ENDORAMA: A 23 year old man with hyperglycemia

Laura Dickens

November 9, 2017
Objectives

1. Review the prevalence and pathophysiology of steroid-induced diabetes.
2. Discuss indications for testing for latent autoimmune diabetes in adults (LADA) in newly diagnosed diabetes, including use of the LADA clinical risk score.
3. Understand the differential diagnosis of hypoglycemia in adults with diabetes, including causes of hyperinsulinemic hypoglycemia.
Chief Complaint

23 year old man with hyperglycemia
HPI

- Pt is a 23 year old man with a PMH of obesity, OSA, asthma, and sickle cell trait admitted for asthma exacerbation.
- He was started on Prednisone 60 mg daily and later in the same day developed hyperglycemia >400
- Pt reports associated symptoms of polyuria and polydipsia.
- Denies prior history of diabetes.
- He has received ~ 1-2 courses of systemic steroids in the last few years and denies hyperglycemia or symptoms of hyperglycemia during these episodes.
February 2017

**PMH:**
- Obesity
- Asthma
- Severe OSA- autoCPAP has been prescribed

**PSH:**
- None

**Meds:**
- Albuterol
- Symbicort
- Ibuprofen PRN

**Allergies:** NKDA

**Social:**
- Former social smoker, no ETOH or drugs.
- Works as a delivery driver.

**Family:** Diabetes in his father (deceased, unknown cause of death)

**ROS:**
- +weight gain (did not specify amount).
- +SOB. +polyuria.
- +polydipsia. Negative for fevers, chest pain, leg swelling, rash, weakness, mood disorders.
February 2017

Physical exam

VITALS: Temp 36, BP 122/51, HR 94, RR 18, O2 sat 100%, 6’2”, 369lbs, BMI 47

Constitutional: No acute distress, conversational, appears well

HEENT: Mucous membranes moist
Neck: Supple, no thyromegaly; +acanthosis circumferential around the neck
Cardiovascular: Regular rate, no extra heart sounds
Pulmonary/Chest: Good respiratory effort, +mid wheezing in RLL
Abdomen: Bowel sounds present, soft, non-tender; no violaceous striae.
Musculoskeletal: Moving all extremities
Neurological: Alert, awake
Skin: Warm, dry.
Psychiatric: Not agitated
February 2017

Labs

<table>
<thead>
<tr>
<th>Anion gap 24</th>
<th>Ca 9.5</th>
<th>Ketones = 0.30</th>
<th>A1c 6.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>138</td>
<td>94</td>
<td>16</td>
<td>454</td>
</tr>
<tr>
<td>4.6</td>
<td>20</td>
<td>1.0</td>
<td>454</td>
</tr>
</tbody>
</table>

Glucose

<table>
<thead>
<tr>
<th>Time</th>
<th>16:52</th>
<th>21:23</th>
<th>07:44</th>
<th>11:25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>277</td>
<td>351</td>
<td>222</td>
<td>252</td>
</tr>
</tbody>
</table>

Current insulin regimen:
- Lantus 10 units daily
- Novolog medium dose (1-9 units) qAC and (1-4 units) qHS
- 24 hr insulin requirements: 24 units
What type of diabetes does he have?

- Type 1
- Type 2
- Steroid induced
Steroid-induced diabetes

• **Definition:** “an abnormal increase in blood glucose associated with the use of glucocorticoids in a patient with or without a prior history of diabetes mellitus”

• **Prevalence:**
  - Oral glucocorticoids have been associated with up to 2% of incident cases of DM in a primary care population
  - 40-56% of inpatient consults to the Endocrinology Consult Service are for new onset steroid-induced DM or type 2 DM exacerbated by steroid use

• A study of NJ Medicaid patients determined relative risk of developing hyperglycemia on oral glucocorticoids was 2.23 compared with no glucocorticoids
  - OR 1.77 for 1 – 39 mg/d Hydrocortisone-equivalents
  - OR 3.02 for 40 – 79 mg/d Hydrocortisone-equivalents
  - OR 5.82 for 80 – 119 mg/d Hydrocortisone-equivalents
  - OR 10.34 for >= 120 mg/d Hydrocortisone-equivalents

Steroid-induced diabetes

How would you treat?

