Beyond Type 1 & 2 Diabetes: Diabetes of the Exocrine Pancreas (DEP)

Pancreatogenic (type 3c) Diabetes

August 19, 2026

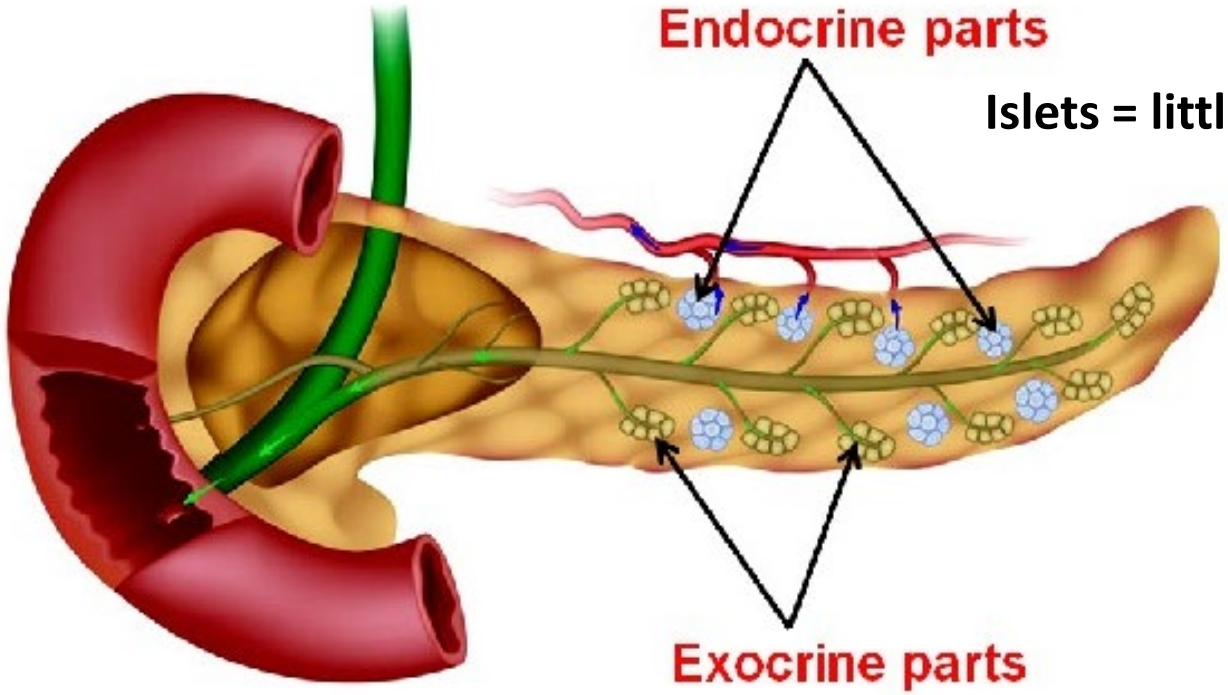
Advancements in Diabetes Webinar

Carol Greenlee MD MACP

Case – William

- 47-year-old male diagnosed with T2D at age 42
- Frustrated & concerned regarding risk of complications due to persistently elevated A1c of 10% despite taking multiple diabetes meds faithfully including:
  - metformin (1 g twice per day)
  - empagliflozin (25 mg once per day)
  - sitagliptin (100 mg once per day)
- C/o erratic BG swings, also c/o loose bowels (blames on metformin)
- PMH/SH: past binge alcohol use w/ a couple episodes of acute pancreatitis (AP) – no alcohol since late 20s, no AP since dc alcohol / occ vapes
- Family Hx: no known IBD or colon cancer, + diabetes in mother & mGM
- BMI 24, BP 118/68, P 88

- What next steps would you consider?

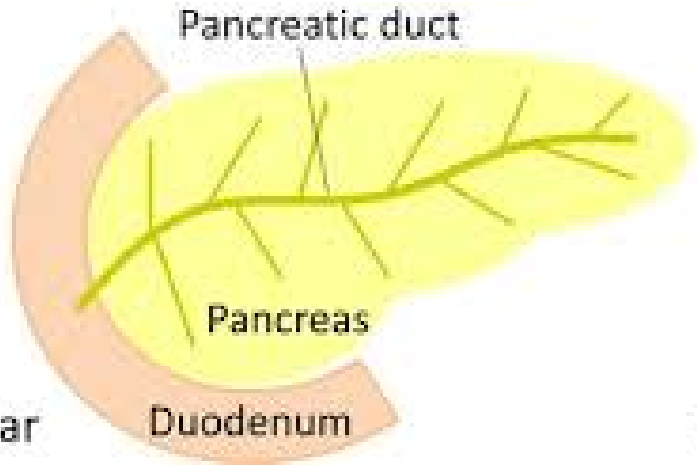


Islets = little islands (2% of pancreatic volume)
Very vascular

Endocrine
Islets of Langerhans

Insulin
Glucagon
Somatostatin

Regulation of blood sugar



Exocrine
Acini

Protease
Lipase
Amylase

Digestion of food

Pancreatic Diabetes or Diabetes of the Exocrine Pancreas (DEP)

- A type of diabetes that develops because of diseases of the exocrine pancreas or damage to the pancreas
  - Also referred to as Pancreatogenic or Type 3c Diabetes
  - Difficult to determine prevalence but likely up to 9-10% of diabetes cases
    - Some analyzes indicate Pancreatic Diabetes is more common than T1D
    - Often misdiagnosed as T2D, occasionally as T1D
  - Traditionally attributed to a variety of exocrine pancreatic diseases with various causes of hyperglycemia - most commonly:
    - Acute or Chronic pancreatitis (inflammation of the pancreas) - ~80%
    - Pancreatic cancer (pancreatic ductal adenocarcinoma) - ~ 8%
    - Cystic fibrosis ~4%
    - Pancreatic surgery
    - Trauma
    - Hemochromatosis

Table 1 Classification of diabetes of the exocrine pancreas.

General inclusions

Post-pancreatitis diabetes mellitus (PPDM)

Post-acute pancreatitis diabetes mellitus (PPDM-A)

Post-chronic pancreatitis diabetes mellitus (PPDM-C)

Pancreatic cancer-related diabetes (PCRD)

Cystic fibrosis-related diabetes (CFRD)

General exclusions

Stress hyperglycemia

Autoimmune diabetes with first recognition after an attack of pancreatitis

Diabetes with first recognition during pregnancy after an attack of pancreatitis

Maturity-onset diabetes of the young

Drug-induced diabetes

Diabetes after pancreatic surgery

Diabetes after blunt pancreatic (abdominal) trauma

Diabetes secondary to pancreatic agenesis/hypoplasia

Diabetes secondary to hereditary hemochromatosis

Special entities

Antecedent diabetes mellitus in pancreatitis (ADMP)

New-onset diabetes in pre-symptomatic pancreatic ductal adenocarcinoma (NOD-PDAC)

Recently proposed renaming & classification

For **Diabetes of the Exocrine Pancreas (DEP)**

Eur J Endocrinol. 2021 Apr;184(4):R151-R163. DIAGNOSIS OF ENDOCRINE DISEASE: Diagnosing and classifying diabetes in diseases of the exocrine pancreas

2026 ADA Standards of Care - Classification

- Recommendation: 2.5 Classify people with hyperglycemia into appropriate diagnostic categories to aid in personalized management. E

- Diabetes is classified conventionally into several clinical categories
  - 1. Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes in adults)
  - 2. Type 2 diabetes (due to a nonautoimmune progressive loss of adequate β-cell insulin secretion, frequently on the background of insulin resistance)
  - **3. Specific types of diabetes due to other causes**, e.g., monogenic diabetes syndromes, *diseases of the exocrine pancreas*, and drug- or chemical-induced diabetes
  - 4. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation or other types of diabetes occurring throughout pregnancy, such as type 1 diabetes)

Table 1 Classification of diabetes of the exocrine pancreas.

