The Gray Area between Type 1 and Type 2 Diabetes

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I have no disclosures.

Objectives

- Review atypical types of diabetes
  - LADA
  - MODY
  - Ketosis prone type 2
  - Double diabetes
- Use cases to:
  - Show clinical presentation
  - Compare and contrast types with each other as well as type 1 and type 2 diabetes

Your patient…

- A 48 y/o female presents with type 2 DM
- She is very intolerant of any carb intake.
- PMH: hypothyroidism
- FH –no DM, mom/sister hypothyroid
- Meds: Glimepiride, Rosiglitazone, Levothyroxine

Physical Exam

- BMI 22
- Bp 130/72
- Skin: vitiligo present
- Lipids
  - Total chol 178 mg/dl
  - HDL 58 mg/dl
  - LDL 106 mg/dl
  - Trigs 84 mg/dl

What type of diabetes?

1. Type 1
2. Type 2
3. Type 1.5
4. LADA
5. Double diabetes
6. Monogenic diabetes
7. Ketosis prone T2DM

What further evaluation will help to sort out the type of diabetes?

- HbA1c
- Glucose tolerance test
- C-peptide and insulin levels
- GAD and islet cell antibodies
- Lipoprotein analysis

Case Summary

- Middle aged adult DM
- Thin
- No family history
- Carbohydrate sensitive
- Positive antibodies

- What type of diabetes does she have?

DM-2, LADA, & DM-1

	DM-2	LADA	DM-1
Age at onset (yrs)			
Range	30 - 90	35 - 70	0 - 35
Predominance	>40	35 - 50	<20
Percentage of diabetic patients	80%	10%	10%
Presence of GAD, ICA, IA2	No	Yes (35%)	Yes (64%)
Increased risk for endocrine autoimmunity	No	Yes	Yes
Yrs to progress to insulin requirement	8 (6 – 10)	4 (2 – 6)	Insulin dependent from diagnosis
Prevalence of macrovascular complications	Very high	High	Low

Adapted from Exp Clin Endocrinol diabetes 109 (2001) Suppl 2: S94 – S108

When to expect LADA

- New diagnosis between age 30-50
- No FH of type 2 DM or Insulin Resistance Syndrome
- Personal or FH of autoimmune disorders
- BMI <25
- Lack of diabetic dyslipidemia
- Previous episode of the “polys” and weight loss
- Carb intolerance

Case 2: Mild diabetes

- 22 year old female found to have hyperglycemia at work function
- No signs or symptoms, no previous labs
- All the women in my family get this. Usually when young. Well at least mom and aunt.
- No other past medical history other than frequent yeast infections
- Had an A1c at work function – A1c 7.1%
- She has a meter-borrowed and has post meal highs

Case 2: Physical Exam/Objective

- BMI 23, vitals normal
- Exam normal

- A1c = 7.1%
- Home SMBG:
  - Fasting glucose 100-130
  - Post meal glucose 140-200
  - Usually returns to normal over time

Case 2: Lab findings

- C –peptide 1.4 (normal 1.1-4.0)
- GAD, islet cell, insulin antibodies- not present
- CMP normal except glucose 126 mg/dl
- Lipids
  - Total chol 158 mg/dl
  - HDL 50 mg/dl
  - LDL 94 mg/dl
  - Trigs 80 mg/dl

What type of diabetes?

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2. Type 2
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7. Ketosis prone T2DM

MODY: A form of monogenic DM

- Autosomal dominant
- Collection of beta cell disease from gene mutations
- Diagnosis most often made by history
- Genetic testing possible
  - Clinical testing
  - Research testing

