Hypoglycemia

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Contents

• Hypoglycemia definition and classification
• Systemic glucose balance and counter-regulation
• Clinical significance of hypoglycemia
• Risk for hypoglycemia
• Treatment of hypoglycemia
• Prevention of hypoglycemia
Definition of hypoglycemia

**Hypoglycemia**

1. Plasma glucose level low (≤70 mg/dL)
2. Autonomic or neuroglycopenic symptoms
3. Symptoms responding to the administration of carbohydrate

**Severe hypoglycemia**

Symptoms that are severe enough to require assistance from another person

## Classification of hypoglycemia

<table>
<thead>
<tr>
<th>Level</th>
<th>Glycemic criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemic alert value (level 1)</td>
<td>( \leq 70 \text{mg/dL} ) ( (3.9 \text{mmol/L}) )</td>
<td>Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy</td>
</tr>
<tr>
<td>Clinically significant hypoglycemia (level 2)</td>
<td>(&lt; 54 \text{mg/dL} ) ( (3.0 \text{mmol/L}) )</td>
<td>Sufficiently low to indicate serious clinically important hypoglycemia</td>
</tr>
<tr>
<td>Severe hypoglycemia (level 3)</td>
<td>No specific glucose threshold</td>
<td>Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery</td>
</tr>
</tbody>
</table>

*ADA Standards of Medical Care in Diabetes 2018*
Systemic glucose balance

• **Plasma glucose**
  – Maintained within a narrow range: 70-140mg/dl
  – Dynamic regulation of glucose influx and utilization
  – During fasting
    • Breakdown of glycogen (glycogenolysis)
      – hepatic stores normally able to maintain glucose levels during 8-12hours of fasting
    • Gluconeogenesis
      – Liver (main) and kidney
      – Precursors from liver, muscle and adipose tissue
## Physiologic Responses to Decreasing Plasma Glucose Concentrations

<table>
<thead>
<tr>
<th>Response</th>
<th>Threshold (mg/dL)</th>
<th>Physiologic Effects</th>
<th>Role in Glucose Counterregulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Insulin (defect in DM)</td>
<td>80–85</td>
<td>↑Ra (↓Rd)</td>
<td>Primary glucose regulatory factor/first defense against hypoglycemia</td>
</tr>
<tr>
<td>↑ Glucagon</td>
<td>65–70</td>
<td>↑Ra</td>
<td>Primary glucose counterregulatory factor: Second defense</td>
</tr>
<tr>
<td>↑ Epinephrine</td>
<td>65-70</td>
<td>↑Ra, ↓Rd</td>
<td>3rd defense. critical when glucagon is deficient</td>
</tr>
<tr>
<td>↑ cortisol and GH</td>
<td>65-70</td>
<td>↑Ra, ↓Rd</td>
<td>Involved in prolonged hypoglycemia, 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 behavioral defense</td>
</tr>
</tbody>
</table>

Ra, rate of glucose appearance, glucose production by the liver and kidneys; Rd, rate of glucose disappearance, glucose utilization by insulin-sensitive tissues such as skeletal muscle.
Glucose in the brain

• The brain
  – **Glucose** is an obligate metabolic fuel for the brain under physiologic conditions
  – Cannot synthesize glucose
  – Stores only a few minutes supply as glycogen
  – Requires a continuous supply of glucose from the arterial circulation.
  – Physiologic mechanisms prevent or rapidly correct hypoglycemia
# Symptoms of hypoglycemia

<table>
<thead>
<tr>
<th>Adrenergic Symptoms</th>
<th>Neuroglycopenic Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms caused by hormones elevating blood glucose</td>
<td>Deficient glucose at the central nervous system</td>
</tr>
</tbody>
</table>

- Shaking, sweating,
- Palpitation
- Tachycardia
- Tingling sensation of arms and legs
- Hunger

- Extreme fatigue, frustration
- Headache, visual impairment, drowsiness
- Dizziness
- Impaired concentration
- Delayed thought, language
- Loss of consciousness, death

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*Korean Diabetes Association, Diabetes Management Guideline 2006*
# Symptoms of hypoglycemia

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capable of self-treatment</td>
<td>May require prompting</td>
<td>Not capable of self-treatment</td>
</tr>
<tr>
<td>Tremors, palpitation, sweating, hunger, fatigue</td>
<td>Headache, mood changes, low attentiveness</td>
<td>Conscious or unconscious</td>
</tr>
<tr>
<td>Adrenergic</td>
<td>Adrenergic + Neuroglycopenic</td>
<td>Neuroglycopenic</td>
</tr>
</tbody>
</table>