General inclusions

Post-pancreatitis diabetes mellitus (PPDM)

Post-acute pancreatitis diabetes mellitus (PPDM-A)

Post-chronic pancreatitis diabetes mellitus (PPDM-C)

Pancreatic cancer-related diabetes (PCRD)

Cystic fibrosis-related diabetes (CFRD)

General exclusions

Stress hyperglycemia

Autoimmune diabetes with first recognition after an attack of pancreatitis

Diabetes with first recognition during pregnancy after an attack of pancreatitis

Maturity-onset diabetes of the young

Drug-induced diabetes

Diabetes after pancreatic surgery

Diabetes after blunt pancreatic (abdominal) trauma

Diabetes secondary to pancreatic agenesis/hypoplasia

Diabetes secondary to hereditary hemochromatosis

Special entities

Antecedent diabetes mellitus in pancreatitis (ADMP)

New-onset diabetes in pre-symptomatic pancreatic ductal adenocarcinoma (NOD-PDAC)

Recently proposed renaming & classification

For **Diabetes of the Exocrine Pancreas (DEP)**

Eur J Endocrinol. 2021 Apr;184(4):R151-R163. DIAGNOSIS OF ENDOCRINE DISEASE: Diagnosing and classifying diabetes in diseases of the exocrine pancreas

Chronic Pancreatitis

- "Chronic pancreatitis is a progressive disorder of the pancreas due to continuous or episodic *inflammation* resulting in *destruction* of pancreatic secretory cells and leading to progressive failure of exocrine and endocrine pancreatic function".
  - Early stages of chronic pancreatitis appear as recurrent, acute pancreatitis, typically presenting with
    - severe epigastric or periumbilical *pain* that may last for days and radiate to the back
    - nausea & vomiting and abdominal distention
  - Inflammation & other processes lead to pancreatic parenchymal (functional tissue) fibrosis and damage → loss of the functional tissue of the pancreas
  - Patients with chronic pancreatitis may eventually develop the *clinical triad* of
    - abdominal pain (which occurs in 85%-97% of patients with chronic pancreatitis)
    - exocrine pancreatic insufficiency
    - pancreatic endocrine insufficiency

Main Causes of Chronic Pancreatitis

- Alcohol consumption is the leading cause of chronic pancreatitis in Europe, the United States, Brazil, Mexico, South Africa, Australia, and South Korea.
  - Alcohol consumption is reported to be the cause of chronic pancreatitis in almost 50% of cases in the United States
- Ductal injury or obstruction – e.g., gallstone pancreatis
- Autoimmune (2 types)
- Hereditary (Familial) - Hereditary chronic pancreatitis is caused by mutation of the cationic trypsinogen gene (PRSS1), which is autosomal dominant with an 80% penetrance (additional genes & mutations being identified)
- Metabolic (hypercalcemia, hypertriglyceridemia)
- Infections (viral, bacterial, parasitic)
- Medications (antivirals/antibiotics, chemotherapy, immunosuppressive, diabetes & BP meds, etc.)

(Susceptibility genes & their interactions with environmental and metabolic risk factors influence individual risk for developing chronic pancreatitis)

Exocrine Pancreatic Insufficiency (EPI)

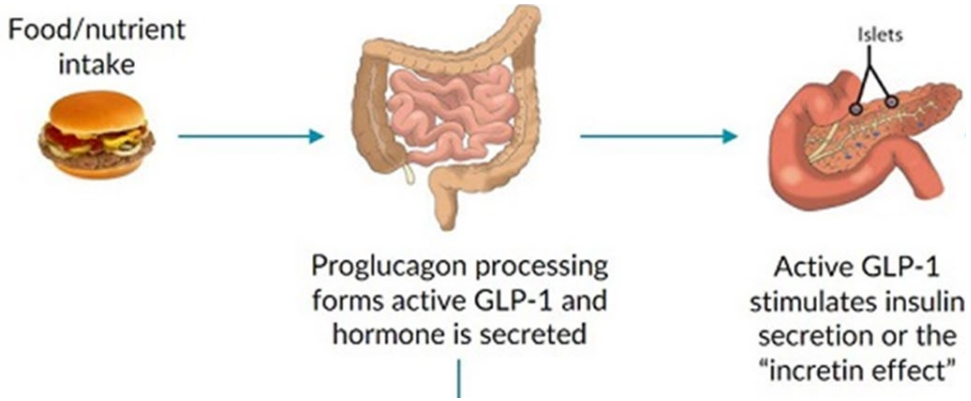
- Exocrine pancreatic insufficiency usually manifests as steatorrhea (an excess of fat in the feces)
  - *Overt steatorrhea* is expected if pancreatic lipase secretion is < 10% of normal
    - Characterized by foul-smelling, fatty/greasy, bulky stools that are difficult to flush away, especially after fatty meals (steatorrhea)
    - More frequent bowel movements, increased gas & bloating may also occur
    - Opioid-associated constipation can confuse the presentation
- Severe cases of exocrine pancreatic insufficiency may result in weight loss, malnutrition, or fat-soluble vitamin deficiency –
  - Symptoms of deficiency vary depending on the deficient vitamin:
    - Symptoms of vitamin E deficiency include ataxia and symptoms of peripheral neuropathy.
    - Symptoms of vitamin A deficiency include impaired night vision.
    - Symptoms of vitamin D deficiency include contraction or muscle spasms /osteoporosis /osteomalacia
  - Weight-related signs of malnutrition include either a BMI < 18.5 kg/m2 or unintentional weight loss (> 5% over 3 months or > 10% over any duration)
- Less severe reductions in pancreatic enzymes may lead to GI symptoms without overt steatorrhea & to nutritional deficiencies, especially lipid-soluble vitamin deficiency (often called *Exocrine Pancreatic Dysfunction*)

Testing for Exocrine Pancreatic Insufficiency (EPI)

- **Fecal elastase-1 (FE-1)** test for diagnosis of EPI (also called PEI) - Elastase is an enzyme produced by the pancreas that helps digest proteins.
- Low FE-1 concentrations increases the suspicion of exocrine pancreatic insufficiency. Although there is no universally agreed upon optimal cut-off - Common cutoff values:
  - Moderate PEI: 100–200 mcg/g - Suggests a moderate decrease in pancreatic enzyme production
  - Severe PEI: <100 mcg/g- Indicates a severe reduction in the pancreas's ability to secrete digestive enzymes.
- Concentrations of FE-1 > 500 micrograms/gram may rule out exocrine insufficiency
- The FE-1 test cannot exclude mild-to-moderate exocrine insufficiency (*exocrine dysfunction*)
  - FE-1 testing is only effective in identifying mild EPI in about 50% of cases.
    - Impaired digestion, even in patients with mild or moderate enzyme insufficiency, can lead to a deficiency of micronutrients and fat-soluble vitamins such as D and K with associated clinical implications.
  - Some sources recommend trial on pancreatic enzyme replacement therapy (PERT) for FE-1 results 200 to 500 range to see if symptoms improve but also critical to r/o other conditions such as celiac disease
- FE-1 results combined with “high-probability” conditions, symptoms, fat-soluble vitamin deficiency more accurate than FE-1 alone – *sample solid or semi-solid stool*
- False + test (falsely low FE-1) with liquid stool, diabetic diarrhea, IBD, celiac disease, orlistat, CKD, etc.

Pancreatic Endocrine Insufficiency

- Development of diabetes mellitus in chronic pancreatitis mainly occurs due to the **destruction of islet cells** by pancreatic inflammation.
  - In contrast to the autoimmune mediated destruction of the **beta-cells** in type 1 diabetes mellitus, **glucagon** secreting **alpha-cells** and **pancreatic polypeptide secreting pancreatic polypeptide-cells** are also subject to destruction in chronic pancreatitis leading to a ***complex deranged metabolic situation***
- Additionally, *nutrient maldigestion* leads to an **impaired incretin secretion** and therefore to a diminished insulin release of the remaining beta-cells.

