Hypoglycemia

Drs Maaz Sohail, FAU Resident and
Bryan Vinik, Endocrinology

Case:

- HPI: 75M referred for hypoglycemia with symptoms that started 18 months ago. Patient states that after drinking wine at night he would up confused and diaphoretic. EMS found him with B<50 which resolved after getting dextrose. Increased frequency of similar episodes since then. He is on a high protein low sugar/carb diet. Majority of symptoms occur overnight and occasionally mid-AM. He feels he needs to eat more frequently to avoid BG drops and using glucose tabs (approx. 1 daily) but without monitoring BG levels. Social drinker, denies any history of liver or pancreatic disease. Denies any hypoglycemic medication.

- ROS: weight gain
- PMH: Aortic valve disease, Hypercholesterolemia, Squamous cell skin cancer.
- PSH: Tonsillectomy, ankle fracture
- Medications:
  - Amlodipine-Benazepril HCL 10-20mg daily
  - Avodart 0.5mg daily
  - Pravastatin 20mg daily
  - HCTZ 25mg daily
- FH: No diabetes in family, noncontributory
- Social: nonsmoker, social drinker
- Allergies: Tetracycline

Physical Exam

BP: 118/70, HR: 70, FS: 75, BMI: 24
HEENT: No adenopathy or thyromegaly
C/V: NSR, no murmurs
GI: soft, NT, ND, no masses
MSK: pulses 2+, no edema
Neuro: normal DTR's, no tremors
Psych: No depression or anxiety

Workup

- Glucose 53, otherwise normal CMP
- elevated pro-insulin
- Normal c-peptide, cortisol, TSH
- Normal CgA normal
- Negative SFU screen
- Normal IGF-2
- MRI of the abdomen w/ contrast negative for any pancreatic lesions.

Follow Up Visit

- Refused hospital stay for 48-72 hour fasting test. He states his hypoglycemia continues but now more frequent however he is still able to manage it with his diet without any significant low BG levels. Hypoglycemic events occur between meals and early am with average BG levels in 50’s; 37 yesterday with symptoms. He is currently not waking up to eat overnight.

Next Step…

- Patient referred to GI for an EUS.
- Findings: No evidence of isolated pancreatic lesions that might account for patient's insulin production. One area biopsied using a 22-gauge needle, not very suspicious however sampled due to lack of other choices.
- Preliminary diagnosis in the room yielded normal acinar cells, formal pathology pending.

Pathology

- Microscopy: Benign acinar cells and a population of atypical cells with mildly pleomorphic nuclei, inconspicuous nucleoli, and a thin rim of cytoplasm. Some atypical cells appear plasmacytoid.
- Immunohistochemical staining: Atypical cells positive for CD56, chromogranin, synaptophysin and negative for CD45. Immunostain for insulin positive.
- Diagnosis: well differentiated pancreatic endocrine tumor

Surgery

- Patient was seen in JFK medical center for surgical enucleation of his insulinoma.

Hypoglycemia

Bryan Vinik MD

With gratitude to:
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Hypoglycemia-Objectives-1:

- 1. Define hypoglycemia: components and severity
- 2. Explain the normal counter regulatory hormone response to hypoglycemia and defects in diabetes
- 3. Describe hypoglycemia unawareness and possible etiologies
- 4. List the causes of non-diabetic hypoglycemia
- 5. Analyze the biochemical findings in the work-up of hypoglycemia
- 6. Assess the key components essential in the diagnosis and management of insulinoma and non-insulinoma pancreatogenous hypoglycemia

Hypoglycemia-Objectives-2:

- 1. DDx and Dx-is it really hypoglycemia and is it causing the Sx
- 2. Determine the cause, detective.
- 3. Treatment

Hypoglycemia

A clinical syndrome characterized by episodes of low blood glucose. Episodes are typically marked by metabolic encephalopathy (neuroglycopenia).

Autonomic manifestations alone do not indicate a hypoglycemic disorder.

