Type 3c Diabetes and Pancreatic Cancer

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Outline of presentation

- Defining Type 3c diabetes
- Causes of Type 3c diabetes
- Characteristics and diagnosis
- Prevalence
- Therapeutic and Nutritional management
- Challenges in this patent group
- Case study
- Take away messages

What is Type 3c Diabetes?

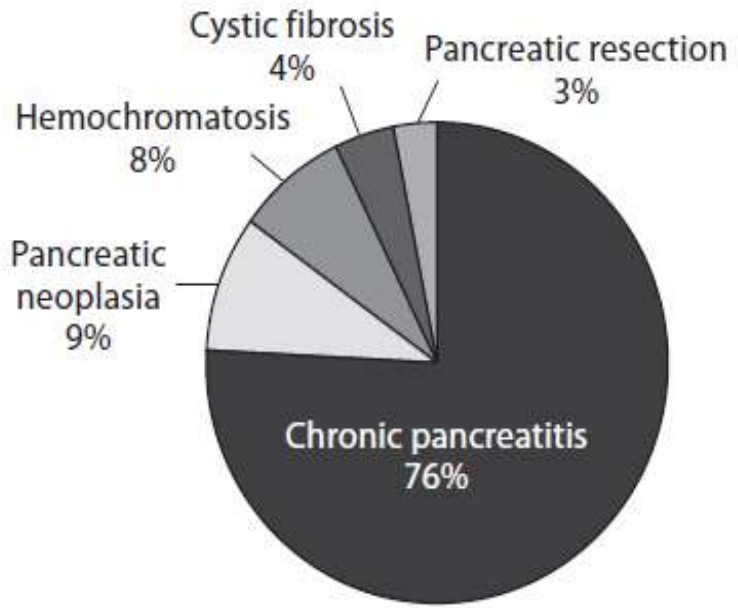
- Form of diabetes that occurs when pancreas is damaged or destroyed
- Synonymous with
  - Secondary pancreatic diabetes
  - Pancreatogenic/pancreatogenous diabetes
  - Diabetes of the exocrine pancreas
- Distinct from Type 1 and Type 2 DM
- Both exocrine and endocrine dysfunction

Table 1 Current classification of diabetes mellitus

I	Type 1 Diabetes Mellitus (β-cell destruction, usually leading to absolute insulin deficiency)
	A: Immune mediated
	B: Idiopathic
II	Type 2 Diabetes Mellitus (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
III	Other Specific Types Of Diabetes Mellitus
	A: Genetic defects of β-cell function
	B: Genetic defects in insulin action
	C: Diseases of the exocrine pancreas
	1: Pancreatitis
	2: Trauma/pancreatectomy
	3: Neoplasia
	4: Cystic fibrosis
	5: Hemochromatosis
	6: Fibrocalculous pancreatopathy
	7: Others
	D: Endocrinopathies
	E: Drug- or chemical-induced
	F: Infections
	G: Uncommon forms of immune-mediated diabetes
	H: Other genetic syndromes sometimes associated with diabetes
IV	Gestational Diabetes Mellitus

American Diabetes Association, 2011

Causes of Type 3c Diabetes



Distribution of causes of T3cDM

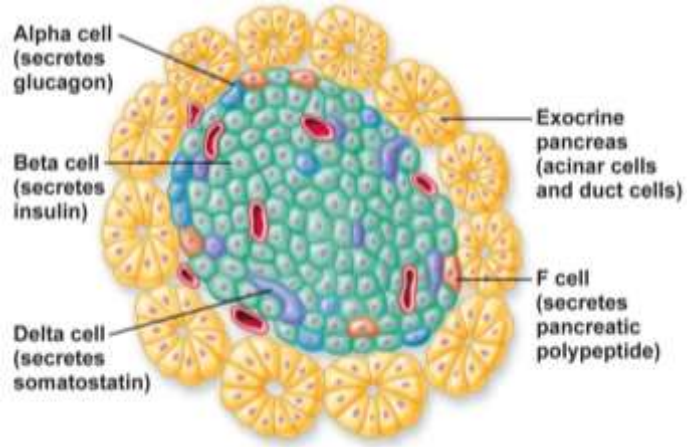
Based on Hardt *et al* (2008)
1,922 hospitalised DM patients
8% reclassified as T3cDM

