

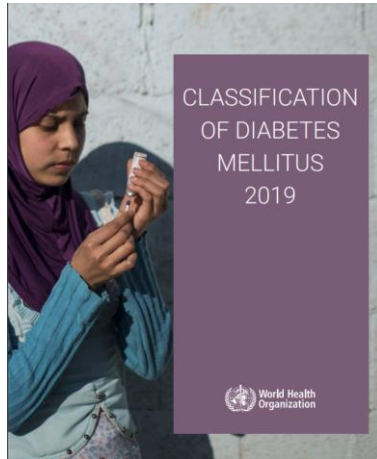
Pancreatic Cancer Related Diabetes (type 3c)

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WHO classification of diabetes - 2019



Diseases of the exocrine pancreas

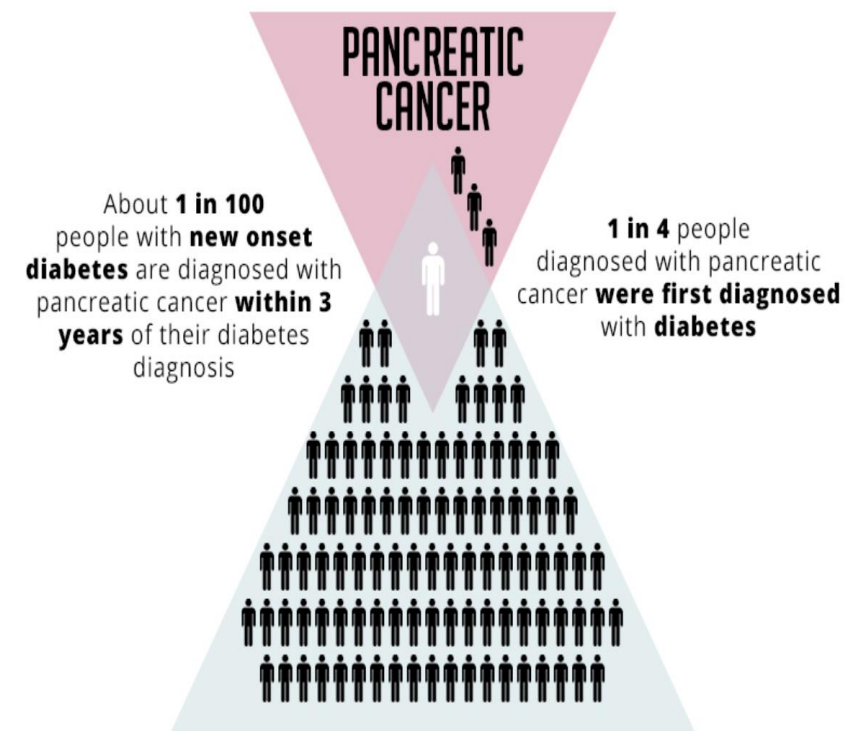
- Any process that diffusely damages the pancreas: pancreatitis, trauma, infection, pancreatectomy.
- Diabetes related to pancreatic adenocarcinoma is caused by other mechanisms than reduction of beta cell mass.

Table 2: Types of diabetes

Type 1 diabetes	
Type 2 diabetes	
Hybrid forms of diabetes	
Slowly evolving immune-mediated diabetes of adults	
Ketosis prone type 2 diabetes	
Other specific types (see Tables)	Diseases of the exocrine pancreas
Monogenic diabetes	Fibrocalculous pancreatopathy
- Monogenic defects of β -cell function	Pancreatitis
- Monogenic defects in insulin action	Trauma/pancreatectomy
Diseases of the exocrine pancreas	Neoplasia
Endocrine disorders	Cystic fibrosis
Drug- or chemical-induced	Haemochromatosis
Infections	Others
Uncommon specific forms of immune-mediated diabetes	
Other genetic syndromes sometimes associated with diabetes	
Unclassified diabetes	
This category should be used temporarily when there is not a clear diagnostic category especially close to the time of diagnosis of diabetes	
Hyperglycemia first detected during pregnancy	
Diabetes mellitus in pregnancy	
Gestational diabetes mellitus	

Diabetes and pancreatic cancer.