Components of Hypoglycemia

- Whipple's Triad:
  - neurogenic and neuroglycopenic symptoms
  - a low plasma glucose concentration
  - relief by raising plasma glucose

It confirms the presence of clinical hypoglycemia, and only those patients in whom Whipple's triad is documented require evaluation and management of hypoglycemia.

Classification

- May be classified as insulin-mediated or non-insulin-mediated.
- Also classified as fasting or postprandial, but:
  - Insulinoma patients may become hypoglycemic postprandially
  - Factitious hypoglycemia occurs without regard to meals

Hypoglycemia in apparently healthy patients

- Single episodes
  - Accidental drug ingestion (ethanol, quinine, salicylates, sulfonylurea, glinides/glitinides)
- Multiple episodes
  - Excessive insulin production (insulinoma or post-gastric bypass syndrome)
  - Factitious use of insulin or secretagogue
  - Side effects of treatment for diabetes

Hypoglycemia in ill patients

- Advanced liver disease
- Chronic renal failure
- Severe congestive heart failure
- Sepsis
- Hospitalized patients at risk for iatrogenic hypoglycemia due to inappropriate insulin or oral medication use

Artifactual hypoglycemia

- Low blood glucose may be an artifact resulting from consumption of glucose in blood collection tube by large numbers of nucleated RBC or leukocytes in patients with hemolysis or leukemia

Diagnosis

- Measure blood glucose when possible
- Detailed history including description of symptoms and circumstances during which symptoms occur
- Medication history extremely important. All meds need to be reviewed and positively identified

Signs and symptoms of hypoglycemia:

- Signs:
  - Diaphoresis and pallor are common signs.
  - Heart rates and systolic blood pressures are raised, but not greatly.
  - Neuroglycopenic manifestations are often observable.
  - Occasionally, transient focal neurological deficits occur.
- Symptoms:
  - **Non-specific.**
  - Neurogenic symptoms: tremor, palpitations, and anxiety/arousal (catecholamine-mediated, adrenergic) and sweating, hunger, and paresthesias (acetylcholine-mediated, cholinergic).
  - Neuroglycopenic symptoms: cognitive impairment, behavioral changes, psychomotor abnormalities and, at lower plasma glucose concentrations, seizure and coma.

Clinical Manifestations

- In a study of patients with insulinomas, 85% had various combinations of diplopia, blurred vision, sweats, palpitations, weakness
- 80% had confusion or abnormal behavior
- 12% had generalized seizures

Clinical Manifestations

- Different patients may have differing symptoms
- Each patient tends to have same symptoms with each episode
- Patients who have only autonomic symptoms without neuroglycopenic symptoms are unlikely to have hypoglycemia
- Many patients have only neuroglycopenic symptoms, which occur at a threshold of about 50 mg/dl

Counterregulatory hormones

- Studies with insulin and glucose infusions to normal young adult volunteers show the threshold for secretion of counterregulatory hormones is about at a glucose of 55 mg/dl

Counterregulatory Hormones

- Insulin is the primary hormone that blunts postprandial hyperglycemia and maintains postabsorptive euglycemia
- Insulin's effects are counterbalanced by several factors to maintain a minimal level of glycemia

Counterregulatory Hormones

- Secreted in response to hypoglycemia
- Effect of hormonal secretion is to raise blood glucose both quickly and over the long term
- In patients with diabetes, secretion of counterregulatory hormones often cause very high blood glucose values after an episode of severe hypoglycemia (rebound)

Counterregulatory Hormones

- 1st defense: **decrease in insulin secretion** as plasma glucose concentrations decline within the physiological range (80–85 mg/dl)
- 2nd defense:
  - Increase in **glucagon.**
  - Acts only on the liver.
  - Increasing glucose production by stimulating both glycogenolysis and gluconeogenesis from alanine, among other amino acids, and glycerol.
  - Glycemic threshold for glucagon is 65 to 70 mg/dL
  - Requires a normally functioning liver.

Counterregulatory hormones

- 3rd defense:
  - Increase in **epinephrine**.
  - Acting via beta-2-adrenergic receptors, epinephrine has similar hepatic effects as glucagon.
  - Also increases the delivery of gluconeogenic substrates from the periphery, inhibits glucose utilization by several tissues, and, via alpha-2-receptors, inhibits insulin secretion.
  - Also requires a normally functioning liver.
  - Glycemic threshold is also at 65-70 mg/dl.

