ENDORAMA –
THE CASE OF THE
DISAPPEARING PANCREAS

Disha Kumar Narang, M.D.
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Our Patient

- 49-year-old woman presents to endocrinology clinic with a 2-month history of polyuria and hypoglycemic episodes
Additional History

Past Medical History:
- Hypertension
- Hodgkin’s lymphoma s/p chemotherapy (MOP and ABVD)
  - C/B CMV hepatitis and strep sepsis
  - Neuropathy from chemotherapy
- Isolated exocrine pancreatic insufficiency

Past Surgical History:
- Splenectomy

Family Hx:
- Father: psoriasis, RA, HLD, CAD, CABG, polymyalgia rheumatica
- Mother: Gallstone pancreatitis, HLD, CAD
- Son: T-cell deficiency; epilepsy

Social History:
- Patient is an attorney
- Ethnic background: Greek and Polish
- Tobacco: Denies
- EtOH: Denies
- Illicits: Denies

Home Meds:
- Atorvastatin 20mg qday
- Cholecalciferol 2000 IU qday
- Clonidine 0.2mg TID
- Diltiazem 180mg qday
- Nebivolol 5mg qday
- Creon 24,000 units 1-2 capsules as needed with meals

Allergies
- Iodinated contrast media
- Penicillin
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Exocrine Pancreatic Insufficiency

• May, 2013 – Started to develop weight loss (10 lbs), with progressive steatorrhea and abdominal pain

• Initial work-up at OSH:
  • Celiac Ab’s: Negative
  • LFT’s: Normal
  • IgG4: Normal
  • ANA, RF, SSA/SSB: Negative
  • TSH: Normal
  • Tg: 205
  • Cystic fibrosis testing: Results unavailable; Negative per patient
  • 25-OH-Vitamin D: 37
  • HbA1C: 5.9%
  • EGD and colonoscopy: Negative
Exocrine Pancreatic Insufficiency

- Abdominal CT: Pancreatic atrophy
- Fecal Elastase (March, 2014): 86
- Trypsin: 8 (low)

- Started on Creon 24, 2-4 tablets with each meal → Improvement in frequency of bowel movements
Exocrine Pancreatic Insufficiency\textsuperscript{3,4}

- **Etiologies:**
  - Cystic fibrosis
  - Chronic pancreatitis
  - Complication of gastric or pancreatic surgical procedures

- **Symptoms:**
  - Steatorrhea, diarrhea, abdominal pain, weight loss

- **Treatment:** Goal to minimize malabsorption and associated malnutrition of lipids and lipid-soluble vitamins
  - Supplemental pancreatic enzyme replacement therapy
<table>
<thead>
<tr>
<th>Tests</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct tests</strong></td>
<td></td>
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<tr>
<td>CCK</td>
<td>Requires specialized laboratory</td>
</tr>
<tr>
<td>Secretin</td>
<td>1-h collection</td>
</tr>
<tr>
<td>Secretin-CCK</td>
<td>Potential for diluted, unreliable enzyme collections</td>
</tr>
<tr>
<td>Endoscopic pancreatic function</td>
<td>None</td>
</tr>
<tr>
<td>Lundh</td>
<td>Confounded in small bowel mucosal diseases</td>
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<tr>
<td><strong>Indirect tests</strong></td>
<td></td>
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<tr>
<td>Faecal elastase-1</td>
<td>Poor sensitivity for early EPI</td>
</tr>
<tr>
<td>24-h and 72-h stool fat</td>
<td>Often inadequate patient compliance</td>
</tr>
<tr>
<td>Secretin-enhanced MRI</td>
<td>Limited assessment</td>
</tr>
<tr>
<td>Serum/urine pancreolaury</td>
<td>Limited in bile salt deficiency, coeliac disease, renal failure and post-gastrectomy</td>
</tr>
<tr>
<td>(^{13})C-mixed triglyceride</td>
<td>Currently under evaluation</td>
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CCK: Cholecystokinin, EPI: Exocrine pancreatic insufficiency, MRI: Magnetic resonance imaging.
Outside Clinic Labs (Spring, 2014)

