Causes of pancreatic insufficiency

Eugen Dumitru
Pancreatic Exocrine Insufficiency (PEI)

1. The Concept
2. The Causes
3. The Consequences
Pancreatic Exocrine Insufficiency (PEI)

1. The Concept
2. The Causes
3. The Consequences
Pancreatic Exocrine Insufficiency

1. The Concept

- A condition characterized by deficiency of the exocrine pancreatic enzymes
- Maldigestion
- Malabsorption
- Malnutrition
- Morbidity & Mortality
Pancreatic Exocrine Insufficiency

1. The Concept

- A condition characterized by deficiency of the exocrine pancreatic enzymes

- Maldigestion

- Malabsorption

- Malnutrition

- Morbidity & Mortality

- PEI allways requires therapy !!!
Pathophysiology of **NORMAL DIGESTION**

The role of **PANCREAS**

- Protein + Carbohydrate = begin to undergo digestion in the stomach
- Triglycerides = mostly unchanged until they reach the small intestine
- **Pancreatic enzymes**: amylase, protease, and lipase
  - Lipase: Triglycerides = F.A. + Monoglycerides
  - Bile salts: micelles
- **Postprandial synchrony**!
Pathophysiology of NORMAL DIGESTION

The role of PANCREAS

- The pancreatic enzymes are inactivated when the pH < 5
- The acidic contents of the stomach must be neutralized
- Pancreatic bicarbonate!
Pathophysiology of NORMAL DIGESTION
The role of PANCREAS

- Pancreatic secretion = neural and hormonal mechanisms
- The hormones = secretin and cholecystokinin (CCK)
- Secretin: water and bicarbonate
- CCK pancreatic enzymes
- Neurohormonal disturbances ---> gall bladder hypomotility + accelerated gastric and intestinal transit

Samer Al-Kaade, 2013
Pathophysiology of **NORMAL DIGESTION**
The role of **PANCREAS**

- **SUMMARY**
  - Pancreas: enzymes + bicarbonate
  - Neurohormonal control: Vagus; Secretin and CCK
  - Postprandial synchrony
Pancreatic Exocrine Insufficiency

How does it develop?

1. Reduced pancreatic secretion due to pancreatic diseases
2. Low CCK release due to duodenal diseases
3. Acidic duodenal pH due to gastric hypersecretion or low bicarbonate secretion
4. Abnormal transit due to surgery
Pancreatic Exocrine Insufficiency

2. Causes

- Acute (necrotising) pancreatitis
- Chronic pancreatitis
- Cystic fibrosis
- Pancreatic cancer & tumors
- Diabetes mellitus
- Pancreatectomy

- Gastrectomy
- Pancreateo-duodenectomy
- Coeliac disease
- IBD
- Zollinger-Ellison syndrome
Acute (necrotising) pancreatitis

CT scan showing a normal pancreas.

Acute Necrotising Pancreatitis.
Acute (necrotising) pancreatitis

- Etiology
- Extent of necrosis
- Location of necrosis
- Complications (duct disruption)
- Necrosectomy

Risks for PEI

B. Boreham, Pancreatologia 2003
Chronic pancreatitis

- the most common cause of PEI
- necrosis, fibrosis and loss of function
- smoking is an independent risk factor for PEI

Residual islets in dense fibrous stroma secondary to loss of exocrine pancreatic tissue in chronic pancreatitis (hematoxylineosin stain, medium magnification).