Counterregulatory Hormones

- Cortisol and growth hormone work slowly over time to maintain glucose levels. They are not involved in acute raising of glucose
- Epinephrine secretion is responsible for autonomic symptoms of hypoglycemia
- Rate of decrease of blood glucose does NOT influence occurrence of symptoms

Counterregulatory Hormones

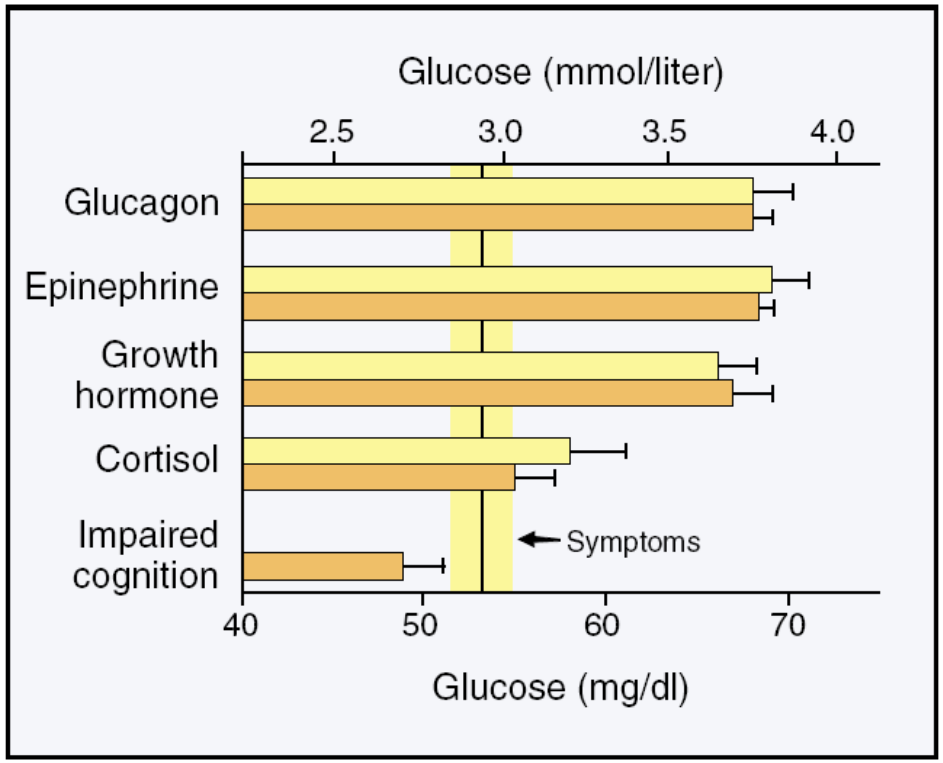


Figure 1. Threshold Plasma Glucose Levels at Which Plasma Levels of Glucagon, Epinephrine, Growth Hormone, and Cortisol Increase, Cognition Is Impaired, and Symptoms of Hypoglycemia Occur in Normal Subjects.

Hypoglycemic Unawareness

- Glucagon and epinephrine are the 2 major defense hormones against prolonged hypoglycemia
- Glucagon secreted by alpha cells of pancreatic islets
- Glucagon response to hypoglycemia diminishes after a few years of type 1 diabetes
- Epinephrine alone may provide adequate defense against hypoglycemia

Hypoglycemic Unawareness

- Epinephrine response to hypoglycemia can be lost after about 10 years of type 1 diabetes
- Can be lost with autonomic diabetic neuropathy
- Hypoglycemia is limiting step in intensive treatment of diabetes (Accord Trial)

