Hypoglycemia

**Definition**

- **In patient with diabetes**
  - Hypoglycemia is defined as all episodes of an abnormally low plasma glucose concentration (with or without symptoms) that expose the individual to harm, (at a Self-Monitored Blood Glucose (SMBG) level ≤70 mg/dL)

- **In patient without diabetes**
  - low plasma glucose concentrations that lead to symptoms and signs, and there is resolution when the plasma glucose concentration is raised

**Whipple’s triad**

1. Patient’s symptoms of hypoglycemia.
2. Documented low patient’s plasma glucose when the symptoms are present.
3. The symptoms can be relieved by administration of glucose.

**Mechanism**

1. **Insulin secretion declines** as the glucose declines to 80 mg/dl in venous blood.
2. **Counter regulatory mechanisms** at mild levels of hypoglycemia (65–70 mg/dl).
   a) Epinephrine release, Glucagon release: The primary defence mechanisms
   b) Cortisol and growth hormone release → If the hypoglycemia persists for several hours.
3. **Hunger** → At glucose levels of 50-55mg/dl.
4. **Neuroglycopenia** → Develop if glucose levels to decline into the mid-50 mg/dl range.

**Counter regulatory response to hypoglycemia**

<table>
<thead>
<tr>
<th>Non-Diabetic</th>
<th>T1DM</th>
<th>T2DM</th>
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</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Decreases</td>
<td>No Decrease*</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Increases</td>
<td>No Increase*</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Increases</td>
<td>Attenuated Increase**</td>
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</table>

* Defective glucose counterregulation.
* Hypoglycemia unawareness.

**Manifestations**

**Neuroglycopenia**

2. Cognitive impairment.
4. Focal neurologic deficits.
5. Visual disturbances.

**Neurogenic (autonomic or Warning symptoms)**

Caused by sympathetic neural response to blood glucose <65
- Sweating
- Palpitations
- Tremor
- Nervousness
- Hunger

**Symptoms**

1. Diaphoresis and pallor.
2. Heart rates and systolic blood pressures are raised.
3. Neuroglycopenic manifestations

**Outcome and complications**

The vast majority of episodes are reversed after the glucose level is raised to normal.

Prolonged untreated hypoglycemia can lead to:
1. Transient neurological deficits, but Permanent neurological damage is rare.
2. Death
**Drugs** are the most common cause

**A- In diabetes**
- Exogenous insulin and insulin secretagogue (sulfonylureas)
- NB: Insulin sensitizers (metformin thiazolidinediones), glucosidase inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase IV inhibitors are much less common causes hypoglycemia.

<table>
<thead>
<tr>
<th>B- Hypoglycemia in patients without diabetes</th>
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</thead>
<tbody>
<tr>
<td>1. Drugs</td>
</tr>
<tr>
<td>• Insulin, sulfonylureas</td>
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<tr>
<td>• Quinolones</td>
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<tr>
<td>• Pentamidine</td>
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<tr>
<td>• Quinine</td>
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<tr>
<td>• Beta blockers</td>
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<td>• ACEI</td>
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<td>• Salicylates</td>
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</table>

**2. Endocrine causes of hypoglycaemia**

**3. Endogenous hyperinsulinism**
- A beta cell secretagogue, such as a Sulfonylurea
  - Insulinoma
    - Pancreatic islet cell tumour that secrete insulin
    - Diagnosed by Whipple's triad, plus
    - Measurement of overnight fasting (16 hours) glucose and insulin levels, C-peptide or proinsulin during a spontaneous episode of hypoglycaemia.
  - Nesidioblastosis,
    - Enlargement of beta cells of the pancreas that produce insulin (nesidioblastosis) may result in excessive insulin release, causing hypoglycemia
  - Insulin autoimmune hypoglycaemia

**4. Tumours**
Mesenchymal tumors, fibromas, carcinoid, myelomas, lymphomas, hepatocellular, and colorectal carcinomas,

**Low glucose is caused by**
1. Secretion of insulin-like growth factor-1,
2. Excessive consumption of glucose by the tumour.
3. True ectopic insulin secretion is extremely rare.

