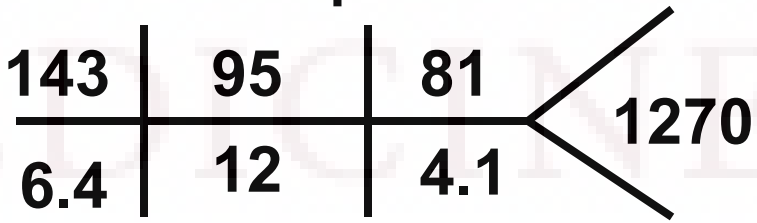
A 71-year-old man with diabetic ketoacidosis

Celeste C. Thomas

July 25, 2013

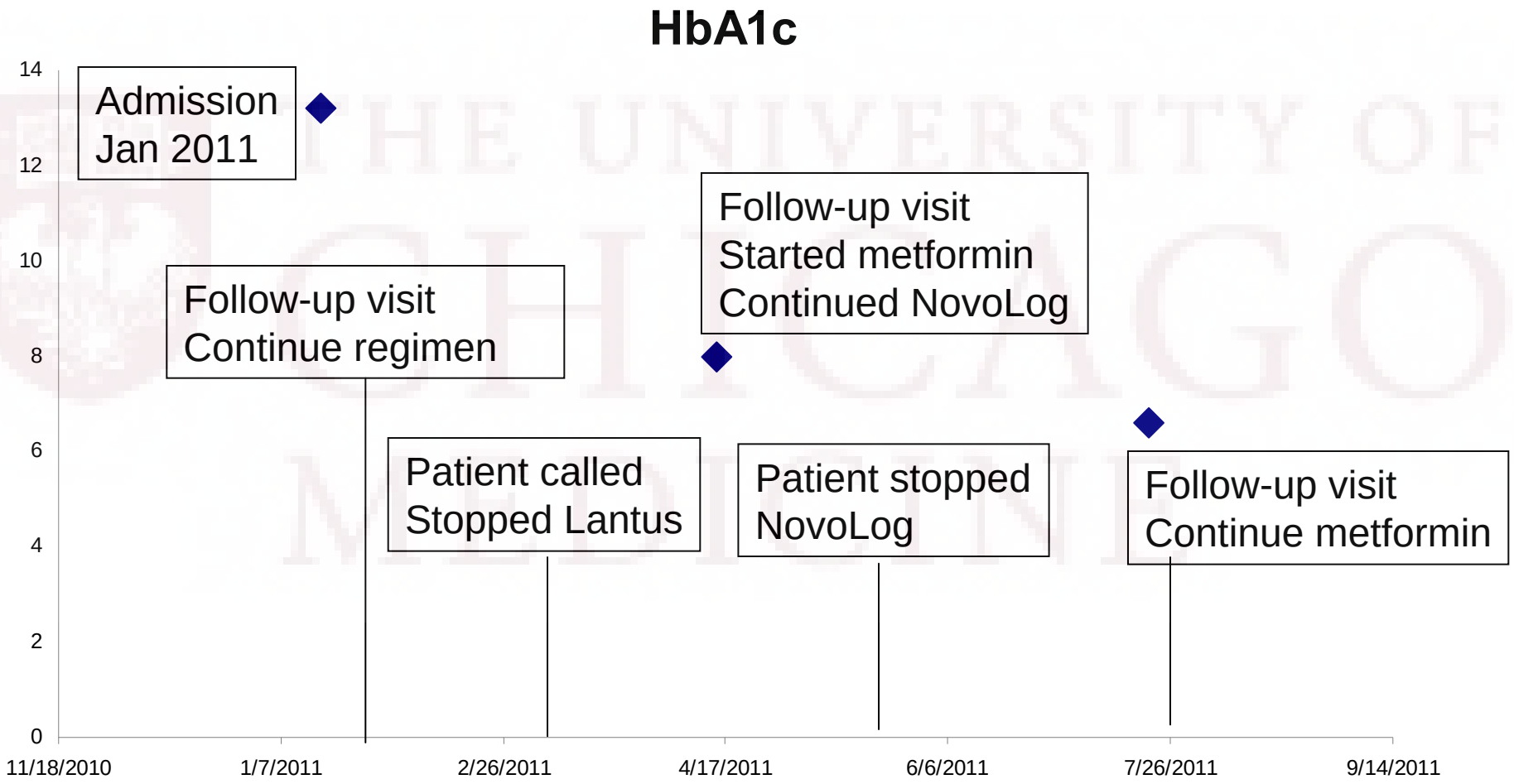
History of Present Illness

- **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
14
12
10
8
6
4
2
0
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
11/18/2010
1/7/2011
2/26/2011
4/17/2011
6/6/2011
7/26/2011
9/14/2011

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 and Social History

- **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

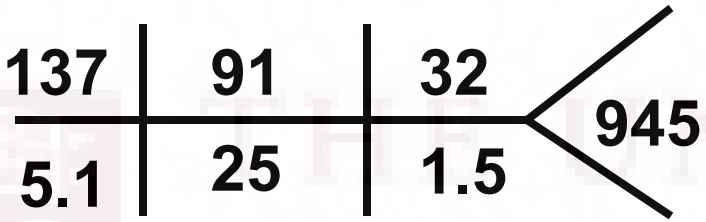
Review of Systems

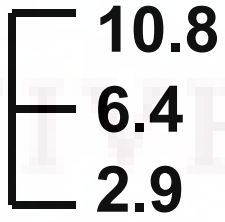
- Constitutional: Positive for weight loss; Negative for fevers, chills
- HEENT: Positive for blurry vision; Negative for sore throat, rhinorrhea, headache
- Respiratory: Negative for cough, wheezing
- CV: Negative for chest pain, shortness of breath, lightheadedness, palpitations
- Gastrointestinal: 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

