ECHO Diabetes

Pancreatogenic Diabetes

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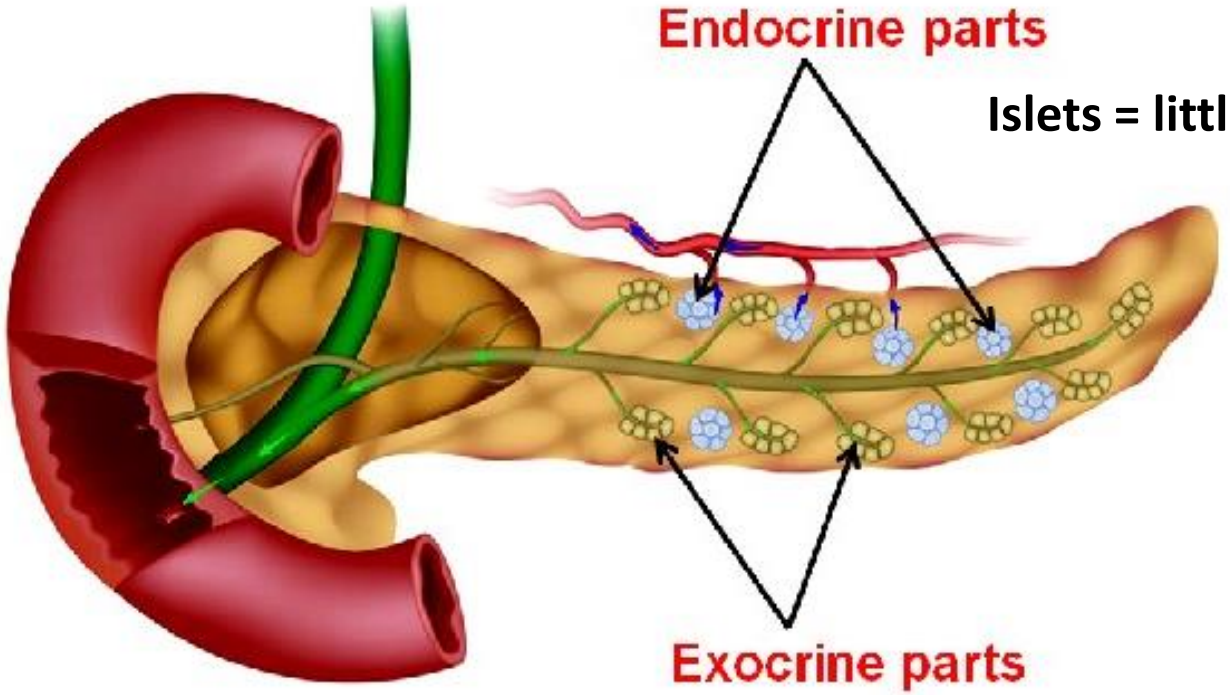
Case -

- 37 yo male from local homeless shelter in isolation at hotel for COVID-19
  - History of mental health issues & diabetes on MDI (basal-bolus insulin)
  - History of youth onset alcohol use disorder
  - History of alcoholic chronic pancreatitis since ~ age 20
  - Onset of diabetes ~ age 27