**Symptoms:**

- Shakiness
- Sweating, chills and clamminess
- Confusion
- Rapid/fast heartbeat
- Hunger and nausea
- Sleepiness
- Headaches
Symptoms of Nocturnal hypoglycemia

Symptoms may include:

• Sweating
• Vivid dreaming
• Restlessness
• Incontinence
• Waking with a headache
• High or low fasting glucose levels
Hypoglycemia in diabetes

- Major limitation in the lowering of glucose in DM

- Type 1 DM
  - 2 to 3 times more frequent than in T2DM
  - Relative hyperinsulinemia (overcorrection)
  - Average 2 times /week of symptomatic hypoglycemia
  - Severe hypoglycemia one episode / year
  - 4-10% of death d/t hypoglycemia

- Type 2 DM
  - Treatment with insulin or sulfonylureas, glinides
  - Frequency increases as absolute insulin deficiency develop
Conventional risk factors

- **Insulin excess**
  - Insulin doses excessive, ill timed or wrong type
  - ↓Influx of exogenous glucose
    - missed meals, fasting
  - ↑Insulin-independent glucose utilization
    - during exercise
  - ↑ Insulin sensitivity
    - Improved glycemic control, middle of the night, late after exercise, increased fitness, weight loss
  - ↓ Endogenous glucose production
    - Following alcohol ingestion
  - ↓ Insulin clearance
    - Renal failure
Risk of hypoglycemia

Risk increases with:

- Recent severe hypoglycemia
- Impaired hypoglycemia awareness
- Liver disease or kidney failure
- Gastroparesis
- Intensive glucose control
- Long duration of diabetes
- T1DM and advanced T2DM (profound insulin deficiency)
- Autonomic neuropathy
- Cognitive impairment
- Alcohol
- Elderly and very young children
**Meta-analysis: Intensive control and Severe hypoglycaemia risk**

### Table 5  Effects of more- vs less-intensive glycaemic control on severe hypoglycaemia

<table>
<thead>
<tr>
<th>Trial</th>
<th>More-intensive</th>
<th>Less-intensive</th>
<th>ΔHbA₁c (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. at risk</td>
<td>No. of events</td>
<td>No. at risk</td>
<td>No. of events</td>
</tr>
<tr>
<td>ACCORD</td>
<td>5,128</td>
<td>538</td>
<td>5,123</td>
<td>179</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>5,571</td>
<td>150</td>
<td>5,569</td>
<td>81</td>
</tr>
<tr>
<td>UKPDS</td>
<td>2,729</td>
<td>194</td>
<td>1,138</td>
<td>23</td>
</tr>
<tr>
<td>VADT</td>
<td>892</td>
<td>189</td>
<td>899</td>
<td>89</td>
</tr>
<tr>
<td>Overall</td>
<td>14,320</td>
<td>1,071</td>
<td>12,729</td>
<td>372</td>
</tr>
</tbody>
</table>

*UKPDS event numbers may be an underestimate as hypoglycaemic episodes were recorded as ‘none’ or ‘one or more’ in each 3 month follow-up period*
Self-reported hypoglycemic episodes were categorized as (1) transient, (2) temporarily incapacitated, (3) requiring third party assistance, and (4) requiring medical attention, recording the most severe episode each quarter.
Consequences of hypoglycemia

- Limits treatment and glycemic control
  - Hypoglycemia is the major limiting factor in the glycemic management of type 1 and type 2 diabetes
- Decreased quality of life / fear of hypoglycemia
- Dementia / cognitive impairment
- Mortality
- Cardiovascular events / cardiovascular death
Hypoglycemia and CVD

• Hypoglycemia has a number of physiological effects on the heart
  – Sympathetic nervous system activation
  – Increases blood flow to myocardium, HR, systolic BP, myocardial contractility, stroke volume, cardiac output → cardiac stress
  – Changes to cardiac repolarization → arrhythmias
  – Inflammatory response → coagulation
  – Endothelial dysfunction → atherosclerosis

• Several studies have shown associations between severe hypoglycemia and cardiovascular events or death

