



THE UNIVERSITY OF
CHICAGO
MEDICINE

**A 79-YEAR-OLD MALE WITH
HYPOGLYCEMIA**

Tara Rajiyah, MD
Med-Peds Endocrine Fellow

LEARNING OBJECTIVES

- Review the differential diagnosis and work up for hypoglycemia
- Distinguish the differences between insulinoma, nesidioblastosis, and autoimmune hypoglycemia
- Explore medical and surgical options for hyperinsulinism

HPI

- 79yo M with a history of mechanical AVR and atrial fibrillation (on coumadin), CHF (EF 45-50%), pulmonary HTN, CKD, COPD, OSA, HLD, hypothyroidism and diet controlled-diabetes
- Transferred from OSH for work up and management of hypoglycemia
- Multiple episodes of symptomatic and asymptomatic hypoglycemia over the last several months
 - Most cases fasting
 - Syncopal episodes with pre-episode amnesia; POC BG <40
 - Most recently, told wife his head felt funny and BG was 33. Improved to 40 after 4 glucose tabs and OJ with 2-teaspoons sugar
- Over last year, patient has had voracious appetite
 - Late night snacking on soda and ice cream d/t waking up not feeling well
 - Improvement of symptoms with eating
- Has gained 10-15 lbs

DIABETES HISTORY

- Diagnosed many years ago
- Was never on insulin
- Was on a ?sulfonylurea until 3 years ago
- Lost 70 lbs prior to diabetes remission, related to decompensation of cardiac disease
- Wife has T2DM but is only on metformin

PAST MEDICAL +SURGICAL HISTORY

- CAD s/p CABG
- Aortic Valve Replacement
- Atrial Fibrillation
- 3rd Degree Heart Block
- HFpEF
- CKD
- Carotid stenosis s/p endarterectomy
- Pulmonary HTN
- HTN
- HLD
- OSA
- Gastric AVMs
- T2DM
- Hypothyroidism
- Dementia

MEDICATIONS

- Lasix 40 mg daily
- Coumadin 5 mg daily
- Donepezil 10 mg daily
- Amiodarone 200 mg daily
- Carvedilol 6.25 mg bid
- Ezetimibe 10 mg daily
- Levothyroxine 125 mcg daily
- Cyanocobalamin 1 tab daily
- Rosuvastatin 10 mg daily
- Loratadine 10 mg daily
- Tamsulosin 0.4 mg daily

FAMILY + SOCIAL HISTORY

- Family History

- Mother: T2DM, CAD
- Brothers (x2): T2DM

- Social History

- Former smoker

PHYSICAL EXAM

- Vitals
 - 161/66 mmHg
 - 60 bpm
 - 36.8 °C
 - 18 breaths per min
 - SpO2 94%
 - BMI 26.6 kg/m²
- General: Well appearing
- Eyes: EOMI, no scleral icterus
- HENT: moist mucous membranes
- CVS: S1+S2, RRR
- Resp: CTA
- GI: soft, NTD, +BS
- MSK: no edema, ecchymotic lesions on UE



Thoughts?

DDx?

Further
Work-Up?

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 |

TABLE 2. Drugs other than antihyperglycemic agents and alcohol reported to cause hypoglycemia (24)

| |
|--|
| Moderate quality of evidence ($\oplus\oplus\oplus\circ$) |
| Cibenzoline |
| Gatifloxacin |
| Pentamidine |
| Quinine |
| Indomethacin |
| Glucagon (during endoscopy) |
| Low quality of evidence ($\oplus\oplus\circ\circ$) |
| Chloroquineoxaline sulfonamide |
| Artesunate/artemisin/artemether |
| IGF-I |
| Lithium |
| Propoxyphene/dextropropoxyphene |
| Very low quality of evidence ($\oplus\circ\circ\circ$) |
| Drugs with >25 cases of hypoglycemia identified |
| Angiotensin converting enzyme inhibitors |
| Angiotensin receptor antagonists |
| β -Adrenergic receptor antagonists |
| Levofloxacin |
| Mifepristone |
| Disopyramide |
| Trimethoprim-sulfamethoxazole |
| Heparin |
| 6-Mercaptopurine |