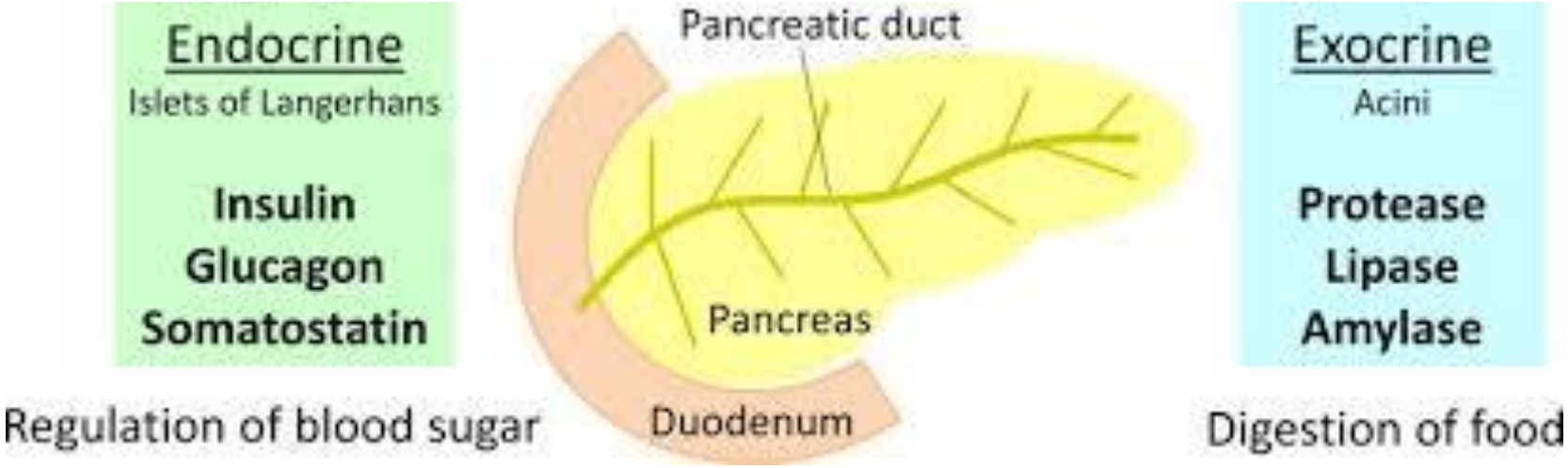
  - What do you need to know to help manage Pancreatogenic Diabetes?

What do you know about Pancreatogenic diabetes?

- When to consider Pancreatogenic diabetes instead of or in addition to type 1 or type 2 diabetes
- How is Pancreatogenic diabetes unique
- Are patients with Pancreatogenic diabetes at risk for the same diabetes complications as type 1 and type 2 diabetes
- What additional factors/risks need to be considered when caring for a patient with Pancreatogenic diabetes

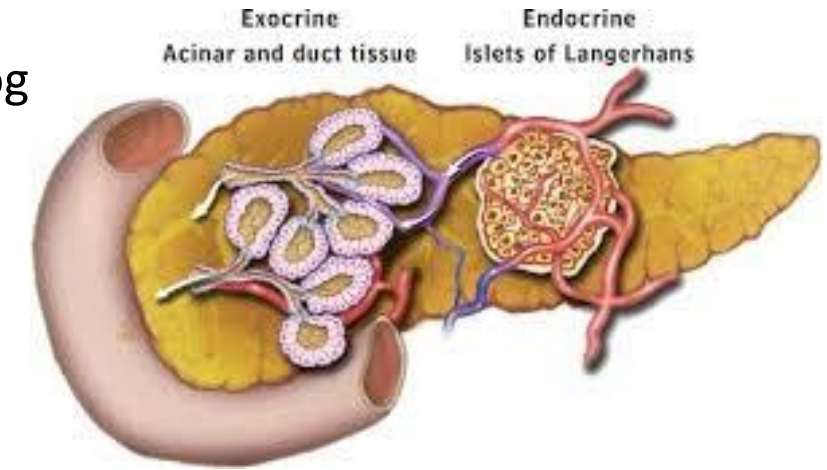


Islets = little islands (2% of pancreatic volume)
Very vascular



Pancreatogenic diabetes

- classified as type 3c diabetes mellitus (T3cDM)
  - refers to diabetes due to ***impairment in pancreatic endocrine function*** related to ***pancreatic exocrine damage*** due to
    - acute, relapsing and chronic pancreatitis (of any etiolog
    - cystic fibrosis
    - hemochromatosis
    - pancreatic cancer
    - pancreatectomy
    - rare causes
      - e.g. neonatal diabetes due to pancreatic agenesis



  - pathogenesis of T3cDM is ultimately due to ***decreased insulin secretion*** caused by both a *reduction in the number of islets and their functional capacity from* ***extensive fibrosis and sclerosis*** *(or resection)*
    - The **pancreatic islets** are distributed throughout the exocrine tissue and receive decreased blood flow with eventual ***ischemic atrophy*** (blood supply cut off by scar tissue build up in the pancreas → islets shrivel up and/or die)