PATHOGENSIS

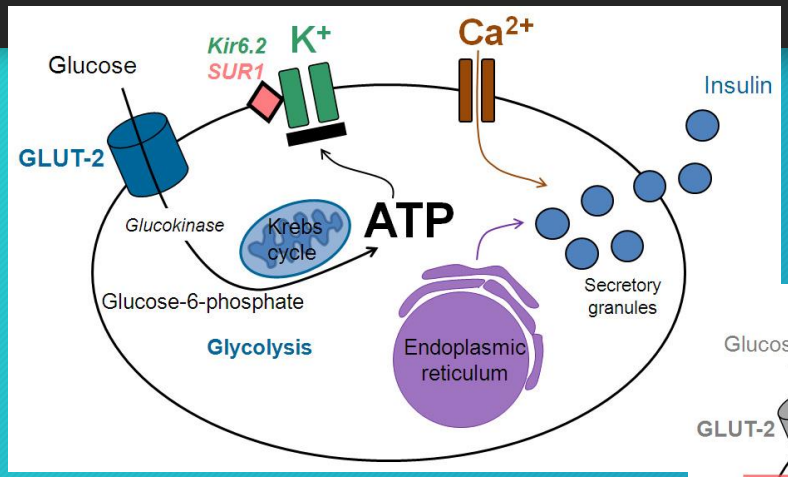

Figure 1
Pancreatic beta cell: the coupling of glucose sensing via GLUT-2 transporters, generation of ATP, membrane depolarization by closing potassium channels, entering of calcium ions, and exocytosis of insulin.

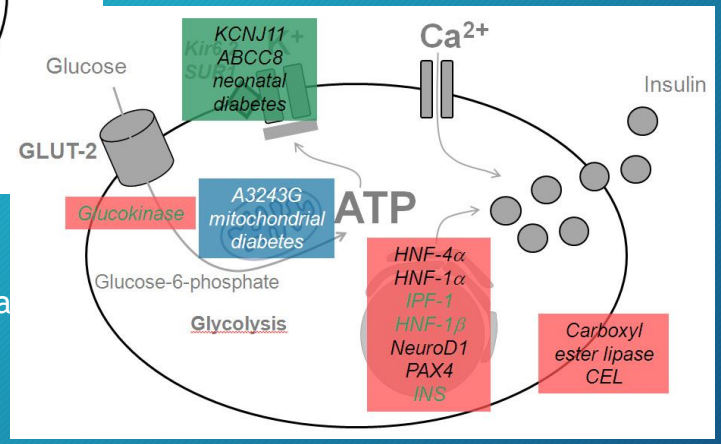

Figure 2
Location of the gene mutations and affected proteins in the pancreatic beta cell in monogenic diabetes mellitus.

MODY (red), mitochondrial diabetes (blue) and neonatal diabetes (green).

Swiss Med Wkly. 2012;142:w13690

Types of MODY

- MODY 1- familial-early onset. Typically responds to SU. Defect HNF4A
- **MODY 2- second most common, may be most common in kids. Long terms stable mild elevations in glucose-may also be present at birth. Glucokinase defect.**
- **MODY 3- most common- young age-responds well to SU. HNF-1A defect.**

Source:http://monogenicdiabetes.uchicago.edu/what-is-monogenic-diabetes/mody-maturity-onset-diabetes-of-the-young/types-of-mody/

Types of MODY (cont.)

- MODY 5 –early diabetes +/- renal disease (cysts) HNF1B defect
- MODY 8- also see exocrine pancreatic insufficiency.
- MODY 4 (IPF 1), MODY 6 (NEUROD1), MODY 7 (KLF 11), MODY 9 (PAX4), and MODY 11 (BLK) –very rare

ource:http://monogenicdiabetes.uchicago.edu/what-is-monogenic-diabetes/mody-maturity-onset-diabetes-of-the-young/types-of-mody/

SUMMARY

Characteristic	MODY	T1DM	T2DM
Age at diagnosis	<25	5-20	>25
Parental Hx	60-90%	<10%	10-40%
Inheritance	Autosomal dominant	autoimmune	polygenic
Obesity Insulin Resistance Metabolic Syndrome	Uncommon	Uncommon	Common
Beta cell Ab	Absent	Present	Absent
C- peptide	Normal	Undetectable	High-low
Optimal Tx	SU MODY(1,3,4)	Insulin	Metformin