LABORATORY WORK UP OF HYPOGLYCEMIA

- Critical Sample
 - Glucose (<55 mg/dl)
 - Insulin
 - C-peptide
 - Pro-insulin
 - Beta-hydroxybutyrate
 - Cortisol
- Sulfonylurea Screen
- Insulin Antibodies

BACK TO OUR PATIENT

- Critical Sample
 - Glucose 41
 - C-peptide 16.21 (N 0.81-3.85)
 - Insulin (N 3-19)
 - Free 59
 - Total 79
 - Pro-insulin 23.9 (N ≤ 8)
- Sulfonylurea screen: Negative
- HbA1c 4.6%

- TSH 6.7
- Cortisol (9 AM, not at time of hypoglycemia) 13

| | | | |
|-----|-----|-----|----|
| 138 | 103 | 44 | 93 |
| 4.7 | 24 | 2.2 | |

| | | | |
|-----|-----|-----|-------------|
| 5.8 | 8.2 | 150 | GFR 29 |
| | 29 | | Albumin 3.3 |
| | | | ALT 25 |
| | | | AST 27 |
| | | | ALP 133 |

TABLE 3. Patterns of findings during fasting or after a mixed meal in normal individuals with no symptoms or signs despite relatively low plasma glucose concentrations (*i.e.* Whipple's triad not documented) and in individuals with hyperinsulinemic (or IGF-mediated) hypoglycemia or hypoglycemia caused by other mechanisms

| Symptoms, signs, or both | Glucose (mg/dl) | Insulin (μ U/ml) | C-peptide (nmol/liter) | Proinsulin (pmol/liter) | β -Hydroxybutyrate (mmol/liter) | Glucose increase after glucagon (mg/dl) | Circulating oral hypoglycemic agent | Antibody to insulin | Diagnostic interpretation |
|--------------------------|-----------------|-----------------------|------------------------|-------------------------|---------------------------------------|---|-------------------------------------|---------------------|-------------------------------|
| No | <55 | <3 | <0.2 | <5 | >2.7 | <25 | No | No | Normal |
| Yes | <55 | \gg 3 | <0.2 | <5 | \leq 2.7 | >25 | No | Neg (Pos) | Exogenous insulin |
| Yes | <55 | \geq 3 | \geq 0.2 | \geq 5 | \leq 2.7 | >25 | No | Neg | Insulinoma, NIPHS, PGBH |
| Yes | <55 | \geq 3 | \geq 0.2 | \geq 5 | \leq 2.7 | >25 | Yes | Neg | Oral hypoglycemic agent |
| Yes | <55 | \gg 3 | \gg 0.2 ^a | \gg 5 ^a | \leq 2.7 | >25 | No | Pos | Insulin autoimmune |
| Yes | <55 | <3 | <0.2 | <5 | \leq 2.7 | >25 | No | Neg | IGF ^b |
| Yes | <55 | <3 | <0.2 | <5 | >2.7 | <25 | No | Neg | Not insulin (or IGF)-mediated |

Neg, Negative; Pos, positive; PGBH, post gastric bypass hypoglycemia.

^a Free C-peptide and proinsulin concentrations are low.

^b Increased pro-IGF-II, free IGF-II, IGF-II/IGF-I ratio.

BACK TO OUR PATIENT

What would you do next?



What do you think is going on with this patient?

INSULINOMA

- Insulin producing tumor of the beta cells of Langerhans
- Incidence is 1-4 per million
- Can occur at any age
- Slightly higher predominance in women
- Less than 10% malignant, multiple tumors or associated with MEN-1
 - RECALL MEN 1: hyperparathyroidism, pituitary adenomas, pancreatic islet cell or gastrointestinal neuroendocrine tumors
- Generally associated with fasting hypoglycemia

NONINSULINOMA PANCREATOGENOUS HYPOGLYCEMIA SYNDROME(NIPHS)

