Atypical Diabetes

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Prior to 1997 terminology was treatment based: “insulin dependent” or “non-insulin dependent”

Confusing, descriptive, not necessarily constant ….

Changed to reflect pathophysiology:

- **Classic T1DM** → autoimmune
  - antibodies to glutamic acid decarboxylase (GAD), islet cell, insulin, the tyrosine phosphatases (insulinoma-associated protein 2 [IA-2] and IA-2 beta), and zinc transporter (ZnT8)

- **Classic T2DM** → insulin resistance + progressive B cell dysfunctions
Non Type 1, Non Type 2 Diabetes Classification

- 10% of diabetes cannot be attributed to T1DM or T2DM
  - Latent Autoimmune Diabetes in Adults (LADA)
  - Ketosis-prone diabetes
  - Maturity-Onset Diabetes of Young (MODY)
  - Lipodystrophy
  - Pancreatic destruction
  - Endocrinopathies
  - Medications
Case 1

- 22 yo **biologic female** presents for new onset hyperglycemia. Was seen in the ED for polyuria and UTI and yeast infection. Bg was **320** and there was **not an anion gap**. There is a very **strong FH of T2DM** diagnosed in first degree relatives in their 20. they were started on metformin 500 mg bid. Of note, they have recently started taking testosterone as **they identify as male**. **BMI is 22**.

- bp is normal. Some acne and terminal hair the the face but **no acanthosis**.

- The savvy EM/IM resident sent out a **GAD ab which was negative**.

- What is the likely diagnosis?
- Transgender man with MODY
- Transgender woman with T1DM
- Woman with T2DM
- Transgender man with T2DM
Transgender man with MODY

Transgender woman with T1DM → GAD+

Woman with T2DM → transgender man and no evidence of T2DM (obesity, acanthosis)

Transgender man with T2DM → no evidence of T2DM (obesity, acanthosis)
Maturity-Onset Diabetes of Young

- Non-obese patients with diabetes at a young age
  - GAD-
  - < 25 years old
  - strong family history (autosomal dominant)
  - > 10 genes associated with these disorders
  - modest hyperglycemia → severe diabetes

- Specific genetic defects are included in the names of the monogenic forms

- Diabetes in the absence of obesity is suspicious for MODY, particularly in adolescents with presumed type 2 diabetes
## MODY

<table>
<thead>
<tr>
<th>Type</th>
<th>Genetic defect</th>
<th>Frequency</th>
<th>Beta cell defect</th>
<th>Clinical features</th>
<th>Risk of microvascular disease</th>
<th>Optimal treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hepatocyte nuclear factor-4-alpha</td>
<td>&lt;10 percent</td>
<td>Reduced insulin secretory response to glucose</td>
<td>Normal renal threshold for glucose</td>
<td>Yes</td>
<td>Sulfonylureas</td>
</tr>
<tr>
<td>2</td>
<td>Glucokinase gene</td>
<td>15 to 31 percent</td>
<td>Defective glucokinase molecule (glucose sensor), increased plasma levels of glucose are necessary to elicit normal levels of insulin secretion</td>
<td>Mild, stable, fasting hyperglycemia, often diagnosed during routine screening, not progressive.</td>
<td>Generally no</td>
<td>Diet</td>
</tr>
<tr>
<td>3</td>
<td>Hepatocyte nuclear factor-1-alpha</td>
<td>52 to 65 percent</td>
<td>Abnormal insulin secretion, low renal threshold for glucose</td>
<td>Low renal threshold for glucose, +glycosuria</td>
<td>Yes</td>
<td>Sulfonylureas</td>
</tr>
<tr>
<td>4</td>
<td>Insulin promoter factor 1</td>
<td>Rare</td>
<td>Reduced binding to the insulin gene promoter, reduced activation of insulin gene in response to hyperglycemia</td>
<td>Rare, pancreatic agenesis in homozygotes, less severe mutations result in mild diabetes</td>
<td>Yes</td>
<td>Sulfonylureas</td>
</tr>
<tr>
<td>5</td>
<td>Hepatocyte nuclear factor-1-beta</td>
<td>Rare</td>
<td></td>
<td>Pancreatic atrophy, renal dysplasia, renal cysts, renal insufficiency, hypomagnesemia</td>
<td>Yes</td>
<td>Insulin</td>
</tr>
<tr>
<td>6</td>
<td>Neurogenic differentiation factor-1</td>
<td>Rare</td>
<td>Pancreatic development</td>
<td></td>
<td>Yes</td>
<td>Insulin</td>
</tr>
</tbody>
</table>

**Data from:**
1. Naylor B, Philpson LH. Who should have genetic testing for maturity-onset diabetes of the young? Clin Endocrinol (Oxf) 2011; 75:422.
2. Ramesh SC, Marshall I. Clinical suspicion of maturity onset diabetes of the young in pediatric patients diagnosed with diabetes mellitus, Indian J Pediatr 2011; Dec 10 [ePub].

