Baylor College of Medicine

Atypical and Ketosis-Prone Diabetes

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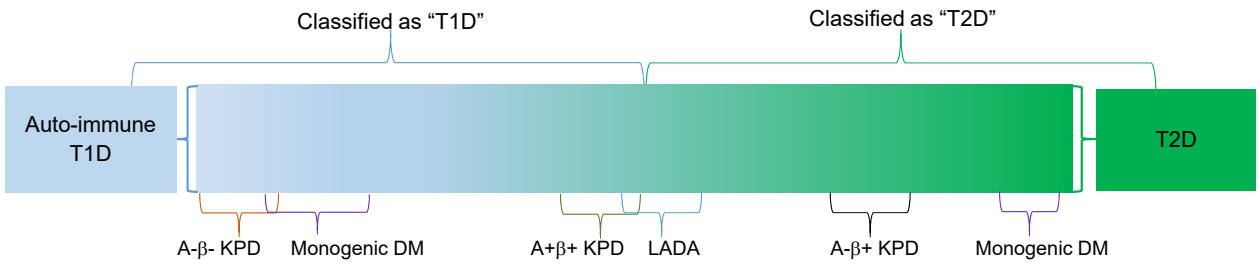
“Atypical” Diabetes in the Spectrum



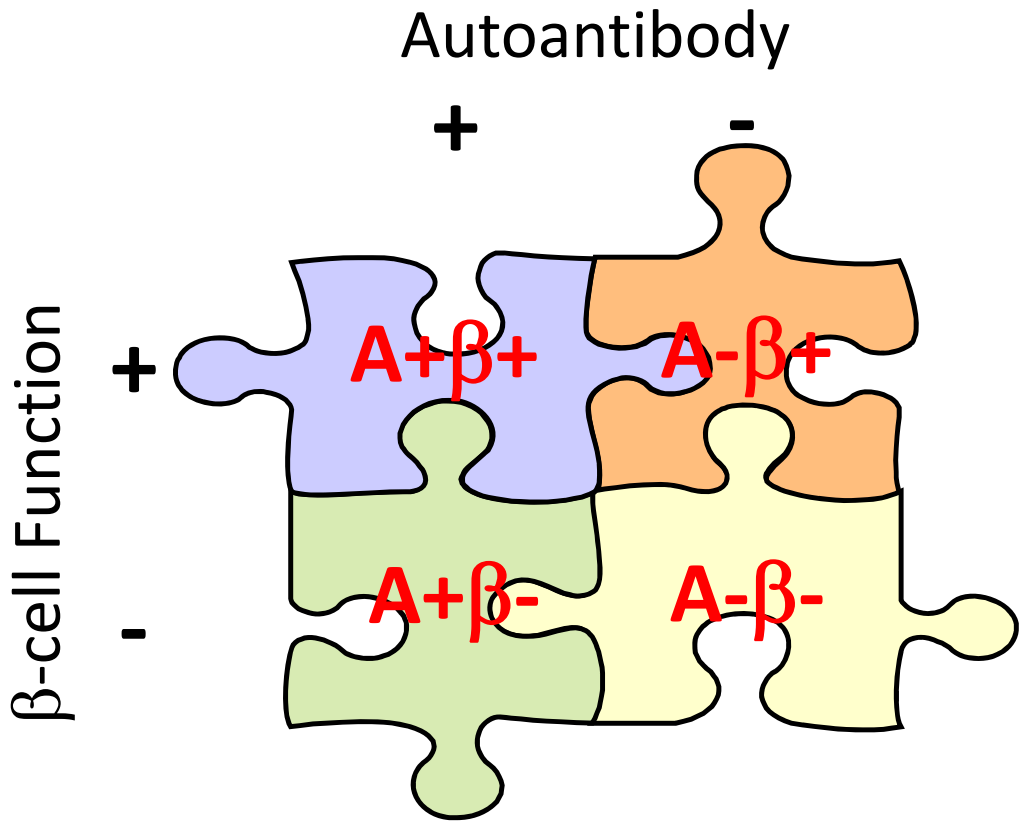
“Atypical Diabetes”

- Mendelian / monogenic / oligogenic; syndromic
- Diabetes due to mutations in genes regulating mitochondrial function
- **Presenting with islet autoantibodies and features of T2D – insulin-independent at onset**
- **Presenting with DKA but able to come off insulin therapy, or with fasting serum C-peptide ≥1 ng/dL**
- **Requiring insulin from diagnosis, without islet autoantibodies, but with low fasting C-peptide level (<1 ng/dL)**
- **Criteria for autoimmune T1D with additional autoimmune conditions**
- Onset of diabetes without islet autoantibodies at <20 years of age
- Clinical evidence of lipodystrophy
- Poor response to metformin within the first 6 months of treatment, or lack of response to GLP-1 agonist
- Long-term “non-progressor,” i.e., with HbA1c < 7% for >10 years on only metformin
- Forms of “secondary diabetes”

“Ketosis-Prone Diabetes”

Patients presenting with DKA (often as the first manifestation of diabetes), but lacking the phenotype of autoimmune type 1 diabetes

Aβ Classification of KPD



Maldonado et al. JCEM, 2003.

