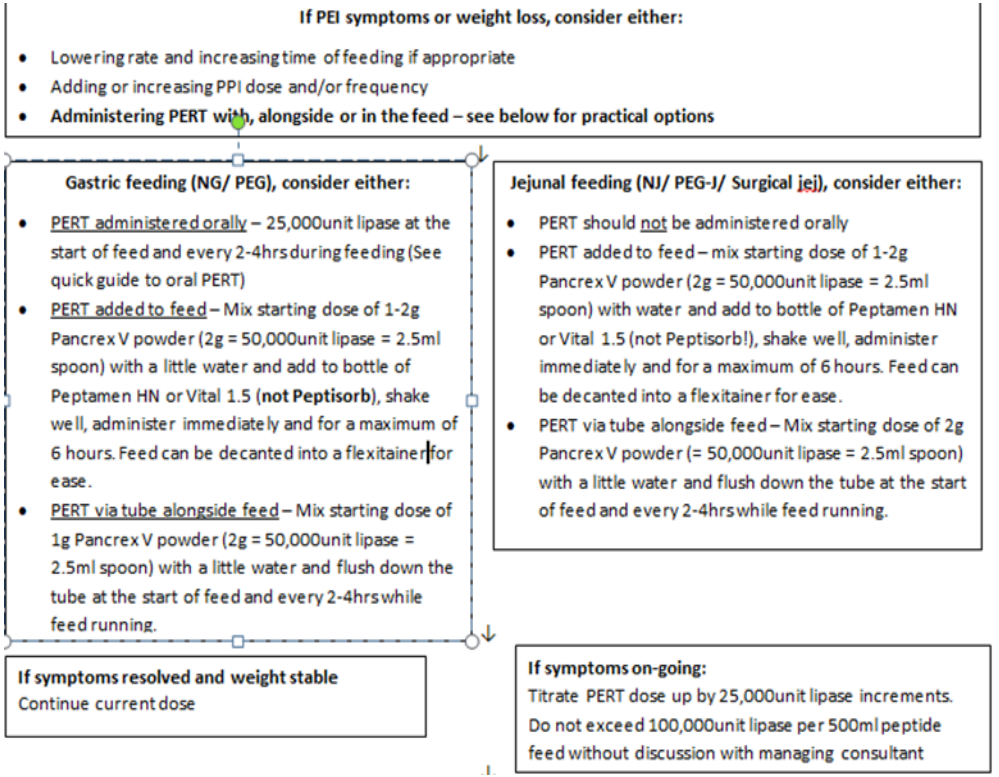
2 week review

- Started creon 75,000 meals and 50,000 with nutritional supplements. Taking at start and spreading. Also taking omeprazole 20mg bd

- Weight stable
- Bowels opening once daily. Improved abdominal pain and bloating
- Ongoing wind, stomach gurgling and smelly stools

- Eventually symptoms controlled with 100,000-125,000 units with meals and 75,000 with nutritional supplements. THERE IS NO MAXIMUM DOSE

PERT and Enteral feeding



Ongoing gastrointestinal symptoms…

Ongoing diarrhoea and other GI symptoms can significantly impact on QOL

If taking high dose PERT and PPI with no improvement, investigate other causes:

- Infective diarrhoea / chemo related
- Bacterial overgrowth
- Bile acid malabsorption

Consider Loperamide / Codeine Phosphate to reduce transit speed

Long-term Quality of Life and Gastrointestinal Functional Outcomes After Pancreaticoduodenectomy

Allen, Casey J., MD; Yakoub, Danny, MD, PhD; Macedo, Francisco Igor, MD; Dosch, Austin R., MD; Brosch, Jessica, BS; Dudeja, Vikas, MD; Ayala, Ronda, RN; Merchant, Nipun B., MD

Annals of Surgery: October 2018 - Volume 268 - Issue 4 - p 657–664
doi: 10.1097/SLA.0000000000002962
PAPERS OF THE 138TH ASA ANNUAL MEETING

Objective: To perform a comprehensive assessment of long-term quality of life (QOL) and gastrointestinal (GI) function in patients following pancreaticoduodenectomy (PD).

Summary of Background Data: Survival after PD has greatly improved and thus has resulted in a larger population of survivors, yet long-term QOL and GI function after PD is largely unknown.

Methods: Patients were identified from a global online support group. QOL was measured using the Short Form-36, while GI function was assessed using the Gastrointestinal Symptom Rating Scale. QOL and GI function were analyzed across subgroups based on time after PD. QOL was compared with preoperative measurements and with established values of a general healthy population (GHP). Multivariate linear regression was used to identify predictors of QOL.

Results: Of the 7605 members of the online support group, 1102 responded to the questionnaire with 927 responders meeting inclusion criteria. Seven hundred seventeen (77.3%) of these responders underwent PD for malignancy. Mean age was 57 ± 12 years and 327 (35%) were male. At the time of survey, patients were 2.0 (0.7, 4.3) years out from surgery, with a maximum 30.7-year response following PD. Emotional and physical domains of QOL improved with time and surpassed preoperative levels between 6 months and 1 year after PD (both $P < 0.001$). Each GI symptom worsened over time (all $P < 0.001$). Independent predictors of general QOL in long-term survivors (> 5 years) included total GSRS score [β = −1.70 (−1.91, −1.50)], female sex [β = 3.58 (0.67, 6.46)], and being a cancer survivor [β = 3.93 (0.60, 7.25)].

Conclusions: Long-term QOL following PD improves over time, however never approaches that of a GHP. GI dysfunction persists in long-term survivors and is an independent predictor of poor QOL. Long-term physical, psychosocial, and GI functional support after PD is encouraged.

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QUESTIONS?