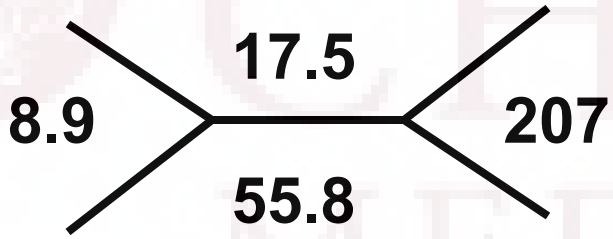
Physical Exam

- **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

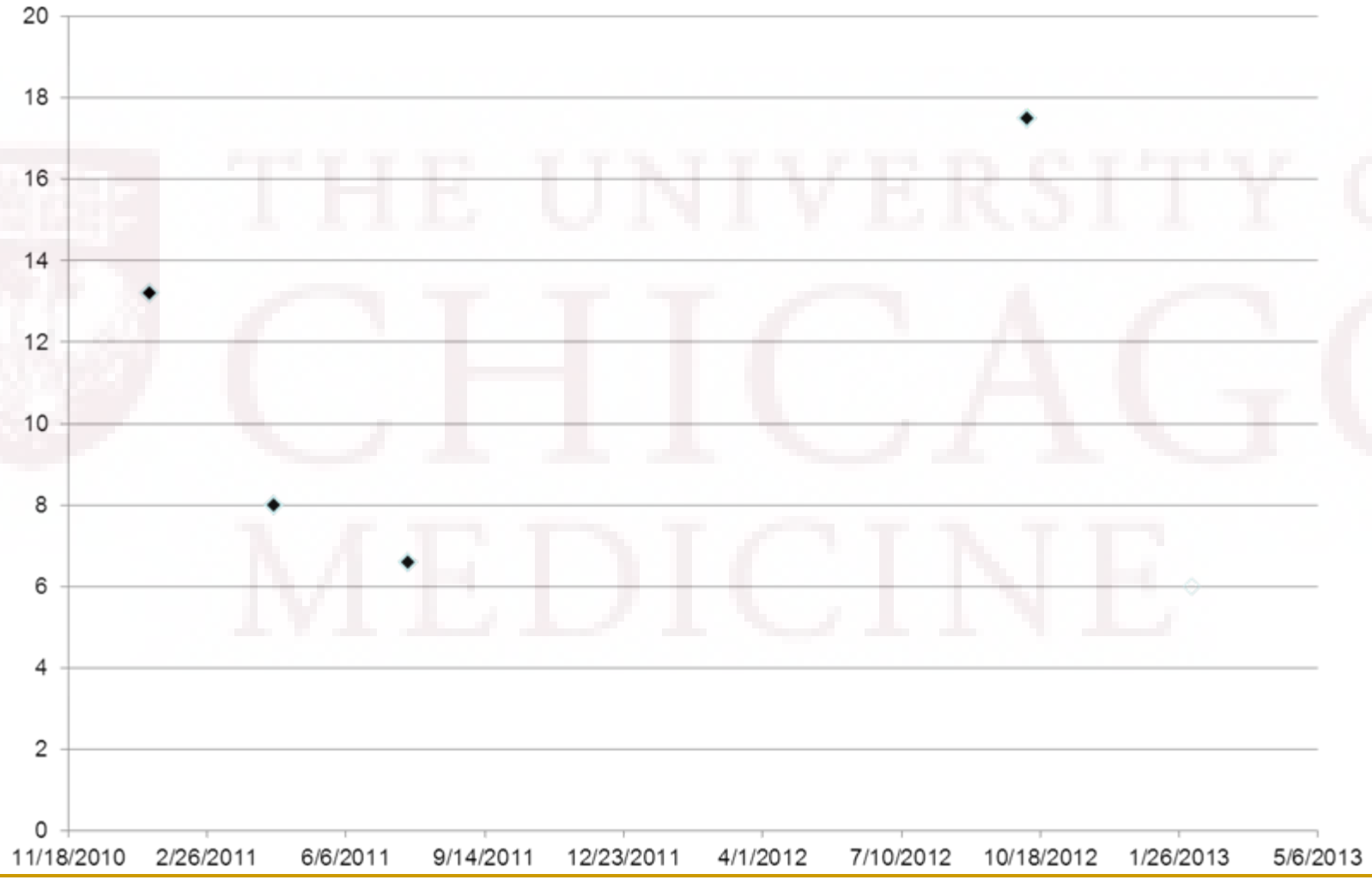
January 2011
GAD65 Ab: Negative
IA-2 Ab: Negative
C-peptide: 0.34 pmol/mL (no simultaneous blood glucose but in between 416 mg/dL and 71 mg/dL)

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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12/23/2011
4/1/2012
7/10/2012
10/18/2012
1/26/2013
5/6/2013

Patient Descriptions

- Dodu SR Diabetes in the tropics. Br Med J 2:747-750. 1967.
  - Patients required revision of their type
- Aadadevoh BK. Temporory diabetes in adult Nigerians. Trans R Soc Trop Med Hyg 62:528-530. 1968
  - “reversible” diabetes
- Oli JM Remittent diabetes mellitus in Nigeria. Trop Georgr Med 30:57-62
  - Series of 7 Nigerian patients with ketosis and then “remission”
- Banerji et al. GAD Ab neg NIDDM in adult black subjects…Flatbush Diabetes. Diabetes 43:741-745. 1994.
- Aizawa et. Al. Ketoacidosis-onset noninsulin dependent diabetes in Japanese subjects. Am J Med Sce 310: 198-201. 1995
- Wilson et al. Ketoacidosis in Apache Indians with non-insulin dependent diabetes mellitus. Arch Intern Med 157:2098-2100. 1997.