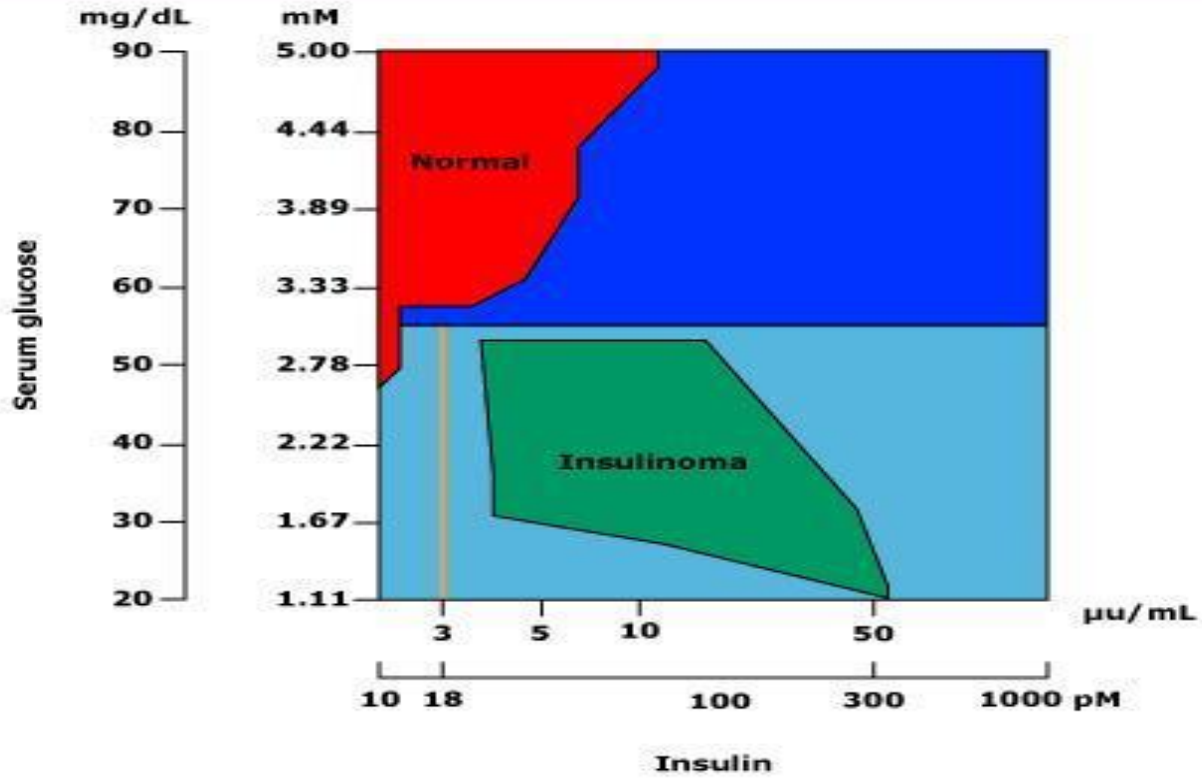
Evaluation of hypoglycemia

- 72 hour fast is the standard evaluation
  - Demonstrate Whipple's triad
  - Determine cause of hypoglycemia
  - Measure Beta-cell peptides and sulfonylurea levels
  - Terminate fast when BS < 55. At this level secretion of Beta-cell polypeptides should be suppressed
  - Terminate fast if patient becomes hypoglycemic
  - Observe closely for signs of neuroglycopenia

Plasma Insulin:

- Plasma insulin concentration of 3 microU/mL by immunochemiluminometric assay (ICMA) when the plasma glucose concentration is below 55 mg/dL (3.0 mmol/L) indicates an excess of insulin and is consistent with insulinoma.
- However, plasma glucose concentrations fall below 50 mg/dL (2.8 mmol/L) in some normal subjects and remain above 50 mg/dL in an occasional patient with an insulinoma.
- Plasma insulin by ICMA may be *lowered* in a hemolyzed blood sample.

