A 71-year-old man with diabetic ketoacidosis

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History of Present Illness

- DM diagnosed in 2011 when presented to hospital
  - Triage note: *Family found him on the floor unresponsive in the kitchen floor after they heard a big "thud".*
  - Presenting basic metabolic panel
    - pH 7.1
    - beta-hydroxybutyrate 6.56 mmol/L
    - lactic acid 5.2 mEq/L
**HPI**

**HbA1c**

- Admission Jan 2011
- Follow-up visit Continue regimen
- Patient called Stopped Lantus
- Follow-up visit Started metformin Continued NovoLog
- Patient stopped NovoLog
- Follow-up visit Continue metformin
HPI

- Returned for education in Oct 2011
- Missed visit in Jan 2012
- Admitted 10 months after last scheduled visit complaining of weakness
- Endocrinology consulted for hyperglycemia
  - Stopped checking blood glucose and taking oral medications when he “found out he was better” at his last visit
HPI

- Pt reports he felt well until two months prior to admission when he experienced increased thirst and polyuria including urinary incontinence
- Drinking a lot of juice
- No new sore throat, fever, headache, abdominal pain, diarrhea, dysuria or other complaints
- Has lost approximately 20 pounds in the last two to three months
History

- **Past Medical History**
  - Diabetes Mellitus
  - Elevated PSA
  - Right UE DVT

- **Past Surgical History**
  - Tonsillectomy/Adenoidectomy

- **Allergies**
  - Strawberries

- **Medications**
  - None
Family History

- No family history of diabetes mellitus
- Father had prostate cancer, deceased at age 85 from pneumonia

Social History

- Retired postal worker, was president of the union for 4 years
- Lives with his mother, assists in her care
- Never married, no children
- Current smoker: ½ ppd for 12 years
- No alcohol
- No illicit drugs
Review of Systems

- Constitutional: Positive for weight loss; Negative for fevers, chills
- HEENT: Positive for blurry vision; Negative for sore throat, rhinorrhea, headache
- Respiratory: Negative for cough, wheezing
- CV: Negative for chest pain, shortness of breath, lightheadedness, palpitations
- Gastrointestinal: Negative for abdominal pain, nausea, vomiting, diarrhea, constipation
- Genitourinary: Positive for urinary frequency, hesitancy, incontinence
- Skin: Negative for diaphoresis, new rash
- Musculoskeletal: Negative for myalgias
- Neurological: Negative for weakness, numbness, tingling
- Psychiatric/Behavioral: Negative for anxiety, depression
Physical Exam

- **Vital Signs**: BP 115/54, pulse 82, Temp 36.5 C, Height 5’7”, Weight 67.2 kg, BMI 22
- **Constitutional**: well-nourished, well-developed male, sitting up in bed in no acute distress, conversant
- **HEENT**: EOMI, oropharynx clear, good dentition, sclera anicteric
- **Neck**: supple, no thyromegaly, no acanthosis nigricans
- **CV**: regular rate, normal S1/S2, no extra heart sounds
- **Pulmonary/Chest**: good respiratory effort, clear to auscultation and percussion b/l
- **Abdomen**: bowel sounds present, soft, non-tender, no straie
- **Musculoskeletal**: no edema, good range of motion
- **Neurological**: vibratory sensation intact in first toes bilaterally
- **Skin**: warm, dry
- **Psychiatric**: flat affect, patient describes mood as “Okay”
Laboratory Studies

Beta hydroxybutyrate = 2.57 mmol/L
Lactic acid = 2.7 mEq/L
HbA1c = 17.5%
Calculated Anion Gap = 21

January 2011
GAD65 Ab: Negative
IA-2 Ab: Negative
C-peptide: 0.34 pmol/mL (no simultaneous blood glucose but in between 416 mg/dL and 71 mg/dL)
Prevalence, Morbidity/Mortality