Graphic 82071 Version 2.0
HNF-1 alpha diabetes (formerly MODY 3)

- Common cause of MODY 60%
- Glucosuria is often part of the clinical presentation
- Diabetic complications are often present
- Treatment is diet intervention and most patients require oral hypoglycemic agents *SU
Glucokinase (GCK) diabetes (formerly MODY 2)

- 2nd most common
- Heterozygous inactivating mutations in glucokinase
  - phosphorylates glucose to glucose-6-phosphate
  - acts as a glucose sensor
- Results in a higher threshold for glucose stimulated insulin secretion.
- Hyperglycemia is often stable, mild, and is not associated with the vascular complications
- Treatment consists basically of dietary (avoiding large quantities of carbohydrate) and lifestyle interventions
<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Type 1 diabetes mellitus</th>
<th>Type 2 diabetes mellitus</th>
<th>MODY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of diagnosis (years)</td>
<td>Majority &lt;25, but may occur at any age</td>
<td>Typically &gt;25 but incidence is increasing in adolescents, paralleling increasing rates of obesity in children and adolescents*</td>
<td>&lt;25</td>
</tr>
<tr>
<td>Weight</td>
<td>Usually thin, but with obesity epidemic overweight and obesity at diagnosis becoming more common</td>
<td>&gt;90 percent at least overweight</td>
<td>Similar to general population</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Insulin-dependent</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Normal when controlled</td>
<td>Decreased</td>
<td>Normal (may be decreased if obese)</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>Infrequent (2 to 10 percent)</td>
<td>Frequent (75 to 90 percent)</td>
<td>Multigenerational, ie, &gt;2 generations</td>
</tr>
<tr>
<td>Risk of diabetic ketoacidosis</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

MODY: maturity onset diabetes of the young.
* In North America, type 2 diabetes predominates in Hispanic, African-American, Native American, Canadian First Nation, Pacific Islander, and Asian-American youth.

Data from:
1. Naylor R, Phillipson LH. Who should have genetic testing for maturity-onset diabetes of the young? Clin Endocrinol (Oxf) 2011; 75:422.
Transgender

- People that have been assigned either male or female at birth yet self-identify as opposite of, neither, or somewhere along, the male-female spectrum
  - Transman
  - Transwoman

- Gender identity is a person’s sense of his or her own gender.

- Sexual orientation is a physical and/or emotional attraction to a specific gender or genders.
36 yo AA was admitted with DKA.

Admit labs were: glucose is 950, co2 is 6 with an anion gap of 26. abg shows pH of 7.1.

Their BMI is 50. There is marked acanthosis

Insulin drip is started.

They tell you diabetes is not a new diagnosis as they were admitted last year for the same and were discharged on insulin but then transitioned to metformin as outpatient.
What is the diagnosis?

- Ketosis prone diabetes
- T1DM
- LADA
- T2DM
What is the diagnosis?

- Ketosis prone diabetes
- T1DM → thin
- LADA → thin
- T2DM → generally do not go into overt DKA
Ketosis-prone Diabetes

- Flatbush diabetes

- Non-autoimmune ketosis-prone diabetes has been described in young African Americans

- Often present with marked hyperglycaemia, ketosis or even ketoacidosis and severe insulin deficiency, but the majority (76%) achieve long-lasting remission from insulin dependency

- Ketotic relapses preceded by progressive hyperglycemia are seen in 90% within 10 years

- Obese males seem to be most vulnerable to this form of diabetes and insulin resistance together with beta-cell dysfunction seem to trigger the ketotic episodes.
Case 3

- 44 yo business man presents for T2DM follow up. He was diagnosed at the age of 38 and was put on metformin and now in on glimiperide and metformin. He is having morning hyperglycemia and occasional lows after exercise. He has never been overweight and current BMI is 23. He does not have HTN or dyslipidemia.

- He denies FH of diabetes.
What is the next best test?

- C peptide
- MODY screen
- GAD antibodies
- Insulin level
What is the next best test?

- C peptide → always pair with glucose
- MODY screen → young and +++FH
- GAD antibodies
- Insulin level → always pair with glucose
Latent Autoimmune Diabetes in Adults

- Previously called type 1.5 diabetes

- 5-14% of patients diagnosed with T2DM of European or Asian descent have pancreatic autoantibodies (GAD+)

- 50% of them will develop marked insulin-deficiency and need treatment with insulin within 5-10 years
  - the rest remain on orals although they are less obese and have less evidence of metabolic syndrome than antibody-negative Type 2 diabetic patients
The higher the titers of GAD65 antibodies $\rightarrow$ the lower the BMI $\rightarrow$ the less endogenous insulin $\rightarrow$ the quicker the progression to insulin dependence