- Represents 0.5-5% of all cases of hyperinsulinemic hypoglycemia
- Due to diffuse islet involvement with islet hypertrophy, hyperplasia and enlarged and hyperchromatic beta-cell nuclei
- Generally associated with post-prandial hypoglycemia
- Can be seen following bariatric surgery

INSULIN ANTIBODIES

- Most commonly seen in patients of Korean or Japanese descent but has been documented in Caucasians
- Usually seen in patients with autoimmune disease or who had had sulfhydryl containing drugs
 - A/w methimazole
 - A/w SLE, MGUS and multiple myeloma
- Hypoglycemic occurs in the late postprandial period as insulin is secreted in response to the meal and then bound to the circulating antibody with dissociation from the antibody in an unregulated fashion
- Very high measured insulin level ($>100 \mu\text{U}/\text{mL}$) due to artifact from high levels of circulating antibodies
- Also high C-peptide and proinsulin

INSULIN RECEPTOR ANTIBODIES

- Severe hyperglycemia, acanthosis nigricans and fasting hypoglycemia episode
- More frequent in black young women
- At low levels, the antibodies act as partial agonists resulting in hypoglycemia
- At high levels, antibodies downregulate the receptor's response to insulin causing hyperglycemia
- Insulin levels, C-peptide and proinsulin are moderately elevated, and insulin receptor antibodies are present
- Often associated with rheumatologic and hematologic diseases

BACK TO OUR PATIENT: IMAGING

- CT Abdomen and Pelvis
 - No comment on pancreas
 - Small hiatal hernia
 - Sludge in gall bladder
 - Sigmoid diverticula without diverticulitis
- Octreotide scan
 - No abnormal activity associated with the pancreas
 - No sites of abnormal activity are identified within the chest or abdomen or pelvis
 - Negative scan

BACK TO OUR PATIENT: EUS

- Small 7mm mass was identified in the uncinate process of the pancreas, unclear if neuroendocrine/insulinoma vs focal fat sparing vs small node

BACK TO OUR PATIENT: SURGICAL PLAN

- Based on these findings, endocrine surgery determined given cardiac history and size of lesion not a suitable surgical candidate
 - Based on size unlikely insulinoma
- Requesting guidance on medical management with diazoxide for hyperinsulinism
 - Per verbal report from surgical team, cardiology said diazoxide was safe to use in this patient but no documentation of this
 - RHC with globally elevated filling pressures

CLINICAL QUESTIONS



- What is the average size of insulinomas?
- Is diazoxide safe in this patient with heart failure and pulmonary hypertension?

INSULINOMA SIZE

- 90% are <2 cm
- Retrospective Polish study (Durczynski et al. 2014)
 - N=530 pancreatic tumor; only 10 insulinomas
 - Average size 1.6 +/- 0.5 cm
 - Location: 10% in uncinate process, 50% in tail, 30% head, 10% body
- Retrospective Serbian study (Tavcar et al. 2014)
 - N=42
 - < 1.0 cm: 17 %
 - 1–1.9 cm: 49%
 - 2–2.9 cm 27%
 - > 3 cm: 7%

DIAZOXIDE

- Binds to the SUR 1 unit of the K-ATP channels of the beta-cells
- Insulin release inhibited by opening the ATP-dependent potassium channel in pancreatic β cells
- Depolarization of beta-cell prevented and therefore insulin secretion is halted
- Effective in >50% of cases
- 100-1500 mg daily in fractionated doses
- Side Effects/Adverse Reaction
 - Cardiac failure/fluid overload (due to sodium and water retention); often given with thiazide diuretic
 - Hyperosmolar coma (nonketotic)
 - Hypertension (transient)
 - Hypotension, palpitations, tachycardia
 - Hyperglycemia
 - Reversible hypertrichosis
 - GI discomfort