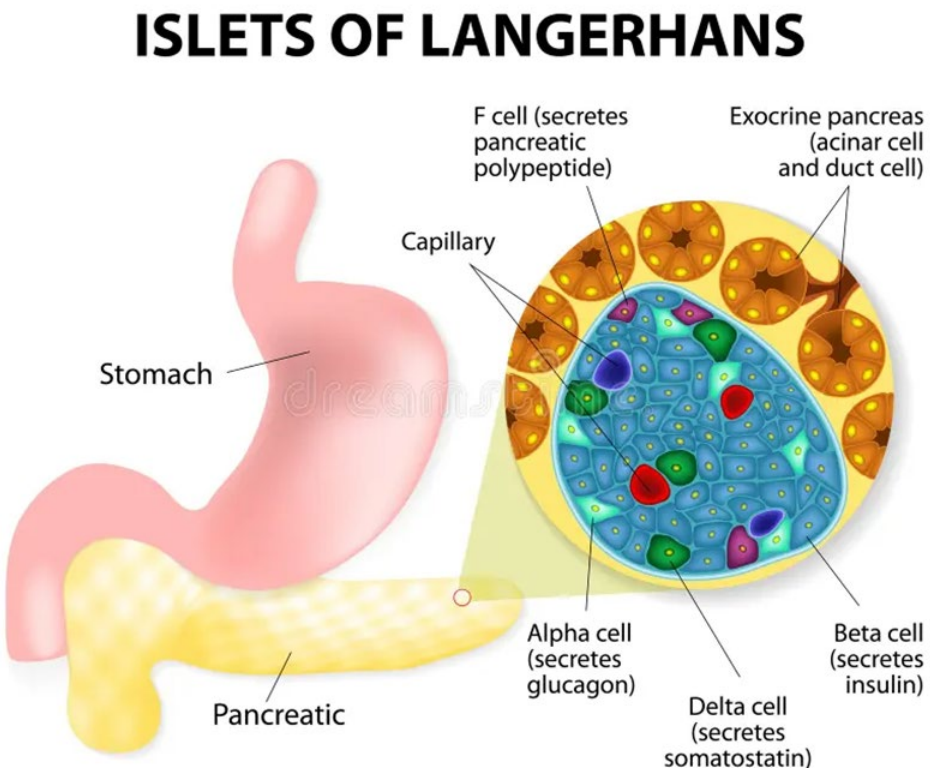


GLP-1 assists Beta-cell

- Insulin secretion based on glucose level
- Survival & growth

Post-pancreatitis Diabetes Mellitus (PPDM)

- Glandular inflammation, chemokines & fibrosis impair and/or destroy the acinar and islet cells
- Loss of acinar function (exocrine insufficiency) affects nutrient absorption & incretin secretion
- Loss of islet function leads to loss of alpha, beta and pancreatic polypeptide cells
  - Loss of glucagon → more hypoglycemia→ erratic glycemia
  - Loss of insulin → hyperglycemia
  - Loss of PPP → hepatic insulin resistance → increased hepatic glucose production



Post-chronic pancreatitis diabetes mellitus (PPDM-C)

- Pancreatic endocrine insufficiency is often asymptomatic, but if present, symptoms can include polyuria, polydipsia, polyphagia, and blurred vision.
  - Any patient with chronic pancreatitis should be monitored for the development of PPDM-c/ type 3c diabetes mellitus.
    - The prevalence of diabetes mellitus among patients with an established diagnosis of chronic pancreatitis is reported to be up to 70%
      - Up to 90% in chronic calcific pancreatitis & 80% in hereditary pancreatitis
    - Increased risk with long-standing duration of the disease, prior partial pancreatectomy (especially distal) and early onset of calcific disease
      - Heavy smoking, male sex, family hx of DEP/type 3c or T2D also increase the risk
  - ADA: Screen for diabetes with **fasting plasma glucose and HbA1c** levels ***annually***, even if there are no clinical symptoms.
    - Malnutrition from malabsorption from EPI can mask PPDM/ type 3c 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

Diagnosing PPDM/type 3c diabetes in a patient with chronic pancreatitis

New-onset Diabetes: Could it be DEP/type 3c Diabetes?

- Even more difficult: determining if a patient first presenting with diabetes or with existing diabetes might have DEP/ type 3c diabetes mellitus:
  - If a patient does not fit into the common presentation and complains about gastrointestinal symptoms the clinician should be aware of the possibility of DEP/type 3c (PPDM) and initiate further diagnostics.
  - There are no universally accepted diagnostic criteria for DEP/ type 3c diabetes. Conceptually, the diagnosis can be made in patients who meet the three following criteria:
    - those who fulfill the diagnostic criteria for diabetes
    - those who have a disease of the exocrine pancreas
    - those whose diabetes is reasonably certain to be secondary to their exocrine pancreatic disease.

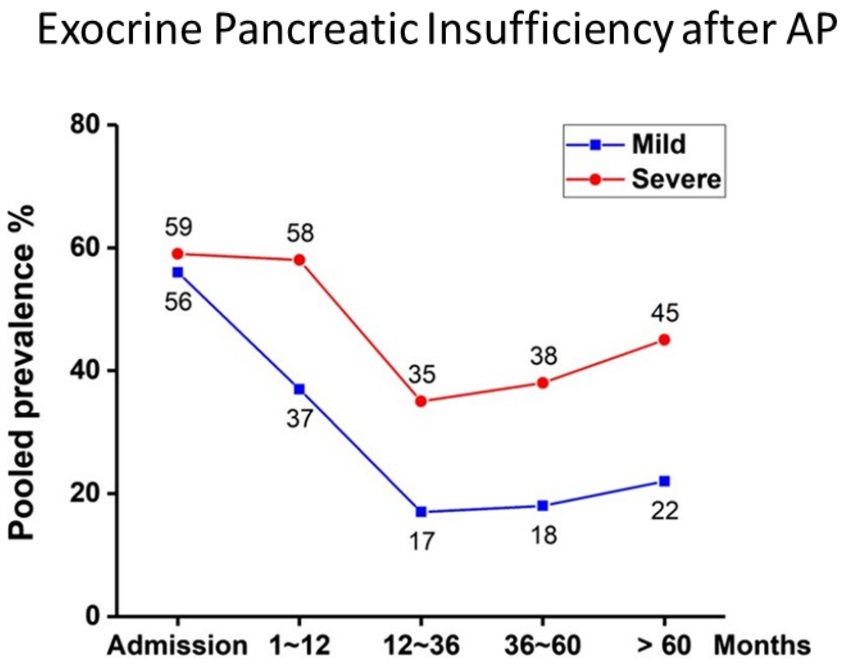
Could It Be DEP/type 3c diabetes?

- It is not always easy to diagnose and classify a patient with DEP/ type 3c diabetes mellitus correctly.
  - Long-standing type 1 and type 2 diabetes mellitus patients are associated with exocrine pancreatic failure.
    - One possible mechanism is impaired entero-pancreatic signaling with reduced secretion of cholecystokinin (CCK) and other hormones that stimulate pancreatic enzyme release - can lead to transient pancreatic exocrine insufficiency/dysfunction.
  - Patients with diabetes mellitus are at a higher risk for developing acute and/or chronic pancreatitis.
    - There are data suggesting diabetes, especially T1D, leads to structural changes in the pancreas potentially predisposing to pancreatitis
    - Hyperglycemic crisis and/or marked hypertriglyceridemia can be associated with pancreatitis
  - Patients with previous episodes of pancreatitis may also develop type 1 or type 2 diabetes independently of their exocrine pancreatic disease.

And it is not just *Chronic* Pancreatitis …

- ***Acute* pancreatitis** - studies have shown that prediabetes and diabetes mellitus (DM) occur following the first attack of AP in ~15% at 1 year, up to 40% of patients over 5 years & beyond (along with exocrine pancreatic insufficiency)
  - Potential residual damage to beta-cell mass & exocrine function

- Some patients have an underlying predisposition toward type 2 diabetes, in whom an additional pancreatic insult becomes diabetogenic
  - Can also manifest later in life with the coexistence of other diabetes risk factors.
  - This may suggest a lower capacity (reduced beta cell reserve) to overcome the individual's underlying degree of insulin resistance and that a shorter duration is sufficient to induce beta-cell failure and hyperglycemia
    - Earlier time to diabetes diagnosis
    - Earlier time to insulin therapy
    - Along with EPI & loss of other islet cells



Acute Pancreatitis

- One of the most common GI disorders
- Usually a self-limiting disorder –
  - mortality ranging from 2–30% in case of persistent organ failure and necrotizing pancreatitis
- The three most common causes of AP are:
  - Gallstone
  - Alcohol
  - Hypertriglyceridemia
- Recurrent Acute Pancreatitis (RAP) is defined as two or more separate attacks of AP with complete resolution with more than three months between the attacks
  - Imaging studies show greater loss of pancreatic volume with RAP vs SAP
  - Shown to evolve into CP in 4% to 24% of cases.