Pancreatogenic diabetes or type 3c diabetes mellitus

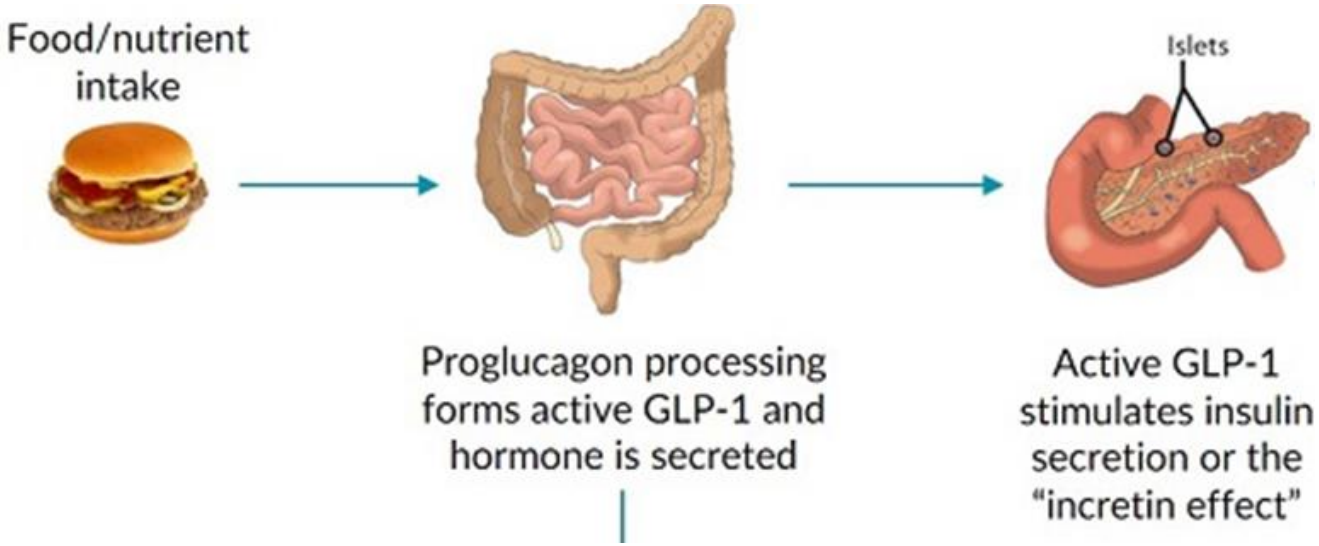
- 5%-10% among all diabetic subjects in Western populations. (more than T1DM)
  - In ~ 80% of cases the underlying disease is ***chronic pancreatitis***
    - Up to 90% of patients with chronic pancreatitis develop diabetes
  - Often misdiagnosed as T2DM or T1DM
  - ***Acute pancreatitis*** - recent studies have shown that prediabetes and diabetes mellitus (DM) occur following the first attack of AP in up to 40% patients and increase over 5 years (along with exocrine pancreatic insufficiency)

pancreatogenic diabetes or type 3c diabetes mellitus

- the endocrinopathy in type 3c is very complex
  - **Destruction of islet cells** by pancreatic inflammation
    - **Loss of *all* islet cells** - Beta cells as well as glucagon secreting alpha-cells and pancreatic polypeptide secreting-cells (in contrast to autoimmune mediated destruction of *only beta-cells* in T1DM)
  - **Nutrient maldigestion** *(exocrine pancreatic insufficiency - EPI)* leads to an ***impaired incretin secretion*** and therefore to a diminished insulin release of the remaining beta-cells
    - ***Maldigestion*** (even without overt malabsorption) can lead to qualitative ***malnutrition***
    - ***Treating exocrine pancreatic insufficiency*** is key feature of medical therapy
      - preventing or treating a lack of fat-soluble vitamins (***especially vitamin D***)
      - restoring impaired fat hydrolysis and ***incretin secretion***