- Chronic Pancreatitis
- Acute Pancreatitis
- Surgical pancreatic resection
- Pancreatic cancer
- Cystic Fibrosis
- Haemochromatosis
- Fibrocalculous pancreatopathy
- Pancreatic Agenesis

Characteristics of Type 3c Diabetes

- Destruction of all islet cells (not just beta cells as in T1DM)
- Loss of all pancreatic hormones -

insulin, glucagon, somatostatin & pancreatic polypeptide (PP)



- Hyperglycaemia
  - *Low insulin levels*
  - *Lack of PP →Hepatic insulin resistance → Unsuppressed glucose production*
  - *PEI → Reduced incretin secretion → Less insulin released*
- Hypoglycaemia common
  - *Glucagon deficiency*
  - *Enhanced peripheral insulin sensitivity*
  - *Alongside PEI, poor dietary intake, Alcohol*

- Swings from hypo to hyperglycaemia, difficult to control (Brittle DM)

Parameter	Type 3cDM	Comparison to T1DM	Comparison to T2DM
Hyperglycaemia	Mild, or severe in 'brittle diabetes'	Severe	Usually mild
Hypoglycaemia	Common and may be severe	Common	Rare
Ketoacidosis	Rare	Common	Rare
Hepatic insulin sensitivity	Decreased	Normal	Normal or decreased
Peripheral insulin sensitivity	Increased	Normal or increased	Decreased
Insulin levels	Low	Low	High
Glucagon levels	Low	Normal or High	Normal or high
PP levels	Low	Normal or Low	High
DM-associated antibodies	No	Yes	Rare
Typical age of onset	Any	Childhood/teens	Mainly adulthood
Overweight/Obese	Uncommon, although CP pts may be overweight but have muscle depletion	Rare	Common
Undernutrition	Common	Uncommon	Rare
Nutrient Deficiency	Deficiency of fat soluble vitamins in CP due to PEI/poor diet	Rare	Rare

Based on earlier table by Duggan & Conlon, 2017

Diagnosis of T3cDM

- **<u>No universally accepted diagnostic criteria</u>**

- Standard DM diagnostic criteria
  - Fasting glucose >7mmol/L or HbA1c >48mmol/mol
- Disease of the exocrine pancreas
- Believe that the pancreatic exocrine disease is the cause

Note - A HbA1c within normal levels does not exclude DM if untreated PEI
- PERT can unmask DM by improved digestion of starches
- So recheck levels once PERT commenced

- Differentiating from T1DM and T2DM
  - potential early identification of PC
  - NICE suggest urgent imaging in people >60 yrs with wt loss & new onset DM (NICE Suspected cancer, 2015)
  - guide treatment options

- No consensus if all DM concurrent with pancreatic disease be considered as T3cDM or if more stringent diagnostic standards should be used

T3cDM diagnostic criteria proposed by Eward and Hardt (2013)

Table 2 Proposed diagnostic criteria for type 3c diabetes mellitus

Major criteria (must be present)
Presence of exocrine pancreatic insufficiency (monoclonal fecal elas tase-1 test or direct function tests)
Pathological pancreatic imaging (endoscopic ultrasound, MRI, CT)
Absence of type 1 diabetes mellitus associated autoimmune markers
Minor criteria
Absent pancreatic polypeptide secretion
Impaired incretin secretion (*e.g.*, GLP-1)
No excessive insulin resistance (*e.g.*, HOMA-IR)
Impaired beta cell function (*e.g.*, HOMA-B, C-Peptide/glucose-ratio)
Low serum levels of lipid soluble vitamins (A, D, E and K)