<table>
<thead>
<tr>
<th>140</th>
<th>104</th>
<th>10</th>
<th>87</th>
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<tbody>
<tr>
<td>3.8</td>
<td>26</td>
<td>0.73</td>
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Total Chol 242
LDL 162
HDL 58
Tg 110

HbA1C 5.7%
C-peptide 1.3
Serum Osmolality 288
Chicago Marathon (October, 2014)

- Towards the end of the marathon, the patient stopped to use the bathroom, and became very confused
  - Confusion improved with Gatorade
- Around this time, she noticed that she was getting up to urinate 6 times per night
  - HbA1C: 5.9%
  - Urine and serum osmolality at OSH: Negative for SIADH
Hyper- and Hypoglycemia

• The patient purchased a CGM
  • Post-prandial BGs: 240s-280s
  • Hyperglycemia caused symptoms of fatigue
• Tried on 2 oral hypoglycemic medications:
  • Nateglinide → Episodes of hypoglycemia
  • Metformin → Diarrhea
• Reported several symptomatic hypoglycemic episodes to 50s with light headedness, diaphoresis, blurry vision
Continued Hypoglycemia

• Upon presentation to our clinic in December, the patient was feeling poorly, trying to eat every 1-2 hours to prevent hypoglycemia, and unable to take her Creon at each meal.

• Hypoglycemic events overnight and during the day without any strenuous activity, not correlated with food intake.
Differential Diagnosis for Hypoglycemia?1,2

- **Drugs**
  - Insulin, insulin secretagogue
  - EtOH
  - Pentamidine
  - Quinine
  - Fluoroquinolones
- **Critical illness**
  - Acute liver failure or cirrhosis
  - Acute renal failure or CKD
  - Heart failure
  - Sepsis
- **Non-islet cell tumors**
  - Mesenchymal tumors, HCC, adrenocortical tumors, carcinoid tumors, leukemia, lymphoma
- **Endogenous hyperinsulinism**
  - Insulinoma
  - Autoimmune hypoglycemia (antibody to insulin or insulin receptor)
  - Functional beta-cell disorders:
    - Non-insulinoma pancreatic tumoreogenic hypoglycemia syndrome
    - Post-gastric bypass hypoglycemia
- **Hormone deficiencies**
  - Adrenal insufficiency
  - Growth hormone deficiency
- **Glycogen storage disease**
Physical Exam

• Vitals: HR 63; BP 155/90; RR 17; Height 170.2cm; Wt 65.45kg; BMI 22.6 kg/m2
• General: well-developed; well-nourished
• HEENT: PERRLA; no thyromegaly; no lymphadenopathy
• CV: RRR; normal heart sounds
• Pulm: CTAB; no wheezes, rales
• Abd: Soft, non-tender, non-distended; positive bowel sounds
• MSK: Normal ROM; no edema or tenderness
• Neuro: AAOx3; no focal deficits
• Skin: Warm and dry; no rashes or lesions
Initial Work-up?
Endocrinology Clinic Labs (Dec, 2014)

- HbA1C – 5.4%
- C-peptide – 0.40
- GAD65 Ab – 0.00
- Insulin Ab – 0.00
- Pro-insulin – 18
- Insulin – 9.5
- Cortisol – 14.8
- FSH – 120.9
- LH – 44.5
- TSH – 1.00
MRCP

- Marked atrophy of the pancreatic parenchyma with predominately fatty replacement
- No abdominal mass lesions identified and no strictures seen in normal caliber pancreatic duct without evidence of obstruction
Clinical Questions

• Why is our patient hypoglycemic? What caused her pancreatic insufficiency?

• Does our patient have diabetes?

• Can insulin-secreting beta cells burn out, thereby causing a surge in insulin secretion prior to losing function?