- CDC reports that from 1996 – 2006 there was a 35% increase in hospital admissions due to DKA
- 4 – 10% mortality
  - Those who have severe underlying disease (for example, acute myocardial infarction, stroke, or septic shock)
  - Patients with marked metabolic derangement, including profound acidosis (pH under 7.0), and those with marked fluid deficits
  - Those with cerebral edema
Diabetic Ketoacidosis

- Absolute or relative deficiency of insulin
- Excess counter-regulatory hormones
- Cytokines (e.g., IL6, IL1, TNFalpha) also oppose the effects of insulin
- Increased hepatic glucose production and diminished glucose uptake by peripheral tissues
Patient Descriptions

  - Patients required revision of their type
  - “reversible” diabetes
  - Series of 7 Nigerian patients with ketosis and then “remission”
Atypical Diabetes/Ketosis-Prone DM

- Some authors argue accounts for 25 – 50% of new diagnosis of diabetes in African-American and Hispanics persons presenting with DKA
- Also reported in Native American, Japanese, Chinese and white populations
- Severe but transient defect in insulin secretion which partially resolves after a few weeks of insulin therapy and is followed by near-normoglycemic remission that lasts for several months to years
Clinical Presentation

- Acute initial presentation
- Polyuria, polydipsia and weight loss for a few weeks to months
- Mean age 40 years
- Several studies report: Two – three fold higher prevalence in men
Disorders of glycemia: etiologic types and stages

American Diabetes Association Dia Care 2008;31:S55-S60

<table>
<thead>
<tr>
<th>Types</th>
<th>Stages</th>
<th>Normoglycemia</th>
<th>Hyperglycemia</th>
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<tr>
<td></td>
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<td>Normal glucose regulation</td>
<td>Impaired Glucose Tolerance</td>
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<td>or Impaired Fasting Glucose</td>
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<td>(Pre-Diabetes)</td>
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<td>Type 1*</td>
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<td>Diabetes Mellitus</td>
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<td>Type 2</td>
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<td>Not insulin requiring</td>
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<tr>
<td>Other Specific Types**</td>
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<td></td>
<td>Insulin requiring for control</td>
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<tr>
<td>Gestational Diabetes **</td>
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<td>Insulin requiring for survival</td>
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*Even after presenting in ketoacidosis, these patients can briefly return to normoglycemia without requiring continuous therapy (i.e., “honeymoon” remission);

**In rare instances, patients in these categories (e.g., Vacor toxicity, type 1 diabetes presenting in pregnancy) may require insulin for survival.
ADA Classification

- **Type 1 diabetes**
  - Immune mediated
  - Idiopathic
    - Permanent insulinopenia
    - Episodic ketoacidosis with varying degrees of insulin deficiency between episodes

- **Type 2 diabetes**

- **Other specific types**
  - Genetic defects of β-cell function
  - Genetic defects in insulin action
  - Diseases of the exocrine pancreas
  - Endocrinopathies
  - Infections
  - Gestational Diabetes Mellitus
  - Others
Other Classifications

- **Modified ADA**
  - Type 1a (Beta cell autoantibodies)
  - KPD insulin-dependent
  - KPD non-insulin dependent
- **BMI-based system**
  - BMI <28, clinical characteristics of T1DM
  - BMI >28, clinical characteristics of T2DM, preservation of Beta-cell function
- **Abeta Classification**
  - A+Beta+ (autoantibodies present, preserved beta cell function)
  - A+Beta- (autoantibodies present, absent beta cell function)
  - A-Beta+ (without antibodies, preserved beta cell function)
  - A-Beta- (without antibodies but absent beta-cell function)
Another Patient

- 50-year-old Nigerian man admitted in DKA
- A1c declined from 15.7% on admission to 5.8% in 5 months
- GAD65 Ab negative
- We communicated via email to decrease insulin requirements
- A1c of 5.8% while prescribed metformin 500 mg BID
- Received fax from pharmacy → patient not requesting refills
Natural History