Acute Pancreatitis and DEP/type 3c diabetes (PPDM-A)

- Because AP is so common, in many analyzes AP is the most common cause of DEP/type 3 diabetes (Post-pancreatitis DM- Acute [PPDM-A])
- Studies highlight that the time course and natural history of diabetes following AP is not clearly defined - it appears to be on the orders of months to years
  - There is a trend for increasing disease prevalence farther from the index AP episode
  - This suggests that the injury associated with AP may not be entirely self-limiting.
    - The injury may set in motion an *inflammatory process with subsequent fibrosis* leading to endocrine insufficiency (more research needed to further delineate this time course to aid surveillance of patients)
- In many studies risk of PPDM-A was increased by increasing *severity* of the episode of AP and by *recurrent* AP episodes (RAP)
  - Several studies found *alcohol* was associated with greater risk of developing PPDM-A
  - Also, patients who had a higher BMI/obesity, age, glucose, triglycerides and low-density lipoprotein at time of admission were associated with increased risk of DM over a 3-month follow-up period.
    - This highlights other comorbid conditions that may contribute to worsened impaired glucose metabolism after an AP episode.

PPDM-A

- Patients should be screened for diabetes *yearly* following AP episode, with particular attention to those with
  - severe episodes
  - alcoholic pancreatitis
  - Diabetes (T2D) risk factors
  - recurrent episodes (RAP)

- ADA 2025 Standards of Care - Recommendation
  - 2.17 Screen people for diabetes within 3–6 months following an episode of acute pancreatitis and annually thereafter.

- These patients typically
  - require insulin earlier than those with T2DM
  - have difficult-to-manage hypo- and hyperglycemic episodes
  - have decreased risk of diabetic ketoacidosis

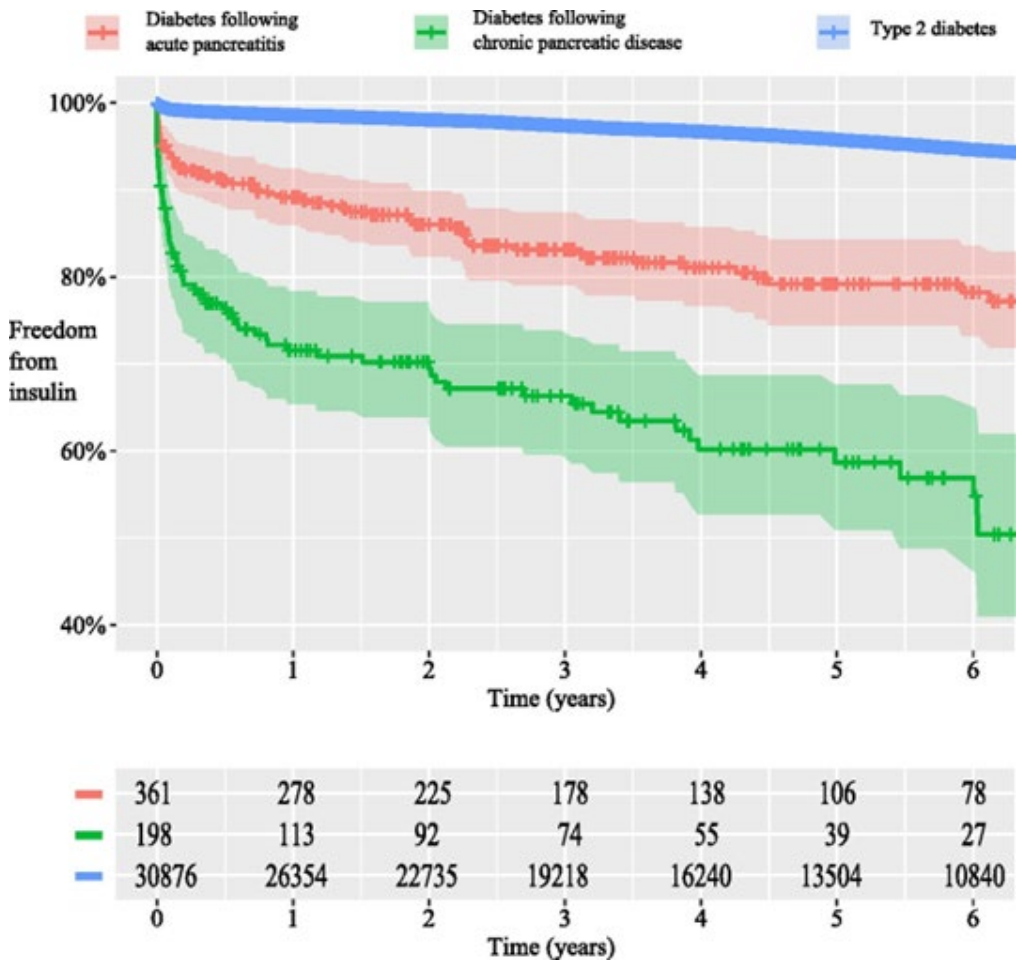
PPDM – Natural History

PPDM has a different natural history to other forms of diabetes;

- Patients are more likely to **require early insulin initiation** compared with those with T2D
  - By 5 years after diagnosis, the group with PPDM was significantly more likely to require insulin (29.6%) compared with T2DM (4.1%)
- PPDM was associated with a 1.7 times increased likelihood of **poor glycemic control** (HbA1c ≥ 7%) at 5 years when compared with T2DM.

Individuals with PPDM are less likely to develop ketoacidosis but should be advised about the symptoms of decompensated hyperglycemia (due to insulinopenia)

Freedom from Insulin Use in T2D, AP, CP



PPDM

- Patients with DEP following pancreatitis (PPDM) have
  - ***Reduced production of insulin*** caused by β-cell dysfunction following pancreatic inflammation or by absolute β-cell loss → **hyperglycemia**
  - ***Loss of pancreatic polypeptide*** which upregulates insulin receptor expression in the liver, and its loss can lead to hepatic insulin resistance & ***increased hepatic glucose production*** → **hyperglycemia**
  - ***Reduced glucagon production*** from pancreatic α-cells, which may explain the episodes of **severe hypoglycemia** that are reported in some patients
  - **Reduced incretin response** due to exocrine pancreatic insufficiency
  - **Nutrient maldigestion/malabsorption** and often unpredictable food intake
- Failure to recognize this altered physiology may result in *suboptimal treatment*.
- The altered physiology also makes insulin therapy challenging – contributing to *poor glycemic control* (twice as likely as T2D)
- Patients with PPDM & insulinopenia could be unfairly ***labeled as poorly compliant*** if they are misclassified as type 2 diabetes and show resistance (poor response) to oral antihyperglycemic agents

PPDM

- In DEP following pancreatitis (PPDM) there is often a *progressive* insulin deficiency, with *mild insulin deficiency* present even before the development of diabetes with more *severe deficiency* developing over time leading to *overt diabetes*
  - Early islet insufficiency might show up only during stress such as an infection or other illness or treatment with glucocorticoids with increase in insulin requirements
  - Endocrine function tends to decline in parallel with exocrine function, with frank diabetes is likely to occur later in the course of the disease
  - Up to 25% of individuals develop a severe form of “brittle diabetes” characterized by rapid fluctuations & wide swings in glucose levels due to
    - the complex deficits in islet hormones
    - impaired incretin secretion
    - maldigestion/malabsorption and/or inconsistent eating patterns due to concomitant pain and/or nausea or chronic alcohol abuse

Complications of PPDM

- Complications include
  - “brittle” diabetes
  - retinopathy, renal dysfunction, and neuropathy, with risks similar to type 1 diabetes
    - The microvascular complications of diabetes mellitus are a *consequence of hyperglycemia* and are reduced by achieving good glycemic control.
    - In patients with DEP, prolonged untreated hyperglycemia results in a similar incidence of microvascular disease as in T1DM
    - Patients with DEP should be under *regular surveillance* for diabetic complications (UACR/eGFR, eye exam, foot exam)
  - Usually not associated with an increased risk of macrovascular complications [thought due to fat malabsorption, however research and longterm studies are lacking and the risks are incompletely understood].