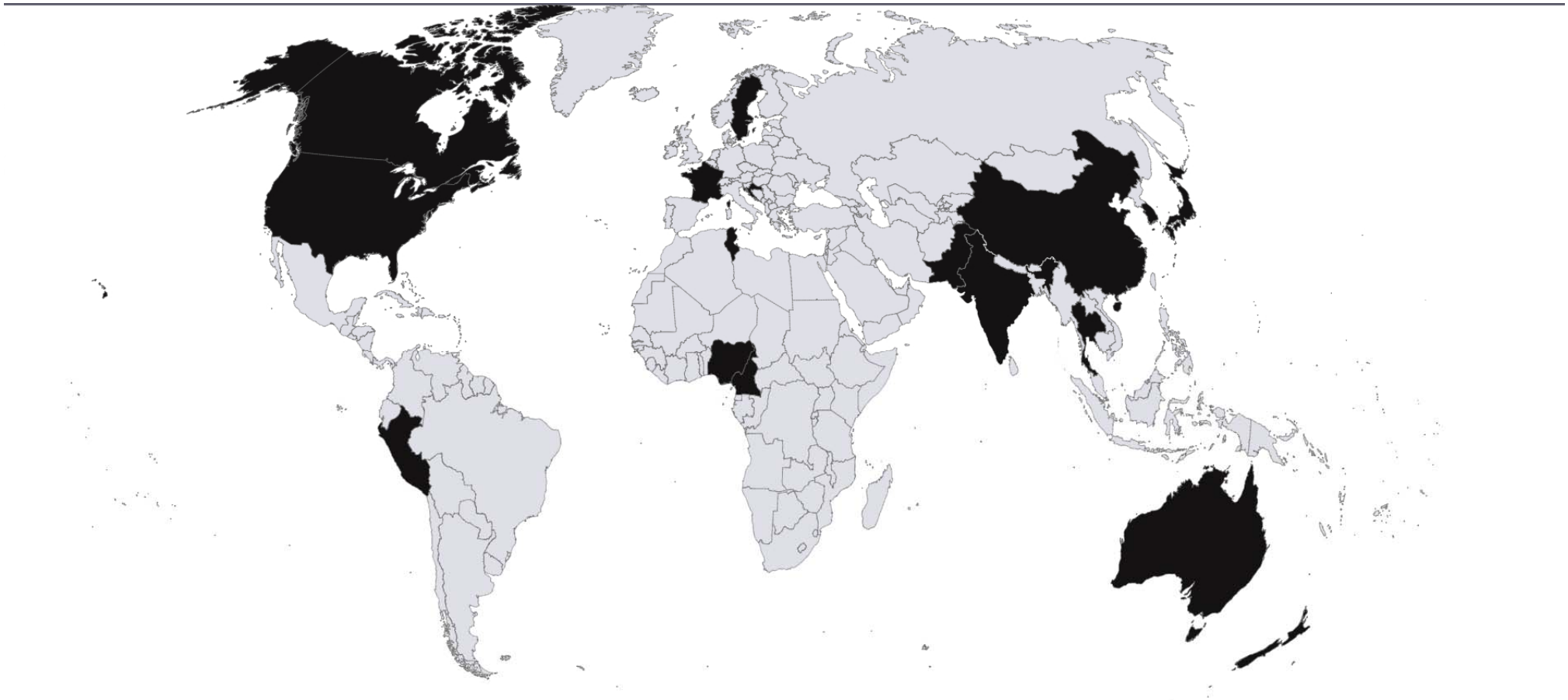
Balasubramanyam et al. Diabetes Care, 2006.

Balasubramanyam et al. Endocrine Reviews, 2008.

