

EARLY CHRONIC PANCREATITIS – ARE YOU MISSING IT?

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ROAD MAP...

- DEFINITION AND SPECTRUM OF CHRONIC PANCREATITIS
- SIGNS AND SYMPTOMS
- WHO IS AT RISK?
- HOW CAN WE IDENTIFY PATIENTS WITH ECP?
- CONSEQUENCES
 - PANCREATIC ENDOCRINE INSUFFICIENCY
 - PANCREATIC MALIGNANCY
- OPTIMAL MANAGEMENT: LIFESTYLE CHANGES AND PHARMACOLOGICAL THERAPIES
- FUTURE DIRECTIONS – DIAGNOSTIC TOOL FOR GENERAL PRACTICE (APC STUDY)

DEFINITION: CHRONIC PANCREATITIS


Chronic pancreatitis is a pathologic fibro-inflammatory syndrome of the pancreas:

- in susceptible individuals (genetic etc)
- environmental risk factors/toxins
- develop *persistent pathologic responses to parenchymal injury or stress*

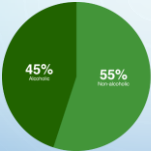
• PANCREATIC ATROPHY	• PANCREATIC ENDOCRINE DYSFUNCTION
• FIBROSIS	• PANCREATIC ENDOCRINE DYSFUNCTION
• DUCT DISTORTION AND STRICTURES	• DYSPLASIA
• CALCIFICATIONS	

TRADITIONAL TEACHING

- RARE - 0.5% OF POPULATION
- ALCOHOLIC OR 'CLOSET ALCOHOLIC'
- PAINFUL, STEATORRHOEA, WEIGHT LOSS
- DIAGNOSIS WITH CT, 72 HOUR FAECAL FATS



AETIOLOGY OF CHRONIC PANCREATITIS




Alcoholic (45%)	Non-alcoholic aetiologies (55%)
	Idiopathic (20%)
	Genetic (5%)
	Obstructive (5%)
	Other (2%)
	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. Gut. Gastroenterology. 2013;96:173.

HOW COMMON IS CHRONIC PANCREATITIS?

There is evidence to suggest that pancreatic disease may exist undiagnosed in medical practice¹⁻⁴



AUTOPSY STUDY

• 1978¹ (DENMARK)



- 394 AUTOPSIES WERE CONDUCTED, WHEREBY THE PANCREAS OF EACH CADAVER UNDERWENT HISTOLOGICAL EXAMINATION
- POST MORTEM RESULTS SHOWED THAT 52 OF THE 394 (13%) EXAMINED BODIES SHOWED EVIDENCE OF CHRONIC PANCREATIC INFLAMMATION
- OF THE BODIES SHOWING EVIDENCE OF CHRONIC PANCREATIC INFLAMMATION, ONLY 2 HAD BEEN DIAGNOSED WITH CHRONIC PANCREATITIS



SCREENING ASYMPTOMATIC PATIENTS 1

• 1991² (FRANCE)



- 180 PATIENTS THOUGHT TO BE FREE OF ANY ABDOMINAL OR PANCREATIC DISEASE AGED FROM 16-83 YEARS OLD HAD THEIR DUODENAL JUICE COLLECTED
- OF THE STUDY GROUP ANALYSED, THE OLDER PATIENTS WERE FOUND TO HAVE A LOWER FUNCTIONING PANCREAS (SUGGESTING PANCREATIC FUNCTION DECREASES WITH AGE) AND 6% OF PATIENTS WERE FOUND TO HAVE PANCREATIC EXOCRINE INSUFFICIENCY (PEI)



SCREENING ASYMPTOMATIC PATIENTS 2

• 2005³ (GERMANY)



