Approach to Hypoglycemia

Diabetics and Non-Diabetics
Incidence

- In (DCCT), 10-30% of type 1 diabetics per year
- Of those, 10% require 3rd party intervention
- In the (UKPDS), (30-35%) of type 2 diabetics on Insulin require 3rd party intervention
Causes

Drugs

- Insulin - most common cause,
- Timing, dose, type
- Clearance of insulin (e.g., renal failure);
- Altered counter regulation
- Sulfonylureas
- Metformin does **not** cause hypoglycemia
- High dose salicylates, β-blockers, quinine, quinolones
Renal failure

- Second gluconeogenic organ
- Decreased clearance of renally excreted drugs or their metabolites (e.g., insulin, chlorpropamide, metabolite of glyburide)

Hepatic Failure

- Decreased glycogenolysis
- Decreased gluconeogenesis
- Large functional reserve, (20% func required to prevent hypoglycemia)
- Genetic defects in glycometabolic pathways
- Finally, compromised drug metabolism (tolbutamide, glyburide, glipizide)
Endocrinopathies

- Adrenal (glucocorticoid) insufficiency
- Growth hormone deficiency
- Glucagon deficiency
- Pituitary disease (decreased combined corticotropin and GH deficiency)
Poisoning
(ethanol, propanolol, salicylates)

- Ethanol inhibits gluconeogenesis

- Ethanol-induced *hypoglycemia* occurs 12-72 hrs after ingestion
Neoplasm

- Non-islet-cell tumors
- Mesenchymal tumors,
- hepatocellular carcinoma,
- adrenocortical tumors,
- carcinoid tumors,
- leukemia, and lymphomas

Most of these tumors secrete IGF-II molecule
Some also secrete Glucagon-like peptide(GLP-1) and Somatostatin
Pancreatic Islets

Islets are distinguished from the surrounding exocrine tissue by a continuous connective tissue capsule and extensive vascularity. Glucagon-secreting alpha cells stain red while the insulin-secreting beta cells stain blue.
Insulinoma

- Pancreatic β-cell tumors that secrete Insulin
- Small, solitary, benign (< 10% malignant)
  - Inability of insulinoma cells to suppress insulin secretion during low levels of circulating glucose, leading to severe hypoglycemia

**Diagnosis and Tumor Localization**

- Very high Insulin levels
- Spiral CT, arteriography, ultrasonography

**Treatment of Choice**

- Enucleation
- Recurrence at 10 yrs is 6% and 20 yrs is 10%
**Islet Hyperplasia**

- Also called nesidioblastosis or diffuse islet hyperplasia or the syndrome of noninsulinoma pancreatogenous hyperinsulinism.

- Represent hyperplastic processes and budding of islet cells from ducts (nesidioblastosis). Now interpreted as precursor to MEN 1, with molecular evidence.

- Heterozygous knockout of the *MEN1* gene in the mouse show multiple giant hyperplastic islets that precede insulinoma.

- Persistent hyperinsulinemic hypoglycemia of infancy (PHHI), these infants have an identifiable genetic mutations in sulfonylurea receptor 1 (SUR1), potassium channel Kir6.2, glucokinase.
Autoimmune causes

- **Anti-insulin receptor antibody**
  - Rarely, **hypoglycemia** is caused by autoantibodies that bind the insulin receptor and mimic the biologic action of insulin.
  - Most patients have elevated ESR, +ve ANA.

- **Anti-insulin antibody**
  - Autoantibodies against insulin bind free circulating plasma insulin when its concentration is high and release insulin when the concentration of free plasma insulin drops.
  - Release of insulin at inappropriate times can cause hypoglycemia.
Symptoms

Adrenergic Symptoms
- Usually seen early with a rapid decline in blood glucose and include tachycardia, tachypnea, vomiting, and diaphoresis.

Neuroglycopenic
- Usually associated with slower or prolonged hypoglycemia, include poor feeding, altered mental status, lethargy, and seizures.
Classification of Hypoglycemia

Fasting hypoglycemia occurs in the postabsorptive period (ie, hours after a meal)

Reactive (postprandial) hypoglycemia.
Reactive hypoglycemia is controversial

Low postprandial plasma glucose levels alone are not sufficient

10% to 30% of normal individuals undergoing oral GTT have plasma glucose <50 mg/dL, with no symptoms

Only patients with severe (eg, loss of consciousness, traumatic injury or accident) attributed to postprandial hypoglycemia require further workup.
Dumping Syndrome/ Alimentary Hypoglycemia

- Alimentary hypoglycemia presents 2 hrs after a meal

**Pathophysiology**

- disruption of controlled gastric emptying
- decreased transit time
- rapid elevation in plasma glucose that triggers exaggerated insulin response.
- abnormal insulin then causes a precipitous drop in blood glucose
Pathophysiology of Hypoglycemia