Plasma glucose and insulin concentrations after a prolonged fast



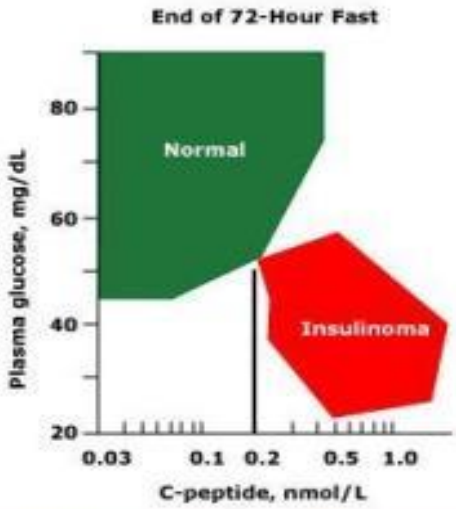
Relation between plasma glucose and insulin concentrations in normal subjects and patients with insulinoma after a prolonged fast.

Data from: Service, FJ. Diagnostic approach to adults with hypoglycemic disorders. Endocrinol Metab Clin North Am 1999; 28:519.

Plasma C-peptide:

- Plasma C-peptide distinguishes endogenous from exogenous hyperinsulinemia.
- In patients who become hypoglycemic, a plasma c-peptide concentration above 0.2 nmol/L is suggestive of an insulinoma.

Plasma C-peptide concentrations after a prolonged fast



Relation between plasma glucose and C-peptide concentrations in normal subjects and patients with an insulinoma after a prolonged fast. In patients who become hypoglycemic, a plasma C-peptide concentration above 0.2 nmol/L is suggestive of an insulinoma. To convert plasma glucose values to mmol/L multiply by 0.056.

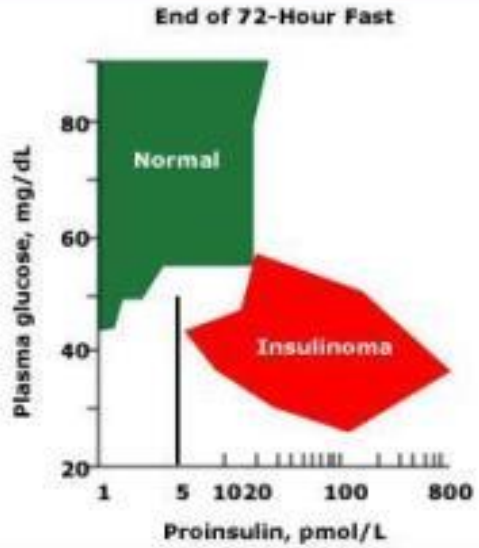
Redrawn from Service, FJ, N Engl J Med 1995; 332:1144.

UpToDate

Plasma Pro-Insulin:

- For plasma proinsulin, the diagnostic criterion for insulinoma is 5 pmol/L or greater.

Plasma proinsulin concentrations after a prolonged fast



Relation between plasma glucose and proinsulin concentrations in normal subjects and patients with an insulinoma after a prolonged fast. In patients who become hypoglycemic, a plasma proinsulin concentration above 5 pmol/L is suggestive of an insulinoma. To convert plasma glucose values to mmol/L multiply by 0.056.

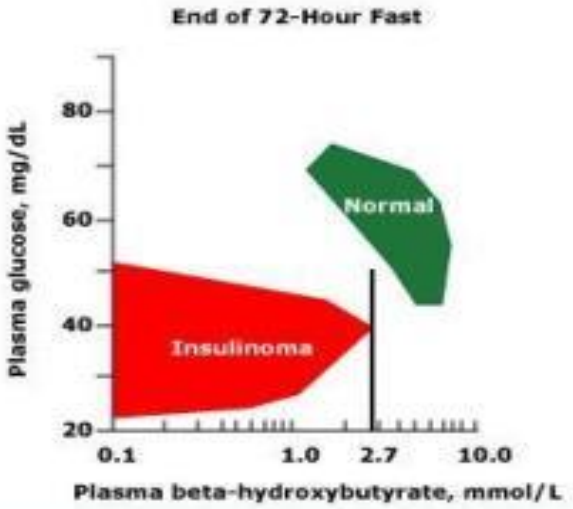
Redrawn from Service, FJ, N Engl J Med 1995; 332:1144.