PREVALENCE OF CARDIAC SIDE EFFECTS IN DIAZOXIDE: NEONATES

- Limited studies; most in neonates
- Neonates
 - Circulatory compromise in HI a/w younger gestational age ($p=0.0372$) and higher maximum dose of diazoxide ($p=0.0146$) (Yoshida et al. 2014)
 - 4.8% (out of 165) with pulmonary hypertension and trend towards higher rates in those with perinatal stress HI vs congenital HI ($p=0.08$) (Thornton et al. 2019)
 - 7% of 133 neonates developed pulmonary hypertension and was associated with the presence of congenital heart disease (CHD) ($P = .008$), and total fluid volume exceeding 130 mL/kg/d in the immediate 24 hours preceding diazoxide ($P = .019$) (Chen et al. 2019)

PREVALENCE OF CARDIAC SIDE EFFECTS IN DIAZOXIDE: ADULTS

- Adults
- In insulinomas, diazoxide caused fluid retention in 50% of patients and was more common in women ($p=0.025$) (Niitsu et al. 2019)
- No comment on pre-existing cardiac history

BACK TO OUR PATIENT

- Asked surgery to wait for preliminary FNA results as would strongly suggest reconsideration of surgery vs ablative procedure
- In follow up note stated would likely recommend octreotide over diazoxide given history of pulmonary hypertension and heart failure
- Surgical team started patient on octreotide 100 mg s/q tid prior to results
 - POC BG ranged from 119-157
- FNA results
 - Mixed, mostly small lymphoid cell population consistent with a reactive process
 - Target cells stain positive with CD-3 and CD-20 (T and B cell lymphoid markers)
 - Cells are negative for synaptophysin, chromogranin, and Ki-67 (0% stain)
 - Cell morphology and stain profile is consistent with a reactive lymph node or chronic inflammation
 - Limited cell; sample not entirely satisfactory

OCTREOTIDE

- Inhibitory effect of insulin secretion by somatostatin analogues
- Presence of somatostatin receptors (SSTR)2A-SSTR5 in a subgroup of insulinomas
- Effective in just under 50% of patients with insulinomas
- Risk of paradoxical hypoglycemia due to suppression of counter-regulatory hormones growth hormone and glucagon
- Side effects
 - GI effects (distension, malabsorption, steatorrhea)
 - Cardiac conduction disturbances
 - Goiter
 - Epistaxis
 - Injection site reaction

BACK TO OUR PATIENT: FOLLOW UP

- Missed endocrine and endocrine surgery follow up appointments
- Did present for DOTATE scan
 - No definitive evidence of Ga-68 DOTATE positive tumor
 - Increased uptake in the prostate most likely prostatitis but cannot r/o tumor
 - Questionable focal activity in left lobe of liver
- DOTATE scans identify up to 90% of insulinomas (Nockel et al. 2016)
 - MRI and CT identify up to 60%
 - Intraoperative US identified almost 94%

WHAT IS THE CAUSE HIS OF HI?

- Occult insulinoma?
- Nesidioblastosis given significant weight loss?
- Cannot diagnose on imaging
- Insulin antibodies vs Insulin receptor antibodies?

Table 2. Nesidioblastosis: differences between neonates and adults [8]

| Parameter | Neonates | Adults |
|---------------------------|--|---|
| Causes | Autosomal recessive and dominant forms affecting <i>SUR1</i> gene, <i>Kir6.2</i> gene, <i>GCK</i> gene, <i>GLUD1</i> gene, <i>H19-IGF2</i> , <i>P257KIP2</i> | Genetic causes widely unknown, MEN-1 syndrome, <i>SUR1</i> and <i>Kir6.2</i> gene not affected Weight loss |
| Frequency | Sporadic: 1/50 000 births Familial: up to 1/2500 births | Unknown, up to 10% of organic hyperinsulinism (0,09/100 000) |
| Histologic findings | Hypertrophic beta cells and islets, Beta cell with pleomorphic nuclei, ductuloinsular complexes, neoformation of islets from ducts | Hypertrophic beta cells and islets, beta cells with pleomorphic nuclei, ductuloinsular complexes, neoformation of islets from ducts |
| Diagnosis | Glycemic response to glucagons Absence of ketonuria, Blood ammonia concentration | Serum glucose <2,2 mmol/l Insulin >6 uU/ml Positive 72 hour fasting test |
| Preoperative localization | Percutaneous transhepatic pancreatic venous sampling Selective arterial calcium test | Endosonography, MRI, multislice CT, selective arterial calcium stimulation test |
| Surgical treatment | Focal form: partial pancreatectomy Diffuse form: 95% pancreatectomy | Gradient-guided extent of pancreatectomy according to results of selective arterial calcium stimulation test |