Duggan *et al* (2017) suggest checking at least once:

DM-associated autoantibodies

C-peptide:glucose ratio (measures beta cell function)

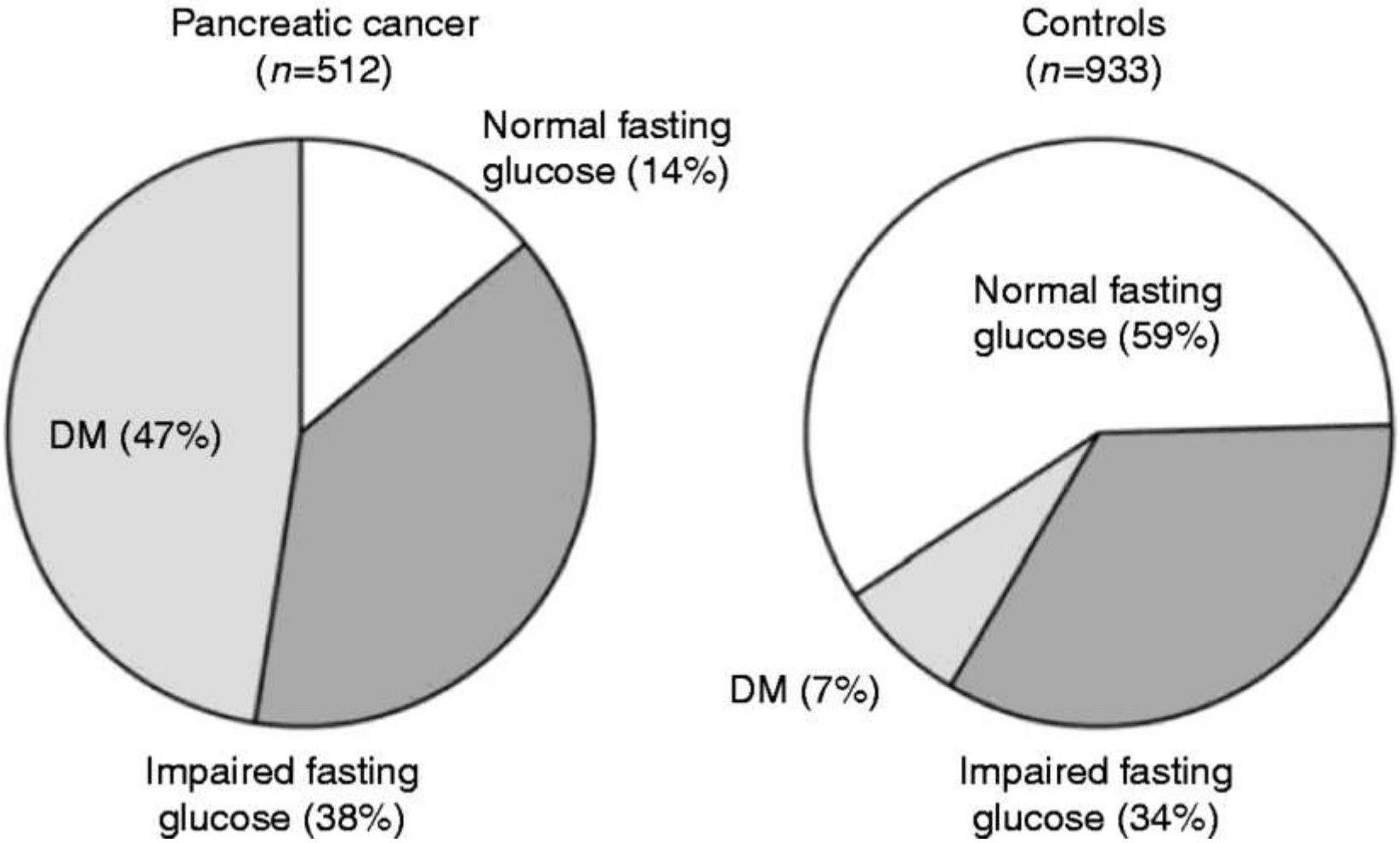
HOMA-IR (measures insulin resistance)

