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

February 2017

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

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

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)

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

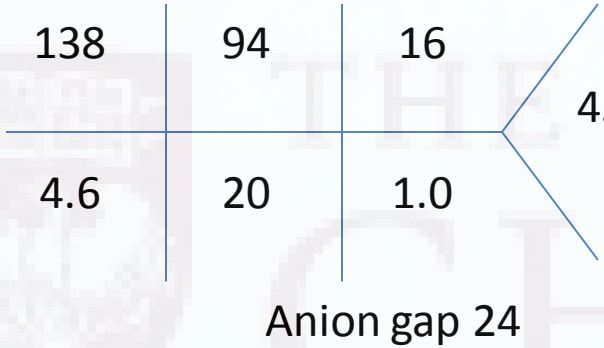
Neurological: Alert, awake

Skin: Warm, dry.

Psychiatric: Not agitated

February 2017

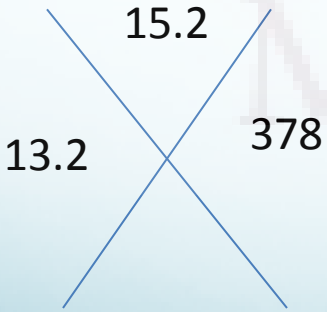
Labs



Anion gap 24

Ca 9.5

Ketones = 0.30
A1c 6.7



	16:52	21:23	07:44	11:25
Glucose	277	351	222	252

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?