• There is little data about optimal management
• GLP1 agonists are promising: Exenatide has been shown to prevent prednisone-induced glucose intolerance
• Basal/bolus insulin is the most flexible option

• Recommendations:
  – Lantus 20 units q AM
  – Novolog 5 units before meals
  – Novolog medium-dose hyperglycemia correction with meals

• While he is on prednisone, continue basal/bolus insulin
• When prednisone is stopped, stop insulin therapy, but continue to monitor blood sugars qac and qhs

February 2017
Readmitted

- **Chief Complaint:** Symptomatic hyperglycemia
- **Labs:** Glucose 709, bicarb 18, AG 24, ketones 0.31, A1c 8.6
- **Meds:** PCP increased doses to Lantus 30 units daily and Novolog 10 units with meals. He took this dose for two days but was still hyperglycemic. Reports dietary changes including more salads and fish and has cut back on juice and soda.
- Recommend the following insulin at discharge
  - Lantus 40 units daily
  - Novolog 15 units with meals
  - Novolog high dose sliding scale
- **F/u with PCP and endocrinology**
Multiple ER Visits and Readmissions

- **April 2017**
  - Lantus 40 units q12 hours
  - Novolog 25 units with meals + high dose sliding scale
- **May 2017**
  - Restarted on same home regimen with rapid improvement, suspect non-adherence contributing
- **June 2017**
  - Lantus 40 units q12 hours
  - Novolog 35 units with meals + high dose sliding scale
  - Start Metformin

<table>
<thead>
<tr>
<th>Date</th>
<th>Hb</th>
<th>A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/26/2017</td>
<td>6.7 (H)</td>
<td></td>
</tr>
<tr>
<td>3/16/2017</td>
<td>8.6 (H)</td>
<td></td>
</tr>
<tr>
<td>4/18/2017</td>
<td>11.0 (H)</td>
<td></td>
</tr>
<tr>
<td>6/12/2017</td>
<td>11.5 (H)</td>
<td></td>
</tr>
</tbody>
</table>
Would you do any additional testing?

- The abrupt onset and rapid progression of his diabetes raised suspicion for LADA

**A Clinical Screening Tool Identifies Autoimmune Diabetes in Adults**

- A study in 2006 proposed a clinical screening tool to identify autoimmune diabetes in adults
- Retrospectively interviewed patients with LADA (n=102) and type 2 diabetes (n=111) to compare clinical features
- Distinguishing clinical features were identified to create a “LADA clinical risk score”

LADA Clinical Risk Score

P <0.0001

Performance of LADA Clinical Risk Score

Table 2—Prospective study: prediction summary

<table>
<thead>
<tr>
<th>LADA clinical risk score*</th>
<th>LADA (GADA+)</th>
<th>Type 2 diabetes (GADA−)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2</td>
<td>9</td>
<td>34</td>
<td>43</td>
</tr>
<tr>
<td>≤1</td>
<td>1</td>
<td>86</td>
<td>87</td>
</tr>
<tr>
<td>Totals</td>
<td>10</td>
<td>120</td>
<td>130</td>
</tr>
</tbody>
</table>

Score is based on the number of distinguishing clinical features for LADA (see Fig. 1).
Additional Labs

How does the positive GAD antibody change your perspective about his diabetes?
Readmitted

- **Chief Complaint:** Symptomatic hypoglycemia
- **Labs:**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb A1C</td>
<td>6.7 (H)</td>
<td>8.6 (H)</td>
<td>11.0 (H)</td>
<td>11.5 (H)</td>
<td>5.0</td>
</tr>
</tbody>
</table>

- **Meds:** Lantus 50 units daily, Novolog 18 units with meals, Metformin 1000mg BID
- **ROS:** Weight loss (40lbs since diagnosis, 360 -> 320 lbs), poor appetite, depressed mood, anhedonia. He recently lost his job doing warehouse work and delivery driving. Denies hypoglycemia at home.