Pancreatic exocrine function and imaging

Interpreting and implementing guidelines

- Previous criteria are useful & best available at present
- Some critique that they are difficult to apply to all clinical settings (Roeyen & De Block, 2017 and Wynne *et al,* 2018)
- All fall short to a certain degree due to potential overlap of different DM types (HaPanEu, 2017)
- PEI & pancreatic atrophy is also found in longstanding T1&T2DM
- T3cDM likely if evidence of pancreatic destruction, pancreatic surgery or recent onset DM in pancreatic ductal adenocarcinoma (Hart *et al,* 2016)
- Could use clinical features to help distinguish from T2DM
  - If no family history of DM, wt loss >2kg, BMI <25kg/m^2 suggest 3c is more likely (Lee *et al*, 2012)
- Difference in opinion regarding diagnosing T3cDM and debate is ongoing

Epidemiology



Pannala et al, 2008

Epidemiology

- The relationship between diabetes and pancreatic cancer is complex
- High prevalence of diabetes in those diagnosed with pancreatic cancer (Pannala et al, 2008)
- Pancreatic cancer in people with diabetes

  - Type 1 (modest), type 2 (significantly), type 3c (highest risk but difficult to distinguish from CP risk)

- Diabetes in people with pancreatic cancer

  - 75-88% new onset DM (<24-36 months) of PC diagnosis (Hart et al, 2016)

- Studies have looked at the prevalence of diabetes in pancreatic diseases and pancreatic diseases in diabetes
- Ewald et al (2012), Woodmansey et al (2017) and Pendharker et al (2017)
- Type 3c diabetes accounts for 1-9% of all diabetes (4-5% reasonable estimate)
- Type 3c diabetes frequently misdiagnosed as type 2 diabetes
- Limited consensus of diagnostic criteria for Type 3c diabetes
- Type 3c diabetes associated with poorer glycaemic control and more likely to require insulin
- The prevalence has tripled over the past 10 years

Underlying pathology

- Thought to differ in PC to other causes of Type 3c DM
- Insulin deficiency

  - Unlikely related to destruction of pancreatic tissue (may become significant with disease progression)

  - Suppression of Beta cell function by toxic secretory products from tumour
- Immunopathogenesis

  - Inhibition of glucose stimulated insulin release by proinflamatory compounds
- Peripheral insulin resistance

  - substantial insulin resistance seen in PC (exact reason is poorly understood)
- Hepatic insulin resistance

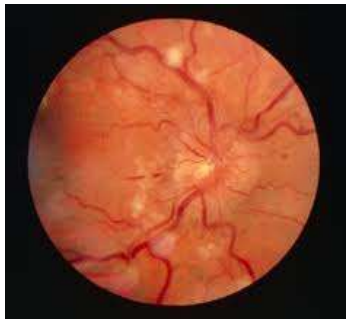
  - demonstrated PC and pancreatic resection
- Reduced incretin effect

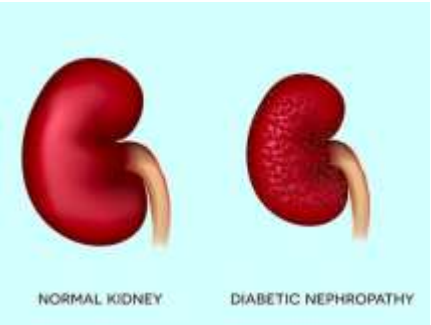
  - untreated PEI leads to reduced incretin response resulting in reduced insulin secretion

(Hart et al, 2016)