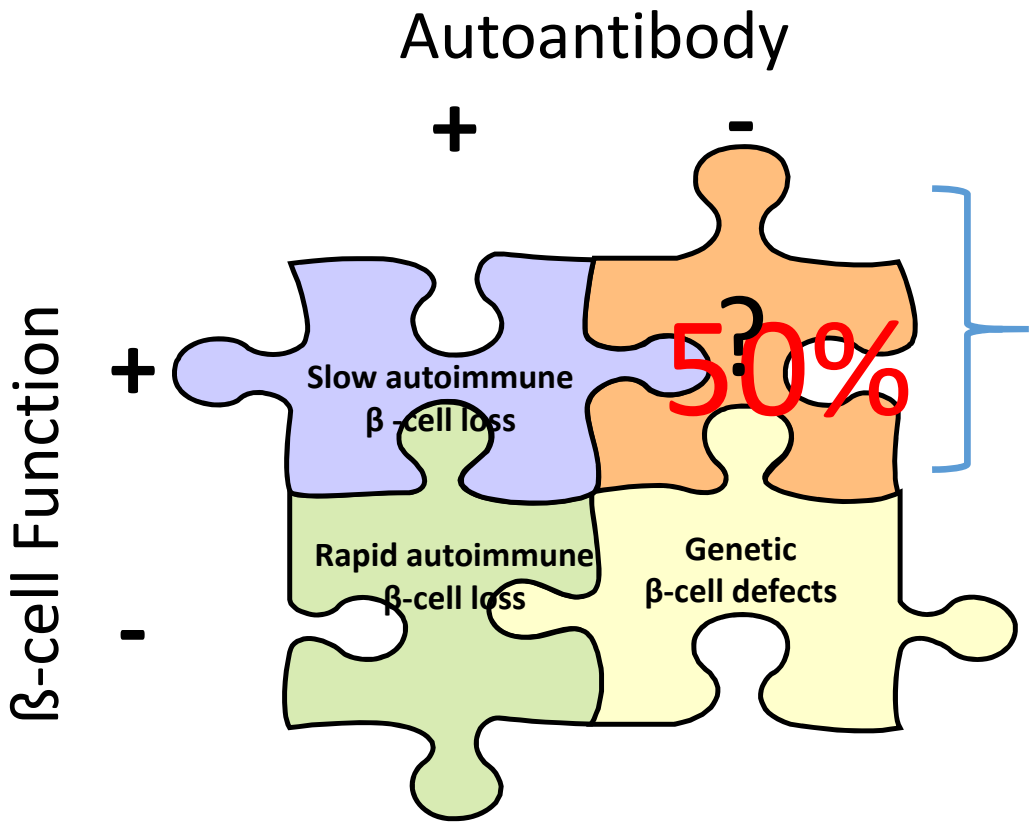
Nalini et al. Metabolism, 2010.

Brooks-Worrell et al. Diabetes Care, 2013.

KPD Around the World



Aβ Classification of KPD



Following recovery from DKA, demonstrate sustained preservation of β-cell function with ability to discontinue insulin treatment while maintaining excellent glycemic control

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Case 1

- 17 yo Hispanic woman presented with DKA after stopping insulin Rx for 3 days.
- Dx diabetes 3 y previously; on MDI insulin from diagnosis
- H/o diabetes in mother (dx in her 30's, on insulin) and maternal grandmother (dx in her 60's, on no medications)
- Past history of DKA
- BMI 24 kg/m^2, physical exam unremarkable
- No evidence of infection, CAD, CVD, renal / liver dysfunction, drugs, alcohol
- ABG consistent with DKA, AG 24
- Standard treatment for DKA, uneventful recovery and discharge on insulin

Case 1

WHAT KIND OF DIABETES DOES SHE HAVE?

Case 1 – additional information

- HbA1c = 13.8%
- Islet autoantibodies: Negative for GAD65Ab, IA-2 Ab, ZnT8 Ab
- C-peptide:

  Fasting: < 0.05 ng/mL

  Peak after glucagon stimulation: < 0.05 ng/mL
- Current Rx: MDI insulin
- HbA1c on follow-up: range from 7.5% (before pregnancy) to 11.2%

Case 1 - Diagnosis

- Dx: A-β- KPD

- 26% monogenic
- This patient does not have a mutation in any known gene associated with monogenic diabetes
- What of the other 74% ??

Case 2

- 56 y.o. African-American man presented with DKA
- No prior history of diabetes
- Polyuria and 25 lb weight loss in the preceding 2 months
- Past history: Hypertension
- Family history: One brother with diabetes on oral medication
- No smoking, alcohol
- BMI 29 kg/m^2
- Mild acanthosis nigricans on neck
- Central obesity, otherwise unremarkable physical exam
- No evidence of infection, CAD, CVD, renal / liver dysfunction, alcohol
- Standard treatment for DKA, uneventful recovery and discharge on insulin

Case 2

WHAT KIND OF DIABETES DOES HE HAVE?