- A TRIAL TOOK STOOL SAMPLES FROM 914 PARTICIPANTS AGED BETWEEN 50-75 YEARS OLD
- THE LEVELS OF ELASTASE-1 (AN ENZYME SECRETED BY THE PANCREAS) WERE MEASURED TO DETECT PANCREATIC FUNCTION
- RESULTS SHOWED THAT 105 (12%) OF PARTICIPANTS DISPLAYED SIGNS OF PANCREATIC EXOCRINE INSUFFICIENCY (PEI) AND 47 (5%) DISPLAYED SIGNS OF SEVERE PEI
- THE FINDINGS FROM THIS STUDY SUGGEST THAT THE PREVALENCE OF PEI INCREASES WITH AGE



SCREENING IBS SYMPTOMS

• 2014⁴ (USA)



- MEDICAL RECORDS OF 2256 PATIENTS WITH IRRITABLE BOWEL SYNDROME (IBS) WERE ANALYSED FOR ABNORMAL FAECAL BIOMARKERS
- APPROXIMATELY 7% OF PATIENTS ASSESSED WERE FOUND TO HAVE LOW FAECAL ELASTASE LEVELS WHICH INDICATES PANCREATIC EXOCRINE INSUFFICIENCY (PEI)
- THE FINDINGS OF THIS STUDY SUGGEST THAT SOME PATIENTS DIAGNOSED WITH IBS MAY HAVE A MORE SINISTER, UNDERLYING CONDITION



EVIDENCE FOR UNDIAGNOSED PANCREATIC EXOCRINE INSUFFICIENCY 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 16-83 years	France	180 prospective	Direct secretin, COX test	6% PEI
Rothkuemper D, et al 2005 ³	General population aged 50-75 years	Germany	914 prospective	Fe-1-2000mg/g	11.5% PEI
Herrig K, et al 2011 ⁴	Persons aged 60-92 years	Germany	108 prospective	Fe-1x 200mg/g	21.7% PEI
Lewis J, et al 2010 ⁵	IBS-D	United Kingdom	314 prospective	Fe-1x100mg/g + CT scan	6.1% severe PEI + 21% CP
Groop J, et al 2014 ⁶	IBS related symptoms	USA	2208 retrospective	Fe-1-2000mg/g	7.1% PEI
Combell J, et al 2014 ⁷	Diarrhoea, abdominal pain, weight loss	United Kingdom	1587 retrospective	Fe-1-2000mg/g + CT, MRI, US scan	11.4% PEI + 33.1% CP or PC

1. Olsen T, Acta Path Microbiol Scand 1978; 86: 48-50; 2. Laugier R, et al. Dig Dis 1991; 36: 200-203; 3. Rothkuemper D, et al. Gut 2005; 54: 1020-1024; 4. Herrig K, et al. Gut 2011; 60: 1011-1015; 5. Lewis J, et al. Clin Gastroenterol Hepatol 2010; 8: 1020-1024; 6. Groop J, et al. Clin Gastroenterol Hepatol 2014; 12: 1020-1024; 7. Combell J, et al. Gut 2014; 63: 1020-1024.

DOES IT MATTER?

THE CONSEQUENCES OF UNDIAGNOSED PANCREATIC DISEASE



* Ehrenstein D, et al. *Gastroenterology* 2006; 130:1019-1024. ** Cohen S, et al. *Gastroenterology* 2006; 130:1019-1024. 3. Ohman A, et al. *Pancreas* 2004; 33:103-107. 4. Ohman A, et al. *Gastroenterology* 2004; 126:1743-1747. 5. Ohman A, et al. *Gastroenterology* 2004; 126:1743-1747. 6. Ohman A, et al. *Gastroenterology* 2004; 126:1743-1747. 7. Ohman A, et al. *Gastroenterology* 2004; 126:1743-1747. 8. Ohman A, et al. *Gastroenterology* 2004; 126:1743-1747. 9. Ohman A, et al. *Gastroenterology* 2004; 126:1743-1747. 10. Ohman A, et al. *Gastroenterology* 2004; 126:1743-1747.