Frier BM. Diabetes Care 2011; 34:S132
Lee AK. Diabetes Care 2018;41:104
Severe hypoglycemia is associated with increased mortality

Accord Annual mortality

![Bar graph showing Accord Annual mortality.](image)

**ACCORD**: Action to Control Cardiovascular Risk in Diabetes

*Symptomatic, severe hypoglycemic event requiring medical assistance

**HA**: Hypoglycaemic events requiring any assistance, medical or non-medical

**HR 1.41 (1.03–1.93)**

Severe hypoglycaemia and risk of CVD and death

Hypoglycemia was defined as a blood glucose level of less than 2.8 mmol per liter (50 mg per deciliter) or the presence of typical symptoms and signs of hypoglycaemia without other apparent cause. Patients with transient dysfunction of the central nervous system who were unable to treat themselves (requiring help from another person) were considered to have severe hypoglycaemia. Patients with transient dysfunction of the central nervous system who were able to treat themselves were considered to have minor hypoglycaemia.

<table>
<thead>
<tr>
<th>Events</th>
<th>Number (%) of patients with event</th>
<th>Hazard ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Hypoglycaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=231)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major macrovascular</td>
<td>33 (15.9%)</td>
<td>3.53 (2.41-5.17)</td>
</tr>
<tr>
<td>Major microvascular</td>
<td>24 (11.5%)</td>
<td>2.19 (1.40-3.45)</td>
</tr>
<tr>
<td>All cause deaths</td>
<td>45 (19.5%)</td>
<td>3.27 (2.29-4.65)</td>
</tr>
<tr>
<td>CVD death</td>
<td>22 (9.5%)</td>
<td>3.79 (2.36-6.08)</td>
</tr>
<tr>
<td>No Severe Hypoglycaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=10909)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major macrovascular</td>
<td>1114 (10.2%)</td>
<td></td>
</tr>
<tr>
<td>Major microvascular</td>
<td>1107 (10.1%)</td>
<td></td>
</tr>
<tr>
<td>All cause deaths</td>
<td>986 (9.0%)</td>
<td></td>
</tr>
<tr>
<td>CVD death</td>
<td>520 (4.8%)</td>
<td></td>
</tr>
</tbody>
</table>
**Hypoglycaemia-related ECG abnormalities**

Simultaneous CGM and Holter Monitoring

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**a** *Sinus bradycardia* (31 beats/min) recorded at 06:10 hours with a CGM of 3.1 mmol/l, having been < 2.2 mmol/l from 04:40 to 05:15 hours.

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**b** *Couplet of multifocal ventricular ectopic beats* preceded by a *QTc interval of 560 ms*. The CGM level at the time was 3.4 mmol/l, but this had varied between 2.9 and 3.2 mmol/l for some time before.
Who is most likely to be harmed?

- Young children
  - Atypical symptoms, most vulnerable to consequences
- Older adults
  - Progressive age-related decrease in beta-adrenergic receptor function and counterregulatory hormone response
  - Geriatric syndromes: more vulnerability
- Prevalent CVD
**Treatment of hypoglycemia**

**Mild to Moderate : Rule of 15**

1. **Test if possible**
2. **If < 70mg/dL**
   - Take 15g of glucose
   - Eat or drink 15 grams of fast sugar (simple carbohydrates)
3. **Wait 15 minutes**
4. **Re-test**
   - If still low treat with another 15g glucose
5. **Snack if next meal is more than 30-60 minutes later**
**Treatment of mild to moderate hypoglycemia**

Examples of 15 g carbohydrate:

- 150 mL (3/4 cup) of juice or regular soft drink
- 3 packets of table sugar
- 15 mL (1 tablespoon) of honey

- Pure glucose: preferred treatment
- Added fat may retard and prolong acute glycemic response
- Carbohydrate sources high in protein should not be used to treat hypoglycemia
  - In T2DM, ingested protein may increase insulin response without increasing plasma glucose concentrations.
Treatment of SEVERE Hypoglycemia in Conscious Person

1. Treat with oral “fast sugar” (simple carbohydrate) (20 g) to relieve symptoms

2. Retest in 15 minutes to ensure the BG> 4.0 mmol/L and retreat with a further 15 g of carbohydrate if needed

3. Eat usual snack or meal due at that time of day or a snack with 15 g carbohydrate plus protein

2018 Diabetes Canada CPG – Chapter 14. Hypoglycemia
Caution

Never give food to an unconscious person

- Position in the left lateral position and withhold any food or fluids. Seek further medical help.

