Outline

• Systemic glucose balance / counterregulation
• Whipple’s triad
• Clinical Manifestations
• Hypoglycemia in diabetes mellitus
• Hypoglycemia in non-diabetes mellitus
• Diagnostic strategy during hypoglycemia
• Treatment
SYSTEMIC GLUCOSE BALANCE

GLUCOSE COUNTERREGULATION
# Physiologic Responses to Decreasing Plasma Glucose Concentrations

**Glycemic threshold (mg/dL)**

<table>
<thead>
<tr>
<th>Response</th>
<th>Glycemic threshold (mg/dL)</th>
<th>Glucose counterregulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin</strong></td>
<td>80-85</td>
<td>Primary glucose regulatory factor/first defense against hypoglycemia</td>
</tr>
<tr>
<td><strong>Glucagon</strong></td>
<td>65-70</td>
<td>Primary glucose counterregulatory factor/second defense against hypoglycemia</td>
</tr>
<tr>
<td><strong>Epinephrine</strong></td>
<td>65-70</td>
<td>Third defense against hypoglycemia, critical when glucagon is deficient</td>
</tr>
<tr>
<td><strong>Cortisol &amp; Growth</strong></td>
<td>65-70</td>
<td>Involved in defense against prolonged hypoglycemia, not critical</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>50-55</td>
<td>Prompt behavioral defense against hypoglycemia (food ingestion)</td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
<td>&lt;50</td>
<td>(Compromises behavioral defense against hypoglycemia)</td>
</tr>
</tbody>
</table>
Whipple’s triad

1) Symptoms, signs, or both consistent with hypoglycemia
2) Low plasma glucose concentration
3) Resolution of those symptoms or signs after the plasma glucose concentration is raised

Non-Diabetes: plasma glucose < 55 mg/dl
Diabetes: plasma glucose < 70 mg/dl

Journal of Clinical Endocrinology & Metabolism, March 2009, 94(3): 709-728
Clinical Manifestations

Neurogenic (or autonomic) symptoms

- CNS-mediated sympathoadrenal discharge triggered by hypoglycemia

- Adrenergic symptoms: palpitations, tremor, and anxiety

- Cholinergic symptoms: sweating, hunger, and paresthesias
Clinical Manifestations

Neuroglycopenic symptoms

• Direct result of central nervous system (CNS) glucose deprivation

• Behavioral changes, confusion, fatigue, seizure, loss of consciousness, and, if hypoglycemia is severe and prolonged, death.
อาการของภาวะน้ำตาลต่ำในเลือด

ลายตาพร่า หัวใจเต้นเร็ว เหงื่อออกมาก ตัวสัน ฉุดเนื้อวาง่าย
ปวดหัว เวียนศีรษะ หัวบ่อย อ่อนเพลีย กังวล
Normal Physiology

Plasma glucose < 55 mg/dl

• Plasma insulin < 3 µU/ml
• C-peptide < 0.6 ng/ml
• Proinsulin < 5.0 pmol/liter
Proinsulin

Insulin + C Peptide
HYPOGLYCEMIA IN DIABETES MELLITUS
HYPOGLYCEMIA IN DIABETES MELLITUS

- Suggest that persons with diabetes become concerned about the possibility of developing hypoglycemia when the self-monitored blood glucose concentration is falling rapidly or is no greater than 70 mg/dl.