Responses to Hypoglycemia is our ability to suppress insulin in response to hypoglycemia

- In Diabetics, it does not occur as Insulin is supplied exogenously
- Main defense is increased release of counterregulatory hormones, as Glucagon, Epinephrine, Cortisol, and Growth hormone
  - Glucagon stimulates both glycogenolysis and gluconeogenesis
  - Epinephrine acts via β-adrenergic receptors and stimulates glycogenolysis and gluconeogenesis
    - Also acts on alpha-2-receptors to inhibit insulin secretion
  - Cortisol and Growth hormone contribute only after prolonged hypoglycemia by limiting peripheral utilization of glucose.
Counterregulatory effects of Epinephrine during Hypoglycemia
Glucagon and epinephrine secretion rises when plasma glucose concentrations fall below 65 to 70 mg/dL (3.6 to 3.9 mmol/L).

Growth hormone secretion increases when plasma glucose concentrations fall below 60 to 65 mg/dL (3.3 to 3.6 mmol/L).

Cortisol secretion increases when plasma glucose concentrations fall below 60 mg/dL (3.3 mmol/L).
Hypoglycemia Unawareness

50% of type 1 patients undergo diminution in their epinephrine response to hypoglycemia,

Further patients lose the autonomic warning symptoms of hypoglycemia and may recognize (or even fail to recognize) the condition only when somatic neurologic function becomes impaired.

Usually associated with duration of diabetes and autonomic neuropathy

May also occur when patients are switched to intensive insulin regimens.

The introduction of intensified treatment regimens can lower the glucose level that triggers epinephrine release and adrenergic symptoms.

The DCCT trial showed that even brief periods of antecedent hypoglycemia can suppress counter-regulatory responses during subsequent hypoglycemic episodes.
Diagnosis

Establishing the cause

- History (liver failure, sepsis, autoimmune disease, neoplasm, alcohol, drugs)

Establishing fasting hypoglycemia

- **Supervised 72 hour fast test**
- In hospital setting to lower risk to the patient
- Usually hypoglycemia develops in first 48 hours of the fast in 95% of cases
72-HOUR FAST Protocol

- Date the onset of the fast as the time of the last intake of calories
- Discontinue all non essential medications
- Allow the patient to drink calorie-free and caffeine-free beverages
- Collect blood specimens for measurement of plasma glucose, insulin, C-peptide, and proinsulin every six hours until the plasma glucose concentration is below 60 mg/dL (3.3 mmol/L) at this point, the frequency of sampling should be increased to every one to two hours.
Test end points and duration

- the plasma glucose concentration is ≤45 mg/dL (2.5 mmol/L)
- the patient has symptoms or signs of hypoglycemia,
- 72 hours have elapsed,
- or when the plasma glucose concentration is less than 55 mg/dL (3 mmol/L) if Whipple's triad is present
- Plasma beta-hydroxybutyrate and sulfonylurea levels are measured
- 1 mg of glucagon is given intravenously and the plasma glucose measured 10, 20, and 30 minutes later.
In normal subjects, the following thresholds have been identified in graded glucose reductions:

- Insulin secretion decreases, (BG < 80), followed by increase in Glucagon and Epinephrine, growth hormone (BG < 65) and Cortisol (BG < 60) respectively.

- Normal subjects do not have symptomatic hypoglycemia after a prolonged fast because Gluconeogenesis accounts for approximately 50 percent of glucose production after an overnight fast and for almost all glucose production after 42 hours or more of fasting.
### Interpretation of values after 72 hour test

<table>
<thead>
<tr>
<th>Insulin</th>
<th>C Peptide</th>
<th>Proinsulin</th>
<th>Sulfonylurea</th>
<th>Insulin Antibody</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>—</td>
<td>—</td>
<td>Exogenous insulin</td>
</tr>
<tr>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>—</td>
<td>—</td>
<td>Insulinoma, CHI</td>
</tr>
<tr>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>+</td>
<td>—</td>
<td>Sulfonylurea</td>
</tr>
<tr>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>—</td>
<td>+</td>
<td>Insulin autoimmune</td>
</tr>
<tr>
<td>±↑</td>
<td>↓</td>
<td>↓</td>
<td>—</td>
<td>－</td>
<td>Insulin receptor autoimmune</td>
</tr>
</tbody>
</table>
## Diagnostic interpretation of the results of a 72-hour fast