October 14, 2017
Endo Consult

• Assessment:
  – Suspect hypoglycemia related to excessive insulin dosing in the setting of weight loss and poor PO intake

• Plan:
  – Hold all insulin
  – Check anti-GAD, anti-IA2, and anti-Znt8 antibodies to help better distinguish type 1 from type 2 diabetes

• Clinical course
  – Weaned off D5, blood sugars in the 100s
Readmitted

- **Chief Complaint:** Symptomatic hypoglycemia
- **Labs:**

![](image)

- **Meds:** Lantus 50 units daily, Novolog 18 units with meals, Metformin 1000mg BID
- **Additional history:** He continued taking same insulin regimen despite counseling to hold insulin. Pt could not explain why.
- **Clinical course:** Readmitted to MICU, on D10, insulin held, psychiatry consulted
Adrenal insufficiency?

- Cortisol = 1.7 (4:12am)
- Pt received Prednisone shortly afterwards but from MAR did not receive steroids prior to this
- He has required prednisone intermittently since February including 5 day bursts in February, March, August, and early October 2017
- He reports last prednisone was a 4 day burst completed 3 ago.

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/17/2017</td>
<td>08:21</td>
<td>7.2</td>
</tr>
<tr>
<td>Cortisol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td></td>
<td>21.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/16/2017</td>
<td>04:38</td>
<td>3.7</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/16/2017</td>
<td>04:38</td>
<td>18.4</td>
</tr>
<tr>
<td>10/16/2017</td>
<td>05:03</td>
<td>17.1</td>
</tr>
<tr>
<td>30 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 minutes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Endo Consult

• Assessment:
  – Still suspect hypoglycemia related to excessive insulin dosing in the setting of weight loss and poor PO intake
  – Cosyntropin stimulation test showed appropriate response but recent-onset secondary adrenal insufficiency possible

• Plan:
  – STOP INSULIN
  – Start Hydrocortisone 20/10, check additional pituitary labs

• Clinical course
  – Weaned off D5, blood sugars in the 100s
### Additional Labs

<table>
<thead>
<tr>
<th>Test</th>
<th>Ref. Range</th>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free T4</td>
<td>1.14</td>
<td>10/17/2017</td>
<td>23:03</td>
</tr>
<tr>
<td>TSH</td>
<td>1.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luteinizing Hormone</td>
<td>6.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>Ref Range: 4.0 - 15.2 ng/mL</td>
<td>10.98</td>
<td></td>
</tr>
<tr>
<td>Te Binding Globulin</td>
<td>Ref Range: 10 - 80 nmol/L</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Calculated Free Testosterone</td>
<td>Ref Range: 90 - 300 pg/mL</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Total Testosterone</td>
<td>Ref Range: 240 - 950 ng/dL</td>
<td>222 (L)</td>
<td></td>
</tr>
</tbody>
</table>

- ZNT8 – negative
- GAD – positive (0.04)
- IA2 – negative
Readmitted

• **Chief Complaint:** Symptomatic hypoglycemia
• **Labs:** Normal renal and hepatic function

• **Meds:** Pt denies taking any insulin, last dose was 4 days ago.
• **Additional History:** Eating normally, lunch was 2 burgers and tater tots, dinner was fried chicken, french fries, and coke
Differential Diagnosis?

Most likely causes in our patient:

- Surreptitious insulin use
- Insulin antibodies
- Insulin-producing tumor (insulinoma)
- Nestidioblastosis?

TABLE 1. Causes of hypoglycemia in adults

<table>
<thead>
<tr>
<th>Ill or medicated individual</th>
<th>Seemingly well individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Drugs</td>
<td>5. Endogenous hyperinsulinism</td>
</tr>
<tr>
<td>Insulin or insulin secretagogue</td>
<td>Insulinoma</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Functional β-cell disorders (nesidioblastosis)</td>
</tr>
<tr>
<td>Others (Table 2)</td>
<td>Noninsulinoma pancreaticogenic hypoglycemia</td>
</tr>
<tr>
<td>2. Critical illnesses</td>
<td>Post gastric bypass hypoglycemia</td>
</tr>
<tr>
<td>Hepatic, renal, or cardiac failure</td>
<td>Insulin autoimmune hypoglycemia</td>
</tr>
<tr>
<td>Sepsis (including malaria)</td>
<td>Antibody to insulin</td>
</tr>
<tr>
<td>Inanition</td>
<td>Antibody to insulin receptor</td>
</tr>
<tr>
<td>3. Hormone deficiency</td>
<td>Insulin secretagogue</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Other</td>
</tr>
<tr>
<td>Glucagon and epinephrine (in insulin-deficient diabetes mellitus)</td>
<td></td>
</tr>
</tbody>
</table>

