INTERACTIONS BETWEEN EXOCRINE AND ENDOCRINE PANCREATIC INSUFFICIENCY

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Conflicts of Interest

- None

Background

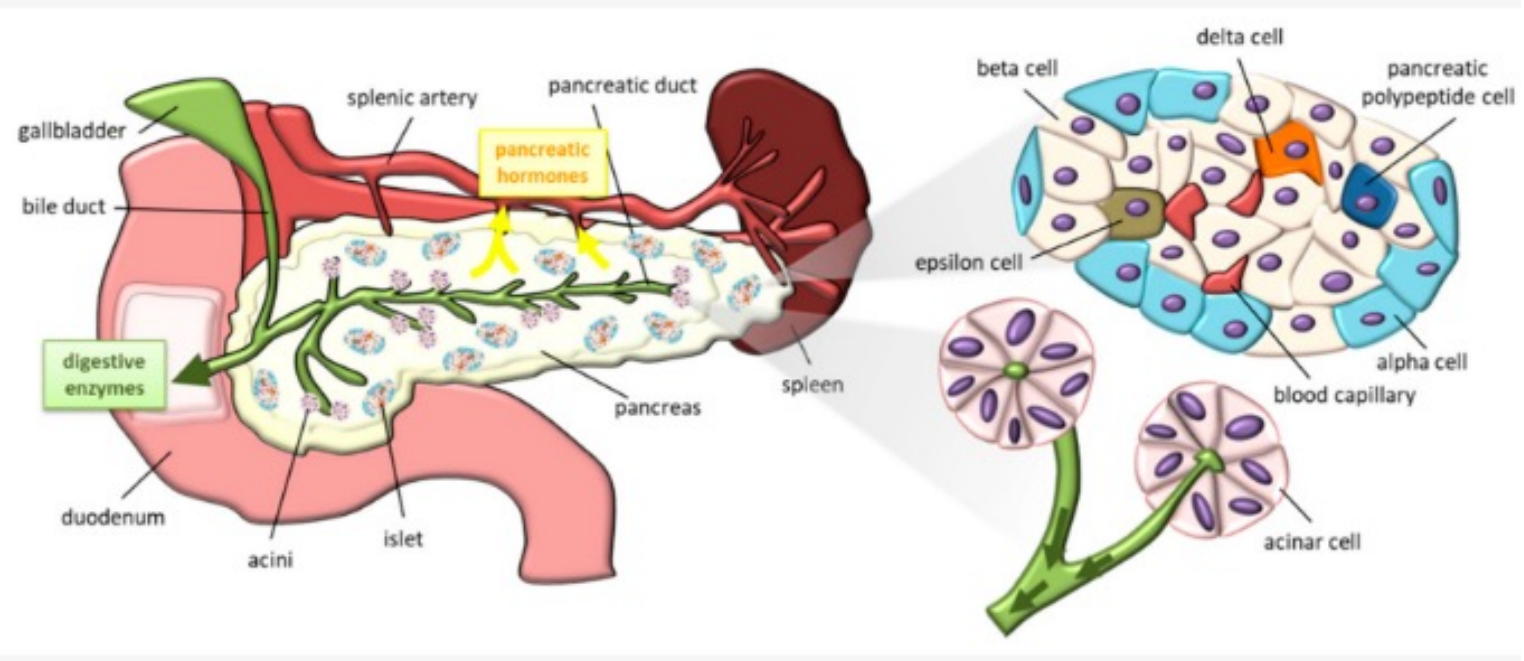
- **Acinar cells produce** and **store** digestive **(pro)enzymes** in zymogens:
  - Proteases (trypsinogen, chymotrypsin, elastase, etc.)
  - Amylase
  - Lipase
  - Nucleases
- **Secretin** and a low **pH stimulate** the secretion of:
  - sodium, chloride,
  - bicarbonate, and
  - water into the pancreatic ducts

- **Fatty and amino acids** in chyme **stimulate**:
  - The release of cholecystokinin (CCK)
    - Activation the vagus nerve
      - Leads to cholinergic stimulation of acinar cells
        - Release of zymogen granules

Foster TP, et al Endocr Pract. 2020
Pandiri AR et al. Toxicol Pathol. 2014
Hart P et al. Pancreapedia 2017

Background

- Islet-acinar vascular axis
- 5 different types of Islets :
  - **α-Cells>>**glucagon
  - **β-cells**>>over 75% of islet cells>>insulin and amylin
  - **δ-cells** >> somatostatin
  - **γ-cells** >> pancreatic polypeptide (PP)
  - **ε-cells**>>ghrelin



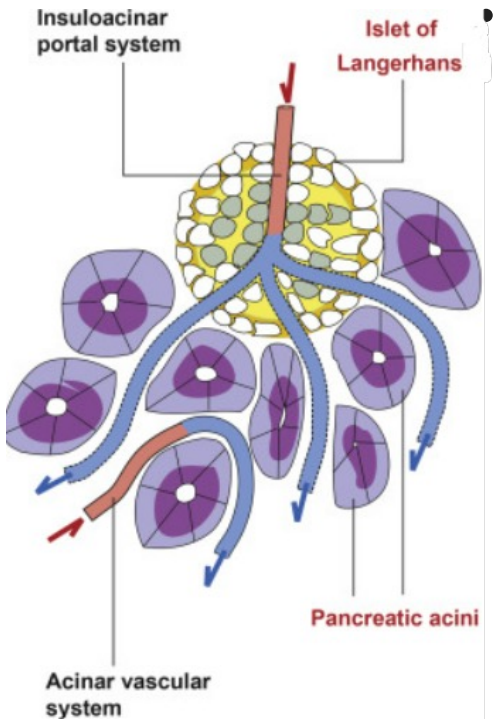
Foster TP, et al Endocr Pract. 2020
Moulle VS, et al Nutrients 2019

Is there any interaction between exocrine and endocrine pancreas?