- If glucagon is available it can be administered subcutaneously, intramuscularly or intravenously.
Treatment of severe hypoglycemia

If unable to treat orally
• Glucagon subcutaneously or intramuscular
  - if no IV access
  - 1mg for adult (0.5mg for child)
• IV dextrose
  - 20-50 ml of D50W given IV over 1-3 minutes
  - Immediate response
• After a severe hypoglycemic episode, people may develop a severe headache
Follow-up management

• If a meal is >1 hour away, a snack (including 15 g carbohydrate and a protein source) should be consumed
• Consider reducing insulin
• Assess cause
• Prevent recurrence
• Avoid BG levels < 70mg/dL
• If BG <100mg/dL before bed, eat a snack with carbohydrate and protein (half-slice apple + 1 cup of milk)
Other management strategies

- Self-management education and support
- Long acting analogues instead of NPH
- Rapid acting analogues instead of regular/soluble insulin
- Correct injection of insulin
Frequent hypoglycemia

- Recognized hypoglycemia more than twice a week
- Up to 50% unrecognized
- Increased frequency may decrease counter-regulatory response and awareness
- Asymptomatic nocturnal hypoglycemia is common, often prolonged
- Severe nocturnal hypoglycemia may result in death

Cryer, Davis, 2003
Frier, 2003
Cryer PE, 2009
Asymptomatic hypoglycemia

- In a cohort of patients with diabetes, more than 50% had asymptomatic (unrecognized) hypoglycemia, as identified by continuous glucose monitoring\(^1\).
- Other researchers have reported similar findings\(^2,3\).

Impaired hypoglycemia awareness

- Diminished ability to perceive the onset of hypoglycemia
- Glycemic thresholds for counter-regulatory responses necessary to restore euglycemia, generation of symptoms, and cognitive impairment are reset at lower levels of blood glucose
- Induced by recurrent exposure to hypoglycemia
- Precludes appropriate behavioral responses, such as eating
- Reliance on recognizing neuroglycopenic symptoms
Managing hypoglycemia unawareness

• Unawareness is sometimes reversible
  – Functional and partially reversible usually
• Encourage hypoglycemia-free state
  – Reversible: require >2-3 weeks of avoidance of hypoglycemia
  – Less stringent glycemic targets up to 3 months
• Medical alert identification
• Monitor blood glucose before certain activities, such as sports, driving a car
Alcohol

Effects of alcohol
- Increased risk of hypoglycemia
- Decreased gluconeogenesis
- Decreased ability to recognize symptoms

Recommendation
- Need to be safe- eat adequate carbohydrates when drinking alcohol

Turner, 2001
Hypoglycemia in older people

- Elderly patients are especially vulnerable to hypoglycemia
- Advanced age, recent hospitalization, polypharmacy are predictors
- Risk of injury from falls
- May be missed or mistaken for dementia
- Malnutrition may increase risk of hypoglycemia
- Avoid long-acting sulfonylureas in older people
- Repaglinide, acarbose and DPP-IV inhibitors may be safer options

Johnson, 2008
Driving safety

- People on insulin or insulin secretagogues should be aware of local regulations and/or guidelines for driving

- Preventive actions
  - Check blood glucose before starting the car
  - If ≤90 mg/dL, eat some carbohydrates before driving
  - Wait to continue driving until BG rises
  - If you are low while driving, **Stop** immediately
  - Carry a source of fast acting sugar

*Cox DJ, Penberthy JK, Zrebiec J. Diabetes Care. 2003*
Hypoglycemia risk factor reduction

- Patient education and empowerment
- Frequent self-monitoring of blood glucose
- Flexible insulin (other drug) regimen
- Rational individual glycemic goals
  - lowest HbA1c that does not cause severe hypoglycemia and preserves awareness of hypoglycemia
- Ongoing professional guidance and support
- Appropriate adjustments of medications, diet and lifestyle
- CGM with automated low glucose suspend shown to be effective in reducing hypoglycemia in type 1 diabetes
Hypoglycemia

- Common
- It is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin or insulin secretagogues
- Incidence can be reduced through education, self-monitoring and self-care
- Higher risk patients should be identified and preventive measures should be implicated
- Must be addressed at every visit to healthcare professionals
- Treatment must be revised if recurrent
Thank you