WHY MISSED:

- CLINICAL SYMPTOMS AT EARLY STAGE ARE NON-SPECIFIC
- MAINSTAY OF INVESTIGATIONS POORLY SENSITIVE IN EARLY DISEASE



Need a high degree of suspicion

HISTORY

- ALCOHOL
- SMOKING
- GENETICS
 - CF
 - HEREDITARY PANCREATITIS
 - PRSS1
 - SPINK1
 - CTRC
- DUCTAL OBSTRUCTION
- SYSTEMIC DISEASES
 - SLE
 - HYPERTRIGLYCERIDAEMIA
 - HYPERCALCAEMIA
 - COELIAC
- AUTOIMMUNE
- TROPICAL

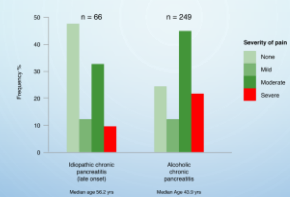
SIGNS AND SYMPTOMS IN CHRONIC PANCREATITIS

- ABDOMINAL PAIN
- PANCREATIC INSUFFICIENCY
 - MALABSORPTION
 - WEIGHT LOSS
 - DIARRHOEA
 - NUTRIENT DEFICIENCIES – PARTICULARLY FAT-SOLUBLE VITAMINS (ADEK)
 - TYPE IIIC DIABETES

PAIN

- USUALLY UNRELATED TO MEALS
- EARLY – PAIN IN DISCRETE ATTACKS; CAN BE MISTAKEN FOR ACUTE PANCREATITIS, NUD
- LATE – CONTINUOUS, CLASSIC
- DOES NOT IMPROVE OVER TIME
 - AMANN, GASTROENTEROLOGY, 1999; MULLADY GUT 2011

WHY DOES CHRONIC PANCREATITIS EXIST UNDETECTED?




- 90% OF PATIENTS WITH IDIOPATHIC CHRONIC PANCREATITIS PRESENTS WITH MILD, MODERATE OR NO PAIN SYMPTOMS


Lutz P, et al. *Gastroenterology* 1998; 112:1461-1467.

WHAT IS PANCREATIC EXOCRINE INSUFFICIENCY (PEI)?


- PROGRESSIVE LOSS OF ACINAR CELLS
- INSUFFICIENT SECRETION OF DIGESTIVE ENZYMES INTO THE DUODENUM¹
 - FUNCTIONALITY OF THE PANCREAS DROPS BELOW 10%¹⁻³
- FOOD IS NOT DIGESTED PROPERLY AND THE NUTRIENTS THAT THE BODY REQUIRES ARE NOT ABSORBED – THIS CAN LEAD TO MALNUTRITION AND OTHER COMPLICATIONS (SUCH AS OSTEOPOROSIS)⁴




