Hypoglycemia in Diabetes

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Introduction:
Hypoglycemia as defined by both the American Diabetes Association(ADA) and European Association for the Study of Diabetes(EASD) is when serum glucose level is less than 70 mg/dL. However this level is neither an indication for treatment nor necessitates presence of symptoms but may just suggest a trend towards low sugars and warrants further exploration. Rather it has been shown in an epidemiological study in south India that 23% of normal subjects have a postprandial sugar less than the fasting. This 70 mg/dl is the lower limit of normal postabsorptive range and is the level at which counter-regulatory hormones get activated in a nondiabetic person. Also, antecedent plasma glucose concentrations of ≤70 mg/dL reduce sympathoadrenal responses to subsequent hypoglycemia and therefore this criterion sets the conservative lower limit for individuals with diabetes.

An alternative definition of hypoglycaemia is a decrease in the blood glucose level or its tissue utilization that results in demonstrable signs or symptoms. These signs or symptoms usually include altered mental status and/or sympathetic nervous system stimulation. The glucose level at which an individual becomes symptomatic is highly variable.

Clinical Classification of Hypoglycemia
Hypoglycemia in diabetes may be classified into the following 5 categories:

1. Severe Hypoglycemia: An event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions.
2. Documented Symptomatic Hypoglycemia: An event when typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤70 mg/dl (≤3.9 mmol/L).
3. Asymptomatic Hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L).
4. Probable Symptomatic Hypoglycemia: An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤70 mg/dl (≤3.9 mmol/L).
5. Pseudo-hypoglycemia: An event when a person experiences typical symptoms of hypoglycemia but with a measured plasma glucose concentration above 70 mg/dl (>3.9 mmol/L).
6. Relative Hypoglycemia: An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration>70 mg/dL. This is due to the fact that patients with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels > 70 mg/dL as plasma glucose concentrations decline toward that level. Though these symptoms cause distress and interfere with the patient's sense of well-being and therefore, potentially limit the achievement of optimal glycemic control, such episodes probably pose no direct harm to the patient.

Pathophysiology of Counter-regulation
As the blood glucose concentration begins to fall, an orchestrated neurohormonal response comes into action to prevent symptomatic hypoglycemia. The three principles of glucose counter-regulation are:
1. Prevention and correction of hypoglycemia involves both waning of insulin and activation of the counter-regulatory hormones.

2. There are redundant counter-regulatory factors like not only glucagon but other hormones like epinephrine, growth hormone and cortisol. Therefore, there is a fail-safe system that prevents hypoglycemia even if one or more components of the system fail.

3. There is hierarchy among the counter-regulatory hormones. Table 1 summarizes the various physiologic responses to falling plasma glucose concentrations.

### Table 1: Physiologic response to falling plasma glucose

<table>
<thead>
<tr>
<th>Hormonal response</th>
<th>Glycemic threshold <em>(mg/dL)</em></th>
<th>Effects</th>
<th>Role in hypoglycemia prevention/correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Insulin</td>
<td>80–85</td>
<td>↑ Ra (↓Rd)</td>
<td>Primary glucose regulatory factor, first defence against hypoglycemia</td>
</tr>
<tr>
<td>↑ Glucagon</td>
<td>65–70</td>
<td>↑ Ra</td>
<td>Primary glucose regulatory factor, second defence against hypoglycemia</td>
</tr>
<tr>
<td>↑ Epinephrine</td>
<td>65–70</td>
<td>↑ Ra ↓ Rd</td>
<td>Involved, Critical when glucagon is deficient, third defence against hypoglycemia</td>
</tr>
<tr>
<td>↑ Cortisol and growth hormone</td>
<td>65–70</td>
<td>↑ Ra ↓ Rd</td>
<td>Involved, not critical</td>
</tr>
<tr>
<td>Symptoms</td>
<td>50–55</td>
<td>↑ Exogenous glucose</td>
<td>Prompt behavioral defense (food ingestion)</td>
</tr>
<tr>
<td>↓ Cognition</td>
<td>&lt; 50</td>
<td>--</td>
<td>Compromises behavioural defence</td>
</tr>
</tbody>
</table>

* Arterialized venous plasma glucose concentration. Ra—Rate of appearance of glucose through production in liver and kidney. Rd—Rate of disappearance of glucose through peripheral utilization in insulin sensitive tissues such as skeletal muscles and not central nervous system.