Case 2 – additional information

- HbA1c 12%
- Islet autoantibodies: GAD65Ab positive (high titer), IA-2 Ab and ZnT8 Ab negative
- Central obesity, otherwise unremarkable physical exam
- C-peptide 2 weeks after DKA:
  - Fasting: 1.5 ng/mL
  - Peak after glucagon stimulation: 1.62 ng/mL
- C-peptide 6 months later:
  - Fasting: 2.6 ng/mL
  - Peak after glucagon stimulation: 5.2 ng/mL
- Insulin discontinued 6 months after DKA episode
- Current Rx: metformin 2g/d, glimepiride 4 mg/d, pioglitazone 15 mg/d
- Remains off insulin 2 years after DKA, no further DKA, HbA1c levels 6.2% - 7.8%

Case 2 - Diagnosis

- Dx: A+β+ KPD

- Have both TID susceptibility and T1D protective HLA Class I alleles
- High frequency of an epitope-specific GAD65 Ab ("DPD")
- Circulating insulin DNA (unmethylated and methylated)
- Natural history: ~ 50% have declining beta cell function over 1 year and become insulin-requiring; ~50% have stable beta cell function over 3-4 years and remain insulin-independent

Case 3

- 44 y.o. Hispanic man presented with DKA
- No prior diagnosis of diabetes
- Polyuria and 30 lb weight loss over 1 month
- Past history: Nil significant
- Family history: Both parents and a sister with diabetes on oral medicatio36
- No smoking, occasional alcohol
- BMI 36 kg/m^2
- Mild acanthosis nigricans on neck
- Central obesity, otherwise unremarkable physical exam
- No evidence of infection, CAD, CVD, renal / liver dysfunction, alcohol
- Standard treatment for DKA, uneventful recovery and discharge on insulin

Case 3

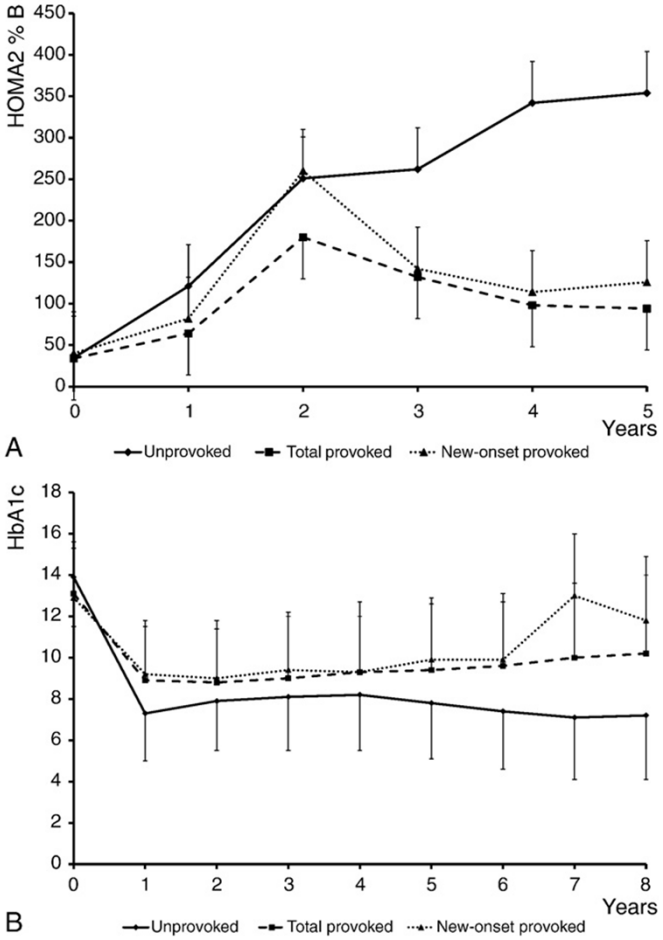
WHAT KIND OF DIABETES DOES HE HAVE?

Case 3 – additional information

- HbA1c 12.4%
- Islet autoantibodies: Negative for GAD65Ab, IA-2 Ab and ZnT8 Ab
- Central obesity, otherwise unremarkable physical exam
- C-peptide 2 weeks after DKA:
  - Fasting: 3.6 ng/mL
  - Peak after glucagon stimulation: 6.6 ng/mL
- C-peptide 6 months later:
  - Fasting: 3.2 ng/mL
- Insulin discontinued 4.5 months after DKA episode
- Current Rx: metformin 1g/d
- Remains off insulin 4 years after DKA, no further DKA, HbA1c levels 5.2% - 6.1%

Case 3 - Diagnosis

- Dx: A-β+ KPD



"Unprovoked"

"Provoked"

Nalini et al. Metabolism, 2010.

Brooks-Worrell et al. Diabetes Care, 2013.

Patel et al. Diabetes, 2013.

Mulukutla et al. J Nutr, 2018.

A-β+ KPD

- "Unprovoked" and "Provoked"

- Different natural histories and pathophysiology

- Unprovoked:
  - Male predominant
  - Low frequency of HLA susceptibility alleles
  - Absent T cell reactivity to islet antigens
  - Defects in branch chain AA metabolism, arginine metabolism
  - Beta cell function stable and insulin-independent for > 4 years (median)
- Provoked:
  - One-third have T cell reactivity to islet antigens
  - Progressive decline in beta cell function; require insulin within 2 years (median)