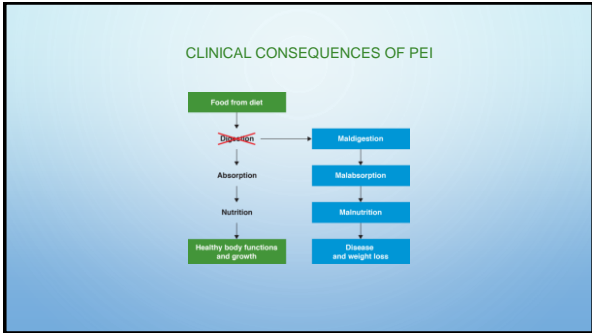
Regularly functioning pancreas



Pancreatic exocrine PE







SYMPTOMS OF PEI

- A COMBINATION OF ANY OF THE FOLLOWING SYMPTOMS IS AN INDICATION THAT A PATIENT COULD HAVE PEI⁴
- **GAS AND BLOATING**
 - FOOD NOT BEING DIGESTED PROPERLY CAN LEAD TO BLOATING IN THE ABDOMEN
- **ABDOMINAL PAIN**
 - GAS PRODUCED BY FOOD NOT BEING DIGESTED FULLY CAN LEAD TO ABDOMINAL PAIN
- **FREQUENT DIARRHOEA**
 - CAUSED BY UNDIGESTED FOOD MOVING TOO QUICKLY THROUGH THE DIGESTIVE TRACT
- **WEIGHT LOSS**
 - DUE TO IMPAIRED DIGESTION AND ABSORPTION OF FATS, PROTEINS AND CARBOHYDRATES, WEIGHT LOSS OFTEN OCCURS IN INDIVIDUALS WITH PEI
- **STEATORRHOEA**
 - GREY, OILY AND VERY FOUL SMELLING STOOLS THAT ARE DIFFICULT TO FLUSH – THIS IS DUE TO EXCESS FAT BEING EXCRETED IN THE FAECES DUE TO POOR FAT DIGESTION AND ABSORPTION
- **MUSCLE WEAKNESS**
 - THE LACK OF PROTEIN BEING PROPERLY DIGESTED AND ASSORBED MEANS THAT THE AN INDIVIDUAL WITH PEI CAN HAVE WEAK MUSCLES

INVESTIGATIONS




RECOMMENDATIONS TO INVESTIGATE FOR PANCREATIC DISEASE AND PEI IN PATIENTS PRESENTING WITH CHRONIC DIARRHOEA SYMPTOMS

Britain 2003	USA 2012	Australasia 2015
<p>British Society of Gastroenterology¹ Guidelines for Investigation of chronic diarrhoea, 2nd Edition</p> <p>"Diarrhoea may result from: (colonic neoplasia/inflammation; (small bowel) inflammation; (small bowel) malabsorption; (malabsorption due to pancreatic insufficiency or (intestinally disorders, and it can be difficult to separate these on clinical grounds."</p>	<p>Mayo Clinic, Rochester, USA³ Evaluating the Patient With Diarrhea: A Case-Based Approach</p> <p>"When belly diarrhea is identified, the initial goal is to distinguish malabsorption from malnutrition."</p> <p>The evaluation focuses on looking for a structural problem involving the small intestine or pancreas."</p>	<p>Australasian Pancreatic Club² Australasian treatment guidelines for the management of pancreatic exocrine insufficiency</p> <p>"PEI may occur in patients with diarrhea predominantly inside bowel symptoms (Level 2). Treatment with PERT may reduce diarrhea and abdominal pain (Level 2b)."</p>


1. Thomas P. et al. Gut 2005; 54(8): 1151-1155. 2. Pancreatology 2015; 15(4): 467-473. 3. Sumner S. Mayo Clin Proc 2012; 87(12): 1288-893.

IS EARLY DETECTION OF CHRONIC PANCREATITIS POSSIBLE?


Endoscopic ultrasound (EUS)



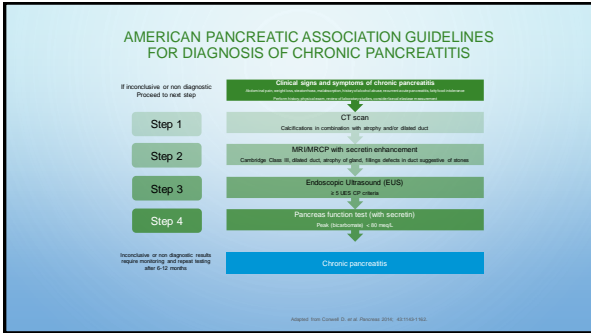
MRI



Computed tomography



Lemon A et al. Cancer Research 74 (13): 1-6, 2014



HOW IS PEI DETECTED?

DIRECT TEST:

- SECRETIN-CAERULEIN TUBULAR TEST

INDIRECT TESTS:

- 3 DAY FAECAL FAT TEST (GOLD STANDARD)
- 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 PRACTICE¹
- IN 2010, IT WAS REPORTED TO BE THE MOST POPULAR TEST USED TO EVALUATE PEI²
- REQUIRES A SINGLE FORMED STOOL SAMPLE²
- MEASURES THE ELASTASE CONCENTRATION IN THE STOOL^{1,2}
- SPECIFICITY: APPROXIMATELY 93%³

