Hypoglycemia T1D and T2D - mechanisms and management

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**Definition of hypoglycemia**

Hypoglycemia refers to abnormally low levels of glucose in the blood. This can lead to symptoms such as shakiness, dizziness, and confusion.

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**The extent of the problem**

The extent of hypoglycemia can vary, but it is a significant concern for those with diabetes and other conditions that affect blood glucose levels.

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**Mechanism of hypoglycemia**

Hypoglycemia occurs when there is a sudden drop in blood glucose levels, which can happen due to various factors such as insulin overuse or insufficient carbohydrate intake.

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**“Scoring” hypoglycemia severity**

Scoring hypoglycemia severity helps in understanding the impact and urgency of the condition.

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**Principles of prevention**

Preventing hypoglycemia involves managing blood glucose levels effectively through diet, exercise, and medication.

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**Treatment**

Treatment of hypoglycemia involves correcting the condition and addressing the underlying causes to prevent future episodes.
Classification of level of hypoglycemia

<table>
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<tr>
<th>Level</th>
<th>Glycemic criteria</th>
<th>Notes</th>
</tr>
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<tr>
<td>Hypoglycemia alert value (level 1)</td>
<td>$\leq 70$ mg/dl (3.9 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>$&lt; 54$ mg/dl (3.0 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>
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</table>

From American Diabetes Association: Glycemic Targets: Standards of Medical Care in Diabetes-2018 Diabetes Care. 2018;41 Suppl 1:S55–S64
What constitutes level 3 hypoglycaemia?

(1) Seizure or coma due to preceding hypoglycemia

(2) Any hypoglycemia requiring glucagon or dextrose to restore blood glucose to normal

(3) Requiring assistance to recognize and/or manage low blood glucose (in some cases this is defined as moderate hypoglycemia).

And new CGM defined criteria

• BG < 3.0 for >15 minutes – can be either moderate or severe hypoglycemia
Rates and predictors of hypoglycaemia in 27 585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study.

Khunti K¹, Alsifri S², Aronson R³, Cigrovski Berkić M⁴, Enters-Weijnen C⁵, Forsén T⁶, Galstyan G⁷, Geelhoed-Duijvestijn P⁸, Goldfracht M⁹, Gydesen H¹¹, Kapur R¹¹, Lalic N¹², Ludvik B¹³, Moberg E¹⁴, Pedersen-Bjergaard U¹⁵, Ramachandran A¹⁶; HAT Investigator Group.

- T1D; n = 8022) or type 2 diabetes (T2D; n = 19 563) 2004 sites in 24 countries treated with insulin >1 year.
- Proportion experiencing at least one hypoglycemic event 6 mth retrospective and 4 week prospective diary records. Hypoglycemia Assessment Tool (HAT)
- During the prospective period, 83.0% with T1D and 46.5% with T2D reported hypoglycaemia
- Glycated haemoglobin level was not a significant predictor of hypoglycemia

<table>
<thead>
<tr>
<th>Events /patient year</th>
<th>Any hypoglycemia</th>
<th>Nocturnal</th>
<th>Severe</th>
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<tbody>
<tr>
<td>T1D</td>
<td>73.3</td>
<td>11.3</td>
<td>4.9</td>
</tr>
<tr>
<td>T2D</td>
<td>19.3</td>
<td>3.7</td>
<td>2.5</td>
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Diabetes Obesity Metabolism 2016; 18:907-915
T1D Exchange

- High rates adverse events with severe hypoglycaemia in T1D exchange
  - 8% in 26-50 yo
  - Up to 25% in > 50 yo

- In 11-14 year olds 8% spend more than 2 hours hypoglycaemic overnight even with intensive monitoring and running pump with CGM
Increased mortality and hypoglycemia

- Seen in trials of intensive diabetes treatment in T2DM and in ICU
  - ADVANCE: 2.5 X increase in CV death and CV events if experience severe hypoglycemia

- Release of catecholamines may increase cardiac workload, which may worsen an already compromised heart, especially in presence of preexisting coronary artery disease