Complications of T3cDM

- Associated with poorer survival at all stages of PC
- Poorer response and increased complications of treatment
- May be more prone to severe episodes of hypoglycaemia due to the absence of other pancreatic hormones
- Patients with longstanding T3cDM are at risk of micro and macrovascular complications similar to T1DM and T2DM





Management goals

- <u>Lack of studies investigating treatment of T3cDM</u>
- Guidelines adopted from treatment of T1DM and T2DM
- Minimise short term metabolic complications

  - potential to reduce QoL and interrupt PC treatment (Hart et al ,2016)

- Aim for fasting glucose 3.9-7.2mmol/L, HbA1c 53
  - Likely inappropriate in more life-limiting conditions or if hypos frequent
- Need to tailor goals according to age/co-morbidities/life expectancy
- Aim to prevent/treat malnutrition, correct PEI and minimise extremes of glycaemia

Duggan *et al,* 2017

Treatment

- Minimal direct studies of diabetes management in PC
- Guidelines adopted from treatment of T1DM and T2DM
- Treatment of PC

  - Diabetes can be improved with surgical resection and response to chemotherapy (Pannala et al, 2008)

- Pharmacological

  - OHAs
  - Insulin
  - PERT

- Dietary

Pharmacological treatment

- Evidence is lacking
- In mild hyperglycaemia – Metformin can be used if not contra-indicated
  - Treats insulin resistance
  - Monitor GI side effects
- In more severe cases – Insulin is the treatment of choice
  - Desirable anabolic effect in malnourished pts
  - Challenging to plan insulin regimen due to rapid fluctuations in BGLs
  - No consensus on the optimal regimen
  - Consider pump therapy

Other oral agents:

- Sulfonylureas (gliclazide) – prolonged hypo risk, avoid in liver disease
- Glinides (repaglinide) – hypo risk but shorter half life so preferred
- Thiazolidinediones (glitazones) – avoid due to risk of fractures, fluid retention, CHF
- Alpha-glycosidase inhibitors (acarbose) – can aggravate PEI, not advised
- SGLT-2 inhibitors (gliflozins) – avoid as DKA risk in T3cDM, loss of kcal
- Incretin therapy, GLP-1 analogues and DPP4 inhibitors (byetta, gliptins)
  - Avoid due to possible risk of pancreatitis
  - Best way to optimise incretin response is to ensure adequate PERT

Rickets et al., 2014 HaPanEU, 2017

Dietary management

Principles of management	Management strategies
Prevent:	• Regular meal pattern with regular starchy CHO
• Hypoglycaemia	• Do not skip meals
• Hyperglycaemia	• Small, frequent meals
• Exacerbation of malnutrition	• Minimize high sugar/GI foods or fluids
• Malabsorption	• Minimise alcohol and smoking
• Co-morbidities associated with diabetes e.g. retinopathy, renal disease	• Ensure adequacy of PERT (will affect BGLs too)
	• Measure BGLs frequently, particularly if on insulin, if diet is poor, after physical activity, if hypo sx
	• Consider diary to record diet/BGLs/PERT/PAL
	• Routine dietitian assessment/monitoring

Adapted from Duggan and Conlon, 2017

- Can be a challenging patient group
  - Conflicting information
  - Access to specialist services
  - Pain, nausea
  - Reduced appetite
- Addressing T3cDM often only one of many potential issues
  - Cancer diagnosis, PEI, weight loss

Case Study

- 68 year old male
- Presented to GP with weight loss

- CT abdomen
  - solid mass in neck and head of pancreas involving hepatic artery, inoperable
  - gross pancreatic duct dilatation

- Histology – pancreatic ductal adenocarcinoma

Seen at HPB clinic

What do we want to find out in regards to his weight loss?