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Symptoms or signs</th>
<th>Serum Glucose mg/dL</th>
<th>Serum Insulin μU/mL</th>
<th>Serum C-peptide pmol/L</th>
<th>Serum Proinsulin pmol/L</th>
<th>Serum β-hydroxybutyrate mmol/L</th>
<th>ΔSerum glucose mg/dL</th>
<th>Sulfonylurea in serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>No</td>
<td>≥40</td>
<td>&lt;3</td>
<td>&lt;200</td>
<td>&lt;5</td>
<td>&gt;2.7</td>
<td>&lt;25</td>
<td>No</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>Yes</td>
<td>≤45</td>
<td>≥3</td>
<td>≥200</td>
<td>≥5</td>
<td>≤2.7</td>
<td>≥25</td>
<td>No</td>
</tr>
<tr>
<td>Factitious hypoglycemia from insulin</td>
<td>Yes</td>
<td>≤45</td>
<td>≥3</td>
<td>&lt;200</td>
<td>&lt;5</td>
<td>≤2.7</td>
<td>≥25</td>
<td>No</td>
</tr>
<tr>
<td>Sulfonylurea-induced hypoglycemia</td>
<td>Yes</td>
<td>≤45</td>
<td>≥3</td>
<td>≥200</td>
<td>≥5</td>
<td>≤2.7</td>
<td>≥25</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypoglycemia mediated by insulin-like growth factor</td>
<td>Yes</td>
<td>≤45</td>
<td>≤3</td>
<td>&lt;200</td>
<td>&lt;5</td>
<td>≤2.7</td>
<td>≥25</td>
<td>No</td>
</tr>
<tr>
<td>Non-insulin-mediated hypoglycemia</td>
<td>Yes</td>
<td>≤45</td>
<td>&lt;3</td>
<td>&lt;200</td>
<td>&lt;5</td>
<td>&gt;2.7</td>
<td>&lt;25</td>
<td>No</td>
</tr>
<tr>
<td>Inadvertent feeding during the fast</td>
<td>No</td>
<td>≥45</td>
<td>&lt;3</td>
<td>&lt;200</td>
<td>&lt;5</td>
<td>≤2.7</td>
<td>≥25</td>
<td>No</td>
</tr>
<tr>
<td>Nonhypoglycemic disorder</td>
<td>Yes</td>
<td>≥40</td>
<td>&lt;3</td>
<td>&lt;200</td>
<td>&lt;5</td>
<td>&gt;2.7</td>
<td>&lt;25</td>
<td></td>
</tr>
</tbody>
</table>
Relation of Plasma Glucose and Proinsulin

![Graph showing the relationship between plasma glucose and proinsulin levels after a 72-hour fast. The graph distinguishes between normal and insulinoma conditions.]
Principles of Treatment

Principles of therapy

- Priority in treating hypoglycemia to maintain plasma glucose greater than 50 mg/dl, either snacks vs IV dextrose

- The second priority is to address the underlying cause. removal or adjustment of the offending drug, appropriate hormone replacement for patients with deficiency, resection of the tumor in Insulioma.

- Patients with autoantibodies against the insulin receptor can be treated with high-dose glucocorticoid (prednisone, 60 mg/d) to prevent hypoglycemia
Most episodes of asymptomatic hypoglycemia and mild to moderate symptomatic hypoglycemia are effectively self-treated by ingestion of glucose tablets or carbohydrate in the form of juices, soft drinks, milk, crackers, candy, or a meal.

A commonly recommended dose of glucose is 16-20 g of oral glucose.

However, the glycemic response to oral glucose is transient, usually less than 2 hours in insulin-induced hypoglycemia.

Parenteral treatment is necessary when a hypoglycemic patient is unable or unwilling (because of neuroglycopenia) to take carbohydrate orally.

Most common 1 amp of D50,(?glucose)
Glucagon is commonly injected subcutaneously or intramuscularly, standard dose, 1 mg.

Less useful in T2DM than in T1DM as it stimulates insulin secretion.

Hypoglycemia related to endogenous hyperinsulinism is often curable by the surgical removal of an insulinoma.

If this is not possible because of multiple or metastatic tumors, Diazoxide can be used, (100-800 mg/day) raises the plasma glucose concentration by suppressing insulin secretion.

Side effects include hypotension, brain edema, gastrointestinal side effects.

Other treatments include octreotide or calcium channel antagonists.
- Short term treatment of hypoglycemia associated with non-beta cell tumors involves short-term measures pending effective medical, surgical, or radiotherapeutic treatment can be done by glucocorticoid or growth hormone.

- Remissions of autoimmune hypoglycemias have been associated with immunosuppressive therapy, including glucocorticoids, but controlled trials are lacking.