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Risk factors for hypoglycemia in diabetes

(1) Insulin excess (insulin or insulin secretagogue) : doses are excessive, ill-timed, or the wrong type

(2) Reduced influx of exogenous glucose  
   e.g. during an overnight fast, missed meals or snacks

(3) Increased insulin-independent glucose utilization  
   e.g. during exercise

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Risk factors for hypoglycemia in diabetes

(4) Increase sensitivity to insulin
   e.g. improved glycemic control, late after exercise, or with increased fitness or weight loss

(5) Reduced endogenous glucose production
   e.g. following alcohol ingestion

(6) Reduced insulin clearance; e.g. renal failure
Risk factors for hypoglycemia in diabetes
HYPOGLYCEMIA IN NON-DIABETES
# 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>1. Endogenous hyperinsulinism</td>
</tr>
<tr>
<td>2. Critical illness</td>
<td></td>
</tr>
<tr>
<td>• Hepatic, renal or cardiac failure</td>
<td></td>
</tr>
<tr>
<td>• Sepsis</td>
<td></td>
</tr>
<tr>
<td>• Inanition</td>
<td></td>
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<tr>
<td>3. Hormone deficiency</td>
<td></td>
</tr>
<tr>
<td>• Cortisol</td>
<td></td>
</tr>
<tr>
<td>• Glucagon and epinephrine (in insulin-deficient diabetes)</td>
<td></td>
</tr>
<tr>
<td>4. Non–islet cell tumor</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Accidental, surreptitious or malicious hypoglycemia</td>
<td></td>
</tr>
</tbody>
</table>
Drugs

• Insulin and insulin secretagogues suppress glucose production and stimulate glucose utilization

• Drugs other than antihyperglycemic agents and alcohol reported to cause hypoglycemia
<table>
<thead>
<tr>
<th>Evidence Level</th>
<th>Drugs/Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>Cibenzoline, Gatifloxacin, Pentamidine, Quinine, Indomethacin, Glucagon</td>
</tr>
<tr>
<td></td>
<td>(during endoscopy)</td>
</tr>
<tr>
<td>Low</td>
<td>Chloroquine, oxaline sulfonamide, Artesunate/artemisin/artemether, IGF-1,</td>
</tr>
<tr>
<td></td>
<td>Lithium, Propoxyphene/dextropropoxyphene</td>
</tr>
<tr>
<td>Very Low</td>
<td>Drugs with &gt;25 cases of hypoglycemia identified:</td>
</tr>
<tr>
<td></td>
<td>Angiotensin converting enzyme inhibitors, Angiotensin receptor antagonists,</td>
</tr>
<tr>
<td></td>
<td>β-Adrenergic receptor antagonists, Levofoxacin, Mifepristone, Disopyramide,</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim-sulfamethoxazole, Heparin, 6-Mercaptopurine</td>
</tr>
<tr>
<td></td>
<td>Drugs with &lt;25 cases of hypoglycemia identified (see Ref. 24)</td>
</tr>
</tbody>
</table>

Journal of Clinical Endocrinology & Metabolism, March 2009, 94(3): 709-728
Drugs other than antihyperglycemic agents and alcohol reported to cause hypoglycemia

Moderate quality of evidence

- Cibenzoline
- Gatifloxacin
- Pentamidine
- Quinine
- Indomethacin
- Glucagon (during endoscopy)

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Ethanol induced hypoglycemia

- Ethanol blocks gluconeogenesis but not glycogenolysis

**Setting 1**
- Typically occurs after a several-day ethanol binge during person eats little food, causing glycogen depletion

**Setting 2**
- Insulin-treated diabetes
  - Gluconeogenesis becomes the predominant route of glucose production during prolonged hypoglycemia
  - Alcohol can contribute to the progression of hypoglycemia

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Ethanol blocks gluconeogenesis.
Critical Illness

- Drugs
- Hepatic failure
- Renal failure
- Cardiac failure
- Sepsis
- Inanition (starvation)
Critical Illness

**Hepatic failure**

- Rapid & extensive hepatic destruction (e.g. toxic hepatitis) causes fasting hypoglycemia
- Liver is the major site of endogenous glucose production

**Renal failure**

- Kidneys are a source of glucose production
- Also caused by the reduced clearance of insulin and reduced mobilization of gluconeogenic precursors
Arterial Glucose

Pancreas

Brain

Liver

Kidneys

Muscle

Fat

Gluconeogenic precursor (lactate, amino acids, glycerol)