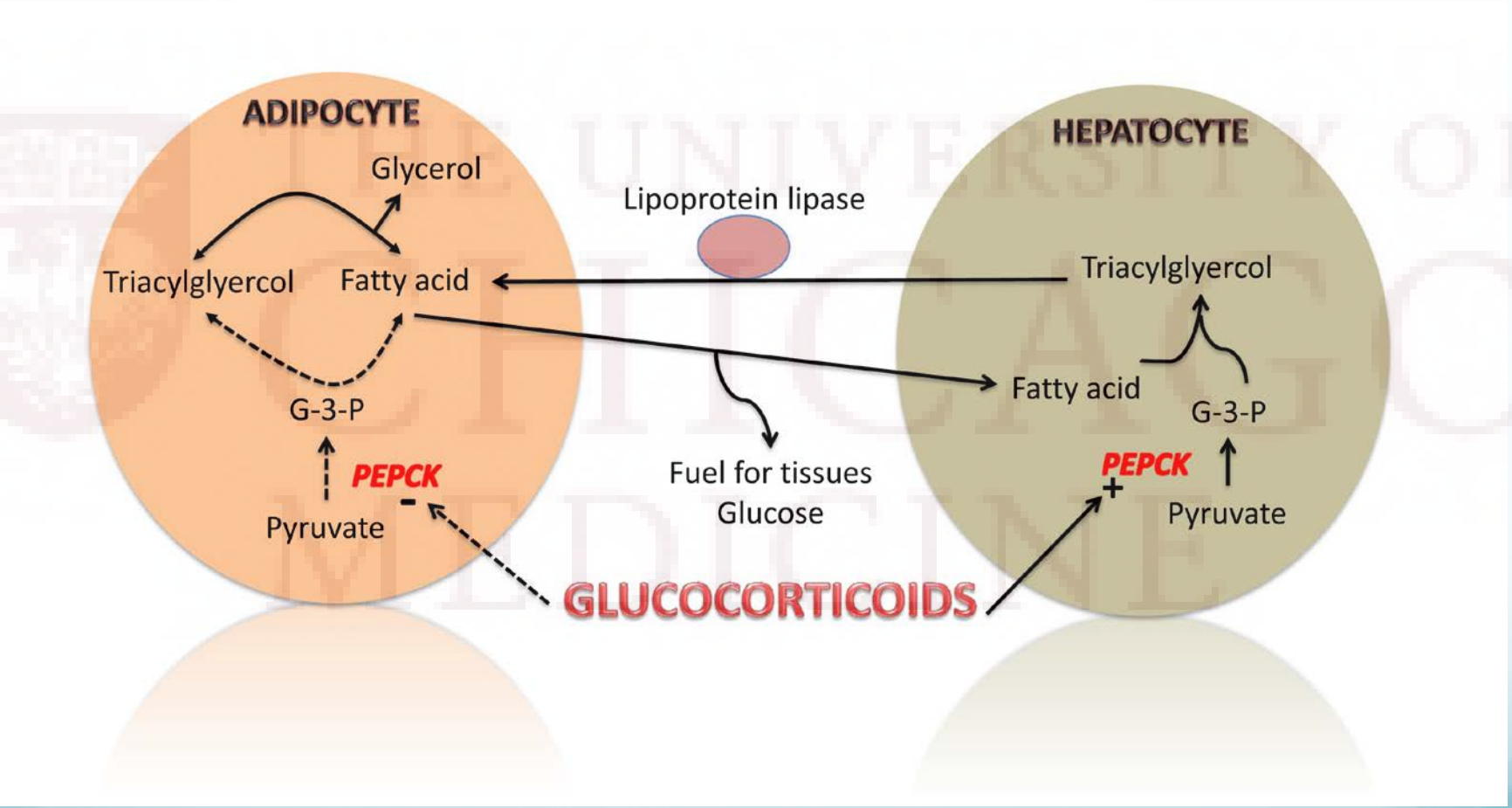
- Type 1
- Type 2
- Steroid induced

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

Gulliford et al. Diabetes Care. 2006 Dec;29(12):2728-9.
Hwang et al. Diabetes Metab Res Rev. 2014 Feb;30(2):96-102.
Gurwitz et al. Arch Intern Med. 1994 Jan 10;154(1):97-101.

Steroid-induced diabetes



Hwang et al. Diabetes Metab Res Rev. 2014 Feb;30(2):96-102.

How would you treat?

- There is little data about optimal management
- GLP1 agonists are promising: Exenatide has been shown to prevent predisone-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

March 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

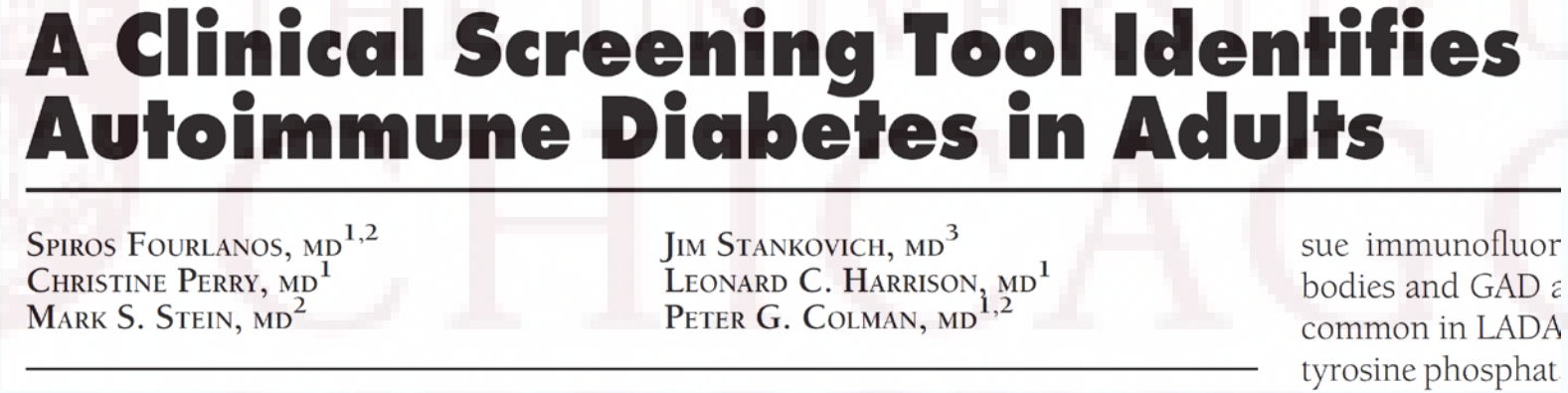
Multiple ER Visits and Readmissions

- 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

	2/26/2017 21:48	3/16/2017 14:36	4/18/2017 20:55	6/12/2017 07:59
Hb A1C	6.7 (H)	8.6 (H)	11.0 (H)	11.5 (H)