**5. Critical illness**
- Sepsis
  - Because of cytokine induced inhibition of gluconeogenesis

  **Chronic kidney disease**
  - Impaired gluconeogenesis, reduced renal clearance of insulin,

  **In fulminant liver failure,**
  - Gluconeogenesis is also impaired.

  **Malnourishment**
  - Due to decreased gluconeogenesis, glycogen depletion

**6. Postprandial hypoglycaemia after meals**
1. After gastric surgery
2. Hereditary fructose intolerance
3. Factitious: due to insulin or sulfonylurea
4. Early or mild type 2 diabetes mellitus.

*occurs within four hours*`

**Factitious hypoglycemia**
- Measurement of C-peptide levels during hypoglycaemia should identify patients who are injecting insulin;
- Sulphonylurea abuse can be detected by chromatography of plasma or urine.

**Special types of hypoglycemia**

**1. Nocturnal hypoglycemia**
- Can lead to disruption of sleep and delays in correction of the hypoglycemia,
- If high morning sugars preceded by an episode of Nocturnal hypoglycaemia = (Somogyi effect).

**2. Hypoglycemia Unawareness**
- It is an impairment of counter regulatory response to hypoglycemia (epinephrine and glucagon),
- Caused by
  1. Overtreatment with insulin or
  2. Autonomic neuropathy.
- It is dangerous because Many patients will develop neuroglycopenic symptoms, without warnings symptoms of hypoglycemia.
### Differential Diagnosis

1. Hyperthyroidism, Pheochromocytoma
2. Cardiac disease (Arrhythmia, Valvular heart)
3. Medications
4. Psychiatric disease

### Management

#### Clinical Evaluation

**History**
- Including relation to meals
- Underlying illnesses or conditions
- Medications taken by the individual, by family members, and social history.

**Clinical Exam** may explore the cause

#### Laboratory Testing

**Fasting or Postprandial** evaluation for:
1. Glucose
2. Insulin
3. C-peptide
4. Proinsulin
5. Sulfonylurea and Meglitinide screen

#### Determining the Cause of Hypoglycemia

1. **In insulinoma, endogenous hyperinsulinism** → Plasma insulin, C-peptide, and proinsulin values are elevated.
2. **Exogenous insulin** → Plasma insulin values are high, but plasma C-peptide and proinsulin values are low.
3. **Nonislet cell tumors** → Plasma insulin, C-peptide, and proinsulin concentrations are not elevated.

#### Localizing Studies

1. **Radiologic studies**
   - Computed tomography, MRI, and ultrasonography can detect most insulinomas.
2. **Arterial calcium stimulation**
   - With hepatic venous sampling to distinguish a focal abnormality (insulinoma).

#### Prevention

1. **Patient education**
   - Keeping a diary of hypoglycemia symptoms
   - Regular check of blood sugar
2. **Modifying**
   - Diet (what, when, and how much you eat).
   - The dosage or types of medicines.
   - The timing and level of physical activity
   - Glycemic targets for individual patients.
3. **Hypoglycemia awareness**
   - Avoidance of hypoglycemia for several weeks may help to improve it.
4. **Nocturnal hypoglycemia**
   - Bedtime snacks
   - Take the intermediate insulin at bedtime rather than before supper
   - Reducing the dose of soluble insulin before supper
   - Changing to a rapid-acting insulin analogue

#### Treatment

**Acute Hypoglycemia**

- For Symptomatic or asymptomatic diabetic with a low glucose value, <70 mg/dL.
- Non diabetic with low glucose (≤55 mg/dL).
- Symptomatic hypoglycemia but rapid blood glucose measurement is not available.
1. If the patient has altered mental status, is unable to swallow, give an IV bolus of 12.5 to 25 gm of glucose (25 percent dextrose).
2. If glucose cannot be given by parenteral or oral routes, and in severe hypoglycemia, give **glucagon** 1 mg IM or SQ.
3. Once the patient is able to ingest carbohydrate safely, providing a mixed meal.

**Treatment of the underlying cause**

1. Adjust dose of antidiabetics
2. Surgical removal of the insulinoma
3. **Non islet tumours** : Oral glucocorticoids, diazoxide and Octreotide, Glucagon.
4. Replacement therapy for **Addison disease**.