Adapted from: Swiss Med Wkly. 2012;142:w13690

Case 3: New Year's Special

- 22 year AA male presents on New Year's eve with nausea, vomiting and abdominal pain
- He has generally been well but has been excessively thirsty and urinating and losing 20 lbs over the past month. Thought he was just stressed
- No meds, no allergies
- Social HX: no tobacco, drinks socially, no specific diet plan, plays basketball 3-4 times a week
- FH: T2DM in mom, and M Aunt, HTN in mom and dad

Physical Exam

- Appears ill, dehydrated and fruity breath
- P 123, R 36, BP 148/88, Afebrile
- Obese BMI 32, exam otherwise normal other than fluid status
- Labs: pH 7.22, HCO- 13, glucose 624 mg/dl, K+ 5.2, β- HOB 6.2
- DX: Diabetic ketoacidosis, dehydration, hyperkalemia, unintentional wt loss

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How would you treat him short/long term?

- Admit to hospital/ insulin for life
- Above plus insulin first/orals later
- Above plus orals now and later
- Above insulin first/life style later

Case Summary

- Support for type 1 DM
  - First diagnosis in DKA
  - Young age at onset
- Support for type 2 DM
  - Phenotype
  - Insulin insensitivity
  - FH of type 2 DM

“Flatbush” diabetes

- Ketosis prone type 2 diabetes
- Seen more commonly in US minority populations
- Initial presentation is DKA
- Antibodies are negative
- Can get off insulin
  - Some with no meds
  - Durability better with some ongoing treatment

Case 4: 10 year old with pre-DM

- 10 year old presents with concerns about diabetes risk
  - Both parents have type 2 DM
  - Child has evidence of NAFLD
  - Family motivated to prevent diabetes
- No past medical history
- No meds
- Family motivated to make changes

Physical Exam

- Child obese
- BMI >95%
- Glucose 94 mg/dl
- Lipids
  - Total 264 mg/dl
  - HDL 26 mg/dl
  - LDL 161 mg/dl
  - Trigs 282 mg/dl
  - AST/ALT 52/68

Case continued

- Went on family dietary program and walking
  - Child (and parents) lost weight
  - However, child kept losing and losing
  - Then developed polys

  - Family monitored glucose- 250mg/dl random
  - Mild ketones, no N/V/ abdominal pain

  - A1c 8.2%

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How will you determine type of diabetes?

- C-peptide/insulin plus glucose
- GAD, islet cell antibodies
- Genetic testing
- Clinical presentation

How will you treat this child?

- Insulin like all type 1
- Oral meds until insulin is needed
- Insulin plus insulin sensitizer
- Lifestyle actions alone
- Transplant
- Other

Summary

- 10%-15% of diabetes is atypical
  - Type 1.5 no longer has descriptive value
- Identifying LADA, MODY and Ketone prone T2DM
  - Affects short terms treatment
  - Changes long term plan
  - Can affect family counseling
- Easy to miss atypical diabetes
  - Non-specific treatments can work but may not be optimal