Nestidioblastosis in T2DM

CASE REPORT

Hyperinsulinemic hypoglycemia due to adult nestidioblastosis in insulin-dependent diabetes

A Raffel, M Anlauf, SB Hosch, M Krausch, T Henopp, J Bauersfeld, R Klofat, D Bach, CF Eisenberger, G Klöppel, WT Knoefel

• Observed in case reports
• 40 year old man with a 6 year history of T2DM, treated with insulin, frequent hospitalizations with glucose >400
• Insulin requirements declined, ultimately pt was admitted with symptomatic hypoglycemia to 25
• Labs documented elevated insulin, c-peptide
• Localizing studies for insulinoma were negative

Nestidioblastosis in T2DM

• Pancreatic tail resection performed
• Histopathology showed no endocrine tumor, multiple enlarged beta cells fulfilling criteria for diffuse nestidioblastosis
• After surgery diabetes recurred and insulin was resumed

How would you evaluate?

ENDO CONSULT

• Assessment:
  – Potential etiologies of hypoglycemia include insulin antibodies, surreptitious insulin use, insulin-producing tumor (insulinoma), or adrenal insufficiency (unlikely to be the cause since pt is on replacement hydrocortisone).

• Plan:
  – Check insulin antibodies
  – Obtain a critical sample
  – Continue Hydrocortisone 20/10

CLINICAL COURSE

• Unable to obtain critical sample, weaned off D5
# Additional Labs

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>464</td>
<td>230</td>
<td>95</td>
</tr>
<tr>
<td>C-Peptide</td>
<td>1.15</td>
<td>0.76</td>
<td>1.27</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Ref. Range</th>
<th>10/20/2017 03:52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td></td>
<td>98</td>
</tr>
<tr>
<td>Insulin</td>
<td>Ref Range: 2.6 - 24.9 mcU/mL</td>
<td>17.2</td>
</tr>
<tr>
<td>PROINSULIN</td>
<td></td>
<td>21 (H)</td>
</tr>
<tr>
<td>PROINSULIN PLASMA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INSULIN ANTIBODIES</td>
<td></td>
<td>0.00</td>
</tr>
</tbody>
</table>
Outstanding Questions

• Was his hypoglycemia caused by endogenous hyperinsulinism?
• Will he develop progressive beta cell failure as his positive GAD antibody suggests?
• Does he really have adrenal insufficiency?

Consult team, be on the lookout for this patient!
UPDATE: Readmission 10/29

- **Chief Complaint:** Symptomatic hypoglycemia
- **History:** Patient reported feeling weak and tired and had one episode of vomiting at home. Blood sugar was in the 60s so he presented to the ER. POC glucose initially 76, dropped to nadir 35 in the ER. Started on D10 and admitted to MICU.
- **Meds:** Denies taking insulin, continues on Hydrocortisone 20/10
- **Labs:** Insulin level 30.2. C-peptide 0.10. No simultaneous glucose but recent POC glucose 69-76
- **Clinical course:** Blood sugars improved on D10, patient left AMA. Unclear if/how he was confronted about lab findings.
Psychiatry Evaluation from Prior Admission

- **History**
  - Raised by mother and grandmother, strained relationship with each
  - At age 17 he was put out of his mother's home and became homeless
  - Previously lived with friends, now living in his Hyundai Sonata
  - Prior arrests for possession of a controlled substance and retail theft

- **Assessment**
  - Major depressive disorder, single episode, moderate severity
  - Patient has decision making capacity to leave AMA
  - Resident: “Differential diagnosis includes a somatic symptom or related disorder including Factitious Disorder… reported he “enjoyed being in the hospital” and exhibits “sick role” behavior.”
  - Attending: “We have increasing concern that he may be invested in being in the hospital but his erratic behavior makes it difficult to determine what his true goals may be.” (Dr. Marcangelo)

Table Source: DSM V
References