Complications

- Malabsorption secondary to pancreatic exocrine dysfunction is common
  - Pancreatic enzyme and vitamin D replacement is required to prevent *malnutrition* and *osteoporotic bone disease*.
- Maldigestion (even without overt malabsorption) can lead to qualitative malnutrition
  - This is especially important concerning the absorption of fat-soluble vitamins (A, D, E and K).
  - Studies show a vitamin D deficiency in > 90% of patients with chronic pancreatitis
- There is a significant correlation of exocrine pancreatic insufficiency and osteoporosis and/or alterations in bone metabolism
- DEP/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*
  - Post-pancreatitis DM (PPDM) > DM-Pancreatitis > Pancreatitis > T2DM
  - Also, 2x increased risk of pancreatic cancer after bout of acute pancreatitis

Management - Lifestyle

- Initial treatment should include all efforts to correct **lifestyle factors** which contribute to *hyperglycemia* and the *risk of pancreatic malignancy* (e.g., abstinence from alcohol and smoking cessation, weight loss in overweight subjects, physical exercise and dietary modifications).

- Attention to nutritional status – avoid or correct malnutrition
  - Dietary considerations (from the United European GI Guidelines):
    - Individualized dietary counseling from an experienced dietician can improve nutritional status
    - Well-nourished patients should follow normal healthy eating advice
      - Normal food supplemented with pancreatic enzymes is adequate for about 80% of patients with chronic pancreatitis.
    - Patients should avoid dietary fat restriction and very high fiber diets
      - Consider dietary fat restriction as a last resort in patients with symptomatic steatorrhea inadequately controlled with pancreatic replacement therapy and proton-pump inhibitors
    - Patients with malnutrition should have small, frequent, high-energy meals
  - Pancreatic enzyme replacement therapy (PERT)

Pancreatic enzyme replacement therapy (PERT)

- PERT is indicated for patients with exocrine pancreatic insufficiency and clinical symptoms or laboratory signs of maldigestion following an appropriate nutritional evaluation (United European GI Guidelines)
  - PERT may *improve the incretin response* to a meal and has been found to *improve glycemia* in small studies
- Screening for fat-soluble vitamins A, D, E, and K can help ensure nutritional sufficiency or detect deficiency and monitor the effectiveness of pancreatic enzyme replacement therapy (PERT) (annual assessment of fat-soluble vitamin levels recommended)
- PERT and vitamin D replacement are both important for nutrition and bone health.
  - United European Gastroenterology guidelines (HAPANEU/UEG) recommends
    - survey patients with chronic pancreatitis for osteoporosis and osteopenia [low bone density] / osteomalacia
      - regularly assess bone density by dual-energy X-ray absorptiometry (DXA)
      - and serum 25(OH)D.
    - To reduce the risk of developing or exacerbating bone-related complications of chronic pancreatitis, encourage basic preventative measures in all patients including
      - an adequate diet with calcium and vitamin D intake
      - regular weight-bearing exercise
      - avoidance of smoking and alcohol intake

Management - Metformin

- The ADA and the EASD recommend metformin as the first-line oral therapy for T2D. Many people with PPDM/type 3c diabetes mellitus patients are initially misdiagnosed with T2D and treated with metformin as a drug of first choice.
  - If *hyperglycemia is rather mild*, therapy with metformin may be a good choice in the absence of contraindications.
    - However, metformin treatment *might not be tolerated* by many patients with PPDM since its main side effects include nausea, abdominal complaints, diarrhea and weight reduction.
  - Since metformin therapy is reported to *reduce the risk of pancreatic cancer* by as much as 70% in T2D and in animal studies - its anti-diabetic and anti-neoplastic effects *may be* beneficial in patients with PPDM/type 3c diabetes mellitus due to chronic pancreatitis.
    - The anti-neoplastic effect of metformin may be due to activation of the liver kinase B-1-adenyl monophosphate protein kinase pathway, a known inhibitor of the mammalian target of rapamycin (mTOR)
    - Patients with CP have a high (5–10%) risk of pancreatic ductal adenocarcinoma - Metformin should be considered as part of the treatment for patients with DEP due to CP; however, outcome studies for this group are not yet available.

Management – Other 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 (this may be changing for some forms of pancreatitis, especially after hypertriglyceridemia or treated GB-disease-associated AP) (less pain with GLP1 RA?)
  - GLP1 RA have a 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) are usually avoided due to the high risk of hypoglycemia in PPDM (which can be prolonged)
  - may be considered with caution, such as use of low dose glinides in early stages
- Alpha-glycosidase inhibitors should be avoided due to aggravation of existing exocrine insufficiency
- TZDs should be avoided due to prominent side effects (e.g., bone fractures, fluid retention) (osteoporosis is common with chronic pancreatitis)
- Some recommend avoiding SGLT-2 inhibitors, due to a possible induction of euglycemic diabetic ketoacidosis in insulin-deficient patients

Management – Insulin Therapy

- PPDM is a progressive disorder -many patients will eventually require insulin therapy
  - Continue metformin therapy if tolerated
  - Use general insulin dosing guidelines as for type 1 diabetes mellitus.
    - Basal and Prandial insulin
  - In patients with severe malnutrition insulin therapy is commonly used as a therapy of first choice due to the desired anabolic effects of insulin
- CGM - In patients with CP and insulin-treated diabetes (PPDM-C), CGM increased time in range and reduced time above and below range. (Diabetes Obes Metab. 2025 Mar18;27(6):3379–3388)
    - These findings highlight the potential of CGM in improving glycemic control.
- AID/Hybrid closed-loop (HCL) insulin delivery (Diabetes Metab. 2024 Jul;50(4):101544)
  - Improved overall glycemia (A1c from 8.5 ± 1.7 % to 7.7 ± 1.3 %)
  - Reduced glucose variability & increased TIR (from 49±24 to 59±19 %)
  - Reduced time below range (from 2.2 ± 2.6 % to 0.8 ± 1.0 %)

Management – Pancreatectomy

- Patients with medically refractory pancreatitis can undergo pancreatectomy, ideally with islet autotransplantation to preserve endogenous islet function and insulin secretion
  - Requires referral to specialized centers
  - In some cases, autotransplant can lead to insulin independence. In others, it may decrease insulin requirements

Case – William

- 47-year-old male diagnosed with T2D at age 42 - Frustrated & concerned regarding risk of complications due to persistently elevated A1c of 10% despite taking multiple diabetes meds faithfully including:
  - metformin (1 g twice per day)
  - empagliflozin (25 mg once per day)
  - sitagliptin (100 mg once per day)
- C/o erratic BG swings, also c/o loose bowels (blames on metformin)
- PMH/SH: past binge alcohol use w/ a couple episodes of acute pancreatitis (AP) – no alcohol since late 20s, no AP since dc alcohol / occ vapes - Family Hx: no known IBD or colon cancer, + diabetes in M & mGM
- BMI 24, BP 118/68, P 88
- Do you think he has PPDM?
- What would you recommend?

"Suggestive factors":

- Relatively young age of onset
- Normal BMI
- Hx of RAP – alcohol-related
- Early need for insulin therapy
- GI symptoms
- Male, +Fam Hx DM

Summary –Key Points

- The most common cause of Diabetes of the Exocrine Pancreas (DEP) (type 3c) is post-pancreatitis diabetes mellitus (PPDM)
  - The risk is higher with Chronic Pancreatitis (CP) → PPDM-C
  - DEP can occur after Acute Pancreatitis → PPDM-A; since AP is a more common GI condition, AP is the most common cause of PPDM
  - Usually misdiagnosed as T2D (need to consider in new-onset diabetes w/ history of pancreatitis) or T1D
    - Often associated with poor glycemic control despite adherence to usual medications for T2D
- In PPDM, Endocrine Pancreatic Insufficiency is usually accompanied by Pancreatic Exocrine Insufficiency (PEI) ranging from maldigestion to overt malabsorption (fecal elastace-1 (FE-1) screen)
  - Fat malabsorption can result in
    - Steatorrhea & GI symptoms
    - Fat-soluble vitamin (A, E, K D) deficiencies
    - Increased risk for bone loss/osteoporosis or osteomalacia
  - Pancreatic Enzyme Replacement Therapy (PERT) is usually needed to restore fat absorption
    - May also improve incretin secretion
- PPDM is associated with an increased risk of adenocarcinoma of the pancreas
- PPDM results from damage to the entire pancreatic islet with loss of not only the Beta cells but also the Alpha cells and Pancreatic Polypeptide (F) cells resulting in both more hyperglycemia and more hypoglycemia, often with wide and rapid swings in glycemia.
  - Metformin can be used in early PPDM if tolerated
    - Potential reduction in risk of pancreatic cancer
  - Insulin replacement is needed as PPDM progresses
    - Insulin Pump therapy with CGM and AID can help improve glycemia
- A diagnosis of PPDM provides an opportunity to provide PERT and select appropriate diabetes medications.