Background

- **Stimulation** of acinar component :
  - Insulin
    - growth
    - amylase synthesis
    - secretion

- **Inhibition** of acinar component**:**
  - P polypetptide
  - Somatostatin
  - Ghrelin
  - Adrenomedullin
  - neuropeptide Y
  - peptide YY inhibit exocrine secretion



- **Alternating effects** on the acinar component**:**
  - Glucagon:
    - **Depends on** the **chronicity** of stimulation>> acinar atrophy
  - Timing fasting vs fed state:
    - **Fasting** or starved state>> **inhibition** of exocrine secretion
    - **Fed** state>> **stimulation** of secretion >> via amino acid stimulation

Piciucchi M et al. Int J Endocrinol 2015
Foster TP, et al Endocr Pract. 2020

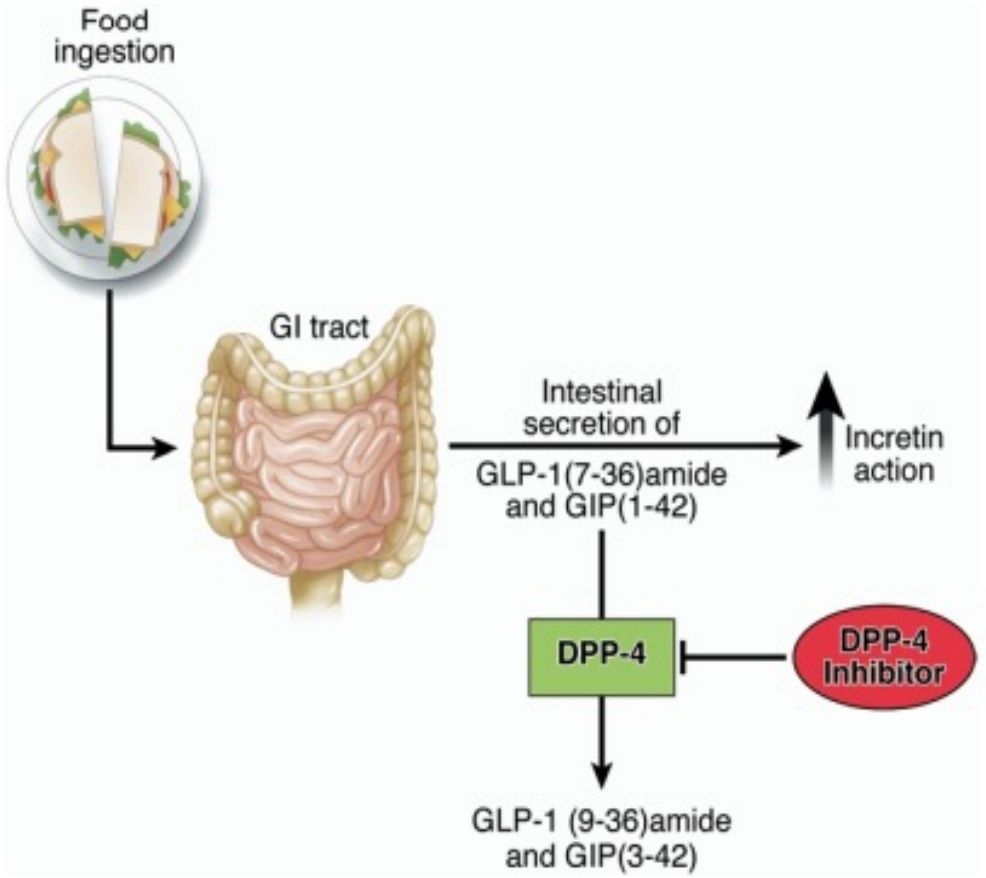
Background

Endocrine cells disseminated in the **small bowel secrete** two peptide known as **incretins**:

- Glucagon-like peptide-1 (**GLP-1**)
- Glucose-dependent insulinotropic hormone (**GIP**)

GLP-1 and GIP are released after lipid and carbohydrate ingestion>> strong stimulus to insulinic production

DPP-4 display the opposite effect and **degrades GLP-1 and GIP**



Piciucchi M et al. Int J Endocrinol 2015
Baggio LL et al Gastroenterology 2007

Pancreatic exocrine insufficiency (PEI)