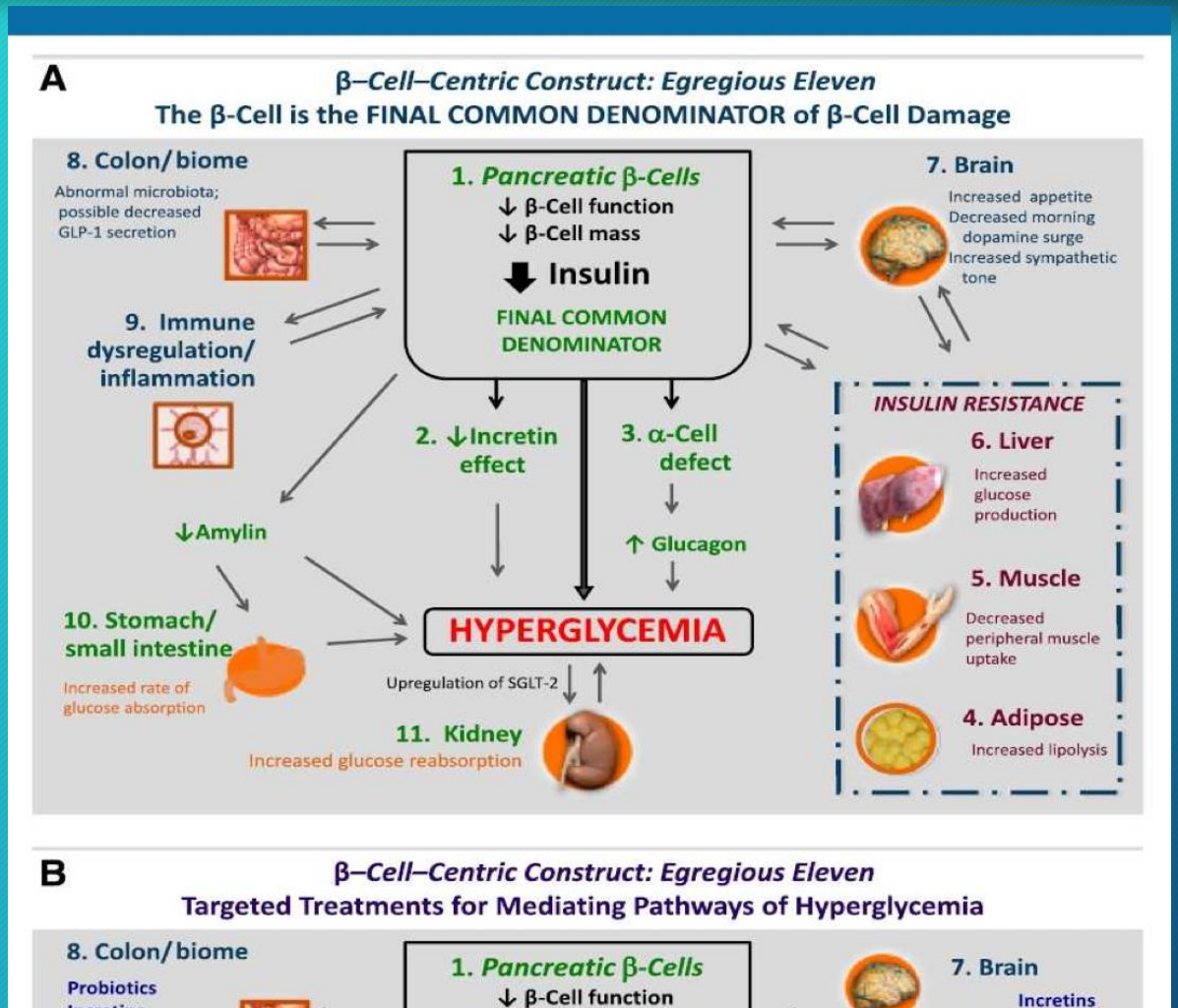
One consideration

- A= antibodies present, B = beta cell function
- A+ B- ====Type 1 A diabetes
- A- B+ ===Type 2 diabetes, ketosis prone type 2, MODY
- A- B- === Type 1 B diabetes or secondary diabetes
- A+B+ === LADA

Another way to classify

- Beta cell function (beta cell-centered)
  - Pathogenic mechanisms lead back to the beta cell
- Relationship between
  - Genetics
    - Polygenic vs. monogenic
  - Insulin resistance
  - Environmental factors
    - epigenetics
  - Inflammation/Immune function
  - Mass of beta cells