Entero-Insular Axis

- The incretin system plays a crucial role in the metabolic control of type 3c diabetes mellitus.
  - The regulation of **Beta cell mass and physiological incretin secretion** are directly **dependent on normal *exocrine* pancreatic function** and fat hydrolysis
  - Chronic pancreatitis and exocrine dysfunction have been associated with **a *functional impairment of the incretin system.***
  - **Impaired GLP-1 secretion can by normalized by *pancreatic enzyme supplementation***

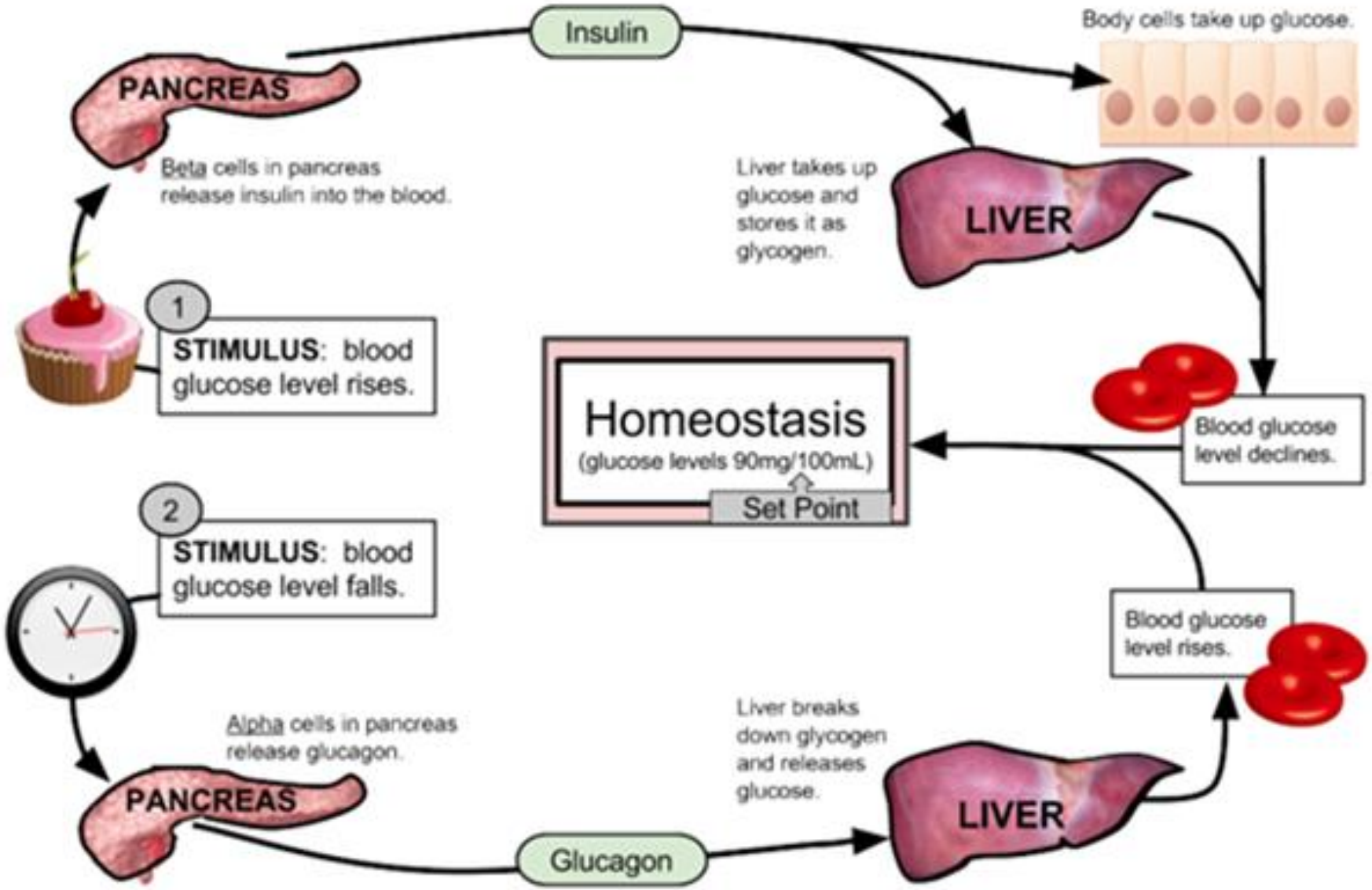


GLP-1 assists Beta-cell

- Insulin secretion based on glucose level
- Survival & growth

Type 3c (Pancreatogenic) diabetes

- Early in the disease - **mild hyperglycemia** - periods of glucose intolerance may *only be evident during stress, illness or high dose glucocorticoid* treatment.
- Later - *progression to "**brittle" diabetes** characterized by **marked glycemic lability** and **frequent hypoglycemia***
  - due to loss of *not only islet β-cell secretion of insulin but also counterregulatory glucagon secretion from islet α-cells* such that **replacement doses of insulin *unpredictably* predispose to hypoglycemia -** blood glucose control may be unstable due to
    - loss of glucagon response to hypoglycemia
    - carbohydrate malabsorption and/or
    - inconsistent eating patterns due to concomitant pain and/or nausea or chronic alcohol abuse
- Unlike T1DM, the β-cell deficit is seldom absolute, and so these patients ***rarely present with diabetic ketoacidosis***


Insulin
PANCREAS
Beta cells in pancreas release insulin into the blood.
Body cells take up glucose.
Liver takes up glucose and stores it as glycogen.
LIVER
1
STIMULUS: blood glucose level rises.
Homeostasis
(glucose levels 90mg/100mL)
Set Point
Blood glucose level declines.
2
STIMULUS: blood glucose level falls.