- Hypoglycemia causes abnormal cardiac repolarization with a prolongation of QTc, an increase that may lead to severe cardiac arrhythmias

- Acute hypoglycemia has also been demonstrated to result in an increased pro-coagulant state, release of inflammatory cytokines, and ultimately to endothelial dysfunction and vascular injury

- Increased MACE and CV mortality not associated with severe hypoglycemia and IAH in T1D
  - Seijling AS et al. Association between hypoglycaemia and impaired hypoglycaemia awareness and mortality in people with Type 1 diabetes mellitus. Diabet Med 2016; 33: 77-83
  - Tu E et al Med J Aust 2008;188:699-702 Sudden death (including Dead in Bed) accounted for 22% of deaths in <40 year olds with T1D
Severe Hypoglycemia, Cardiovascular Outcomes, and Death—The LEADER Experience

- Patients with type 2 diabetes and high risk for CV disease (n = 9,340) were randomized 1:1 to liraglutide or placebo, + standard treatment, for 3.5–5 years.
- The primary end point was time to first major adverse cardiovascular event (MACE) and secondary end points included incidence of hypoglycemia.
- A total of 267 patients experienced severe hypoglycemia (liraglutide n = 114, placebo n = 153; rate ratio 0.69; 95% CI 0.51, 0.93).
- Characteristics of those with hypoglycemia included:
  - longer diabetes duration (16 years cf 12 years)
  - higher incidence of heart failure and kidney disease
  - used insulin more frequently at baseline
- MACE event 6.3 fold more likely within 7 days of a severe hypoglycemia event
- CV Death 9.6 x more likely within 7 days of a severe hypoglycemia event

Diabetes Care 2018 Jun; dc172677 Zinman et al.
Normal glucose regulation

- As glucose enters the stomach incretins are secreted, so when glucose enters the bloodstream, insulin is already secreted and further enhanced by rise in glucose.
- Glucose leaves the bloodstream and enters muscle and liver with storage of glucose as glycogen.
- Between meals, glycogen metabolized to glucose to maintain glucose and supply energy needs.
- When blood glucose levels are relatively low, endogenous insulin secretion is suppressed and glucagon secreted to increase hepatic glucose production/hepatic glycogenolysis.
- If insufficient, adrenalin release from the sympatho-adrenal system stimulates additional hepatic glucose production and causes symptoms of hunger.
Mechanism of hypoglycemia

Hypoglycemia – explainable vs unexplainable

- **Explainable** - accepted by the person with diabetes as a consequence of treatment eg.
  - insufficient carbohydrate eaten
  - delay in food intake after taking insulin
  - intercurrent illness with vomiting
  - excess of alcohol
  - excess insulin taken for food or to correct high BG

- **Unexplainable** - usually linked to unrecognised hypoglycemia
Hypoglycemia – explainable

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

2. Exogenous glucose delivery is decreased (as following missed meals and during the overnight fast, with gastroparesis or coeliac disease).

3. Glucose utilization and sensitivity to insulin are increased (as during and shortly after exercise, in the middle of the night, following weight loss or improved glycemic control).

4. Endogenous glucose production is decreased (as following alcohol ingestion or in liver failure).

5. Insulin clearance is decreased (as in renal failure).
Hypoglycemia - unexplainable

- Causes considerable disruption to patients’ lives.
- Responses to hypoglycemia wane over time.
- Contribute to significant increase in glycemic variability.
- The main factors in IAH
  - Complete insulin deficiency so no capacity to switch off insulin
  - Reduced secretion of glucagon
  - Reduced sympato-adrenal response

- Hypoglycemic unawareness from recurrent hypoglycemia in its early phases may be partially reversible by reducing insulin doses (but responses do not return to normal).
- Loss of glucagon and catecholamine response may be irreversible and response to hypoglycemia thereafter relies only on the pituitary–adrenal axis to produce growth hormone and cortisol.