Atypical Diabetes/Ketosis-Prone DM

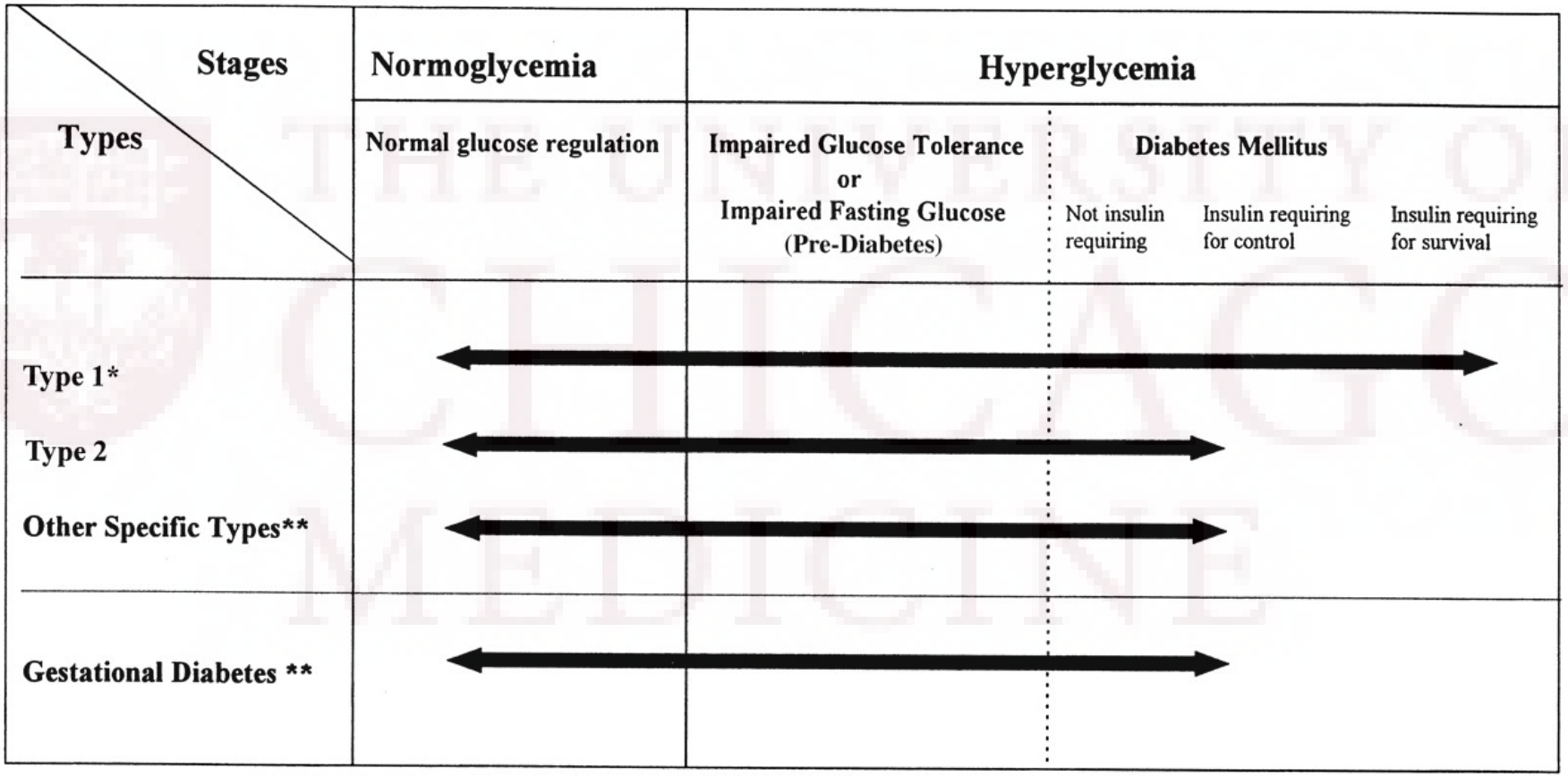
- Some authors argue accounts for 25 – 50% of new diagnosis of diabetes in African-American and Hispanics persons presenting with DKA
- Also reported in Native American, Japanese, Chinese and white populations
- Severe but transient defect in insulin secretion which partially resolves after a few weeks 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



*Even after presenting in ketoacidosis, these patients can briefly return to normoglycemia without requiring continuous therapy (i.e., “honeymoon” remission);