Blood glucose level rises.
Alpha cells in pancreas release glucagon.
Liver breaks down glycogen and releases glucose.
PANCREAS
LIVER
Glucagon

Long-term Diabetes Risks

- Patients with T3cDM appear to share a **similar risk for the micro- and macro-vascular complications** of diabetes as seen in T1DM and T2DM
  - Patients should be monitored for the development of retinopathy, nephropathy, neuropathy, and follow the same cardiovascular disease risk reduction guidelines as for patients with T1DM and T2DM
- Higher risk of **pancreatic cancer** with both diabetes and chronic pancreatitis
  - Other risk factors
    - Smoking cigarettes
    - Obesity
    - Cirrhosis of liver
  - On the other hand, ***new-onset diabetes may indicate subclinical pancreatic cancer***, especially if associated weight loss – uncertainty regarding screening

Treatment of type 3c diabetes

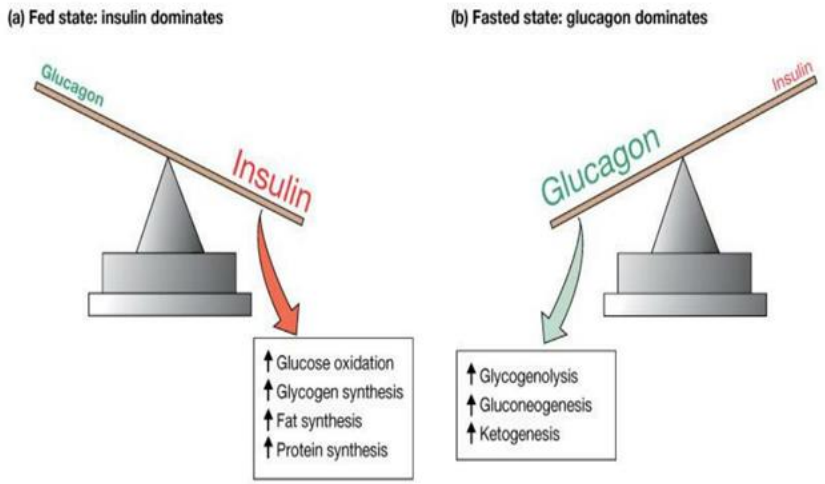
- As in other diabetes types, initial treatment should include all efforts to *correct lifestyle factors* which
  - contribute to hyperglycemia
  - contribute to the risk of pancreatic malignancy (*e.g.*, ***abstinence from alcohol and smoking cessation***, weight loss in overweight subjects, physical exercise and dietary modifications (SSBs & red or processed meat))
- Pharmacologic agents
  - **metformin** is first-line oral therapy for T2DM
    - many type 3c diabetes patients are initially treated with metformin if hyperglycemia is mild
    - Often not be tolerated by patients with chronic pancreatitis due to side effects (nausea, abdominal complaints, diarrhea and weight reduction)
    - **metformin therapy reduces the risk of pancreatic cancer by as much as 70%,** (***chronic pancreatitis and diabetes mellitus are both well accepted risk factors for the development of pancreatic cancer***)