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

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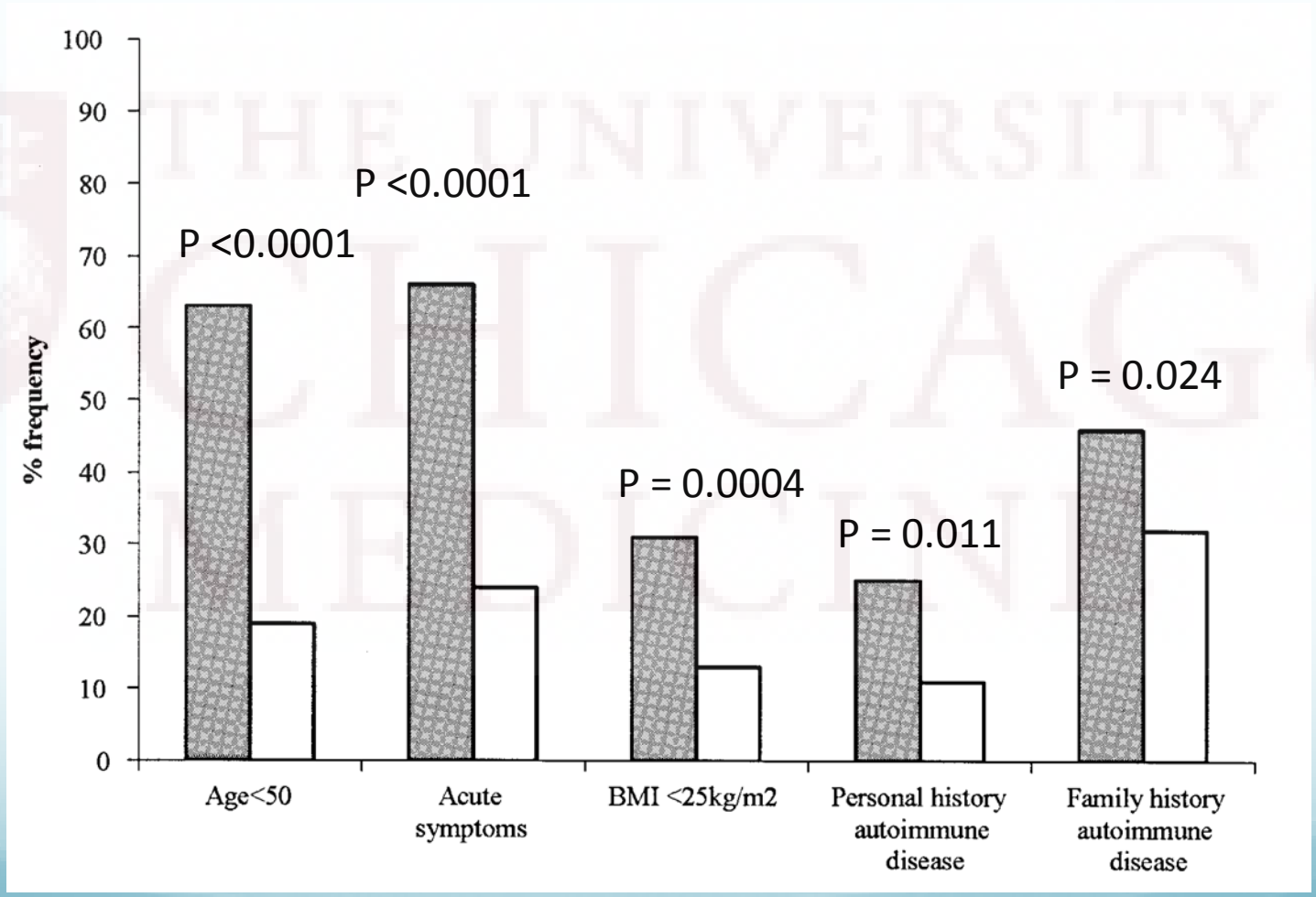
sue immunofluor
bodies and GAD a
common in LADA
tyrosine phosphat

- 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”

Fourlanos et al. Diabetes Care. 2006 May;29(5):970-5.