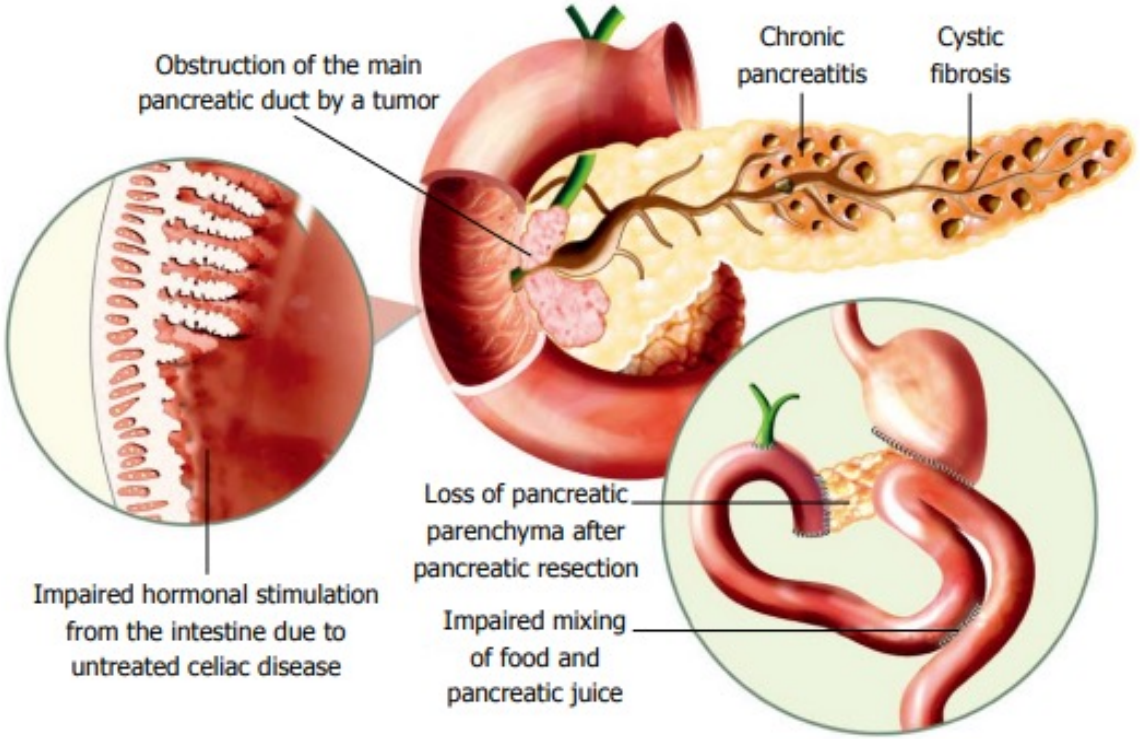
- Pancreatic exocrine insufficiency (**PEI**) can be defined as a **reduction in pancreatic enzyme activity in the intestinal lumen to a level that is below the threshold required to maintain normal digestion**

- Pancreatic exocrine **secretion can be significantly reduced without PEI** being present:
  - Steatorrhea does not occur until 95% of the exocrine component is impaired

- Moderately **reduced bicarbonate or enzyme output** is a reliable indicator of chronic pancreatitis (CP) but does not necessarily indicate PEI

B. Lindkvist WJG 2013

Pancreatic exocrine insufficiency (PEI)



Second, **any pathology**, including extra-pancreatic conditions, **that interrupt the chain of events required for the normal digestion** of ingested food **by pancreatic digestive enzymes may cause PEI**

B. Lindkvist WJG 2013

Pancreatic exocrine insufficiency (PEI)

- The prevalence of PEI in the general population is unknown
- PEI is most associated with diseases of the exocrine pancreas, being a common late-stage manifestation of CP
- Pancreatic function and pancreatic secretion are not synonymous, and PEI can be due to extra-pancreatic diseases

Capurso G. et al Clin Exp Gastroenterol. 2019

Diagnosis of PEI

- The gold standard for the diagnosis of PEI is three-day fecal fat quantification and determination of the coefficient of fat absorption
  - Unpleasant for both the patient and laboratory personnel
  - Strict diet and collection of the complete volume of feces for three days
  - The test is very rarely performed

- Pancreatic elastase 1 is an enzyme of the pancreatic juice that is highly stable during passage through the gastrointestinal tract
  - Single spot of fecal sample>>> enzyme-linked immunosorbent assay (FE-1)
  - FE-1 levels correlate with more sensitive tests
  - Low FE-1 levels correlate with morphological tests for CP (ERCP, MRCP)

B. Lindkvist WJG 2013

Diagnosis of PEI

FE-1 concentration of < 15 μg/g feces detects PEI with high sensitivity and specificity in patients with CP without prior pancreatic surgery.

Intermediate FE-1 values (15-200 μg/g feces) are more difficult to interpret and likely warrant testing with more sensitive methods.

FE-1 assessment is not a reliable test for PEI in patients post-pancreatic resection.