DISTINGUISHING BETWEEN INSULINOMA AND NESIDIOBLASTOSIS

- Selective arterial calcium stimulation (SACST) with hepatic venous sampling can localize occult insulinomas with 90% sensitivity
- IV administration of calcium stimulates insulin release from insulinoma but not from normal beta cells
- Cannulation of the femoral vein and artery with passage of a sampling catheter to the right hepatic vein for sampling for insulin levels
- A catheter is also placed into the splenic, superior mesenteric and gastroduodenal arteries and calcium gluconate injected into these arteries
- Hepatic vein insulin concentration was significantly higher in insulinomas compared to nesidioblastosis (25.1 ± 4.4 vs 6.4 ± 0.5 , respectively, $P < .001$) (Thompson et al. 2015)
- A maximum hepatic venous insulin concentration of $91.5 \mu\text{IU/mL}$ was 95% specific for insulinoma and $263.5 \mu\text{IU/mL}$ was 100% specific (Thompson et al. 2015)

DISTINGUISHING BETWEEN INSULINOMA AND NESIDIOBLASTOSIS

- Histological differences
 - Insulinoma
 - Uniform nuclei with fine chromatin pattern and small nuclei
 - Nesidioblastosis
 - Budding of islet cells from pancreatic duct epithelium with increase in size, shape, and number of islet cells

MANAGEMENT OF HYPERINSULINISM: SURGICAL

- Surgical Management
 - Tumor Enucleation (75-98% cure)
 - Recurrence up to 7% in spontaneous cases and up to 21% in insulinomas
 - Partial pancreatectomy
 - Occult tumors
 - NIPHS
- Loco-regional Therapies
 - Radiofrequency ablation
 - High-intensity focused ultrasound ablation
 - Ultrasound-assisted alcoholization or selective chemoembolization
 - Many patients require repeat procedures in 5 weeks to 9 months

MANAGEMENT OF HYPERINSULINISM: MEDICAL

Table 2 Medical treatment of hyperinsulinemic hypoglycaemia (HH) according to the pathology

| Cause of HH | Treatments | References |
|--|---|--------------------------|
| Benign insulinoma | Diazoxide (from 100 to 600 mg up to 1500 mg per day) | Gill et al. [34] |
| | Somatostatin analogues | Vezzosi D et al. [36] |
| | Steroids | De Herder WW et al. [33] |
| Malignant insulinoma | Everolimus | Bernard et al. [55] |
| | Sunitinib | De herder WW et al. [56] |
| | Chemotherapy | Eriksson et al. [80] |
| | Peptide receptor radionuclide therapy (PRRT) | Baudin et al. [62] |
| Nesidioblastosis | Diazoxide, octreotide, alpha-glucosidase inhibitors (acarbose) or calcium channel blockers (verapamil and nifedipine) | Kapoor et al. [124] |
| Hirata syndrome Insulin Antibodies | Steroids (prednisone, 30–60 mg/day) | Wong et al. [135] |
| | Plasmapheresis | Yaturu et al. [136] |
| Autoimmune hypoglycaemia type B Insulin receptor antibodies | Steroids (prednisone 80 mg/day), azathioprine (100 mg/day) | Chon et al. [138] |
| | Combination of rituximab, cyclophosphamide and pulse steroids | Malek et al. [140] |