Treatment of type 3c diabetes

- Pharmacologic agents
  - **Incretin based therapies** - use should best be ***avoided*** at present time
    - GLP-1 receptor analogues, **DPP-4-inhibitors -** possible association with a higher risk of pancreatitis
    - high frequency of prominent gastrointestinal side effects (e.g., nausea, delayed gastric emptying, weight loss)
    - A better and safer way to **positively influence the incretin system** might be **supplementation with pancreatic enzymes**
  - **Insulin secretagogues** (sulfonylurea and glinides) may be considered with ***caution*** regarding high risk of hypoglycemia (& common associated liver disease) – possible use in early T3c DM
  - **TZDs** should be ***avoided*** due to prominent side effects (e.g., bone fractures, fluid retention) (osteoporosis is common with chronic pancreatitis)

Treatment of type 3c diabetes

- Pharmacologic agents
  - Chronic pancreatitis is a progressive disorder -many patients will eventually require **insulin therapy**
    - Use general insulin dosing guidelines as for type 1 diabetes mellitus.
    - In patients with severe malnutrition insulin therapy is commonly used as a therapy of first choice due to the desired anabolic effects of insulin
    - Insulin pump therapy may be considered for patients who experience the brittle form of diabetes mellitus (Very challenging due to lack of glucagon and frequent hypoglycemia)



Distinguishing type 3c diabetes from other types

- It is not always easy to diagnose and classify a patient with type 3c diabetes mellitus correctly –
  - can be misclassified as or combined with either type 1 or type 2 diabetes
    - Patients with diabetes mellitus are at a higher risk for developing acute and/or chronic pancreatitis
      - Alcohol-induced, gallstone, hypertriglyceridemia, familial-genetic, autoimmune, medications, anatomic, other
    - Patients with previous episodes of pancreatitis may also develop type 1 or type 2 diabetes independently of their exocrine pancreatic disease

- Criteria for diagnosing type 3c diabetes mellitus
  - the presence of pancreatic exocrine insufficiency (according to monoclonal fecal elastase 1 test or direct function tests),
  - evidence of pathological pancreatic imaging (by endoscopic ultrasound, MRI or CT)
  - the absence of type 1 diabetes mellitus (T1DM)-associated autoantibodies