Hypoglycemia-Associated Autonomic Failure

Early T2DM (Relative β-Cell Failure)
- Marked Absolute Therapeutic Hyperinsulinemia
- Falling Glucose Levels
- Isolated Episodes of Hypoglycemia

Advanced T2DM and T1DM (Absolute β-Cell Failure)
- Relative or Mild-Moderate Absolute Therapeutic Hyperinsulinemia
- Falling Glucose Levels
- β-Cell Failure → No Insulin and No Glucagon
- Episodes of Hypoglycemia
- Exercise, Sleep
- Attenuated Sympathoadrenal Responses to Hypoglycemia (HAAF)
- Adrenomedullary Epinephrine Responses:
  - Defective Glucose Counterregulation
- Sympathetic Neural Responses:
  - Hypoglycemia Unawareness
  - Recurrent Hypoglycemia

Clarke/Gold Score

1. Tick the category that best describes you (tick one only):
   - I always have symptoms when my blood sugar is low 0
   - I sometimes have symptoms when my blood sugar is low 1
   - I no longer have symptoms when my blood sugar is low 1

2. Have you lost some of the symptoms that used to occur when your blood sugar was low?
   - Yes 1
   - No 0

3. In the past 6 months, how often have you had hypoglycaemic episodes, where you might feel confused, disoriented, or lethargic and were unable to treat yourself?
   - Never 0
   - Once a month 1
   - More than once a month 1

4. In the past year, how often have you had hypoglycaemic episodes, where you were unconscious or had a seizure and needed glucagon or intravenous glucose?
   - Never 0
   - 1 time 1
   - 2 times 1
   - 3 times 1
   - 4 times 1

5. How often in the last month have you had readings <3.5mmol/l with symptoms?
   - Never 0
   - 1-3 times 1
   - 4-6 times 1
   - Almost daily 1

6. How often in the last month have you had readings <3.5mmol/l without any symptoms?
   - Never 0
   - 1-3 times 1
   - 4-6 times 1
   - Almost daily 1

7. How low does your blood sugar need to go before you feel symptoms?
   - 3.4-3.9mmol/l 0
   - 2.8-3.3mmol/l 1
   - 2.3-2.7mmol/l 1
   - <2.2mmol/l 1

8. To what extent can you tell by your symptoms that your blood sugar is low?
   - Never 1
   - Rarely 1
   - Sometimes 1
   - Often 1
   - Always 0

GOLD SCORE

“Do you know when your hypos are commencing?”

<table>
<thead>
<tr>
<th>Awareness</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
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Prevention of hypoglycemia in diabetes

- Acknowledge and address the problem in every person treated with insulin or an insulin secretagogue at every consultation
  - What frequency does low blood glucose occur- explainable or unexplainable?
    - Review SMBG and CGM records
  - At what level does the person detect/develop symptoms of hypoglycemia?
  - Do others ever detect hypoglycemia before the person with diabetes?
- Conventional risk factors for hypoglycemia
  - Risk factors that result in relative or absolute hyperinsulinemia
  - Timing/type and dose of insulin or insulin secretagogue – MDI increases risk in T2DM vs basal insulin
  - Situations in which exogenous or endogenous glucose delivery is decreased
  - Situations in which glucose utilisation or insulin sensitivity is increased or insulin clearance is decreased
Prevention of hypoglycemia in diabetes

• Consider risk factors indicative of HAAF
  • History of severe hypoglycemia- a red flag! Regardless of changes made the likelihood of a further event remains high
  • Evidence of impaired awareness of hypoglycemia

• Apply the relevant principles of intensive glycemic therapy with a view to minimising the risk of further iatrogenic hypoglycemia including
  • Drug/dose selection
  • Individualized glycemic goals – appropriate to age, duration diabetes, complications
  • Structured patient education-scrupulous avoidance of hypoglycemia
  • Selective application of diabetes technologies
Structured patient education

• Little SA et al. Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 × 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). Diabetes Care 2014;37:2114-22

• Little SA et al. Sustained reduction in severe hypoglycemia in adults with type I diabetes complicated by impaired awareness of hypoglycemia: Two-year follow up in the HypoCOMPaSS randomized clinical trial. Diabetes Care. 2018;41:1600-1607