>200 µg/g stool: normal value²

<200 µg/g stool: mild PEI¹

<100 µg/g stool: severe PEI¹

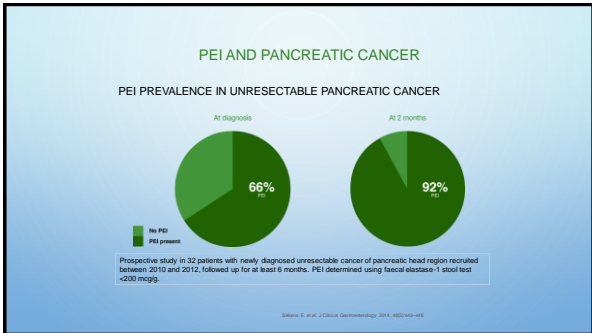
1. Tsoh J, et al. MAJ 2010; 2. Silvers D, et al. Best Pract Res Clin Gastroenterol 2010; 24:327-347; 3. Lohri C, et al. GJ 1996; 20: 585-588.

PEI DIAGNOSTIC PATHWAY

PATIENT GROUPS ¹	PRESENTING SYMPTOMS ¹	PREVALENCE OF PEI ²	SCREENING/DIAGNOSTIC TESTS ^{3,4}	DIAGNOSIS	TREATMENT
Pancreatic Cancer Post-pancreatic resection Chronic Pancreatitis (>10 yrs) Cystic Fibrosis	Non-specific symptoms: - Diarrhoea - Abdominal pain - Weight loss Over symptoms: - Steatorrhea - Low serum nutritional markers	High (>80%)	Without testing: Sensitivity <50% Specificity <50% With testing: e.g. Faecal elastase-1 test: Sensitivity >90% Specificity >90%	PEI	Pancreatic enzyme replacement therapy (PERT)

1. Tsoh J, et al. MAJ 2010; 184:467-469; 2. Thomas P, et al. Gut 2002; 51:244-245; 3. Lohri C, et al. Gastroenterology 2010; 118: 585-590; 4. Silvers D, et al. Best Pract Res Clin Gastroenterol 2010; 24:327-347; 5. Lohri C, et al. GJ 1996; 20: 585-588; 6. Silvers D, et al. GJ 2014; 28: 159-173; 7. Dunaway G, et al. J Gastroenterology 2004; 39(7): 1050-1054; 8. Lohri C, et al. Gut 1996; 20: 585-590.

A FEW WORDS ABOUT PEI AND PANCREATIC CANCER...



QUALITATIVE RESEARCH: IMPACT OF PEI ON QOL IN UNRESECTABLE PANCREATIC CANCER

"Participants identified that their priority limited supportive care needs 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, if please & need!"
Carer, Male (Dad)

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

"You've got this lack of food intake / can't eat as much of what I used to and more and 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.

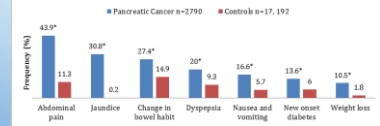
Guidon M, & Walsh K. Support Care Cancer 2015.

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:e005726.

MANAGEMENT

LIFESTYLE MODIFICATION

- AVOID EXPOSURE TO OBVIOUS RISK FACTORS
 - ALCOHOL
 - SMOKING
- ENZYME SUPPLEMENTATION (PERT)
- SMALL MEALS FREQUENT MEALS

ADDITIONAL MANAGEMENT

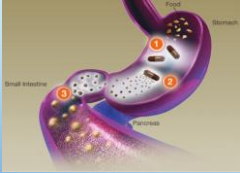
- ANALGESIA
 - SIMPLE
 - NEUROLEPTICS EG TCA, GABAPENTOIDS
- DECOMPRESSION
 - ENDOSCOPIC
 - SURGICAL
 - ESWL

PERT TREATMENT GOALS¹

- ELIMINATE MALDIGESTION
- ELIMINATE MALABSORPTION
- MAINTAIN ADEQUATE NUTRITION

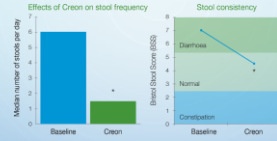
1. Todd et al. BMJ 2005; 330: 461-467

DELIVERY OF PANCREATIC ENZYMES USING A MODERN ORAL FORMULATION



1. The capsule containing pancreatic enzymes enters the stomach along with the food.
2. The outer capsule dissolves rapidly to release enteric-coated mini-microspheres
3. The mini-microspheres pass through the pylorus together with the chyme.
4. 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 on 85-0 patients with normal Fe-1 levels
Open label study, n=18, n=12 weeks, all patients with PEI, Fe-1 <100 µg/g stool.
Dose: Creon 50,000 Units three times daily.