The fecal fat concentration was consistently higher in relation to FE-1 levels in operated compared with non-operated cases: inadequate mixing of food with the pancreatic juice

B. Lindkvist WJG 2013
Benini L et al. Pancreatology 2013

Diagnosis of PEI

The 13C-mixed triglycerides (13C-MTG) breath test directly measures the clinically most relevant end-effect of exocrine pancreatic function: the degradation of triglycerides

The patient ingests a small amount of 13C-marked triglycerides (2-octanoyl (1-13C)-1,3 distearoyl glycerol), together with butter on a piece of toasted bread, after an overnight fast

In the presence of normal lipase activity, 13C-triglycerides will be degraded in the intestinal lumen

13C-marked fatty acids will then be absorbed, metabolized in the liver, and excreted as 13CO2 in exhaled air

Values below 29% are considered as pathological, and the test detects fat maldigestion with a sensitivity of > 90%

B. Lindkvist WJG 2013
Benini L et al. Pancreatology 2013

EPI caused by pancreatic disorders		
Disease	EPI prevalence	Factors associated with EPI occurrence
Chronic pancreatitis	30%–90%	• Long disease duration • Alcoholic etiology • Extensive calcifications • Ductal obstruction
Acute pancreatitis	Mild pancreatitis: 15%–20% Severe pancreatitis: 30%–40%	• Necrosis extent (>30%) • Alcoholic etiology
Autoimmune pancreatitis	30%–60%	Extensive mass/calcification
Unresectable pancreatic cancer	20%–60%	• Head localization • Large size • Ductal obstruction • Coexistent chronic pancreatitis
Pancreatic neoplasms after surgery	Pancreaticoduodenectomy: 80%–90% Distal pancreatectomy: 20%–50%	• Whipple intervention* • Gastropancreatic anastomosis*
Benign pancreatic tumor (before surgery)	30%–60%	• Head localization • Large size • Ductal obstruction • Coexistent chronic pancreatitis
Cystic fibrosis	80%–90%	Classes I, II, III, VI CFTR mutations
Shwachman–Diamond syndrome	80%–90%	–
EPI caused by extrapancreatic disorders		
Type I diabetes	30%–50%	• High insulin requirement • Poor glycemic control • Early diabetes onset
Type II diabetes	20%–30%	• Insulin requirement • Poor glycemic control • Long diabetes duration
Inflammatory bowel disease	Ulcerative colitis: 10% Crohn's disease: 4%	• Disease reactivation (only for temporary EPI) • Long disease duration • Surgical patients
Celiac disease	5%–80%	Untreated disease (no gluten-free diet)
Pediatric intestinal transplantation	10%	
HIV syndrome	10%–50%	Retroviral therapy
Gastrointestinal surgery	Total/subtotal gastrectomy: 40%–80% Esophagectomy: 16%	• Extensive intestinal resection • Vagal denervation
Sjogren's syndrome	10%–30%	
Aging	15%–30%	Age >80 years
Tobacco usage	10%–20%	Alcohol usage
Somatostatin analogs therapy	20%	

Causes of PEI

PEI in Type I Diabetes

- **The size of the pancreas** in individuals with Type I Diabetes is significantly **smaller** than controls despite β-cells only comprising a small percentage of pancreatic mass

- At Histology: **atrophy, fibrosis, changes in size, and morphology**

- Compared to age-matched controls, **the weight** of **postmortem** Type I Diabetes pancreas is **reduced** by 35 to 45%

- **Imaging studies** of those living with T1D have demonstrated that **the volume** of the pancreas is **reduced 18 to 52%** compared to controls

Gepts W. Diabetes. 1965
Foster TP, et al Endocr Pract. 2020

Changes in the Exocrine Pancreas and Enzymes in T1D

Changes	Significant findings	Source (Reference)
Reduced pancreas size[a]	• 35%, mean weight at autopsy aged 14 and over • 52%, median area via ultrasound • 37%, mean volume at autopsy • 32%, mean PVI via CT • 31%, mean PVI via MRI • 45%, mean weight from cadaveric organ donors • 26%, mean PVI[c] via MRI • 33%, mean PVI via CT • [illegible] mean volume via MRI • 47% mean volume via MRI or CT; 4/25 T1D with ~6% progressive volume loss per year • [illegible] median volume via MRI; 7.2% relative volume loss over first year of new onset T1D • 18% mean transverse area via ultrasound • 22%, mean RPV of recent onset via MRI • 45%, mean weight from cadaveric organ donors	MacLean 1959 (22) Fonseca 1985 (9) Löhr 1987 (20) Goda 2001 (15) Gaglia 2011 (13) Campbell-Thompson 2012 (6) Williams 2012 (31) Lu 2016 (21) Regnell 2016 (24) Virostko 2016 (28) Virostko 2019 (32) Augustine 2019 (5) Campbell-Thompson 2019 (7) Wright 2020 (33)
Acinar atrophy	• Compressed, atrophic glandular acini; many acini replaced with connective tissue • Small acini with depleted zymogens in prolonged diabetes • [illegible] atrophy with smaller acinar cells • Acinar atrophy in 21% • [illegible] reduced compared to controls and AAb+ • Less acinar cells, but similar in size	Cecil 1908 (3) Foulis 1986 (10) Löhr 1987 (20) Waguri 1997 (29) Tang 2020[c] Wright 2020 (33)
Fatty infiltration & Fibrosis	• Adipose infiltration of stroma; adipose tissue replaced acini in 11%; fibrosis around vessels and ducts; 24% significant sclerosis, worse with age • Intra-lobular and peri-lobular sclerosis, worse with chronicity • Fatty changes in 32%; Inter-acinar fibrosis in 66% • Fatty degeneration and fibrosis, worse with age, irrespective of T1D duration • Increased fibrosis: thickened inter-acinar septa and intraparenchymal deposits of connective tissue	Cecil 1908 (3) Gepts 1965 (14) Waguri 1997 (29) Bonnet-Serrano 2018 (46) Wright 2020 (33)
Immune histopathology	• Lymphoid, eosinophil, plasma, and PMNs • PMNs in 6/119; diffuse lymphocytes in 9/119 cases • Peri-insular lymphocytes, reticular cells, PMNs • Lymphocytic infiltration in 47% • Increased C4d (product of complement) in vascular endothelium and extracellular matrix • Neutrophils in exocrine pancreas in new onset and chronic cases • High numbers of cytotoxic T-cells, helper T-cells, and monocytes	Cecil 1908 (3) Foulis 1986 (10) Gepts 1965 (14) Waguri 1997 (29) Rowe 2013 (26) Valle 2013 (27) Rodriguez-Calvo 2014 (25)
Vascular changes	• Thickening of pancreatic vessels with small arteriole destruction, worse with age • Arteriosclerosis, worse with chronicity • Microvasculature has smaller diameters & increased density in insulin negative islets, but no difference in exocrine vessel diameter/density	Cecil 1908 (3) Gepts 1965 (14) Canzano 2019 (51)
Decreased exocrine enzymes[b]	• 54% ↓ amylase (DEF) • 65% ↓ amylase, 80% ↓ trypsin (DEF) • 78% ↓ trypsin (DEF) • 36% ↓ amylase, 37% ↓ lipase, 26% ↓ trypsin (DEF) • Significantly lower trypsinogen levels in T1D and multiple AAb+ subjects	Pollard 1943 (23) Frier 1976 (12) Frier 1980 (11) Lankisch 1982 (18) Li 2017 (19)