Adapted from William’s Textbook of Endocrinology, Eleventh Edition.

### Causes

Causes of hypoglycemia are varied, but in diabetic patients, it is most often iatrogenic.

- Hypoglycemia may result from medication changes or overdoses, infection, diet changes, metabolic changes over time, or activity changes; however, no acute cause may be found. Careful consideration should be given to all diabetic patients presenting with hypoglycemia. New medications, activity changes, and infection should be considered.
- Early in the course of type 2 diabetes, patients may experience episodes of hypoglycemia several hours after meals. The symptoms generally are brief and respond spontaneously.
- Drugs that may be related to hypoglycemia include the following: oral hypoglycemics, sulfonylurea, insulin, salicylates, p-aminobenzoic acid, haloperidol, ethanol, quinine, thiazide diuretics.
- Cultural and social factors. Eg. Religious fasting during ramzan

- Other causes in nondiabetic and in patients with diabetes include the following:
  - GI surgery (Especially gastric surgery)
  - Hepatic disease
  - Islet cell tumor/extra-pancreatic tumor (Rare)
  - Adrenal insufficiency
  - Hypopituitarism
  - Sepsis
  - Starvation.

### Clinical Recognition of Hypoglycemia

#### History

- A history of insulin usage or ingestion of an oral hypoglycemic agent may be known, and possible toxic ingestion should be considered. Inquire if the patient is taking any new medications
- Obtaining an accurate medical history may be difficult if the patient’s mental status is altered
- The medical history may include diabetes mellitus, renal insufficiency/failure, alcoholism, hepatic cirrhosis/failure, other endocrine diseases, or recent surgery
Review systems for weight reduction, fatigue, somnolence, nausea and vomiting, and headache.
Look for other symptoms suggesting infection.
Adrenergic symptoms and neuroglycopenic symptoms summarized in Table 2.

Table 2: Symptoms of hypoglycemia

<table>
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<td>Cognitive impairment</td>
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<tr>
<td>– Palpitations</td>
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<td>Psychomotor abnormalities</td>
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<tr>
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<td>Coma</td>
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<td>– Sweating</td>
<td></td>
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<tr>
<td>– Hunger</td>
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</tr>
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<td>– Paresthesia</td>
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CMI disturbances may include nausea and vomiting, dyspepsia, and abdominal cramping.
Skin may be diaphoretic and warm or show signs of dehydration with decrease in turgor.
Neurologic conditions include coma, confusion, fatigue, loss of coordination, combative or agitated disposition, stroke syndrome, tremors, convulsions, and diplopia.

### Laboratory Studies

- Treatment and disposition of hypoglycemia are guided by the history and the clinical picture. Serum glucose should be measured frequently and used to guide treatment, because clinical appearance alone may not reflect the seriousness of the situation.
- Hypoglycemia is defined* according to the following serum glucose levels.\(^5\)
  - <50 mg/dL in men
  - <45 mg/dL in women
  - <40 mg/dL in infants and children

*More than definition, these are operational thresholds
- If the cause of hypoglycemia is other than oral hypoglycemic agents or insulin in a diabetic patient, other lab tests may be necessary. Check liver function tests, cortisol and thyroid levels (if clinically indicated).
- Search for a source of infection. Studies should be considered to rule out the possibility of a concurrent occult infection contributing to the new hypoglycemic episode.

- Complete physical examination
- Blood counts and chest radiograph (if indicated)
- Urinalysis and renal function tests.
- Continuous glucose monitoring system is useful in identifying asymptomatic or subtle hypoglycaemias as shown in Fig. 1.

Hypoglycemias may be suspected in the following category of patients:
- Being a male: young adult or Elderly
- Low HbA1c (<5.0%)
- Long duration of diabetes
- A history of hypoglycaemia
- Hypoglycaemia unawareness
- Recent bouts of severe hypoglycaemia
- Low C-peptide level, daily insulin dose
- Insulin dosage >0.85 U/kg/day
- Recreational activity

### Physical Examination

Physical findings are nonspecific in hypoglycemia and generally are related to the central and autonomic nervous systems.
- Assess vital signs for hypothermia, tachypnea, tachycardia, hypertension, and bradycardia (neonates)
- Cardiovascular disturbances may include tachycardia (bradycardia in children), hypertension or hypotension and dysrhythmias. Respiratory disturbances may include dyspnea, tachypnea, and acute pulmonary edema

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Fig. 1 - **Somogyi effect**: Early morning hypoglycemics leading on to fasting hyperglycemia in an asymptomatic patient, detected on free style libre – A new concept in glucose monitoring providing much more information at an affordable cost.