UpToDate

Plasma Beta-Hydroxybutyrate:

- Because of the antiketogenic effect of insulin, plasma beta-hydroxybutyrate (BHOB) concentrations are lower in insulinoma patients than in normal subjects.
- All patients with insulinoma had plasma BHOB values of 2.7 mmol/L or less.
- Can be used to *confirm* (as can response to glucagon stimulation) the diagnosis in patients in whom the insulin and C-peptide values are in the borderline range or to indicate the action of an insulin-like factor.

Plasma beta-hydroxybutyrate concentrations after a prolonged fast

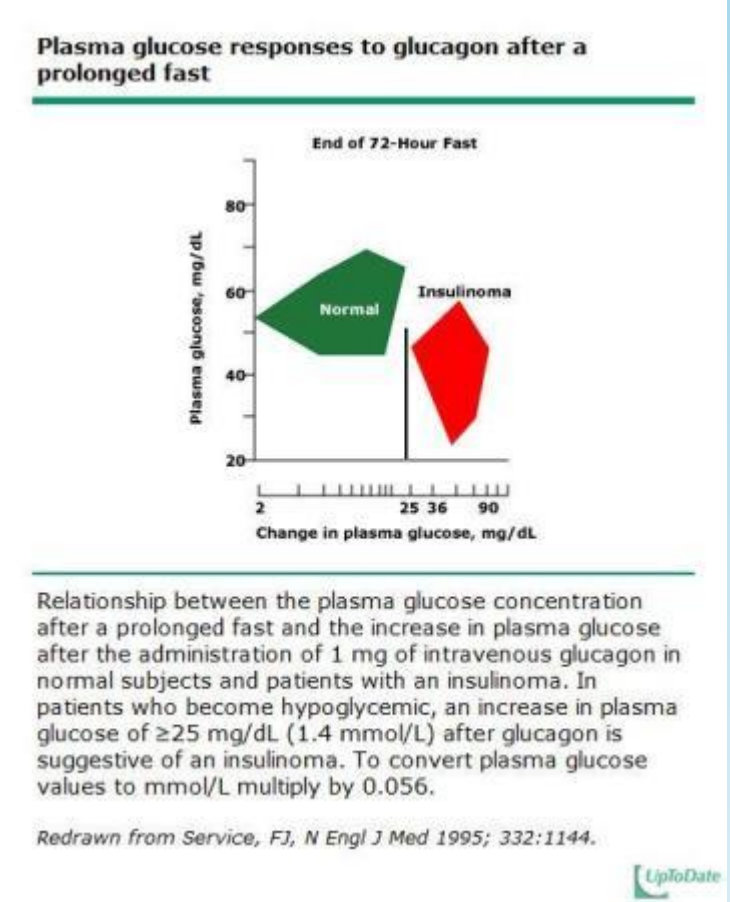


Relation between plasma glucose and beta-hydroxybutyrate concentrations in normal subjects and patients with an insulinoma after a prolonged fast. In patients who become hypoglycemic, a plasma beta-hydroxybutyrate concentration below 2.7 mmol/L is suggestive of an insulinoma. To convert plasma glucose values to mmol/L multiply by 0.056.

Redrawn from Service, FJ, N Engl J Med 1995; 332:1144.

Glucagon Stimulation:

- Recall that insulin is antiglycogenolytic and hyperinsulinemia permits retention of glycogen within the liver.
- Patients with insulin-mediated hypoglycemia respond to 1 mg of intravenous glucagon (a potent glycogenolytic agent) by releasing glucose.
- Normal subjects will have released virtually all glucose from the liver at the end of the 72-hour fast and cannot therefore respond as vigorously.
- At the end of the fast, patients with an insulinoma have an increase in plasma glucose of 25 mg/dL (1.4 mmol/L) or more in 20 to 30 min.