- Period of near-normoglycemic remission lasts from a few months to several years
- Mauvais-Jarvis et al, characterized a cohort of 223 newly-diagnosed patients from sub-Saharan Africa for a period of 10 years
  - Ketosis-prone type 2 diabetes (n = 111) was defined as new-onset diabetes without precipitating illness (infection, stress), with the presence of strong ketosis (urine ketones >80 mg/dl) or DKA, and in the absence of ICAs and GAD 65 autoantibodies.
  - 76% were able to discontinue insulin after initial insulin dependence
  - 90% of those only transiently insulin dependent, relapsed within 10 years.
  - 77% presented with relapse-remission within 2 years of diagnosis and with each relapse, there was a progressive risk of becoming chronically insulin dependent
  - ~50% remained insulin independent after 10 years
**β-Cell function**

![Graph showing ΔC-peptide levels over years of follow-up for different groups: Controls (n=7), KPT2D-NID (n=21), KPT2D-ID (n=15), T2DM (n=19), and T1DM (n=12).](image)
What’s the best treatment?

- 20 obese black patients with new-onset KPDM after euglycemia
  - 2.5 mg of glipizide or placebo daily
  - Followed for 17.4 months
  - Remission was prolonged with glipizide

- 35 obese African-American patients
  - Diet and low-dose glyburide versus diet alone
  - Followed for 16 months
  - Hyperglycemia recurred in 72% treated with diet alone compared with 20% with glyburide
Best Treatment

- 44 overweight KPDM patients
  - Pioglitazone or placebo
  - Followed for 3 years
  - Pioglitazone reduced hyperglycemic relapse
    68 vs 32%
  - Pioglitazone allowed for longer remission
    (median 809 vs 162 days)
Ongoing studies

- NIH clinical trial: ketosis-prone diabetes mellitus (KPDM): metformin versus sitagliptin treatment
Genes Implicated

- A missense mutation (Arg121Trp) of PAX4 has been implicated in early and insulin deficient type 2 diabetes in Japanese subjects.
- PAX4 is a transcription factor essential for the development of insulin-producing pancreatic beta-cells.
Genes Implicated - Baylor

- Screened 101 KPD subjects
- Found a new variant in the PAX4 gene (Arg133Trp), specific to a population of west African ancestry
  - Predisposes to KPD under a recessive model
  - Homozygous Arg133Trp PAX4 carriers were found in 4% of subjects with KPD but not in 355 controls or 147 subjects with common type 2 or type 1 diabetes
Genes Implicated - Baylor

- In vitro, the Arg133Trp variant showed a decreased transcriptional repression of target gene promoters in an alpha-TC1.6 cell line.
- In addition, one KPD patient was heterozygous for a rare PAX4 variant (Arg37Trp) that was not found in controls and that showed a more severe biochemical phenotype than Arg133Trp.
- Clinical investigation of the homozygous Arg133Trp carriers and of the Arg37Trp carrier demonstrated a more severe alteration in insulin secretory reserve, during a glucagon-stimulation test, compared to other KPD subjects.
Intracellular Signaling

Patterns of insulin-stimulated AKT phosphorylation and protein expression in muscle biopsy samples

- Immediately after hyperglycemic crisis
  - AKT-2 expression and insulin stimulated phosphorylation were impaired

- Follow-up with near euglycemia
  - AKT-2 expression and phosphorylation improved
Back to our Original Patient

- Last Visit in May 2013
- Saw ophthalmology – no retinopathy
- s/p radiation therapy for prostate cancer
- Patient continues on insulin glargine 15 units daily and insulin aspart 10 units with meals (twice daily)
- Regained weight, BMI 28
Take Home Points

- Ketosis-prone diabetes is a heterogeneous syndrome, phenotypically defined.
- Many patients are able to discontinue insulin after initial episode of ketosis but many relapse with progressive loss of beta-cell function.
- Best management in the “remission” period is yet to be defined but patient education and continued glucose monitoring are critical.
- Investigation of these forms of diabetes could be of great value in uncovering novel mechanisms of beta cell dysfunction.
References (not previously listed)

- Smiley et al. Update on diagnosis, pathogenesis and management of ketosis-prone Type 2 diabetes mellitus. *Diabetes Management (Lond)* 1(6):589-600. 2011