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

American Diabetes Association, 2011
Causes of Type 3c Diabetes

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

Based on Hardt et al (2008)
1,922 hospitalised DM patients
8% reclassified as T3cDM
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)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type 3cDM</th>
<th>Comparison to T1DM</th>
<th>Comparison to T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycaemia</td>
<td>Mild, or severe in ‘brittle diabetes’</td>
<td>Severe</td>
<td>Usually mild</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>Common and may be severe</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>Rare</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Hepatic insulin sensitivity</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal or decreased</td>
</tr>
<tr>
<td>Peripheral insulin sensitivity</td>
<td>Increased</td>
<td>Normal or increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Insulin levels</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Glucagon levels</td>
<td>Low</td>
<td>Normal or High</td>
<td>Normal or high</td>
</tr>
<tr>
<td>PP levels</td>
<td>Low</td>
<td>Normal or Low</td>
<td>High</td>
</tr>
<tr>
<td>DM-associated antibodies</td>
<td>No</td>
<td>Yes</td>
<td>Rare</td>
</tr>
<tr>
<td>Typical age of onset</td>
<td>Any</td>
<td>Childhood/teens</td>
<td>Mainly adulthood</td>
</tr>
<tr>
<td>Overweight/Obese</td>
<td>Uncommon, although CP pts may be overweight but have muscle depletion</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Undernutrition</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
<tr>
<td>Nutrient Deficiency</td>
<td>Deficiency of fat soluble vitamins in CP due to PEI/poor diet</td>
<td>Rare</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Based on earlier table by Duggan & Conlon, 2017
Diagnosis of T3cDM

- **No universally accepted diagnostic criteria**

- 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>
<thead>
<tr>
<th>Table 2</th>
<th>Proposed diagnostic criteria for type 3c diabetes mellitus</th>
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</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong> (must be present)</td>
<td></td>
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<tr>
<td>Presence of exocrine pancreatic insufficiency (monoclonal fecal elastase-1 test or direct function tests)</td>
<td></td>
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<tr>
<td>Pathological pancreatic imaging (endoscopic ultrasound, MRI, CT)</td>
<td></td>
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<tr>
<td>Absence of type 1 diabetes mellitus associated autoimmune markers</td>
<td></td>
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<tr>
<td><strong>Minor criteria</strong></td>
<td></td>
</tr>
<tr>
<td>Absent pancreatic polypeptide secretion</td>
<td></td>
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<tr>
<td>Impaired incretin secretion (e.g., GLP-1)</td>
<td></td>
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<tr>
<td>No excessive insulin resistance (e.g., HOMA-IR)</td>
<td></td>
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<tr>
<td>Impaired beta cell function (e.g., HOMA-B, C-Peptide/glucose-ratio)</td>
<td></td>
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<tr>
<td>Low serum levels of lipid soluble vitamins (A, D, E and K)</td>
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</table>

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

Pancreatic cancer
(n=512)

Normal fasting glucose (14%)

DM (47%)

Impaired fasting glucose (38%)

Controls
(n=933)

Normal fasting glucose (59%)

DM (7%)

Impaired fasting glucose (34%)

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
  - 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 proinflammatory 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

• Lack of studies investigating treatment of T3cDM
• 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

<table>
<thead>
<tr>
<th>Prevent:</th>
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<tbody>
<tr>
<td>Regular meal pattern with regular starchy CHO</td>
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<tr>
<td>Do not skip meals</td>
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<tr>
<td>Small, frequent meals</td>
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<tr>
<td>Minimize high sugar/GI foods or fluids</td>
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<tr>
<td>Minimise alcohol and smoking</td>
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<tr>
<td>Ensure adequacy of PERT (will affect BGLs too)</td>
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<tr>
<td>Measure BGLs frequently, particularly if on insulin, if diet is poor, after physical activity, if hypo sx</td>
<td></td>
</tr>
<tr>
<td>Consider diary to record diet/BGLs/PERT/PAL</td>
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<tr>
<td>Routine dietitian assessment/monitoring</td>
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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?
- Weight: 94 kg, BMI 30.7 kg/m²
- 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
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

- Roeyen & De Block (2017) A pleas for more practical and clinically applicable criteria defining type 3c diabetes. *Pancreatology*, 17:875