Insulin Secretagogues

- Sulfonylureas or meglitanides are used as oral hypoglycemics to treat diabetes
- Patients with hypoglycemia from inappropriate use of these medications will have concentrations of B-cell peptides identical to those with insulinoma
- Therefore plasma assays for these drugs are an essential part of an evaluation for hypoglycemia

Insulin Antibodies

- Part of standard workup for hypoglycemia
- Used to be very common in those receiving insulin injections when beef-pork insulin was standard
- Current human and analog insulins cause very little antibody production
- High titers may be diagnostic of insulin autoimmune hypoglycemia

Oral Glucose Tolerance Test

- Should NOT be used as part of an evaluation for hypoglycemia
- At least 10% of healthy people have glucose values <50 during this test
- Results do not correlate with serum glucose responses to a mixed meal

Mixed Meal

- For patients with neuroglycopenic symptoms within 5 hrs after eating, a mixed meal test could be performed
- Test is positive if there are symptoms of neuroglycopenia and a blood glucose <50
- Positive test does NOT provide a diagnosis, only biochemical confirmation of the history

Insulinoma:

- Incidence 3-10 cases per million people/yr (1:250,000 patient years) (50% of NETs)
- Mayo clinic data shows patients with insulinoma have age range 8 to 82
- 8% had multiple endocrine neoplasia type 1
- 6% had malignant insulinoma
- Insulinomas have been found in pregnant patients, and in patients with Type 2 diabetes
- One case of insulinoma in a patient with Type 1 diabetes has been reported

Insulinoma

- Hypoglycemia caused by excessive insulin secretion
- Islet cell pancreatic tumor secreting insulin
- Confirmation of diagnosis requires exclusion of hypoglycemia from exogenous sources

Localization on Insulinoma

- Transabdominal ultrasound
- High resolution CT
- Best localization is intraoperative ultrasound with palpation of pancreas by experienced surgeon
- This approach has 98% success rate in the identification of insulinoma
- After localization, patients proceed to surgical removal

Treatment of Insulinoma

- Surgical removal
- Medical therapy includes diazoxide, which suppresses insulin secretion
- Side effects include edema and hirsutism
- Other meds that have been used include verapamil, phenytoin, and octreotide, all of which inhibit insulin secretion
- Medical therapy used in patients who are not acceptable surgical risks

NIPHS

- Noninsulinoma Pancreatogenous Hypoglycemia Syndrome
- Unique clinical syndrome reported 1999
- Typical patient is an adult who does not have insulinoma but who does have hypoglycemia resulting from pancreatic postprandial insulin hypersecretion

NIPHS

- Ages of patients 16-78
- All have severe neuroglycopenia with loss of consciousness or seizures
- Predominantly occurs in males (70%)
- At Mayo clinic it occurs 1/5th as frequently as insulinoma

NIPHS

- Symptoms of hypoglycemia occur 2-4 hours after eating
- Low glucose levels and high insulin levels are found postprandially
- 72 hour fasts are normal vs Patients with insulinoma very rarely have negative 72 hour fasts
- Radiographic localization studies are negative

NIPHS Treatment

- Because NIPHS results from diffuse B-cell hyperplasia and no discrete tumor, partial pancreatectomy is the treatment
- Symptoms may recur after several years

Factitious Hypoglycemia

- Self-induced hypoglycemia
- More common in women
- Usually occurs in health care workers or someone with access to medications
- Factitious hypoglycemia in diabetics probably more common than recognized, since diagnosis very difficult

Factitious Hypoglycemia

- Results from administration of insulin or insulin secretagogues
- Less often a parent may administer insulin to a child
- Insulin has been used to attempt suicide or homicide
- Mistaken prescription for hypoglycemic drugs

Factitious Hypoglycemia

- Should be considered in every patient undergoing evaluation for hypoglycemia
- Should be especially considered when hypoglycemia episodes have no pattern
- All medications need to by positively identified
- Diagnosis can be established by measuring c-peptide, insulin, and sulfonylurea/glitinide when hypoglycemia occurs

Factitious Hypoglycemia

- When due to orally administered pharmacologic agent (sulfonylurea or meglitinide), drug will be present in blood
- When due to insulin, serum insulin is high and c-peptide is suppressed
- C-peptide levels are near zero in type 1 diabetics, but confirmation that values are low eliminates consideration of endogenous hyperinsulinism