Foster TP, et al Endocr Pract. 2020

PEI in Type I Diabetes

- It remains to be determined exocrine insufficiency in type I DM is due to:
  - **Primarily β-cell loss:**
    - (1) endocrine dysfunction
    - (2) vascular damage
    - (3) autonomic neuropathy
  - **A disease of the entire pancreas:**
    - Inflammatory infiltrate

Piciucchi M et al. Int J Endocrinol 2015
Foster TP, et al Endocr Pract. 2020

PEI in Type I Diabetes

- The damage is probably multifactorial:
    - Lack of the trophic action of insulin/glucagon/somatostatin
    - Autoimmune damage
    - Autonomic diabetic neuropathy >>> enteropancreatic reflex impairment
    - Microvascular damage >>hypoxic damage
    - Immune cells infiltration of the exocrine pancreas, supporting a model of generalized pancreatic inflammation

Piciucchi M et al. Int J Endocrinol 2015
Foster TP, et al Endocr Pract. 2020

PEI in Type I Diabetes

PEI seems to occur earlier and more frequently in type I diabetes:

- 10% of severe and 45% of moderate PEI in **children** 2-25 years

- Higher prevalence in screened **adults**>> 10–30% severe and 22–56% moderate PEI

Type I diabetes is characterized by:
- Early occurrence
- Severe insulin deficiency,
- Long standing disease
- High rate of neural and vascular complications