How are they related?



National Cancer Institute

- ▶ 1% of newly diagnosed diabetes in adults will go on to be diagnosed with pancreatic cancer within 3 years.
- ▶ Diagnosis - HbA1c 48mmol/mol
- ▶ Identifying diabetes relating to pancreatic cancer has significant implications for earlier diagnosis, treatment options and increased survival.

Identifying Pancreatic Cancer Related Diabetes (PCRD)

PCRD /Type 3c misdiagnosed in 87.5% as type 2 diabetes (Woodmansey et al, 2017)

New Onset type 2 DM vs. Pancreatic Cancer Related Diabetes (PCRD)

- ▶ Sudden weight loss
 - ▶ Lower BMI
- ▶ Rapid onset of hyperglycaemia
 - ▶ Deteriorating BG control
- ▶ Lack of response to escalating diabetes medication
 - ▶ Malnutrition
 - ▶ GI symptoms

Implication of methods used to diagnose diabetes in pancreatic cancer patients

	Patient history or medical records	Fasting blood glucose	HbA1c	OGTT 75g
% diagnosed as having diabetes	12 - 29%	47%	41.7%	77% (diabetes and glucose intolerance)

Pathophysiology of diabetes specific to pancreatic cancer

- ▶ Proposed mechanisms of hyperglycaemia
- ▶ Insulin deficiency due to beta cell loss/dysfunction
- ▶ Inflammatory mediators
- ▶ **Paraneoplastic mechanism causing IR and beta cell dysfunction**
- ▶ Immunopathogenesis
- ▶ Hepatic insulin resistance caused by reduction in pancreatic polypeptide
- ▶ Peripheral insulin resistance
- ▶ Reduced incretin effect
- ▶ Genetic
- ▶ Adrenomedullin and Vanin 1 as mediators of inflammation causing beta cell toxicity
- ▶ Gut microbiome



Medication class	Name	Mode of action	Pros/Cons and considerations
Biguanides	Metformin *First line	Decreasing gluconeogenesis by opposing the action of glucagon. Increasing peripheral use of glucose. Requires some residual functioning pancreas. Insulin resistance	Reduces risk of pancreatic cancer First line if hyperglycaemia mild Sensitisation to chemo - gemcitabine GI side effects and weight loss Avoid with ongoing alcohol excess - lactic acidosis risk B12 malabsorption
Sulfonylureas (SUs)	Gliclazide, Glibenclamide, Glimepiride Glipizide Gliclazide	Stimulate beta cells in the pancreas to produce more insulin.	Hypoglycaemia risk Hyponatraemia Avoid in severe renal and hepatic impairment Absorption reduced by colessevelam
Glinides	Nateglinide, Repaglinide	Stimulate beta cells in pancreas to produce more insulin	Useful in milder hyperglycaemia prior to starting insulin Hypoglycaemia risk Shorter half life than sulfonylureas
Thiazolidinediones (Glitazones) (TZDs)	Rosiglitazone, Pioglitazone	Binds to a receptor which promotes deposition of fat cells into peripheral tissue which improves a person's sensitivity to insulin.	Should be avoided due to osteoporosis, fluid retention, congestive heart disease. Weight gain due to increase in peripheral fat mass. Avoid in patients with chronic pancreatitis
Alpha-glycosidase inhibitors (AGIs)	Acarbose Miglitol	Block and slow down the absorption of carbohydrates from the GIT.	Increases PEI and weight loss DKA and acute pancreatitis risk Little or no evidence - should be avoided
Incretin based therapies GLP-1 analogues - injection DPP-4 inhibitors - tablet	Exenatide Liraglutide Sitagliptin Saxagliptin Linagliptin	GLP-1 incretin mimics - increases levels of incretins. DPP-4 works by blocking the action of the enzyme which destroys the hormone incretin. Incretin signals the pancreas to produce more insulin and reduce hepatic glucose production.	GI side effects Increased risk of acute pancreatitis Pancreatic cancer risk Current recommendation is to avoid in type 3cDM
Sodium glucose co-transporter-2 (SGLT-2)	Dapagliflozin Canagliflozin Empagliflozin	Reduce renal reabsorption of glucose without stimulating insulin release	DKA in insulin deficient patients and should not be prescribed
Insulin		Insulin replacement therapy	Anabolic effect for treating malnutrition Hypoglycaemic risk Carcinogenic

Clinical example 1 - undiagnosed DM

Setting - Pancreatic surgical outpatients.