LADA Clinical Risk Score



Fourlanos et al. Diabetes Care. 2006 May;29(5):970-5.

Performance of LADA Clinical Risk Score

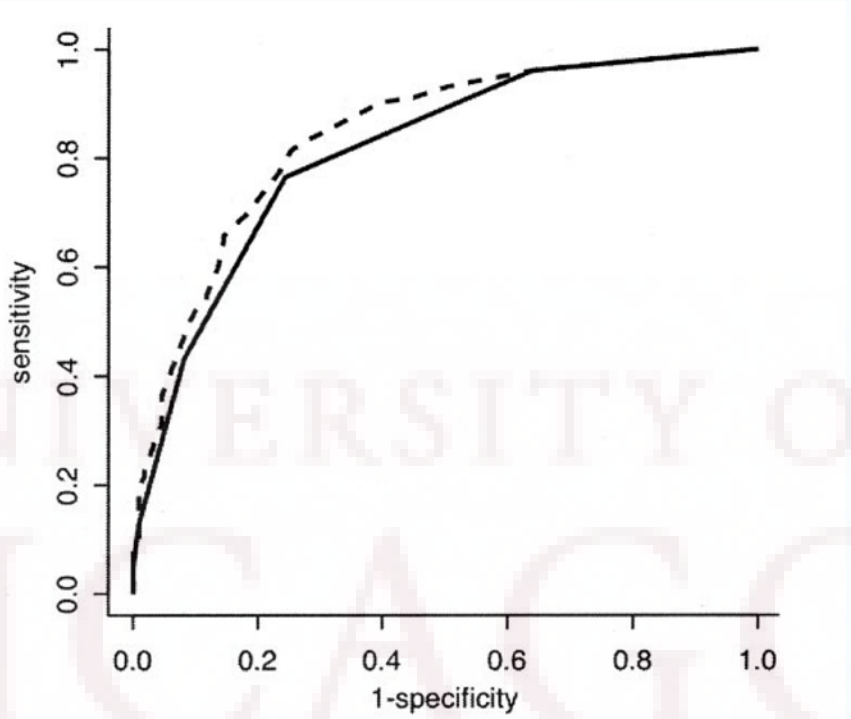


Table 2—*Prospective study: prediction summary*

LADA clinical risk score*	LADA (GADA+)	Type 2 diabetes (GADA−)	Total
≥2	9	34	43
≤1	1	86	87
Totals	10	120	130

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

Fourlanos et al. Diabetes Care. 2006 May;29(5):970-5.

Additional Labs

	3/22/2017 05:52	4/19/2017 17:53
GAD65 AB ASSAY	Insufficient quantity	**0.05 (H)**

	3/16/2017 14:36	5/4/2017 04:06
Glucose	464	230
C-Peptide	1.15	0.76

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

October 14, 2017

Readmitted

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

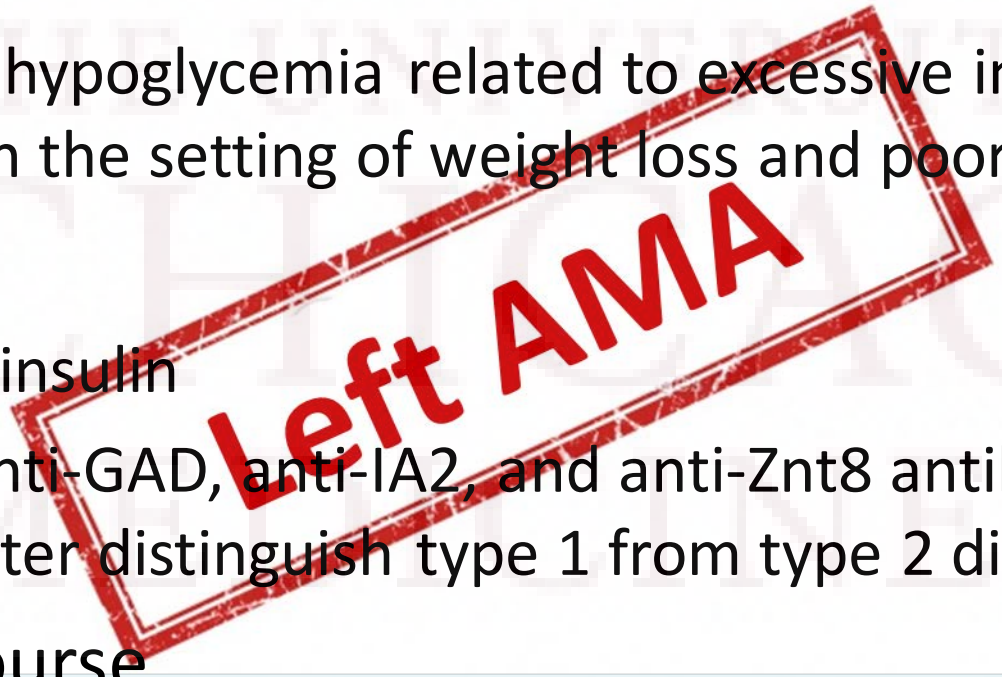
	No department found			Mitchell Adult Emergency Dept. University of Chicago 10/13 0700 - 10/14 0659					
Time:	1811	1819	1833	1840	1928	2019	2059	2220	2306
Glucose (mg/dL)	Graphs cannot display in the current view								
▼Accucheck									
POC Glucose	34	40	180		33	136	48	43	85
▼Serum Glucose									
Serum Glucose				54					