Piciucchi M. et al. Int J Endocrinol 2015
Foster TP, et al Endocr Pract. 2020

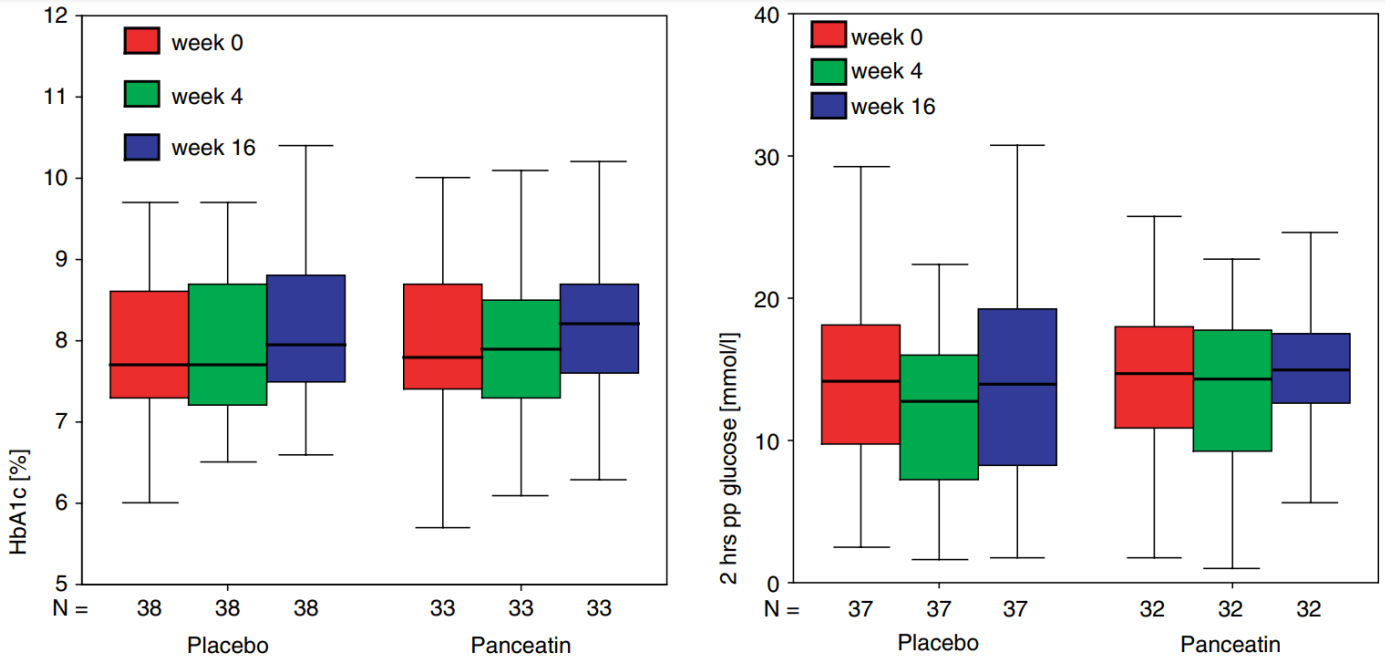
PEI in Type I Diabetes

- **PEI** in T1D clinically presents with **diarrhea, bloating, cramping, and/or weight loss**
- Such symptoms can be in **overlap with** other **complications of diabetes**: GI autonomic neuropathy, celiac disease or bacterial overgrowth
- **Celiac disease** should always be ruled out in type I DM patients (RR=5)
- The clinical relevance of PEI in T1D is still largely unknown as **many patients with PEI** are **asymptomatic**

Piciucchi M et al. Int J Endocrinol 2015
Foster TP, et al Endocr Pract. 2020

PEI in Type I Diabetes

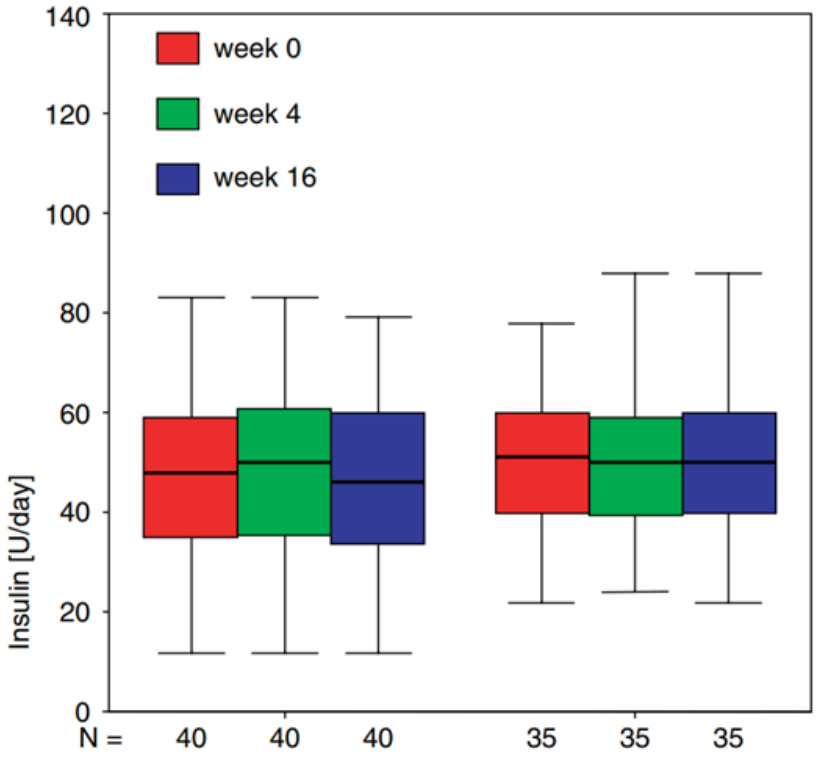
- One prospective observational study on 115 patients randomized patients to receive PERT *vs* placebo
- 42% of patients with DM (type 1 and 2) had GI symptoms had PEI:
  - **PERT did not improve symptoms**, but the **follow-up was short** (3 months)
  - **no** significant **differences** concerning **HbA1c, fasting glucose levels, 2-h pp glucose levels**