Beta cell centered visual



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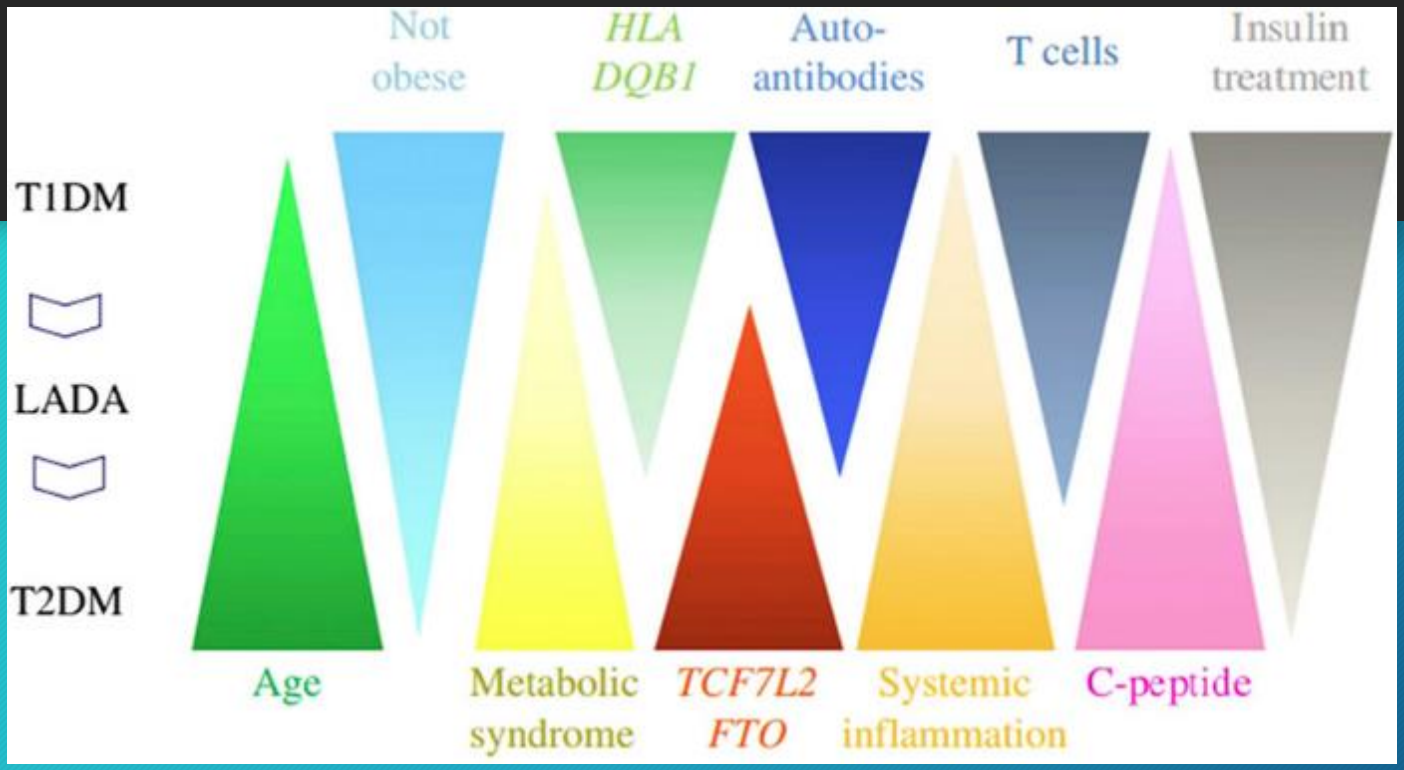

Figure 1—Qualitative illustration of the spectrum of factors associated with different forms of DM, including the variable age at onset, lack of obesity, metabolic syndrome, genetic associations, different forms of immune changes, C-peptide secretion, and the need for insulin therapy.

T1DM, type 1 DM; T2DM, type 2 diabetes.

Schwartz S. et al. Diabetes Care 2016

Questions?

References

- American Diabetes Association. Classification of Diabetes Mellitus. Diabetes Care 2012:1:S64-S71.
- Umpierrez GE, Smiley D, Kitabchi AE. Narrative Review: Ketosis Prone Type 2 Diabetes Mellitus. Annals of Internal Medicine 2006.144:350-357.
- Shubrook JH. LADA:Classifying Type 1.5 Diabetes Mellitus. JAOA 2009. Supplement-Health Watch 21-25.
- Liese AD, D'Agostino RB, Hamman RF, et al. The Burdent of Diabetes Mellitus Among US Youth: Prevalence Estimates from the SEARCH for Diabetes in Youth Trial. Pediatrics 2006.118:1510-1518.
- Schwartz SS. Et al. The Time is Right For a New Classification System for Diabetes: Rationale and Implications of B-cell-Centric Classification Schema. Diabetes Care: 2016. 39:179-186.