**Clinical Management of Hypoglycemia** (Fig.2)

- Treatment should not be withheld while waiting for a laboratory glucose value, since the brain uses glucose as its primary energy source, neuronal damage may occur if treatment of hypoglycemia is delayed.
- A hyperglycemic patient with an altered mental status may receive a bolus of glucose. This procedure is unlikely to harm the patient with high glucose; however, the delay in giving glucose to the hypoglycemic patient may be detrimental.
- The mainstay of therapy for hypoglycemia is glucose/carbohydrates.
Clinical management of hypoglycemia

Hospitalized/emergency room patient with hypoglycemia (BG < 60 mg)

Patient able to eat then provide 30 gm (2 tablespoon) of oral glucose or milk (for patients on α-glucosidase inhibitors)
Follow up with some complex carbohydrate
1. 1 cup fruit Juice
2. 1 slice bread
3. 1 cup of milk
4. 2–3 biscuits (unsweetened)

Patient not able to eat
Administer 20 mL of 50% dextrose bolus intravenously and then 5 or 10% dextrose fluids at 100 mL/hr until stabilized
If available Injection glucagon 1.0 mg (1 mL) stat can also be administered instead of dextrose

Monitor blood glucose q30 min till > 100 mg

Once blood glucose > 100 mg evaluate cause and decide if further monitoring and observation required

Fig. 2: Clinical management of hypoglycaemia

Management of Recurrent Hypoglycemias

History of Recurrent Hypoglycemia

Clues to drugs, critical illnesses, organ failure, hormone deficiencies, non-islet cell tumors, Oral hypoglycemic agents

Liver function test
Renal functions
Cortisol

Exclude Factitious hypoglycemia
Autoimmune hypoglycemia

Imaging

Fig. 3 – Management of Recurrent Hypoglycemias
**TOPIC IN FOCUS - Hypoglycemia in diabetes**

**Long-term Management**
Ten percent glucose IV infusion in water by venous line @ 100 mL/hr; avoid vein sclerosis that may occur with peripheral infusion
- The following patients require admission and 10 percent dextrose infusion after initial hypoglycemia is corrected because of the risk of further hypoglycemia
  - No obvious cause
  - Oral hypoglycemic agent
  - Long-acting insulin
  - Persistent neurologic deficits
- Education /Prevention: Patients must be counselled as to the causes and the early signs and symptoms of hypoglycemia. General outpatient diabetic education or inpatient diabetic teaching is indicated.¹

**Recurrent Hypoglycemias**
The protocol in Fig. 3 is suggested in individuals with recurrent hypoglycemias in whom over dosage of medications and life style change alone cannot explain the hypoglycemias. Though rare, if all the mentioned causes are excluded then rarely patient may require evaluation and imaging for Insulinoma.²

**Consequences:**
Delay in treatment can result in profound sequelae, including death, though uncommon.³
- Acute sequelae include coma, cardiac dysrhythmia and death
- The risk of permanent neurological deficits increases with prolonged hypoglycemia; such deficits can include hemiparesis, memory impairment, diminished language skills, decreased abstract thinking capabilities and ataxia
- Because the consequences of hypoglycemia can be devastating and an antidote is readily available, diagnosis and treatment must be rapid in any patient with suspected hypoglycemia, regardless of the cause.
- In patients with cardiac autonomic neuropathy, repetitive hypoglycaemia may lead to unresponsiveness and ultimately death which is known as death in bed syndrome. Cardiac autonomic neuropathy is more seen in patients with fibrocalcific pancreatic diabetes.⁴
- Recurrent hypoglycaemia in children can cause intellectual impairment as therefore have relaxed glycemic targets. They also require additional care during adolescence due to the higher incidence in this age group. This is often due to lack of motivation busy educational responsibilities, changing physical activities and poor dietary habits.

**References:**