Glucose production

Arterial glucose

Sympathoadrenal outflow

Pituitary

Growth hormone

Adrenal medullae

Epinephrine

Norepinephrine

Acetylcholine

Adrenal cortex

Cortisol

Ingestion

Symptoms

Glucose clearance


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Critical Illness

Cardiac failure

- Mechanism of hypoglycemia in patients with cardiac failure is unknown.
- It may involve hepatic congestion and hypoxia

Sepsis

- Increased glucose utilization is induced by cytokine
- Cytokine-induced inhibition of gluconeogenesis in the setting of nutritional glycogen depletion, in combination with hepatic and renal hypoperfusion, may also contribute to hypoglycemia

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Cytokine-induced glucose utilization

Sepsis

Cytokine blocks gluconeogenesis


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Critical Illness

Starvation

• Loss of whole-body fat stores and subsequent depletion of gluconeogenic precursors (e.g., amino acids), necessitating increased glucose utilization
Critical Illness

- Drugs
- Hepatic failure
- Renal failure
- Cardiac failure
- Sepsis
- Inanition (starvation)

- Found in → Rapid & extensive hepatic destruction
- Decrease glucose production
  And reduced clearance of insulin
- Unknown mechanism
- Increased glucose utilization
- Depletion of fat stores
gluconeogenic precursors
Hormone Deficiencies

- **Cortisol and Growth hormone**: Involved in defense against prolonged hypoglycemia, **not critical**
  
  - Occur with prolonged fasting in patients with primary adrenocortical failure (Addison's disease) or hypopituitarism
  - Cortisol deficiency: impaired gluconeogenesis and low gluconeogenic precursors, in setting of glycogen depletion

- Growth hormone deficiency can cause hypoglycemia in young children

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Non–Beta-Cell Tumors

- Feature >>> Fasting hypoglycemia
- Occurs occasionally in large mesenchymal/epithelial tumors
  - Hepatomas, adrenocortical carcinomas, carcinoids

- Glucose kinetic patterns resemble “hyperinsulinism”
- Overproduction of an incompletely processed form of insulin-like growth factor II ("big IGF-II")
  - Insulin secretion is suppressed appropriately during hypoglycemia
Endogenous Hyperinsulinism

(1) Primary beta-cell disorder,
   - Typically a beta-cell tumor (insulinoma)
   - Sometimes multiple insulinomas, or a functional beta-cell disorder with beta-cell hypertrophy or hyperplasia

(2) Antibody to insulin or to the insulin receptor

(3) Beta-cell secretagogue: sulfonylurea

(4) Ectopic insulin → Very rare
Insulinomas

- Uncommon
- Incidence is estimated to be 1 in 250,000
- >90% are benign
- Potentially fatal hypoglycemia
- Median age at presentation is 50 years in sporadic cases
- >99% of insulinomas are within the substance of the pancreas and usually small (90% <2.0 cm)
- CT or MRI detects ~ 70–80% of insulinomas
- Endoscopic ultrasound has a sensitivity ~90%

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Diagnostic strategy during hypoglycemia

- Plasma glucose
- Insulin
- C-peptide
- Proinsulin
- β-hydroxybutyrate concentrations
- Screen for circulating oral hypoglycemic agents

**Document Whipple's triad**

- Symptoms & signs with hypoglycemia
- Low plasma glucose concentration
- Resolution of symptoms or signs after plasma glucose concentration is raised

Cortisol

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Proinsulin

\[ \text{NH}_3 \rightarrow \text{COOH} \]

Insulin

\[ \text{NH}_3 \rightarrow \text{COOH} \]

C Peptide

\[ \text{NH}_3 \rightarrow \text{COOH} \]
Normal Physiology

Plasma glucose < 55 mg/dl

- Plasma insulin < 3 µU/ml
- C-peptide < 0.6 ng/ml
- Proinsulin < 5.0 pmol/liter

Suppress Insulin

Journal of Clinical Endocrinology & Metabolism, March 2009, 94(3): 709-728
Diagnostic strategy and treatment during hypoglycemia in non DM