- **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.

	2/26/2017 21:48	3/16/2017 14:36	4/18/2017 20:55	6/12/2017 07:59	10/3/2017 04:06
Hb A1C	6.7 (H)	8.6 (H)	11.0 (H)	11.5 (H)	5.0

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



October 16, 2017

Readmitted

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

	No de...	Mitchell Adult Emergency Dept. University of Chicago								N09S	
	10/15 0700 - 10/16 0659										
Time:	1513	1609	1618	1628	1743	1806	1901	1947	2018	2058	2156	2301
Glucose (mg/dL)	Graphs cannot display in the current view											
Accucheck												
POC Glucose	62			126	54		37	43	64	42	72	119
Serum Glucose												
Serum Glucose		61										
Dextrose												
DEXTROSE IV (g)			25			25						

- **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?

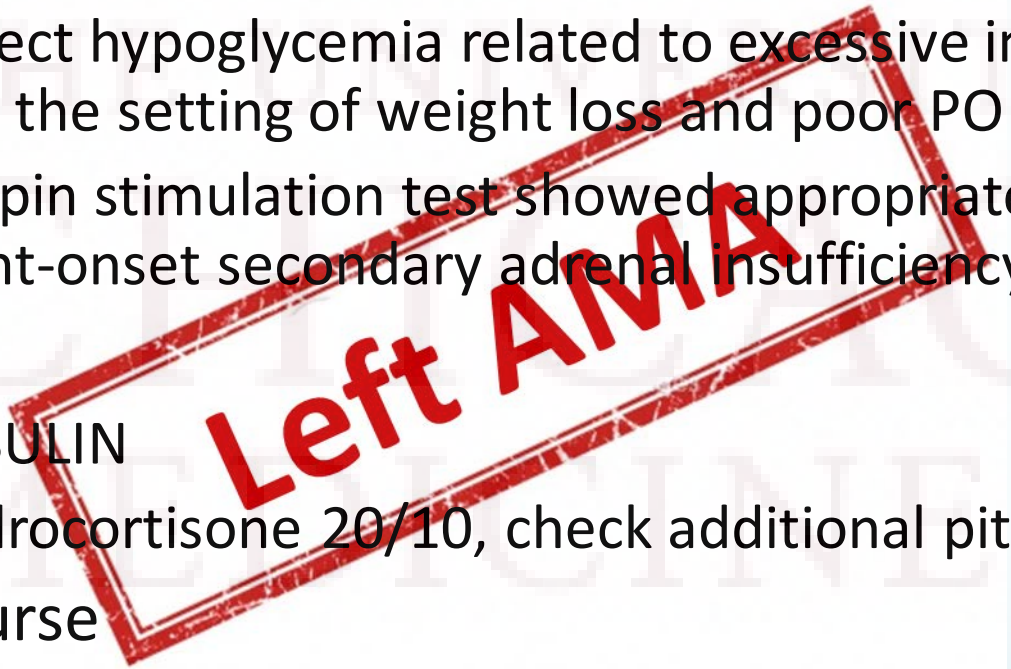
- Cortisol = 1.7 (4:12am)
- Pt received Prednisone shortly afterwards but from MAR did not receive steroids prior to this
- He has required prednisone intermittently since February including 5 day bursts in February, March, August, and early October 2017
- He reports last prednisone was a 4 day burst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