- The treatment of hypoglycemia related to hepatic or renal disease, cardiac failure, or sepsis includes short-term measures and, treatment or management of the underlying disease process.
Hypoglycemic Coma

Recovery from hypoglycemia may be delayed, because of cerebral edema. Unconsciousness lasting more than 30 minutes after plasma glucose is corrected is called posthypoglycemic coma, IV mannitol (40 g as a 20% solution over 20 minutes) or glucocorticoids (e.g., dexamethasone, 10 mg), or both can be used along with maintenance of normal plasma glucose levels
CASE 1 — A 39-year-old man was referred for evaluation of repeated episodes of sweating, slurred speech, and confusion during the last four years that could be aborted by eating. On two occasions, he drove his car off the side of the road; both times he was found to be confused, his serum glucose concentrations ranged from 30 to 40 mg/dL (1.7 to 2.2 mmol/L), and he improved after intravenous glucose administration.

After fasting for 12 hours, he began to sweat and became confused and combative. Serum values at that time were as follows:
- Glucose - 22 mg/dL
- Insulin - 110 microU/mL (660 pmol/L)
- C-peptide - 3200 pmol/L (0.03-1 nmol/L)
- Proinsulin - 800 pmol/L (2-31 pmol/L)
- Glucose increase after glucagon - 39 mg/dL (2.2 mmol/L)

Sulfonylurea – negative

What is the most likely Diagnosis?
A) Surreptitious Insulin use
B) Antibodies to Insulin receptor
C) Insulinoma
D) None of the above

Comment — This is a classic case of insulinoma. The patient was healthy but had episodes of neuroglycopenia. Whipple’s triad (symptoms of hypoglycemia, low serum glucose concentrations at the same time, and relief of symptoms by glucose administration) was satisfied. That the hypoglycemia was caused by endogenous insulin was confirmed by the high serum insulin, C-peptide and proinsulin concentrations, and supported by the low serum beta-hydroxybutyrate concentration and the small rise in serum glucose after intravenous glucagon administration.
CASE 2 — A 27-year-old man was referred by his local physician for evaluation of hypoglycemia found incidentally during a work-up for peptic ulcer disease. Past medical history included gastric bypass surgery for morbid obesity 2 years ago. During the last four months, he had several episodes of weakness and feeling "shaky inside" late in the evening. During the night he would periodically drink soda. When symptomatic, reflectance meter blood glucose values measured by the patient using equipment purchased for his seven-year-old daughter (diagnosed with type 1 diabetes one year earlier) had been in the range of 40 to 50 mg/dL (2.2 to 2.8 mmol/L). Serum values after an overnight fast were:

- Glucose: 36 mg/dL (2.0 mmol/L)
- Insulin: 140 microU/mL (840 pmol/L)
- C-peptide: <33 pmol/L (0.03-1 nmol/L)
- Proinsulin: 0.9 pmol/L (2-31 pmol/L)

What is his most likely diagnosis?

A) Insulinoma
B) Insulin antibodies
C) Exogenous Insulin administration
D) Alimentary hypoglycemia

The low serum C-peptide and proinsulin values indicate that the hyperinsulinemia (140 microU/mL (840 pmol/L)) was due to exogenous insulin administration.
Thanks.
CASE 8 — A 76-year-old woman was referred for the evaluation of postprandial adrenergic symptoms with occasional visual changes. There was one episode of confusion while on a telephone call to her daughter. During an episode of light headedness, sweating, weakness and irritability two hours after breakfast (which occurred while under observation), serum values were as follows:

<table>
<thead>
<tr>
<th>Glucose</th>
<th>51 mg/dl (2.8 mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>6.4 microU/mL (45.9 pmol/L)</td>
</tr>
<tr>
<td>C-peptide</td>
<td>2.6 ng/mL (858 pmol/L)</td>
</tr>
<tr>
<td>Betahydroxybutyrate</td>
<td>0.1 mmol/L</td>
</tr>
<tr>
<td>Glucose increase after glucagon</td>
<td>46 mg/dL (2.6 mmol/L)</td>
</tr>
</tbody>
</table>

Sulfonylurea negative

A mixed meal test was performed because of the presence of postprandial symptoms accompanied by biochemical evidence of insulin-mediated hypoglycemia. Biochemical testing 180 minutes after a mixed meal revealed the following:

<table>
<thead>
<tr>
<th>Glucose</th>
<th>43 mg/dl (2.4 mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>22.0 microU/ml (157.8 pmol/L)</td>
</tr>
<tr>
<td>C-peptide</td>
<td>4.7 ng/ml (1551 pmol/L)</td>
</tr>
</tbody>
</table>

The biochemical tests confirmed insulin-mediated hypoglycemia. The differential diagnosis included noninsulinoma pancreatogenous hypoglycemia (Islet cell hypertrophy/nesidioblastosis), which is associated with postprandial hypoglycemia, insulin autoimmune hypoglycemia (postprandial or fasting hypoglycemia), or insulinoma, which more commonly presents as fasting hypoglycemia. (See “Noninsulinoma pancreatogenous hypoglycemia” and see “Insulinoma”).