REFERENCES

- Anderson B, Nostedt J, Girgis S. Insulinoma or non-insulinoma pancreatogenous hypoglycemia? A diagnostic dilemma. *J Surg Case Reports*. 2016. 11:1-4.
- Chen SC, Dastamani A, Pintus D *et al*. Diazoxide-induced pulmonary hypertension in hyperinsulinaemic hypoglycaemia: Recommendations from a multicentre study in the United Kingdom. *Clinical endocrinol*. 2019. 91:770-775.
- Church D, Cardoso L, Kay RG *et al*. Assessment and management of anti-insulin autoantibodies in varying presentations of insulin autoimmune syndrome. *JCEM*. 2018. 103(10): 3845-3855. Dravecka I and Lazurova I. Nesidioblastosis in adults. *Neoplasma*. 61(3): 252-256.
- Cryer PE, Axelrod L, Grossman AB *et al*. Evaluation and management of adult hypoglycemic disorders: An Endocrine society clinical practice guidelines. *JCEM*. 2009. 94(3): 709-728.
- Davi MV, Pia A, Guarnotta V. The treatment of hyperinsulinemic hypoglycemia in adults: an update. *J Endocrinol Invest*. 2017. 40(1): 9-20.
- Durczynski A, Hogendorf P, Szymanski D *et al*. Insulinoma—rare but important clinical problem. Analysis of a series of 530 patients who underwent surgical treatment for the pancreatic tumor. *POLSKI PRZEGLĄD CHIRURGICZNY*. 2014, 86(11): 505–510.
- Garcia Guerrero A, Huix-Gonzalez F, Levy MJ. *Et al*. Ablative therapy in pancreatic cystic lesions. *Gastroenterol Hepatol*. 2019. 42(1): 43-50.
- Niitsu Y, Minami I, Izumiyama H *et al*. Clinical outcomes of 20 Japanese patients with insulinoma treated with diazoxide. *Endocrine Journal*. 2019. 66(2): 149-155.
- Nockel P, Babic B, Millo C. Localization of Insulinoma us 68-Ga DOTATE PET/CT. *JCEM*. 2017. 102(1):195-199.
- Jabri AL and Bayard C. Nesidioblastosis associated with hyperinsulinemia hypoglycemia in adults: review of literature. *European J of Internal Medicine*. 2004. 15:407-410.

REFERENCES

- Kandaswamy L, Raghavan R, and Pappachan JM. Spontaneous hypoglycemia: diagnostic evaluation and management. *Endocrine*. 2016. 53: 47-57.
- Komatsu Y, Nakamura A, Masahiro T *et al*. Safety and tolerability of diazoxide in Japanese patients with hyperinsulinemic hypoglycemia. *Endocrine Journal*. 2016. 63(3): 311-314
- Starke A, Saddig C, Krich B. Islet Hyperplasia in Adults: Challenge to Preoperatively Diagnose Non-Insulinoma Pancreatogenic Hypoglycemia Syndrome. *World J Surg*. 2006. 30: 670-679.
- Shao S, Zeng Z and Hu S. An observational analysis of insulinoma from a single institution. *QJM*. 2018. 237-241.
- Shah P, Rahman SA, Demirbilek H *et al*. Hyperinsulinemic hypoglycemia in children and adult. *Lancet Diabetes Endocrinol*. 2017. 5:729-42.
- Tavcar I, Kikovic S, Bezmarevic M *et al*. A 60-year experience in the treatment of pancreatic isulinoma in the Military Medical Academy, Belgrade, Serbia. *Vojnosanit Pregl*. 2014. 71(3): 293–297.
- Thompson SM, Vella A, Thomas GB *et al*. Selective calcium stimulation with hepatic venous sampling differentiates insulinoma from nesidioblastosis. *JCEM*. 2015. 100(11): 4189-4197.
- Throton P, Truong L, Reynolds C. Rate of serious adverse events associated with diazoxide treatment of patients with hyperinsulinism. *Horm Res Paediatr*. 2019. 91(1): 25-32.
- Unal B, Uzun OC, Cumhr I. A rare of complication of fastric bypass (weight loss) Surgery: Nesidioblastosis. *Interventional J of Surg Path*. 2015. 23(1): 68-70.
- Valente LG, Kwado A, Guillaume P *et al*. Clinical presentation of 54 patients with endogenous hyperinsulinemic hypoglycemia: neurological chameleon. *Swiss Med Wkly*. 2018. 148:w14682.