D. Rothenbacher, Scand J Gastroenterol 2005
Probability of remaining free of PEI for patients with chronic pancreatitis.

Years from the onset

PETER LAYER, GASTROENTEROLOGY 1994
Cystic fibrosis

- mutations in the CFTR gene
- reduced chloride transport in the pancreas
- reduced water content of secretions
- precipitation of proteins, and plugging of ductules
- autodigestion of the pancreas
Obstructions of the pancreatic duct

- pancreatic cancer
- ampullary tumors

- These conditions hinder pancreatic exocrine secretions from reaching the gut
Obstructions of the pancreatic duct

Pancreatic Insufficiency

Pancreatic Hypofunction
Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region

<table>
<thead>
<tr>
<th>Treatment parameter</th>
<th>Placebo*</th>
<th>Pancreatic enzyme therapy*</th>
<th>P Value</th>
<th>Mean difference</th>
<th>95% CI for the difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in body weight (%)</td>
<td>-3.7 (4.4)</td>
<td>+1.2 (4.3)</td>
<td>0.02</td>
<td>4.9</td>
<td>0.9 to 8.9</td>
</tr>
<tr>
<td>Change in body weight (kg)</td>
<td>-2.2 (2.7)</td>
<td>+0.7 (2.5)</td>
<td>0.02</td>
<td>2.8</td>
<td>0.4 to 5.2</td>
</tr>
<tr>
<td>Change in fat absorption coefficient</td>
<td>-8 (25)</td>
<td>+12 (25)</td>
<td>0.13</td>
<td>20</td>
<td>-6 to 45</td>
</tr>
<tr>
<td>Change in stool frequency per day</td>
<td>+0.2 (1.0)</td>
<td>-1.0 (1.9)</td>
<td>0.07</td>
<td>1.2</td>
<td>NA</td>
</tr>
<tr>
<td>Daily total caloric intake (MJ)</td>
<td>6.66 (1.78)</td>
<td>8.42 (1.88)</td>
<td>0.04</td>
<td>1.76</td>
<td>0.08 to 3.44</td>
</tr>
<tr>
<td>Daily fat intake (MJ)</td>
<td>2.65 (0.94)</td>
<td>3.31 (1.07)</td>
<td>0.15</td>
<td>0.66</td>
<td>-0.26 to 1.58</td>
</tr>
<tr>
<td>Daily protein intake (MJ)</td>
<td>0.92 (0.24)</td>
<td>1.27 (0.30)</td>
<td>&lt;0.01</td>
<td>0.36</td>
<td>0.11 to 0.61</td>
</tr>
<tr>
<td>Daily carbohydrate intake (MJ)</td>
<td>3.10 (0.95)</td>
<td>3.81 (1.00)</td>
<td>0.11</td>
<td>0.71</td>
<td>0.18 to 1.61</td>
</tr>
</tbody>
</table>

*Mean (SD).
Celiac disease

- decreased pancreatic stimulation
- PEI in about one third of patients
- unrecognized cause of treatment failure
PEI and adult coeliac disease

• In patients with CD compliant with their gluten-free diet who have on-going diarrhoea

• One possible cause is exocrine pancreatic insufficiency
  Impaired release of CCK

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**Table 1. Group demographics and Fel-1 results**

<table>
<thead>
<tr>
<th>Group</th>
<th>Group</th>
<th>N (male)</th>
<th>Patients with Fel-1 &gt;200</th>
<th>Patients with Fel-1 &lt;200</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole CD group</td>
<td>209 (55)</td>
<td>178/209 (85%)</td>
<td>31/209 (15%)</td>
</tr>
<tr>
<td>A</td>
<td>New diagnosis CD</td>
<td>57 (13)</td>
<td>51/57 (89%)</td>
<td>6/57 (11%)</td>
</tr>
<tr>
<td>B</td>
<td>CD asymptomatic (on GFD)</td>
<td>86 (24)</td>
<td>81/86 (94%)</td>
<td>5/86 (6%)</td>
</tr>
<tr>
<td>C</td>
<td>CD with chronic diarrhoea (on GFD)</td>
<td>66 (18)</td>
<td>46/66 (69%)</td>
<td>20/66 (30%)*</td>
</tr>
<tr>
<td>D</td>
<td>Controls with diarrhoea</td>
<td>50 (13)</td>
<td>48/50 (96%)</td>
<td>2/50 (4%)†</td>
</tr>
</tbody>
</table>

Pancreatic enzyme supplementation may provide symptomatic benefit

J. S. LEEDS, Aliment Pharmacol Ther, 2007
Crohn disease / UC

- Increased risk for Acute Pancreatitis (including drug-induced) $> 250 \times$
- Autoimmune pancreatitis $> 15 \times$
- Chronic pancreatitis
- PEI

- Pancreatic autoantibodies (Anti-GP2 Ab.)