Distinguishing type 3c diabetes from other types

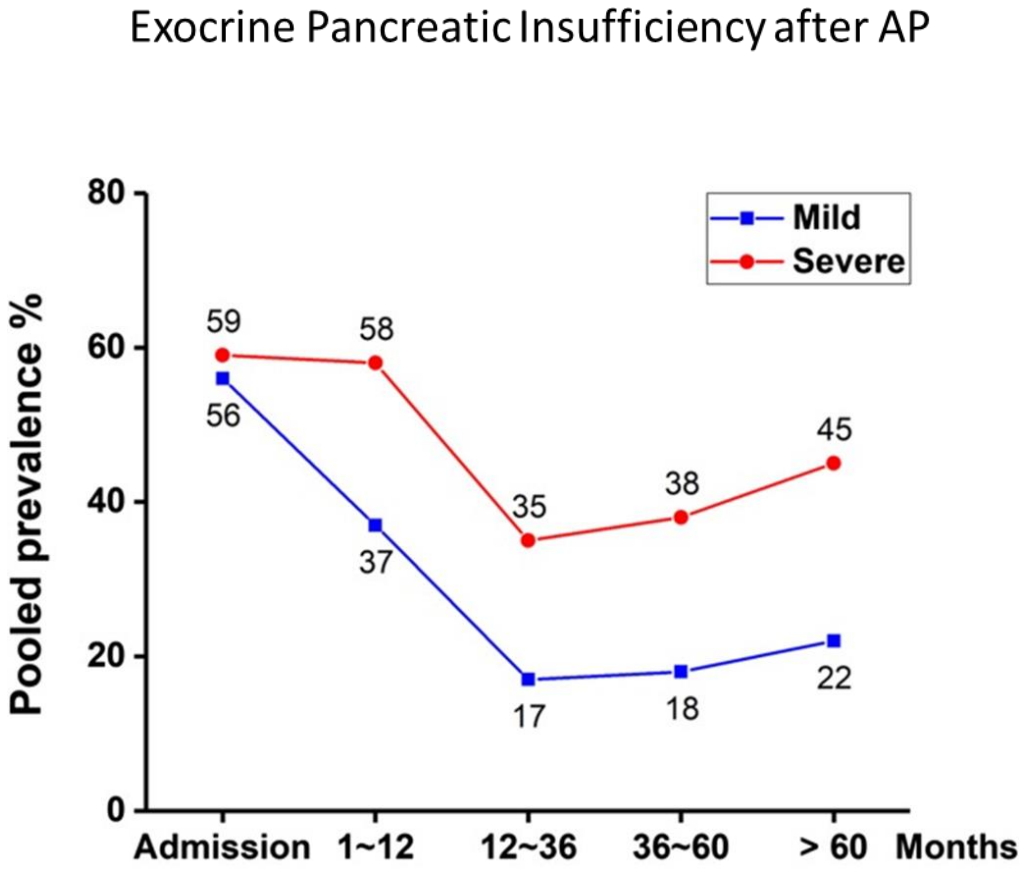
- Any patient with chronic pancreatitis should be monitored for the development of type 3c diabetes –
  - higher risk with
    - long-standing duration of the disease
    - prior partial pancreatectomy (especially resection of tail of pancreas)
    - early onset of calcific disease
  - The initial evaluation of patients with chronic pancreatitis should include fasting glucose and HbA1c repeated at least annually. **

** ***malnutrition from malabsorption*** from EPI can ***mask T3c diabetes*** (normal BG/A1c)(not absorbing many nutrients so doesn't require much insulin) –

then following Pancreatic Enzyme Replacement Therapy (PERT) (and improved nutrient absorption) hyperglycemia can (rapidly) appear (now insufficient insulin to cover the nutrients due to islet destruction by fibrosis)

Acute Pancreatitis – residual effects

- Clinical resolution of acute pancreatitis as judged by standard clinical measures may not detect some **residual damage to beta-cell mass & exocrine function**
- Rather, this may manifest later in life with the coexistence of other diabetes risk factors.
  - The average age of diabetes diagnosis was younger by 4 years among those with a history of acute pancreatitis (**reduced beta cell reserve)**
  - Also nutritional status compromise from EPI
- This may suggest a **lower capacity** to overcome the individual's underlying degree of insulin resistance and that a **shorter duration is sufficient to induce beta-cell failure and hyperglycemia**
- Need to think of, do assessment & monitoring



Clinical Pearls

- type 3c diabetes mellitus due to chronic pancreatitis might be referred to as a ***premalignant condition*** since both diseases are well accepted risk factors for the development of pancreatic cancer
  - Postpancreatitis DM **>** DM-Pancreatitis **>** Pancreatitis **>** T2DM
  - Also, 2x increased risk of pancreatic cancer after bout of *acute pancreatitis*
- the *progression* to endocrine failure appears accelerated with *alcohol*-associated pancreatitis (both chronic & acute)
- *Combined effects of cirrhosis* (ALD and/or NAFLD) not uncommon
  - Especially if alcohol-associated chronic pancreatitis, obesity and/ or hypertriglyceridemia
  - Hepatogenic diabetes + Pancreatogenic diabetes

What do you know about Pancreatogenic diabetes?