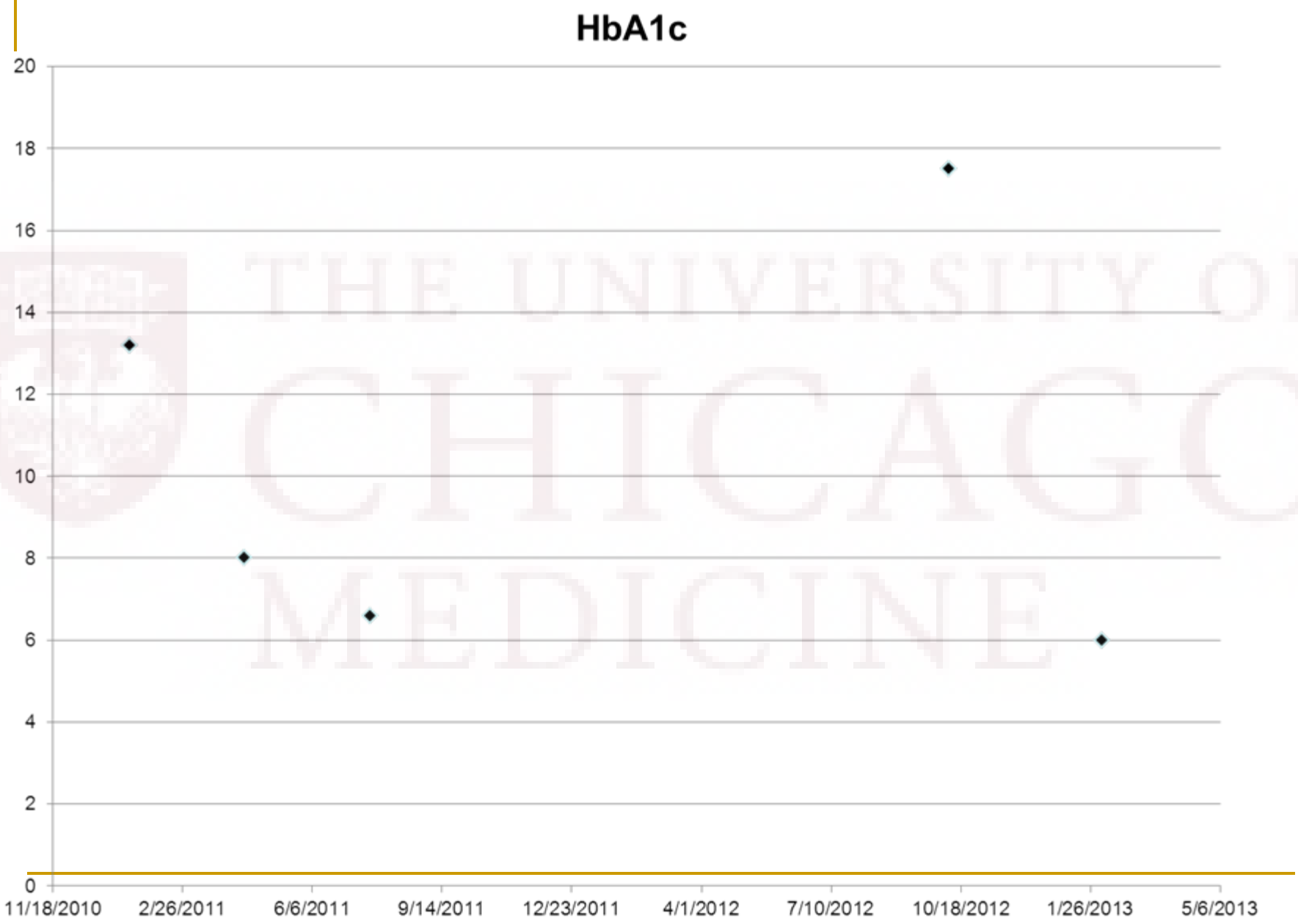
∗∗In rare instances, patients in these categories (e.g., Vacor toxicity, type 1 diabetes presenting in pregnancy) may require insulin for survival.