Whipple's triad

Plasma glucose <55 mg/dL

- Insulin
- C-peptide
- Cortisol
- Other

Treat
Diagnostic strategy and treatment during hypoglycemia in non DM
<table>
<thead>
<tr>
<th>Symptoms, signs, or both</th>
<th>Glucose (mg/dl)</th>
<th>Insulin (µU/ml)</th>
<th>C-peptide (nmol/liter)</th>
<th>Proinsulin (pmol/liter)</th>
<th>β-Hydroxybutyrate (mmol/liter)</th>
<th>Glucose increase after glucagon (mg/dl)</th>
<th>Circulating oral hypoglycemic</th>
<th>Antibody to insulin</th>
<th>Diagnostic interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>&lt; 55</td>
<td>&lt; 3</td>
<td>&lt; 0.2</td>
<td>&lt; 5</td>
<td>&gt; 2.7</td>
<td>&lt; 25</td>
<td>No</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt; 55</td>
<td>&gt; 3</td>
<td>&lt; 0.2</td>
<td>&lt; 5</td>
<td>≤ 2.7</td>
<td>&gt; 25</td>
<td>No</td>
<td>Neg (Pos)</td>
<td>Exogenous insulin</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt; 55</td>
<td>≥ 3</td>
<td>≥ 0.2</td>
<td>≥ 5</td>
<td>≤ 2.7</td>
<td>&gt; 25</td>
<td>No</td>
<td>Neg</td>
<td>Insulinoma, NIPHS, PGBH</td>
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<tr>
<td>Yes</td>
<td>&lt; 55</td>
<td>≥ 3</td>
<td>≥ 0.2</td>
<td>≥ 5</td>
<td>≤ 2.7</td>
<td>&gt; 25</td>
<td>Yes</td>
<td>Neg</td>
<td>Oral hypoglycemic agent</td>
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<td>Yes</td>
<td>&lt; 55</td>
<td>&gt; 3</td>
<td>&gt; 0.2°</td>
<td>&gt; 5°</td>
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<td>No</td>
<td>Pos</td>
<td>Insulin autoimmune</td>
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<td>Neg</td>
<td>IGF b</td>
</tr>
<tr>
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<td>&lt; 0.2</td>
<td>&lt; 5</td>
<td>&gt; 2.7</td>
<td>&lt; 25</td>
<td>No</td>
<td>Neg</td>
<td>Not insulin (or IGF)-mediated</td>
</tr>
</tbody>
</table>
Urgent Treatment

If patient is able to take oral treatment

- Oral treatment with glucose tablets or glucose-containing fluids, candy, or food is appropriate
- Initial dose is 20 g of glucose

If patient is unable to take oral treatment

- Intravenous glucose (25 g) should be given and followed by a glucose infusion guided by serial plasma glucose

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Prevention of Recurrent Hypoglycemia

- Prevention of recurrent hypoglycemia requires an understanding of the hypoglycemic mechanism.

- Offending drugs can be discontinued or their doses reduced.

- Hypoglycemia caused by a sulfonylurea can persist for hours, or even days.
Prevention of Recurrent Hypoglycemia

• Cortisol and growth hormone can be replaced if they are deficient.

• Surgical resection of an insulinoma is curative.

• Medical therapy with diazoxide or octreotide can be used if resection is not possible and in patients with a nontumor beta-cell disorder.
Prevention of Recurrent Hypoglycemia

- Partial pancreatectomy may be necessary in the latter patients.

- Failing these treatments, frequent feedings and avoidance of fasting may be required.

- Administration of uncooked cornstarch at bedtime or even an overnight intragastric infusion of glucose may be necessary in some patients.