- Weight: 94 kg, BMI 30.7 kg/m^2
- Usual weight ~ 110 kg, has lost 15% in 2 months
- Diet Hx:
  - BF – ½ bowl cereal + skimmed milk
  - L – soup +/- low fat yoghurt
  - EM – beans on toast + jelly
  - Snacks – rich tea biscuit or fruit
- PMHx: Enlarged Prostate
- Reduced intake owing to loss of taste, poor appetite, feeling unwell
- Bowels – had been loose but now normal
- Random blood glucose – 7.3 mmol/L

Any thoughts?

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What happened next…

- Sent faecal elastase sample
  - Came back <15
  - Started on PERT
- Given oral nutrition support advice – encouraged with milky drinks, food fortification etc

- 2 weeks later returned to clinic…
  - Still losing weight
  - Feeling thirsty, increased urinary frequency
  - Oral thrush

Then what happened…

- BGL checked – 27.8 mmol/L!!
- Pt admitted into the hospital and started on insulin

Now...

- Eating better
- Taking PERT
- BGLs well controlled on basal bolus insulin regime
- Weight stabilised
- Pt having chemotherapy and managing well

What can we learn from this case study?

- Malabsorption can be masked by low fat diets
- Diabetes can be masked by malabsorption
- Important to think about the wider picture
- MDT approach

Take away messages

- Many research gaps regarding diagnosis and management
- Patients with PC should be monitored for diabetes
- Poor awareness and misclassification of Type 3c diabetes
- Early recognition allows optimal treatment and f/up
- Expect the clinical picture to change quickly
- Close monitoring essential for good glycaemic control, prevent malabsorption and optimising nutritional status

Any Questions?

References

- American Diabetes Association (2011) Diagnosis and classification of diabetes. *Diabetes Care,* 34(s1): 62-S69
- Cui Y & Andersen D (2011) Pancreatogenic diabetes: special consideration for management. *Pancreatology* 11 (3); 279–294
- Duggan S & Conlon K (2017) Pancreatogenic Type 3c Diabetes: Underestimated, Underappreciated, and Poorly Managed. *Practical Gastroenterology,* 14-23
- Ewald N, Kaufman C, Raspe A, Kloer H *et al* (2012) Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c), *Diabetes Metabolism Research and Reviews* 28:4 (338-342)
- Hardt, P, Brendel M, Kloer H, Bretzel R (2008) Is Pancreatic Diabetes underdiagnosed and misdiagnosed? *Diabetes Care*, 31(s2), 165-169
- Hart P *et al* (2016) Type 3c diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. Lancet. *1(3) 226-237*
- Lee J, Kim S, Park H *et al* (2012) New-onset diabetes patients need pancreatic screening? *Journal of Clinical Gastroenterology,* 46(7); e58–61
- Magruder J, Elahi D and Andersen, D (2011) Diabetes and Pancreatic Cancer. *Pancreas.* Vol 40 (3) 339-351
- Muniraj T & Chari S (2012) Diabetes and Pancreatic Cancer. *Minerva Gastroenterology Dietol,* 58(4), 331-345
- NICE guideline (2015) Suspected cancer: recognition and referral https://www.nice.org.uk/guidance/ng12
- Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM & Chari ST 2008 Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. *Gastroenterology* 134 981–987.
- Pendharkar S, Mathew J & Petrov M (2017) Age- and sex-specific prevalence of diabetes associated with diseases of the exocrine pancreas: a population-based study *Digestive Liver Disease*, 49, 540–544
- Roeyen & De Block (2017) A pleas for more practical and clinically applicable criteria defining type 3c diabetes. *Pancreatology*, **17:**875
- Woodmansery C, McGovern A, McCullough K, Whyte M *et al* (2017) Incidence, Demographics, and Clinical Characteristics of Diabetes of the Exocrine Pancreas (Type 3c): A Retrospective Cohort Study. *Diabetes Care*, 40(11):1486-1493
- Wynne K, Devereaux B & Dornhorst A (2018) Diabetes of the exocrine pancreas: Review. *Journal of Gastroenterology and Hepatology,* 1-9