Table 1 Classification of diabetes of the exocrine pancreas.

General inclusions

Post-pancreatitis diabetes mellitus (PPDM)

Post-acute pancreatitis diabetes mellitus (PPDM-A)

Post-chronic pancreatitis diabetes mellitus (PPDM-C)

Pancreatic cancer-related diabetes (PCRD)

Cystic fibrosis-related diabetes (CFRD)

General exclusions

Stress hyperglycemia

Autoimmune diabetes with first recognition after an attack of pancreatitis

Diabetes with first recognition during pregnancy after an attack of pancreatitis

Maturity-onset diabetes of the young

Drug-induced diabetes

Diabetes after pancreatic surgery

Diabetes after blunt pancreatic (abdominal) trauma

Diabetes secondary to pancreatic agenesis/hypoplasia

Diabetes secondary to hereditary hemochromatosis

Special entities

Antecedent diabetes mellitus in pancreatitis (ADMP)

New-onset diabetes in pre-symptomatic pancreatic ductal adenocarcinoma (NOD-PDAC)

Recently proposed renaming & classification
For Diabetes of the Exocrine Pancreas (DEP)

Eur J Endocrinol. 2021 Apr;184(4):R151-R163.
DIAGNOSIS OF ENDOCRINE DISEASE: Diagnosing and classifying diabetes in diseases of the exocrine pancreas

Pre-question: Which one answer is correct?

- New onset diabetes caused by pancreatic cancer
  A. Is primarily due to destruction of beta-cells by the cancer cells
  B. Is associated with markedly increased insulin resistance
  C. Is associated with rapid weight gain
  D. Appears to be due to a paraneoplastic suppression of beta-cell function

Paraneoplastic – signs and symptoms that occur due to the production of chemical signaling molecules by tumor cells (not due to cancer destroying tissue)
Tumor-induced diabetes – tumor cells secrete substances that cause insulin resistance or interfere with insulin production

Pancreatic Ductal Adenocarcinoma (Pancreatic Cancer)

- Pancreatic ductal adenocarcinoma (PDAC) is a malignant tumor of the pancreas that accounts for approximately 90% of all pancreatic carcinomas – called *"Pancreatic Cancer"*
  - Most tumors (about 60%-70%) occur in the head of the pancreas.
  - The peak incidence is in individuals aged 60-80 years, with > 90% of cases reported in adults > 55 years old.
  - The highest incidence is in Northern America
  - Male adults are slightly more affected in the United States and worldwide.
    - Pancreatic cancer is the 10th most common cancer for male persons and the eighth most common cancer for female persons in the United States.
    - African Americans are more commonly affected than persons of other races and ethnicities in the United States.
    - Native American and Alaskan Native (AI/AN) populations have
      - higher incidence of PDAC than US Whites
      - the worst survival outcomes for PDAC among all major US racial/ethnic groups

Major Risk Factors for Pancreatic Cancer

- Major risk factors include:
  - Tobacco use
  - Genetic predisposition and family history
    - ~10% of pancreatic cancers are inherited, caused by inherited gene mutations (like BRCA1/2, PALB2, ATM)
  - Obesity/central adiposity
  - Chronic pancreatitis
  - Diabetes
  - Heavy alcohol use (> 3 drinks (30-45 g of ethanol) /day)

- Other risk factors include:
  - Low physical activity
  - Dietary factors - Consumption of red meat (especially processed meat), foods high in sugars, foods containing saturated fatty acids
  - Insulin resistance
  - Sulfonylureas (suggestive) https://pubmed.ncbi.nlm.nih.gov/23399556/

Major Risk Factors for Pancreatic Cancer

- Major risk factors include:
  - Tobacco use
  - Genetic predisposition and family history
    - ~10% of pancreatic cancers are inherited, caused by inherited gene mutations (like BRCA1/2, PALB2, ATM)
  - Obesity/central adiposity
  - **Chronic pancreatitis**
  - **Diabetes**

  } **Postpancreatitis DM > DM-Pancreatitis > Pancreatitis > T2DM**

  - Heavy alcohol use (> 3 drinks (30-45 g of ethanol) /day)

- Other risk factors include:
  - Low physical activity
  - Dietary factors - Consumption of red meat (especially processed meat), foods high in sugars, foods containing saturated fatty acids
  - Insulin resistance
  - Sulfonylureas (suggestive) https://pubmed.ncbi.nlm.nih.gov/23399556/

Bidirectional Relationship between Diabetes & Pancreatic Cancer

- Diabetes is both a risk factor for and a complication of pancreatic cancer.
  - Long-term type 2 diabetes (≥ 2 years) is associated with (predisposes to) an increased risk of pancreatic cancer, with risk ratios ranging from 1.5 to 2.0.
  - New-onset diabetes (NOD) may be *caused by* early-stage pancreatic cancer as a ***paraneoplastic syndrome*** with a poorly understood pathophysiology (**Pancreatic ductal adenocarcinoma-related diabetes mellitus (PDAC-DM**)) or **PCRD**
    - Up to 85% of patients with pancreatic cancer have diabetes or hyperglycemia, which frequently manifests as early as *2-3 years before* a diagnosis of pancreatic cancer.
    - Glucose control worsens in patients with PDAC-DM in the face of ongoing, often profound, *weight loss*.
    - **Diabetes & weight loss are paraneoplastic phenomena induced by pancreatic cancer**.
      - These pancreatic cancer-induced metabolic alterations are likely mechanisms to promote the survival and growth of pancreatic cancer

PDAC-DM/PCRD - potential clues to earlier diagnosis?

- Pancreatic cancer is one of the deadliest cancers
  - due to aggressive invasion & spread and late diagnosis (7 to 9% 5-year survival)
  - ~75% of people with PDAC die from their disease within 1 year of diagnosis
- Earlier diagnosis is the key for improved survival
  - Localized (stage 1-2) allows resection (40 to 50+% 5-year survival)
- No reliable screening tests for early detection
  - The metabolic dysregulation caused by invasive pancreatic cancer leads to new-onset glycemic abnormalities (NOGA) in the ***months to years preceding*** pancreatic cancer diagnosis
  - These metabolic changes could enable early diagnosis of pancreatic cancer, if they can be distinguished from the ones that occur in patients with type 2 diabetes (NOD due to pancreatic cancer vs T2D, etc.)
    - Currently research looking at blood biomarkers for earlier diagnosis

Probability of Pancreatic Cancer in NOD

- For patients with new-onset diabetes (NOD) – the clinical risk for PDAC shows a substantially increased probability within two years if combination of
  - age 50 years or older
  - unintentional weight loss
  - rapid glycemic deterioration/rapid A1c rise/early insulin requirements
- PDAC-DM/PCRD is often clinically confused with type 2 diabetes (most cases of NOD), resulting in delayed cancer detection
  - UK guidelines recommend urgent imaging to assess for pancreatic cancer in people aged over 60 years with weight loss and new-onset diabetes
    - Imaging can include CT, MRI and endoscopic US
- PDAC developing in pre-existing T2D can also be associated with worsening glycemia & unintentional weight loss but most pronounced in NOD

Metabolic Defects in PDAC-DM vs other forms of Diabetes

- ***PDAC-DM and type 2 diabetes are metabolically distinct***, with different defects responsible for hyperglycemia:
  - PDAC-DM is characterized **predominantly by insulin deficiency** and displays higher insulin sensitivity (less insulin resistance) than type 2 diabetes.
    - Compared with type 2 diabetes, individuals with **PDAC-DM showed ~2.5-fold greater insulin sensitivity, ~81% lower insulin secretion** and **~40% lower beta cell function**
  - ***PDAC-DM has been shown to exhibit α-cell disinhibition*** *(increased glucagon levels)*
    - whereas ***Chronic pancreatitis type 3c (PPDM-c)*** often shows **α-cell deficiency** (*decreased glucagon levels*) **and a high hypoglycemia risk**
- These findings identify biological characteristics that may have implications for individualized treatment of PDAC-DM (insulin therapy) and *guide diagnostic biomarker discovery for early PDAC diagnosis* – focus of ongoing research