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)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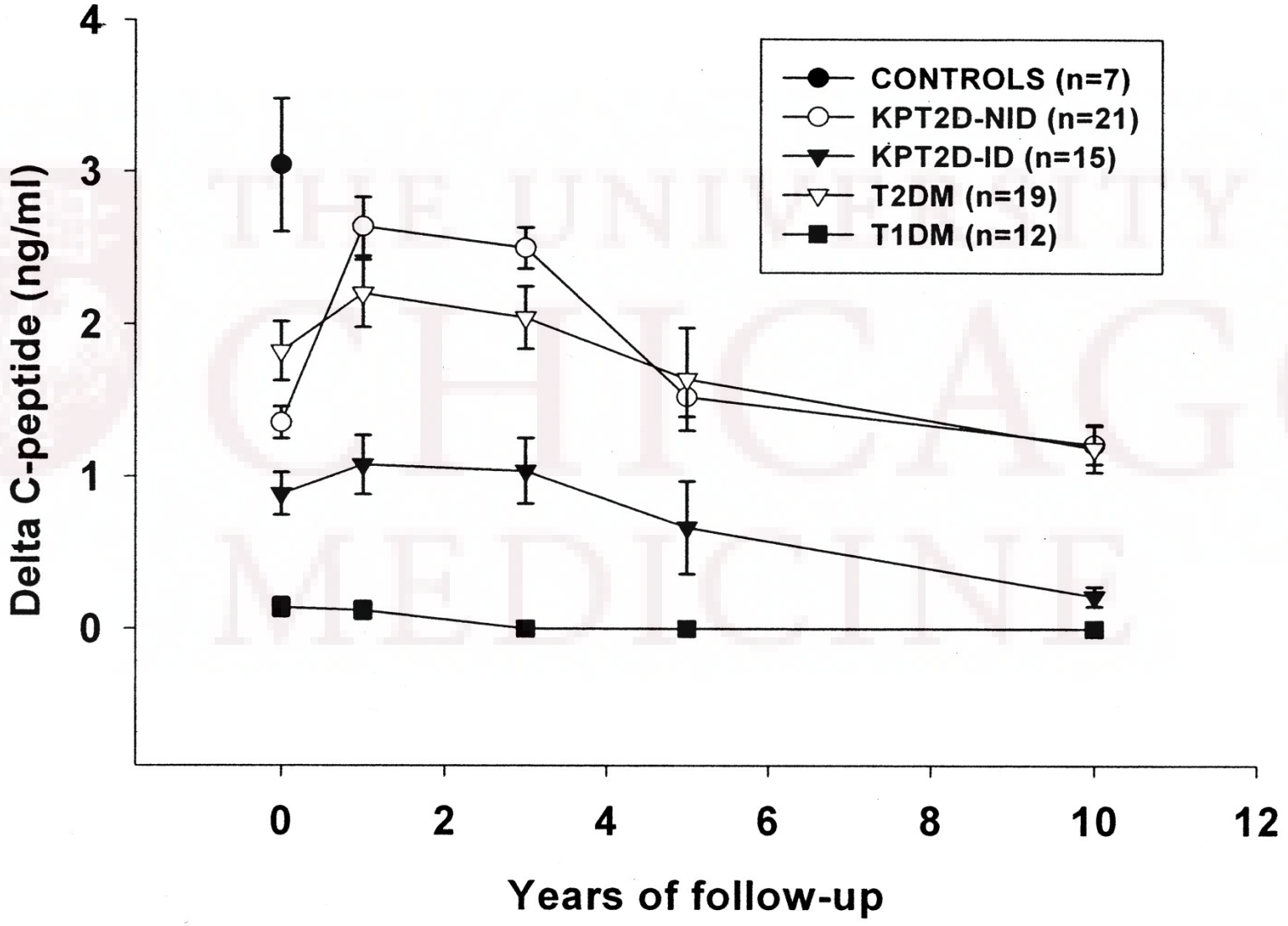
Another Patient

- 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



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 expresson 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)

- Balasubramanyam et al. Syndromes of Ketosis-Prone Diabetes Mellitus. *Endocrine Reviews* 29:292-302. 2008
- Smiley et al. Update on diagnosis, pathogenesis and management of ketosis-prone Type 2 diabetes mellitus. *Diabetes Management (Lond)* 1(6):589-600. 2011
- Umpierrez et al. Narrative Review: Ketosis-Prone Type 2 Diabetes Mellitus. *Annals of Internal Medicine.* 2006
- Tan KC, Mackay IR, Zimmet PZ, Hawkins BR, Lam KS: Metabolic and immunologic features of Chinese patients with atypical diabetes mellitus. Diabetes Care23 :335 – 338,2000