- When to consider Pancreatogenic diabetes instead of or in addition to type 1 or type 2 diabetes
  - History of chronic pancreatitis, exocrine pancreatic insufficiency or even a bout of acute pancreatitis (also pancreatic cancer, partial pancreatectomy, cystic fibrosis, etc.)
    - New onset diabetes with weight loss – as indicator of pancreatic cancer
- How is Pancreatogenic diabetes unique
  - Damage to **all** the cells in the islet, not just beta cells – wide swings in glucose ("brittle"), high risk of hypoglycemia, lower risk of DKA -
  - Also impaired Incretin system due to maldigestion

What do you know about Pancreatogenic diabetes?

- Are patients with Pancreatogenic diabetes at risk for the same diabetes complications –
  - yes – micro-vascular complications & macro-vascular disease
- What additional factors/risks need to be considered when caring for a patient with Pancreatogenic diabetes
  - Maldigestion/malabsorption/malnutrition – need for digestive enzyme replacement
  - Higher risk of hypoglycemia
  - High risk of Pancreatic cancer

exocrine pancreatic insufficiency

- In patients with type 3c diabetes *exocrine* pancreatic insufficiency is nearly *ubiquitous*
- Many patients with chronic pancreatitis manifest some degree of fat malabsorption, *regardless of the presence of symptoms.*
  - overt steatorrhea is usually not observed until over 90% of exocrine pancreatic function is lost
  - relevant ***maldigestion***, which is present in the majority of patients with chronic pancreatitis, may cause *qualitative malnutrition*. This is especially important concerning the absorption of fat-soluble vitamins (A, D, E and K).
  - significant correlation of exocrine pancreatic insufficiency and *osteoporosis* and/or alterations in bone metabolism can be observed

Diagnosing Exocrine Pancreatic Insufficiency

- Either direct pancreatic function tests, including the Lundh meal test, secretin-caerulein (or pancreozymin) test (SCT), amino acid consumption test (AACT), fecal chymotrypsin test - or
- Fecal elastase-1 (FE-1) test* - or
- Indirect tests including the triolein breath test, serum fluorescein-dilaurate test, serum pancreolauryl test, urinary pancreolauryl test, urinary N-benzoyl-l-tyrosyl-P-aminobenzoic acid (NBP-PABA) test, urinary d-xylose excretion test and fecal fat excretion (FFE) test.

*An FE-1 of 100–200 µg/g was defined as mild to moderate EPI and < 100 µg/g as severe EPI.

*While the FE-1 test is easy to perform and cost-effective for severe cases(sensitivity and specificity > 90%), the sensitivity for mild/moderately severe cases is low (~60%) and fails to identify many patients with EPI.

Pancreatogenic diabetes – diabetes (damage to endocrine pancreas) caused by disease of exocrine pancreas …

Can Diabetes (disease of endocrine pancreas) cause damage to exocrine pancreas

Exocrine Pancreas Dysfunction & TID

Endocr. Pract. 2020;26(No. 12), 1505-1513

Foster, T., et al (Schatz, Desmond)

- "Exocrine pancreas abnormalities often occur in T1D. Whether exocrine dysfunction occurs simultaneously with Beta Cell destruction, as a result of Beta Cell loss, or as a combination of both remains to be definitively answered.
- In TID with gastrointestinal complaints, PEI should be evaluated, usually via fecal elastase measurements [need to test for Celiac disease and other causes of GI symptoms first].
- PERT is recommended for T1D patients with symptoms and laboratory evidence of PEI [relief of GI symptoms, improved quality of life, better glycemic control and optimal nutrition]."

If screen / look for pancreatic cancer, which method to use?

- Endoscopic US (EUS) (highest yield of high-risk lesions, especially solid)
- MRI (complimentary with EUS, better than EUS for cystic lesions)

- CT scan - lower yield (11%) + higher load of ionizing radiation

Diabetes Medication in COVID-19