• Does the patient have a genetic mutation pre-disposing her to loss of pancreatic function and therefore diabetes?
Diabetes Classification

Fig. 1. Diabetes Classification.
Diabetes Classification\textsuperscript{18}

Fig. 1. Diabetes Classification.
The Pancreas and Diabetes

• Relationship established after pancreatectomy in a dog in 1889
• Chey first described in 1963 that diabetes could be due to various pancreatic diseases
• 1-2% of human diabetes is due to pancreatic disease
• 70-80% of beta cells need to be removed from the pancreas (i.e. extensive pancreatic damage) to cause diabetes
  • Surgical excision
  • Acute, chronic pancreatitis
  • Pancreatic fibrosis
  • Tropical chronic pancreatitis (fibro-calculous pancreatic disease)
  • Carcinoma of the pancreas
  • Inherited disorders affecting the pancreas such as CF
## Pancreatic Disease

### Acute Pancreatitis
- Premature activation of enzyme precursors produced by acinar cells → inflammatory cascade
- More common in T2DM patients
- Islet cells often spared, but acute hyperglycemia develops in >50% of cases and permanent DM in 5%

### Chronic Pancreatitis
- Persistent inflammation of pancreas resulting in loss of exocrine function
- 50% develop DM
  - Disturbed beta-cell regeneration
- Predisposes to pancreatic carcinoma
### Pancreatic Disease\(^{14}\)

#### Tropical Chronic Pancreatitis
- Seen in developing countries
- Can result in fibrocalculous pancreatic diabetes
- Young patients – present with abdominal pain from pancreatic calculi
- DM develops up to 10 years after pancreatitis occurs
- Etiology: Unknown
  - Impoverished, malnourished areas
  - Genetic mutations in *SPINK1* gene
  - Micronutrient deficiency or toxins

#### Pancreatic Carcinoma
- Ductal adenocarcinoma in 90% of cases
- Twice as common in obese patients or T2DM
- DM present in 50% of those with pancreatic carcinoma
  - Tumor-associated humoral factors that cause insulin resistance
  - *KRAS* gene mutation involved in progression to cancer
Pancreatic Diabetes (Type 3c?)

- Hardt, et al. (Diabetes Care, 2008) reclassified all patients with diabetes treated at their hospital in Germany over a 1-year period\textsuperscript{15}
- Type 3 – No autoantibodies; both exocrine pancreatic insufficiency and typical morphologic pathology
- Records of 1922 patients examined for patients meeting T1DM, T2DM, and T3cDM criteria
  - 8\% $\rightarrow$ Reclassified as diabetes type 3c
  - 12\% $\rightarrow$ T1DM
  - 80\% $\rightarrow$ T2DM
Pancreatic Diabetes

- Ewald, et al. studied 1868 patients diagnosed with diabetes, who were admitted to their hospital over 24 months. Patients were reclassified according to ADA classifications.¹⁹
- Misclassification is frequent
- Found that 172 (7.2%) had pancreatic disease, including 135 with chronic pancreatitis (78.5%), 12 with hereditary hemochromatosis, 14 with pancreatic cancer, and 7 with cystic fibrosis
  - Underlying diagnosis had been missed in half of these patients
Pancreatic (Type 3C) Diabetes?\textsuperscript{5}

- Limited data available
- Previously: 0.5-1.15% prevalence among DM cases in North America\textsuperscript{6} \Rightarrow Now more common than previously reported: 5-10% of Western diabetic populations\textsuperscript{7}
- Diabetes mellitus secondary to pancreatic diseases
  - Exocrine pancreatic diseases
    - Hemochromatosis, cystic fibrosis, fibrocalculous pancreatopathy, pancreatic trauma, pancreatectomy, pancreatic agenesis, pancreatic cancer
  - Most common cause (78.5% of T3cDM patients): \textit{chronic pancreatitis}
Exocrine Pancreatic Insufficiency and Diabetes

• Frequent co-morbidity of both exocrine and endocrine pancreas in diabetic patients
• About every second patient with T1DM (26-74%) and about every third patient with T2DM (28-36%) suffers from exocrine pancreatic insufficiency
  • Dysregulation of exocrine secretion due to diabetic neuropathy
  • Atrophy of exocrine tissue due to lack of local trophic insulin effects
  • Local or general vascular damage
  • Autoimmune-mediated inflammation induced by beta-cell specific and exocrine tissue antigens
  • Genetic defects of exocrine and endocrine cells
CEL Mutations\textsuperscript{15,16}