Higher risk for autoimmune thyroid disease and celiac disease
Lipodystrophy

- Loss of subcutaneous adipose tissue associated with severe insulin resistance, hepatosteatosis and diabetes
- They can either be congenital or acquired
  - Treatment of HIV with protease inhibitors
Pancreatic Destruction

- 60-70% loss of the pancreas $\Rightarrow$ diabetes
- Acquired etiologies include: pancreatitis, trauma, infection, pancreatic carcinoma, pancreatectomy
- Inherited disorders that affect both the exocrine and endocrine pancreas include hemochromatosis and cystic fibrosis
Pancreatectomy

- T1DM + pancreatic exocrine deficiency + alpha cell deficiency
  - w/o Alpha cells → no glucagon → hepatic glucose production → hypoglycemia risk!
- Low insulin requirements
- Pancreatic enzyme supplements is always needed!
Pancreatitis

- The mechanism of diabetes in pancreatitis is either acute or chronic inflammation or fibrosis of the beta cells.
- 70% of patients with long term pancreatitis (over 20 years) have DM.
- 90% of patients with fibrocalcific pancreatitis have diabetes.
- Hypoglycemia risk and pancreatic enzyme supplements is often needed.

  - Conflicting data on whether treatment with DPP4-inhibitors or GLP1-analogues can cause pancreatitis.
Hemochromatosis

- Autosomal recessive
- Increased iron absorption by the GI tract and increased total body iron stores
- Excess iron is sequestered in many different tissues including the liver, the endocrine and exocrine pancreas, and the pituitary
- Classic triad of hemochromatosis is diabetes mellitus, hepatomegaly, and increased skin pigmentation
Cystic Fibrosis

- Autosomal recessive disorder due to a defect in the chloride transport channel

- Symptoms are mostly pulmonary, but patients also have exocrine pancreatic dysfunction and need pancreatic enzyme supplements

- Share features with both type 1 and type 2 diabetes → decreased insulin production and insulin resistance

- Per ADA screening:
  - Annual screening for CFRD in all patients using OGTT
# Diabetes risk

## Approximate frequency of diabetes mellitus in different types of pancreatic disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pancreatectomy</td>
<td>100</td>
</tr>
<tr>
<td>Pancreatectomy</td>
<td></td>
</tr>
<tr>
<td>Distal pancreatectomy</td>
<td>20 to 40</td>
</tr>
<tr>
<td>40 to 86 percent resection</td>
<td>40</td>
</tr>
<tr>
<td>80 to 95 percent resection</td>
<td>&lt;60</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>2 to 18</td>
</tr>
<tr>
<td>Chronic catar calling</td>
<td>60 to 70</td>
</tr>
<tr>
<td>Chronic noncatar calling</td>
<td>15 to 50</td>
</tr>
<tr>
<td>Hemachromatosis</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>75</td>
</tr>
<tr>
<td>Secondary</td>
<td>15</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>40 to 50</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>10</td>
</tr>
</tbody>
</table>


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Endocrinopathies

- Acromegaly
- Cushing’s syndrome*
- Pheochromocytoma
- Hyperthyroidism
- Neuroendocrine tumors
  - Glucagonoma and somatostatinoma
Cushing’s syndrome

- Excess secretion of glucocorticoids from the adrenal glands can be caused by adrenal, pituitary, or ectopic tumours secreting glucocorticoids or exogenous administration
- Marked insulin resistance, increase gluconeogenesis
- Treatment of choice is insulin*
Drug Induced Diabetes

- **Glucocorticoids**
  - Inhaled, topical and PO

- **Immunosuppressive drugs**
  - Tacrolimus and cyclosporine have been shown to impair insulin secretion and insulin action dose-dependently
  - mtor antagonists sirolimus and everolimus has been associated with post-transplant diabetes

- **Statins**
  - Association is dose-dependent and the size of the effect varies for different statins
  - Not a reason not to use in a statin benefit groups!
Psychototropic medicines

- Increase appetite that can lead to weight gain, hypertension and dyslipidaemia, as well as diabetes
- Clozapine, olanzapine, quetiapine and chlorpromazine are the most risky

Interferon-alpha

- T1DM and other autoimmune diseases
Chromosomal anomalies

- **Down’s syndrome**
  - Trisomy 21
  - Autoimmune disorders: type 1 diabetes (4x) and hashimotos

- **Klinefelter syndrome**
  - XXY
  - hypergonadotrophic hypogonadism ➔ low testosterone, decreased muscle and increased fat mass ➔ T2DM
  - Rx ➔ trt

- **Turner syndrome**
  - 45X
  - Increased in T2DM and possibly T1DM
Learning points

- It can be difficult to distinguish between type 1, type 2 and atypical diabetes.

- It is important to diagnose MODY because the optimal treatment and risk for diabetes complications varies with the underlying genetic defect.

- Those with LADA are at risk for other autoimmune diseases.

- Any disease that damages the pancreas, or removal of pancreatic tissue, can result in diabetes.
Lalala Lalala
My mom says I'm special