	10/17/2017 08:21
Cortisol	7.2
ACTH	21.8

	10/16/2017 04:38	10/16/2017 04:38	10/16/2017 05:03
	Baseline	30 minutes	60 minutes
Cortisol	3.7	18.4	17.1

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

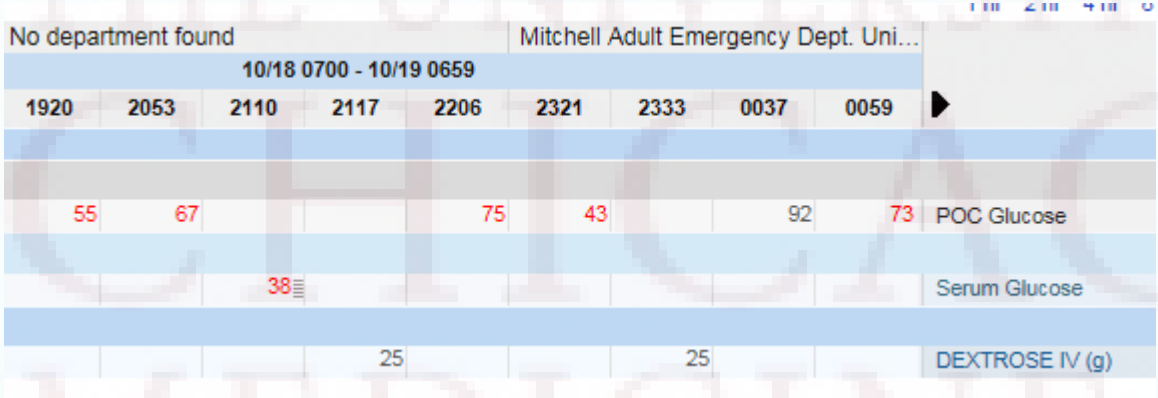
	Ref. Range	10/17/2017 23:03
Free T4		1.14
TSH		1.49
Luteinizing Hormone		6.8
Prolactin	Ref Range: 4.0 - 15.2 ng/mL	10.98
Te Binding Globulin	Ref Range: 10 - 80 nmol/L	18
Calculated Free Testosterone	Ref Range: 90 - 300 pg/mL	103
Total Testosterone	Ref Range: 240 - 950 ng/dL	222 (L)

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

October 18, 2017

Readmitted

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



No department found					Mitchell Adult Emergency Dept. Uni...				
10/18 0700 - 10/19 0659									
1920	2053	2110	2117	2206	2321	2333	0037	0059	
55	67			75	43		92	73	POC Glucose
		38							Serum Glucose
			25			25			DEXTROSE IV (g)

- **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?

TABLE 1. Causes of hypoglycemia in adults

Ill or medicated individual
1. Drugs
   - Insulin or insulin secretagogue
   - Alcohol
   - Others (Table 2)
2. Critical illnesses
   - Hepatic, renal, or cardiac failure
   - Sepsis (including malaria)
   - Inanition
3. Hormone deficiency
   - Cortisol
   - Glucagon and epinephrine (in insulin-deficient diabetes mellitus)
4. Nonislet cell tumor

Seemingly well individual
5. Endogenous hyperinsulinism
   - Insulinoma
   - Functional β-cell disorders (nesidioblastosis)
     - Noninsulinoma pancreatogenous hypoglycemia
     - Post gastric bypass hypoglycemia
   - Insulin autoimmune hypoglycemia
     - Antibody to insulin
     - Antibody to insulin receptor
   - Insulin secretagogue
   - Other
6. Accidental, surreptitious, or malicious hypoglycemia

- Most likely causes in our patient:
  - Surreptitious insulin use
  - Insulin antibodies
  - Insulin-producing tumor (insulinoma)
  - Nestidioblastosis?