- Blockage of pancreatic duct by pancreatic cancer can result in pancreatic exocrine insufficiency with need for PERT

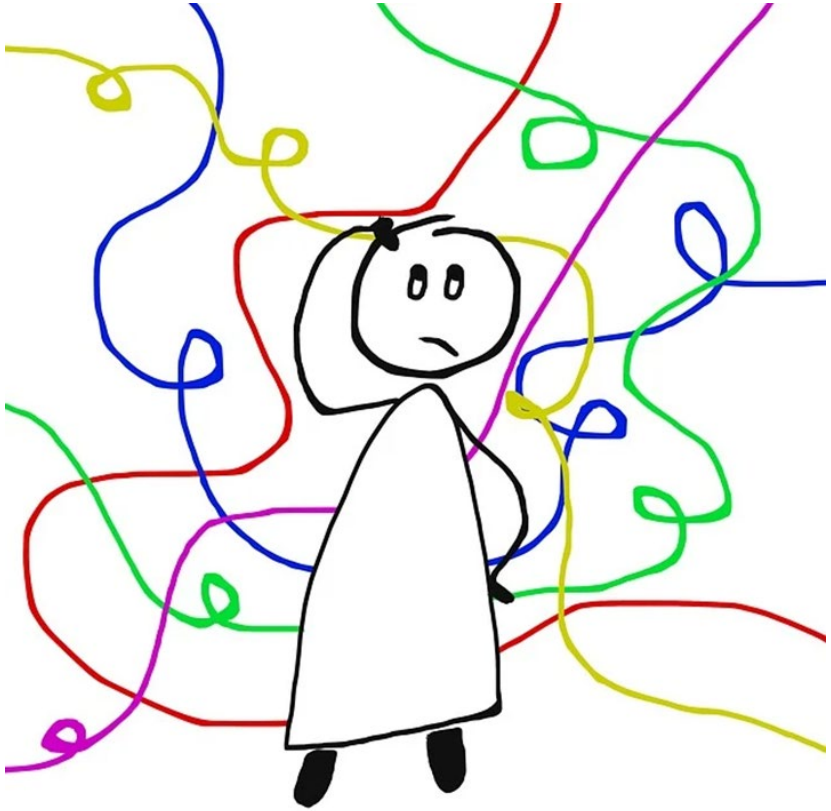
Summary - Key Points

- **Pancreatic cancer-related diabetes (PCRD) [Pancreatic Ductal Adenocarcinoma Diabetes (PDAC-DM)]** is considered a ***paraneoplastic*** phenomena induced by the PDAC
- In a subset of people, new-onset hyperglycemia/diabetes (NOD) is due to PDAC – most often in people over age 50, with associated unintentional weight loss & rapid deterioration in glycemia/ rise in A1c or early requirement for insulin therapy
- Currently no reliable screening test – potential for biomarkers with further research on PCRD
  - Think about PCRD in people with NOD, especially if weight loss, rapid worsening glycemia

Post-question: Which one answer is correct?

- New onset diabetes caused by pancreatic cancer
  A. Is primarily due to destruction of beta-cells by the cancer cells
  B. Is associated with markedly increased insulin resistance
  C. Is associated with rapid weight gain
  D. Appears to be due to a paraneoplastic suppression of beta-cell function

Questions, Comments, Clarification



Do you think you have patients in your clinic that might have DEP instead of T2D or T1D?

Extra Slides

References

- https://pubmed.ncbi.nlm.nih.gov/33460395/ DIAGNOSIS OF ENDOCRINE DISEASE: Diagnosing and classifying diabetes in diseases of the exocrine pancreas. Eur J Endocrinol. 2021 Apr;184(4):R151-R163.
- https://diabetesjournals.org/care/article/40/11/1486/36928/Incidence-Demographics-and-Clinical
- https://pmc.ncbi.nlm.nih.gov/articles/PMC5495015/ Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer(CPDPC). Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. Lancet Gastroenterol Hepatol. 2016 Nov;1(3):226-237.
- 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2026 | Diabetes Care | American Diabetes Association
- Eur J Endocrinol. 2021 Apr;184(4):R151-R163. doi: 10.1530/EJE-20-0974.DIAGNOSIS OF ENDOCRINE DISEASE: Diagnosing and classifying diabetes in diseases of the exocrine pancreas
- Majumder S, Chari ST. Chronic pancreatitis. Lancet. 2016 May 7;387(10031):1957-66. World J
- Gastroenterol. 2013 Nov 14;19(42):7276–7281. Ewald N, Hardt PD. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. World J Gastroenterol. 2013 Nov 14;19(42):7276-81. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis – PMC
- World J Gastroenterol. 2013 Nov 14;19(42):7276–7281.

References

- Lancet Gastroenterol Hepatol 2016 Nov;1(3):226
- Majumder S, Chari ST. Chronic pancreatitis. Lancet. 2016 May 7;387(10031):1957-66.
- Dig Dis Sci 2017 May;62(5):1119
- https://pmc.ncbi.nlm.nih.gov/articles/PMC10423608/ Frontline Gastroenterol. 2023 Feb 9;14(5):371–376.
- https://pmc.ncbi.nlm.nih.gov/articles/PMC3831209/#:~:text=Development%20of%20diabetes%20mellitus%20in,misdiagnosed%5B6%2C7%5D.
- StatPearls 2017 Nov 1, Pancreatology 2005;5(2-3):122PDF).
- World J Gastroenterol. 2013 Nov 14;19(42):7276–7281.
- Acute pancreatitis and diabetes mellitus: a review. Korean J Intern Med. 2021 Jan;36(1):15-24.
- Clinico-radiological comparison and short-term prognosis of single acute pancreatitis and recurrent acute pancreatitis including pancreatic volumetry. PLoS One. 2018 Oct 25;13(10)
- Dynamed Plus - United European GI Guidelines
- New insights into pancreatic cancer-induced paraneoplastic diabetes – PMC/Diabetes and pancreatic cancer: a complex and confounding interplay | Gut
- https://pmc.ncbi.nlm.nih.gov/articles/PMC4224068/ metformin and pancreatic cancer

Definitions

- Pancreatic exocrine insufficiency (PEI) (or exocrine pancreatic insufficiency) is the insufficient secretion of pancreatic enzymes (due to acinar dysfunction) and/or sodium bicarbonate (due to ductal dysfunction)
  - Exocrine insufficiency may be due to pancreatic parenchyma loss, main pancreatic duct obstruction, decreased exocrine pancreas simulation, and decreased activation of pancreatic enzymes
- Pancreatic endocrine insufficiency is the insufficient secretion of pancreatic endocrine hormones such as glucagon, insulin, somatostatin, ghrelin, and pancreatic polypeptide
  - Pancreatic endocrine dysfunction, called type 3c diabetes or pancreatogenic diabetes, may be due to damaged pancreatic parenchyma and progressive beta cell loss.

Fecal Elastace-1 testing

- FE-1 testing is not affected by concomitant pancreatic enzyme replacement therapy.
- The monoclonal FE-1 test is more specific than the polyclonal test.
- Diarrhea increases the likelihood of false positive results.
- The reported diagnostic performance of FE-1 tests for detecting exocrine pancreatic insufficiency in 7 cohort studies of patients with suspected chronic pancreatitis (with secretin-based direct function testing as the reference standard):
- Sensitivities ranged from 25% to 67% in patients with mild impairment, 35% to 100% in patients with moderate impairment, and 85% to 100% in patients with severe impairment.
- Specificities ranged from 55% to 100%.
- Reference - Dig Dis Sci 2017 May;62(5):1119

Fecal Elastace-1 testing

- Our findings emphasize the importance of interpreting FE-1 results within the appropriate clinical setting.
  - FE-1 allows the diagnosis (high PPV) but not the exclusion (limited NPV) of PEI in cases with a high probability of this condition (e.g., patients with cystic fibrosis or advanced chronic calcifying pancreatitis).
  - On the contrary, FE-1 allows to exclude (high NPV) but not to diagnose PEI (limited PPV) in case of low probability of this condition.
  - Therefore, a low FE-1 result should be considered with caution in scenarios with a low probability of PEI, and a normal FE-1 result should be considered with caution in scenarios with a high probability of PEI.
  - These findings support the current statement that FE-1 should be considered together with a global assessment of symptoms and nutritional status in an appropriate clinical scenario for PEI diagnosis.
  - Diagnostic Accuracy of Fecal Elastase-1 Test for Pancreatic Exocrine Insufficiency: A Systematic Review and Meta-Analysis - de la Iglesia - 2025 - United European Gastroenterology Journal - Wiley Online Library