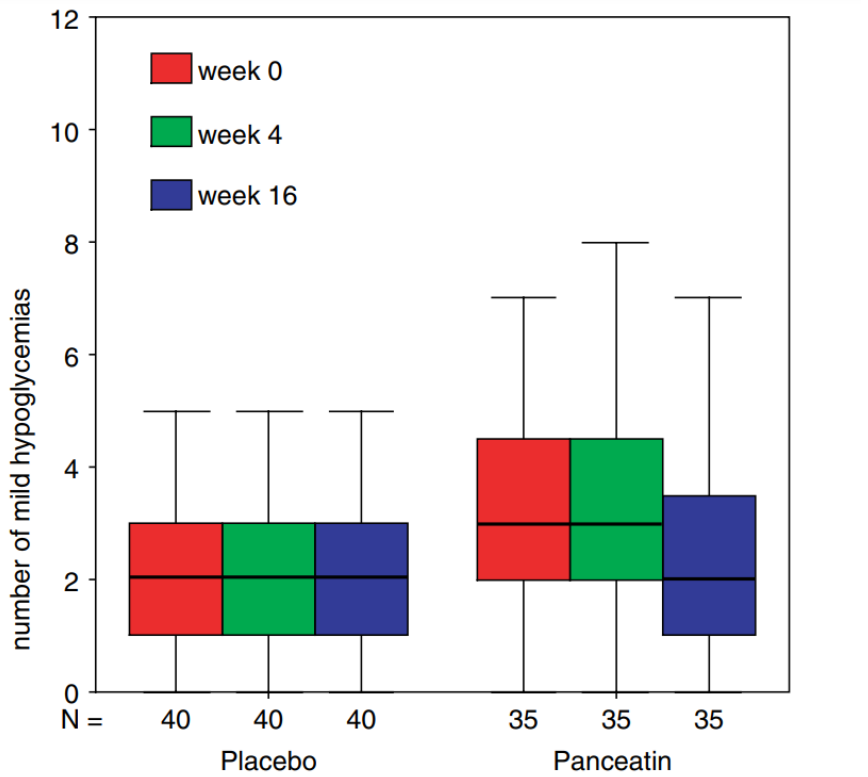


Ewald N et al. Diabetes Metab Res Rev 2007

PEI in Type I Diabetes

The study has shown a possible reduction in mild and moderate hypoglycemia





Ewald N et al. Diabetes Metab Res Rev 2007

PEI in Type II Diabetes

- Data about the prevalence of **PEI** in adult patients with **t2DM** are **numerous**, although more **heterogeneous**

- In a large prospective study on 1231 diabetic patients, the prevalence of PEI was 35% in the 697 patients with t2DM

- **Correlations with disease duration and insulin therapy** in the general population of 1231 subjects were **not confirmed** in the subgroup analysis of type II diabetes patients

- **Notably, this study did not** specifically **exclude** cases with **previous** history of **pancreatic disease**, thus leading to a possible bias

- Subsequent **smaller series**, confirmed a prevalence of PEI of about **30–40%** in type II diabetes

Piciucchi M et al. Int J Endocrinol 2015
Hardt P. D. Et al. Pancreatology 2003

PEI in Type II Diabetes

- **Kumar HRP** et al. reported data about the prevalence of PEI in t2DM in a **C-CC s**tudy on **123** patients, 88 diabetic (cases), and 35 were nondiabetic healthy volunteers (control group)

Relationship of various parameters with fecal elastase-1 activity

Parameters/ factors/variables	FE-1 level			Total	*P*
	Normal	Moderate	Severe		
Age					
<30	1 (16.7)	4 (66.6)	1 (16.7)	6 (4.9)	0.5051
31-40	8 (25.0)	18 (56.2)	6 (18.8)	32 (26)	
41-50	14 (34.1)	15 (36.6)	12 (29.3)	41 (33.3)	
51-60	11 (25.0)	18 (40.9)	15 (34.1)	44 (35.8)	
Total	34 (27.6)	55 (44.7)	34 (27.7)	123 (100.1)	
Retinopathy					
Absent	15 (20.8)	39 (54.1)	18 (25.0)	72 (81.8)	0.001
Present	1 (6.2)	3 (18.7)	12 (75.0)	16 (18.1)	
Total	16 (18.2)	42 (47.7)	30 (34.1)	88 (100.0)	
Neuropathy					
Absent	13 (17.1)	39 (51.3)	24 (31.6)	76 (86.3)	0.2
Present	3 (25.0)	3 (25.0)	6 (50.0)	12 (13.7)	
Total	16 (18.2)	42 (47.7)	30 (34.1)	88 (100)	
Peripheral pulses					
Abnormal	2 (10.0)	4 (20.0)	14 (70.0)	20 (22.7)	0.001
Normal	14 (20.6)	38 (55.9)	16 (23.5)	68 (77.3)	
Total	16 (18.2)	42 (47.7)	30 (34.1)	88 (100.0)	

FE: Fecal elastase-1

Distribution of FE-1 levels between diabetic and non- diabetic controls

Fecal elastase Levels	Non-Diabetic	Diabetic	Total
Normal	18 (51.4)	16 (18.2)	34 (27.6)
Moderate	13 (37.1)	42 (47.7)	55 (44.7)
Severe	4 (11.4)	30 (34.1)	34 (27.6)
Total	35 (100.0)	88 (100)	123

P value<0.0001, chi- square test

Relationship of glycemic parameters with FE-1 activity

Glycemic Parameters	Non-Diabetic			*P*	Diabetic			*P*
	Normal	Moderate	Severe		Normal	Moderate	Severe	
FBS	87.1±12.4	83.76±9.2	90.00±6.3	0.53	123.56±29.9	130.9±30.8	174.10±58.2	0.001
PPBS	125.1±15.4	122.6±16.2	120.2±25.8	0.84	146.31±55.6	185.1±65.2	226.20±51.4	0.012
HbA1C	5.05±0.79	5.3±0.71	5.4±0.51	0.84	8.1±1.64	8.3±1.5	10.1±1.47	0.001