Table: Cryer et al. J Clin Endocrinol Metab. 2009 Mar;94(3):709-28.

Nestidioblastosis in T2DM

CASE REPORT

Hyperinsulinemic hypoglycemia due to adult nesidioblastosis in insulin-dependent diabetes

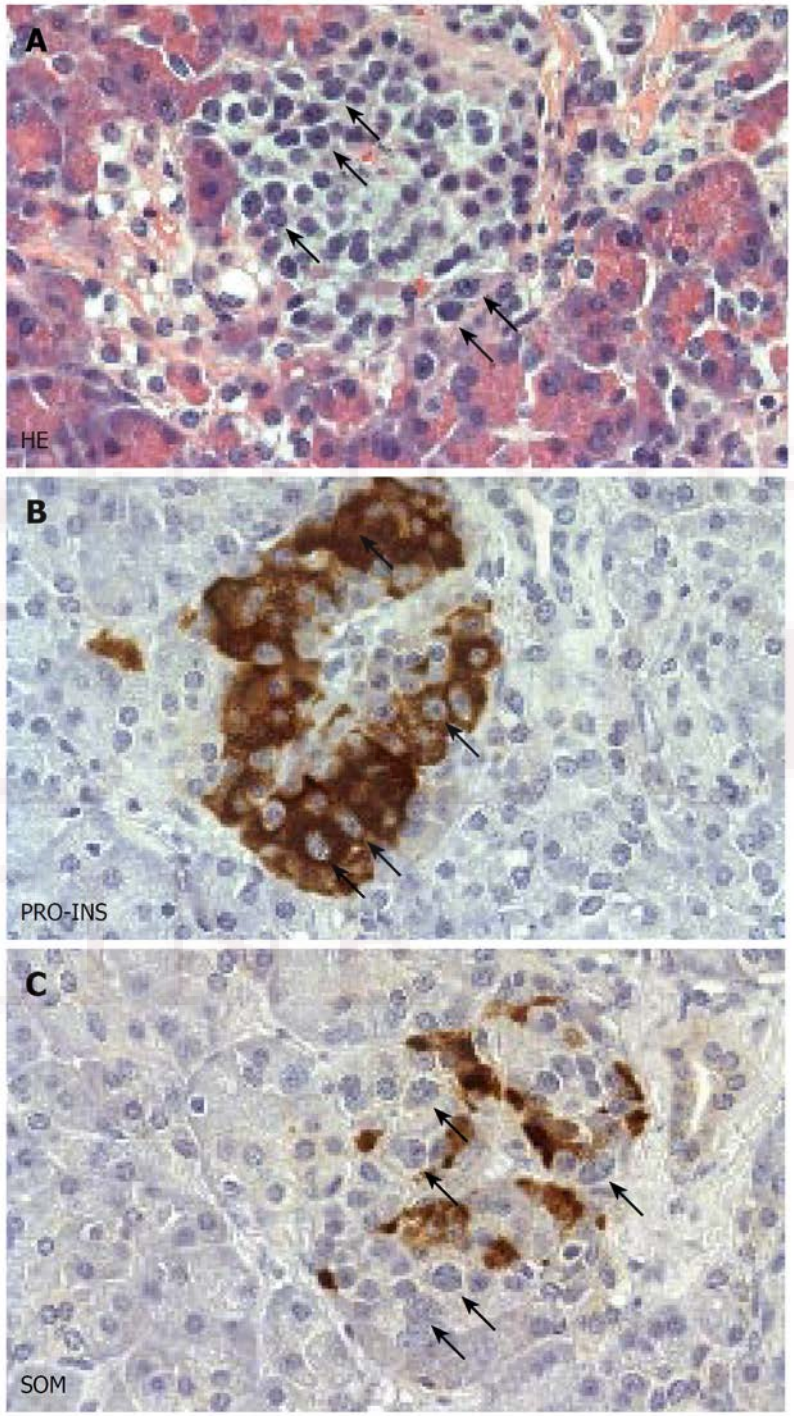
A Raffel, M Anlauf, SB Hosch, M Krausch, T Henopp, J Bauersfeld, R Klofat, D Bach, CF Eisenberger, G Klöppel, WT Knoefel

- 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

Raffel et al. World J Gastroenterol. 2006 Nov 28;12(44):7221-4.