Pancreatic head adenocarcinoma

- ▶ Struggling with:
 - ▶ Poor appetite, lethargy, weight loss (8kg over previous 8 weeks), steatorrhea, taste changes, polyuria and thirst.
- ▶ Random blood glucose - 20mmol/l
- ▶ BMI 23kg/m²
- ▶ Commenced pancreatic enzyme replacement
 - ▶ 75 000 with meals and 50 000 with snacks
- ▶ First line dietary advice - nutritional support avoiding high GI/sugary drinks and snacks
- ▶ Referred to oncology for assessment for chemotherapy
- ▶ Diabetic medication started by oncologist Friday pm - gliclazide 40mg bd

Clinical example 2 - misdiagnosed DM Setting - Pancreatic surgical outpatients. Pancreatic head adenocarcinoma

- ▶ Diagnosed Type 2 diabetes 8 months ago.
- ▶ Following healthy eating advice for weight loss
- ▶ Weight loss - 10kg, BMI 22kg/m²
- ▶ Appetite reasonable but reduced portion sizes and avoiding “sugary foods, desserts and choosing low fat options.
- ▶ Prescribed metformin by GP
- ▶ Struggling with abdominal pain, bloating, wind, urgency with slightly paler than usual stools.
- ▶ Not monitoring BG
- ▶ Offered group type 2 diabetes support session by GP practice.
- ▶ MDT - work up for possible Pylorus Preserving Pancreaticoduodenectomy (PPPD)
- ▶ Unpick and explain type 2 diabetes and diabetes related to pancreatic cancer.
- ▶ Reframe nutritional goals.
- ▶ Start on PERT - review and assess considering GI side effects of Metformin and optimise PERT.
- ▶ Repeat BG and HbA1c (implication of starting PERT)
- ▶ Tertiary DM centre review depending outcome of BG results.
- ▶ Nutritional support - high protein/high kcal/low simple sugars and low GI.
- ▶ Exercise - Prehab service
- ▶ Goal - optimise nutrition, glycaemic control and physical function in preparation for pancreatic surgery.

Nutritional aims

In-line with cancer pathway and diabetes treatment

- ▶ Prevent hypoglycaemic events (<4mmol/L)
- ▶ Minimise hyperglycaemia
- ▶ Optimise nutritional status
- ▶ PEI management
- ▶ Monitor and correct any micronutrient deficiency
- ▶ Aim HbA1c <53mmol/mol
 - ▶ Minimise risks of longer-term complications
- ▶ Consider lifestyle factors
- ▶ Education and understanding
 - ▶ Challenging type of DM to manage - reassure and support.



Care planning

- ▶ Hypoglycaemic awareness and treatment plan.
- ▶ Regular eating pattern, including starchy carbohydrates.
- ▶ Avoid missing meals.
- ▶ Small frequent meal pattern.
- ▶ Limit simple sugars and refined carbohydrates - especially sugary drinks and sweets.
- ▶ Nutritional drinks
 - ▶ Slow, avoid juice style
 - ▶ insulin
 - ▶ CHO 25 - 67g per bottle
- ▶ Lower glycaemic index foods and meal composition.
- ▶ Avoid 'diabetic foods'
- ▶ Monitor BG regularly
 - ▶ Intensive insulin regimen: 6 - 10 x per day or CGM
 - ▶ Monitor BG, diet, exercise and PERT 'brittle diabetes'
- ▶ Ensure adequate PERT and monitor for glycaemic consequences.
- ▶ Lifestyle changes - alcohol, smoking and exercise (prehab and beyond).

Adapted for pancreatic cancer patients from: Duggan et al (2017)

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