Pancreatic enzyme replacement therapy (PERT)

- From Summary in Dynamed: PERT is indicated for patients with exocrine pancreatic insufficiency and clinical symptoms or laboratory signs of maldigestion following an appropriate nutritional evaluation (United European GI Guidelines)
  - Take PERT with meals and snacks
  - Start with a lipase dose of at least 40,000 units with main meals, and about half of that with snacks
    - Lower doses (25,000-40,000 units per meal) may be effective in some patients, but most patients will require higher doses.
  - PERT preparations of choice are enteric-coated microspheres or mini-microspheres with < 2 mm diameter

Another reference: Evaluation and Management of Exocrine Pancreatic Insufficiency (EPI): Pearls and Pitfalls

Previous Diagnostic Criteria
(not all patients with DEP meet the suggested criteria)

The diagnosis of DEP is based upon standard criteria for diabetes mellitus:

- clinical symptoms of hyperglycemia and glucose of ≥ 11.1 mmol/L
- in asymptomatic individuals with at least two abnormal biochemical tests: fasting glucose 7.0 mmol/L, 2-h glucose ≥ 11.1 mmol/L after 75-g oral glucose ingestion, or HbA1c ≥ 6.5% (48 mmol/mol).
- The 75-g glucose tolerance test remains the gold standard for diagnosis of DEP.

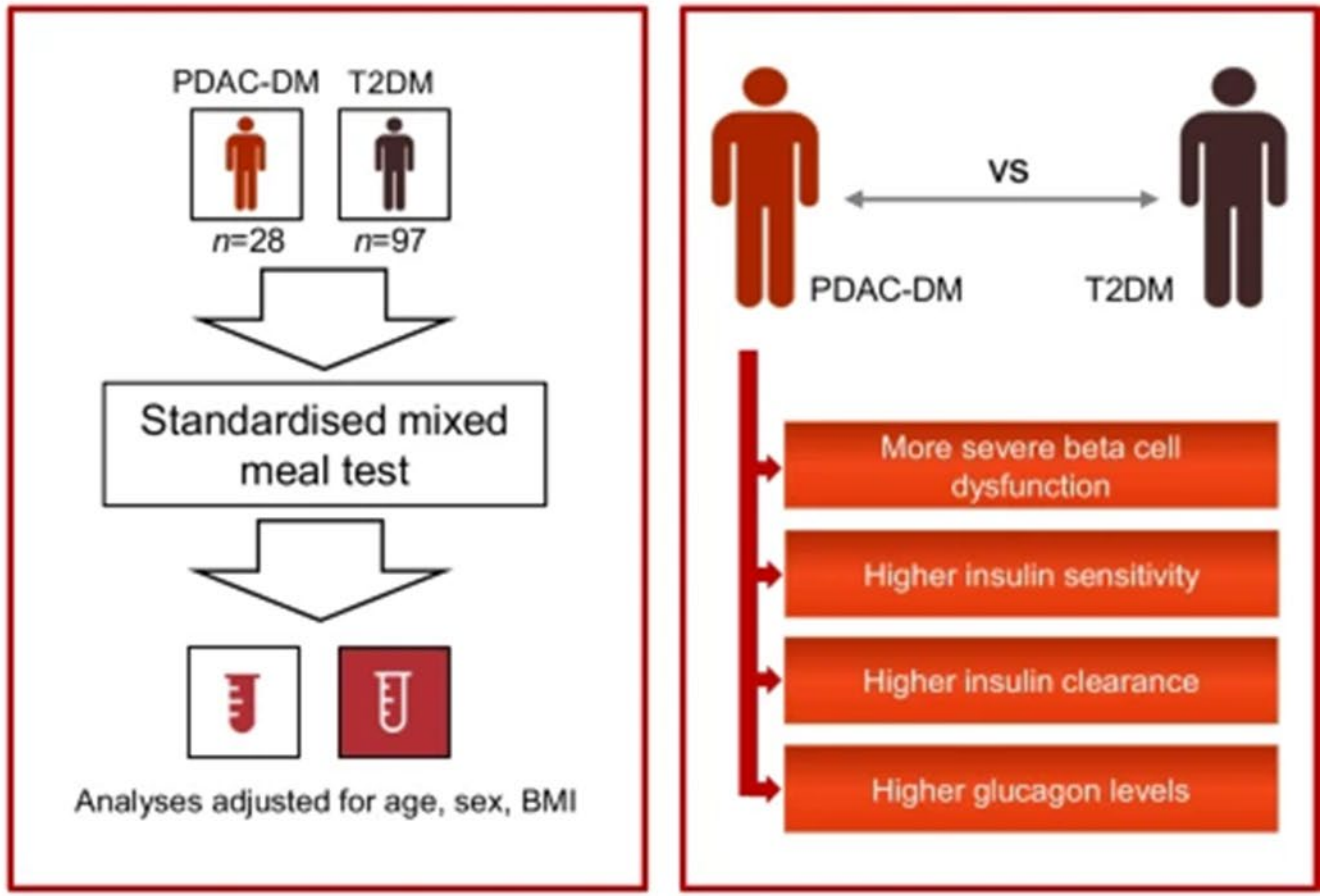
- However, currently, there is no consensus as to whether all diabetes concurrent with pancreatic disease should be considered as DEP or if more stringent diagnostic standards should be used. Ewald and Bretzel proposed the following diagnostic criteria
  - A diagnosis of diabetes mellitus
  - Evidence of exocrine pancreatic insufficiency (fecal elastase-1 < 200 μg/g or abnormal direct function testing)
  - Abnormal pancreatic imaging (endoscopic ultrasound, magnetic resonance imaging, and computed tomography)
  - Absence of type 1 diabetes associated autoimmune markers (antibodies against glutamine acid decarboxylase, islet cell antigen, or insulin)
  - But not all DEP have abnormal imaging, etc.
- Characteristics of DEP include
  - impaired β cell function;
  - lack of insulin resistance;
  - deficiency of lipid-soluble vitamins A, D, E, and K;
  - impaired release of GLP-1 and PP. a reduced PP response to mixed nutrients (less than twice the basal level) has been identified as a specific marker.

Diabetes caused by pancreatic cancer shows metabolic differences compared to type 2 diabetes

Gap: New-onset diabetes mellitus caused by pancreatic ductal adenocarcinoma (PDAC-DM) affects middle-aged and older adults, similar to type 2 diabetes mellitus (T2DM).

Little is known about the pathophysiology of PDAC-DM and how it differs from T2DM.

Hypothesis: PDAC-DM and T2DM differ in their underlying metabolic defects.



Research reported in this publication was supported by the National Cancer Institute (NCI) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health

Pancreatic Diabetes or Diabetes in the Context of Disease of the Exocrine Pancreas

- ADA 2026 Standards of Care - Recommendation
  - 2.23 Screen people for diabetes within 3–6 months following an episode of acute pancreatitis and annually thereafter. Screening for diabetes is recommended annually for people with chronic pancreatitis. E

Case Report that Illustrates Diagnosis & Management (hereditary pancreatitis)

- https://pmc.ncbi.nlm.nih.gov/articles/PMC12093095/

- Issues with C-peptide measurements
  - Call for Standardization of C-Peptide Measurement – PMC
    - The effect of an error of 30% in C-peptide determination is illustrated by the following considerations: a difference of 30% between different assays would lead to a range of 140 to 260 pmol/L for the suggested cut-off of 200 pmol/L and 420 to 780 pmol/L for the suggested cut-off of 600 pmol/L, respectively. Thus, a patient with a true C-peptide of 200 pmol/L who obtains a C-peptide result of 160 pmol/L, this result will be interpreted as low, while a result of 240 pmol/L measured in another laboratory will be interpreted as not decreased, ie, “normal.” Thus, based on these C-peptide values, a diabetologist would start an insulin treatment when the patient has obtained a result of 160 pmol/L, while the same patient would not receive an insulin treatment when a C-peptide value of 240 pmol/L was determined. The corresponding considerations are also valid for the upper C-peptide cut-off.