Insulin Autoimmune Hypoglycemia

- Very rare disorder
- Usually occurs in persons of Japanese or Korean ethnicity
- May occur at any age
- Usually self-limited in Asians, may be persistent in Caucasians
- No gender predilection

Insulin Autoimmune Hypoglycemia

- Many patients have ongoing autoimmune disorder
- Some patients have history of treatment with sulfhydryl containing drug such as anti-thyroid medication
- No patient has a history of insulin exposure

Insulin Autoimmune Hypoglycemia

- Presence of autoantibodies to insulin or insulin receptor
- Mechanism for generation of these antibodies is unknown
- Patients experience postprandial hypoglycemia resulting in neuroglycopenia
- Serum insulin levels very high because of antibody interference (can be >1000 uU/ml)

Insulin Autoimmune Hypoglycemia

- Very low titers of insulin antibodies may be observed in healthy patients without hypoglycemia
- Treatment is supportive, including frequent small meals
- For those with more severe symptoms, partial pancreatectomy is used
- Medications are of no value

Post Gastric Bypass Hypoglycemia

- Roux-en-Y gastric bypass
- More often occurs in women
- Occurs several times more frequently than insulinoma
- Gastric bypass may lead to increased secretion of gut hormones that stimulate insulin secretion (incretins) such as GLP-1

Post Gastric Bypass Hypoglycemia

- In turn increased GLP-1 may lead to islet cell hypertrophy
- Some patients may have insulinoma which can lead to overeating and obesity
- Patients with post bypass hypoglycemia have post-prandial hypoglycemia
- Insulinoma patients have fasting hypoglycemia
- Management may include partial pancreatectomy

Interpretation of 72 hour fast

Symptoms, signs, or both	Glucose (mg/dl)	Insulin (μU/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	>>3	<0.2	<5	≤2.7	>25	No	Neg (Pos)	Exogenous insulin
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	No	Neg	Insulinoma, NIPHS, PGBH
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	Yes	Neg	Oral hypoglycemic agent
Yes	<55	>>3	>>0.2*	>>5*	≤2.7	>25	No	Pos	Insulin autoimmune
Yes	<55	<3	<0.2	<5	≤2.7	>25	No	Neg	IGF•
Yes	<55	<3	<0.2	<5	>2.7	<25	No	Neg	Not insulin (or IGF)-mediated

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

Neg: negative; Pos: positive; PGBH: post gastric bypass hypoglycemia; NIPHS: noninsulinoma pancreatogenous hypoglycemia syndrome; IGF: insulin-like growth factor.
* Free C-peptide and proinsulin concentrations are low.
• Increased pro-IGF-II, free IGF-II, IGF-II/IGF-I ratio.

Review and Summary

- Hypoglycemia is a syndrome characterized by episodes of low blood glucose
- Symptoms can be neuroglycopenic or autonomic
- Patients with autonomic symptoms only are unlikely to have hypoglycemia

Review and Summary

- Counterregulatory hormones which defend against hypoglycemia include glucagon, epinephrine, cortisol, and growth hormone
- Epinephrine and glucagon work quickly to raise blood glucose by increasing hepatic glucose output

Review and Summary

- Diabetics lose glucagon production over time
- Epinephrine becomes main defense against hypoglycemia when glucagon production is lost
- Epinephrine production can be lost over time
- When both glucagon and epinephrine are missing, patients have hypoglycemic unawareness

Review and Summary

- Causes of non-diabetic hypoglycemia include
  - Insulinoma
  - Factitious hypoglycemia
  - Medication errors
  - Liver disease, renal disease, congestive heart failure, sepsis
  - Non insulinoma pancreatogenous hypoglycemia

Review and Summary

- Biochemical findings for insulinoma include inappropriately elevated insulin and c-peptide levels when blood glucose is low
- Key components for diagnosis of hypoglycemia include positive 72 hr fast and insulin secreting islet cell adenoma
- NIPHS usually causes post-prandial hypoglycemia and 72 hr fast usually negative
- NIPHS is due to b-cell hyperplasia

THANK YOU