Triantafillidis, ANNALS OF GASTROENTEROLOGY 2010
Exocrine Pancreatic Insufficiency in Diabetes Mellitus

Philip D. Hardt, Experimental Diabetes Research 2011
• Abnormal Pancreatic Exocrine Function in Diabetes Mellitus (DM)
  • 51% (26–74%) of IDDM
  • 32% (28–36%) of NIDDM
• direct and indirect function tests
• steatorrhea - 60% of DM

• Pancreatic Exocrine Morphology in Diabetes Mellitus
  • chronic inflammatory changes
  • pancreatic atrophy
• Autopsy studies, ERCP, US, CT and MRI

Philip D. Hardt, Experimental Diabetes Research 2011
Hypothesis Explaining Pancreatic Damage in Patients with Diabetes Mellitus

- Insulin as a Trophic Factor for Exocrine Tissue
- Changes in Secretion/Action of Other Islet Hormones
- Pancreatic atrophy might result from a lack of trophic insulin effects
- Glucagon and somatostatin elevation

Philip D. Hardt, Experimental Diabetes Research 2011
Hypothesis Explaining Pancreatic Damage in Patients with Diabetes Mellitus

- Autoimmunity
- Diabetic neuropathy

• Antibodies against exocrine antigens
• Interruption of the enteropancreatic reflexes
Zollinger-Ellison syndrome

- acid inactivation of pancreatic enzymes
- it is corrected by controlling the acid secretion
GI and pancreatic surgical procedures

- loss of postprandial synchrony
- decreased pancreatic stimulation
- loss of pancreatic parenchyma

- PEI contributes to postoperative morbidity in patients who undergo esophagectomy

Samer Al-Kaade, 2013
PEI after GI surgery

- Gastric emptying and pancreatic secretions
- Antro-fundic reflexes
- Vagal reflexes
- CCK-releasing peptide
- CCK

J. Enrique Domínguez-Muñoz, HPB 2009
PEI after GI surgery

- disturbance of fundus relaxation
- absence of neurally stimulated pancreatic secretion
- reduction in CCK mediated stimulation of pancreatic secretion
- large and hard-to-digest nutrient particles
- pancreatic resection
- asynchrony

As a consequence, maldigestion develops in up to 80% of patients who have been operated upon for gastric or pancreatic diseases.

Friess, Am J Gastroenterol 1996

J. Enrique Domínguez-Muñoz, HPB 2009
Risk factors for development of PEI after pancreatic surgery

- Duodenectomy
- Stricture of pancreatic duct anastomosis
- Extent of pancreatic distal resection
- Preoperative pancreatic fibrosis
- Test used for diagnosis of PEI

Nakamura et al, J Gastrointest Surg 2009
Speicher and Traverso, J Gastrointest Surg 2010
Meta-analysis of PEI after surgery

Duodenum preserving surgery > pancreatoduodenectomy

3. The Consequences

Clinical Consequence of PEI

- EPI = deficiency of exocrine pancreatic enzymes ---> maldigestion
- Pancreatic lipase = 90% of fat digestion
- Maldigestion of fat > proteins and carbohydrates
- Impaired fat digestion when lipase output < 10%
- Steatorrhea
3. The Consequences

Clinical Consequence of PEI

- **Malnutrition**, and not diarrhea, is the main clinical consequence of PEI

- A deficient nutritional status, in chronic pancreatitis, is associated with:
  - more pain episodes
  - more hospitalization
  - cardiovascular events
  - fracture risk
  - infection risk
Thank you!