- Genetic factors may contribute to exocrine dysfunction in diabetes
- Mutation in 2 Norwegian families with diabetes and exocrine pancreas dysfunction
  - Diabetes characterized by primary beta-cell failure and simultaneous pancreatic exocrine dysfunction
  - Heterozygous frame-shift mutation was identified in the carboxyl-ester lipase (CEL) gene
- CEL mutations and exocrine dysfunction were also identified in 182 unrelated subjects with diabetes
- Findings linked diabetes to the disrupted function of a lipase in the pancreatic acinar cells
Diagnosis of Pancreatic Diabetes

- Proposed major criteria:
  - Presence of exocrine pancreatic insufficiency
  - Pathological pancreatic imaging (EUS, MRI, CT)
  - Absence of T1DM-associated autoimmune markers

- Proposed minor criteria:
  - Impaired beta cell function (HOMA-B, C-peptide/glucose-ratio)
  - No excessive insulin resistance
  - Low serum levels of lipid soluble vitamins
Clinical Characteristics

• Frequent episodes of hypoglycemia – labile blood sugars
  • Paradoxic combination of normal or enhanced peripheral insulin sensitivity and decreased hepatic insulin sensitivity → enhanced peripheral insulin sensitivity and deficiency of counter-regulatory pancreatic glucagon secretion

• Ewald, et al. found that in pancreatic diabetes patients, 60.5% of subjects were male, and 39.5% female

• No statistically significant differences in HbA1C between diabetes subtypes
Treatment?

- No generally accepted guidelines
  - Pancreatic diabetes patients have most typically been treated with Metformin → shown to reduce risk of pancreatic cancer in patients with chronic pancreatitis by up to 70%\(^\text{13}\)
  - Depending on beta cell function, patients may become fully insulin-dependent
- Chronic pancreatitis and exocrine dysfunction have been associated with a functional impairment of the incretin system
  - May be an additional therapeutic target, but incretin-based therapy is associated with a higher risk of pancreatitis
1-Week Follow-Up in Endocrinology Clinic

- Patient increased her carbohydrate intake with each meal, in addition to snacks between meals
- When attempting to run, her BG’s would drop from 150s → 60s, despite hydrating with Gatorade
- Despite eating carbohydrate-rich meals, her BG would drop to 40s on occasion, with hypoglycemia unawareness
  - BG’s would routinely drop to 60s-80s in the late afternoon
- Our patient was ruled out for a pituitary disorder, adrenal insufficiency, hyper- or hypothyroidism
  - Repeat AM cortisol: 16.9
• Started on a trial of hydrocortisone 30/15 to maintain blood sugars, but the patient was unable to tolerate
  • She had agitation per her family, and continued to have hypoglycemia to 50s → Hydrocortisone was discontinued
• Encouraged to continue eating a high-carbohydrate diet
2 Weeks Later in Endocrinology Clinic

• Patient reported much improved energy levels
• One episode of hypoglycemia to 50s over 2 weeks, likely due to increased activity and decreased carbohydrate intake that day
• Having more frequent high’s: 280s – low 300s
# Overview of Labs Through Clinic Visits

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<thead>
<tr>
<th></th>
<th>12/12/14</th>
<th>12/19/14</th>
<th>1/9/15</th>
</tr>
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<tbody>
<tr>
<td>HbA1C</td>
<td>5.4%</td>
<td>5.7%</td>
<td>5.8%</td>
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<tr>
<td>C-peptide</td>
<td>0.40</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>14.8</td>
<td>16.9</td>
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</table>
Remaining Questions and Conclusions

• Has the patient had indolent chronic pancreatitis that suddenly manifested itself in the last 1.5 years?
• Will the patient continue to have intermittent episodes of hypoglycemia and have labile blood sugars?

• The patient likely has pancreatic diabetes, which will require insulin therapy.

• Important to keep a broad differential in mind in a patient who presents with exocrine pancreatic insufficiency, and its connection to development of diabetes
References

5. Ewald N, Bretzel RG. Diabetes mellitus secondary to pancreatic diseases (Type 3c)--are we neglecting an important disease? Eur J Intern Med. 2013 Apr;24(3):203-6.
References