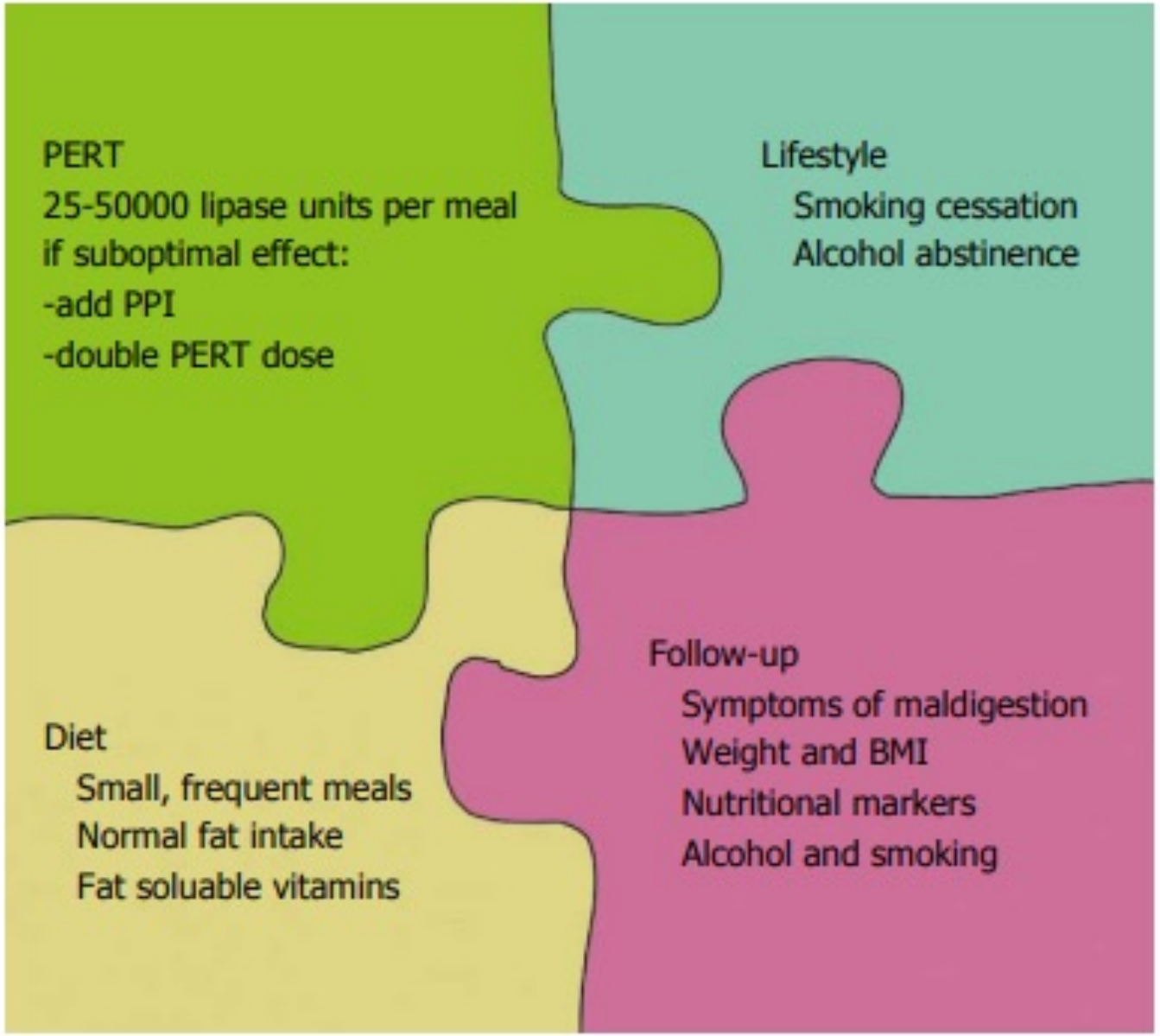
Prasanna Kumar HR et al. Indian J Endocrinol Metab. 2018

PEI in Type II Diabetes

- **Physio-pathological mechanisms** involved in PEI occurrence in type II diabetes seems to be **similar** to that reported above for **type I diabetes**

- In particular, in these subjects, without autoimmune damage and insulin deficiency, autonomic neuropathy and microvascular damage may play a key role in inducing pancreatic atrophy and fibrosis.

Treatment



B. Lindkvist WJG 2013
Löhr M. et al UEG Journal 2018

Is there any interaction between exocrine and endocrine pancreas?

Conclusions

- **Yes!!! There is an interaction between the exocrine and endocrine pancreas**

- The interactions between the endocrine and exocrine pancreatic function is **poorly investigated and understood**

- **Most studies** on PEI in both type I and type II carry **several limitations**:
  - "**Cross-sectional**" design
  - Evaluation of the **prevalence** and **NOT** its **incidence** over time

Conclusions

- **Fecal elastase** measurement is also **highly variable**

- Impaired reliability due to the **dilution of elastase** enzyme in stools **in cases diarrhea,** often present in diabetic subjects because:
  - Bacterial overgrowth
  - Medications
  - Diabetes-induced vascular or neuropathic complications

Conclusions

- The reported prevalence of PEI observed in **type I (25–74%)** and **type II (28–54%)** diabetes

- Long duration of disease
- High insulin requirement
- Poor glycemic control

- In **type I diabetes**, the primary reduction of insulin levels results in a decreased **trophic action** on the exocrine cells

- In **type II diabetes:**
  - a **more severe** form
  - **autonomic neuropathy**
  - **microvascular damage**,
  - **Fibrosis and atrophy**
  - **Loss of the islet-acinar-ductal axis**

THANKS FOR THE ATTENTION