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

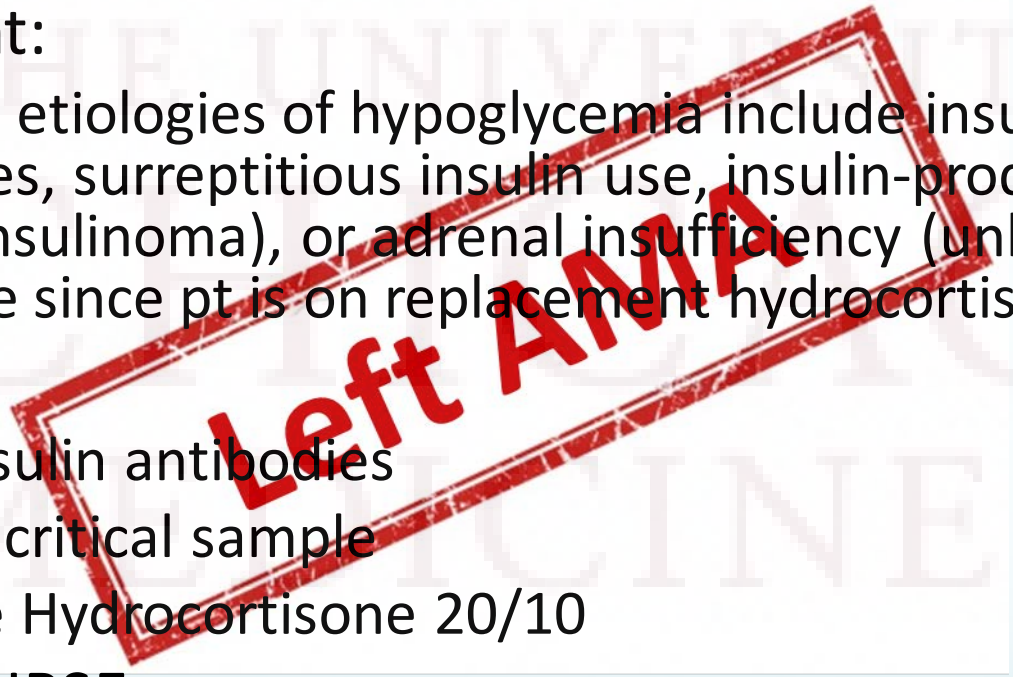


Raffel et al. World J Gastroenterol. 2006 Nov 28;12(44):7221-4.

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

	3/16/2017 14:36	5/4/2017 04:06	10/17/2017 08:33
Glucose	464	230	95
C-Peptide	1.15	0.76	1.27

	Ref. Range	10/20/2017 03:52
Glucose		98
Insulin	Ref Range: 2.6 - 24.9 mcU/mL	17.2
PROINSULIN PLASMA		**21 (H)**
INSULIN ANTIBODIES		0.00

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

- Hist
  - each
  - meless
  - theft
- Asse
  - joyed
  - 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)

Diagnostic Criteria **300.19 (F68.10)**

Factitious Disorder Imposed on Self

A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, associated with identified deception.

B. The individual presents himself or herself to others as ill, impaired, or injured.

C. The deceptive behavior is evident even in the absence of obvious external rewards.

D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Specify:

Single episode

Recurrent episodes (two or more events of falsification of illness and/or induction of injury)

Table Source: DSM V

References

1. Gulliford MC, Charlton J, Latinovic R. Risk of diabetes associated with prescribed glucocorticoids in a large population. Diabetes Care. 2006 Dec;29(12):2728-9. PubMed PMID: 17130214.
2. Hwang JL, Weiss RE. Steroid-induced diabetes: a clinical and molecular approach to understanding and treatment. Diabetes Metab Res Rev. 2014 Feb;30(2):96-102. doi: 10.1002/dmrr.2486. Review. PubMed PMID: 24123849; PubMed Central PMCID: PMC4112077.
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