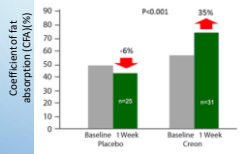
Patients on pancreatic enzyme therapy (Creon) showed a clinically significant response:

- 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 (ongoing) - patients followed over 12 months. Stool frequency and consistency of Creon 50,000 units three times daily 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

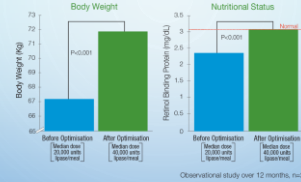


58 patients with pancreatic exocrine insufficiency after pancreatic resection due to malignancy or chronic pancreatitis.

PERT SIGNIFICANTLY IMPROVES FAT ABSORPTION BY 35% AFTER ONE WEEK.

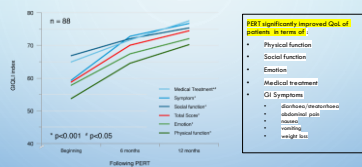
Sobor C. et al, Aliment Pharm & Ther, 2013

EFFECTS OF PERT ON BODY WEIGHT AND NUTRITIONAL STATUS



Observational uncontrolled study involving 20 patients with pancreatic exocrine insufficiency associated chronic pancreatitis. At baseline, these patients were treated with pancreatic exocrine replacement therapy with the dosage titrated to reach the symptoms of weight loss and diarrhoea. The dosage was increased and titrated to achieve normal fat absorption as observed by 125 stool triolein levels test. This treatment was continued for one year.

EFFECTS OF PERT ON THE QUALITY OF LIFE (QOL) OF PATIENTS WITH CHRONIC PANCREATITIS



Observational prospective, multicentre study which assessed symptoms and quality of life over one year in patients with newly diagnosed PD in patients with chronic pancreatitis without prior pancreatic exocrine replacement. Quality of life was measured using questionnaire quality of life score (QOL).

PERT ADULT DOSE RANGE



* Adults: Please refer to the Summary of Product Characteristics (SPC) for further information. ¹ Creon, also manufactured by Abbott Nutrition, also manufactured by Abbott Nutrition.

² Australian Guidelines for Management of Pancreatic Exocrine Insufficiency (PanE), et al. (2010) 1000-1010.

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. Clinch Protein Metabolism. A. Todd. J. et al. GJA (2015) 102 481-487

SUMMARY

- MORE COMMON THAN PREVIOUSLY THOUGHT
- SIGNIFICANTLY UNDER-DIAGNOSED
- UNRECOGNISED DISEASE CAN LEAD TO POOR QOL, HEALTH COMPLICATIONS AND REDUCED SURVIVAL
- SYMPTOMS CAN BE NON-SPECIFIC
- COMMON CONDITIONS STILL COMMON BUT...
 - NEED TO THINK OF IT!!!

FUTURE DIRECTIONS

- APC INITIATED DEVELOPMENT OF A DIAGNOSTIC TOOL
- BASED ON WORK DONE IN UK FOR PANCREATIC CANCER
- BROADENED TO ALSO INCLUDE
 - CHRONIC PANCREATITIS
 - PANCREATIC EXOCRINE INSUFFICIENCY
- PHASE 1 - DEVELOPMENT PHASE (CURRENT)
 - LITERATURE REVIEW
 - DELPHI PROTOCOL
- PHASE 2 - VALIDATION PHASE
 - GENERAL PRACTICES TO UTILIZE PROSPECTIVELY