• 2x2 factorial design comparing CSII and MDI and CGM vs SMBG, 96 subjects
• IAH defined as GOLD score >4
• After 6 months study period patients chose treatment MDI/CSII with or without CGM
• IAH improvement sustained: Gold score baseline 5.1 ± 1.1 vs. 24 mths 3.7 ± 1.9; P < 0.0001
• Severe hypoglycemia: reduced from 8.9 ± 12.8 episodes/person-year prestudy to 0.4 ± 0.8 at 24 months (P < 0.0001)
• Improvement in treatment satisfaction and reduced fear of hypoglycemia were sustained
Structured patient education

• Single 1-2 hour education session
• The four points of HypoCOMPaSS established the imperatives:
  • never delay hypoglycemia treatment;
  • recognize personalized times of increased risk
  • Identify and detect subtle symptoms
  • confirm low glucose levels through regular self-monitoring, particularly for nocturnal hypoglycemia.
• Also included
  • advice on self-adjustment of insulin doses according to carbohydrate intake
  • SMBG in relation to planned activity
  • recommendation for oral carbohydrate administration for all glucose levels <4.0mmol/L
• Weekly calls between study visits from week 4-24 to reinforce rigorous hypoglycemia avoidance and insulin titration
Selective application of diabetes technology

- CGM and prevention of hypoglycemia
  - Early meta-analyses including Cochrane analysis did not show any advantage of CGM with CSII (did not incorporate later iterations with LGS or PLGS)
  - More recent studies have shown CGM devices improve glycemic control and reduce duration of hypoglycemia regardless of CSII or MDI in type I DM
    - DIAMOND
    - HypoDE
    - (GOLD)
  - Limited studies of CGM in T2D with few focusing on T2D treated with MDI for whom there is the greatest risk of hypoglycemia
    - DIAMOND
  - Potential for improvement in hypoglycemia awareness without change in A1c


Cgm outcomes in MDI users in DIAMOND

- High adherence to CGM – mean 6 days per week
- HbA1c reductions cf controls
  - Reduced by 0.6% in type 1
  - Reduced by 0.3% in type 2
  - Greater benefit with higher baseline HbA1c
- In **T1DM** time in range increased, time hyperglycemic decreased and **time hypoglycemic decreased by 50%**- 80 mins per day control vs 43 mins/day CGM,
- In **T2DM** time in range increased and time hyperglycemic decreased but **no change in time hypoglycemic**
- In **T1DM** no difference in rates of severe hypoglycemia but trials not powered to detect difference in hypoglycemia and low number of events
Impact of CGM on quality of life in adults with T1D

DIAMOND

- CGM was associated with
  - Greater increase in hypoglycemic confidence
  - Greater decrease in diabetes distress
- CGM satisfaction
  - Was not associated with glycemic changes
  - Was associated with reduction in diabetes distress
  - Was associated with improved glycemic confidence

HypoDE study


- A 6-month, multicentre, open-label, parallel, randomised controlled trial done at 12 diabetes practices in Germany
- All participants wore masked rtCGM system for 28 days and then randomly assigned to 26 weeks of unmasked rtCGM ( Dexcom G5) or control group with SMBG
- 149 participants (n=74 control; n=75 rtCGM)
- 141 completed the follow-up phase (n=66 control, n=75 rtCGM).
- The mean number of hypoglycaemic events per 28 days in the rtCGM group reduced from 10·8 (SD 10·0) to 3·5 (4·7); reduction among control negligible (14·4 [12·4] to 13·7 [11·6])
- Incidence of hypoglycaemic events decreased by 72% for participants in the rtCGM group (incidence rate ratio 0·28 [95% CI 0·20–0·39], p<0·0001).
- No change in hypoglycemia unawareness scores despite 6 months of CGM and reduced number of events
- Reduced glycemic variability in rt-CGM group- CV reduction from 39% to 34%
Continuous Glucose Monitoring for Hypoglycemia Avoidance and Glucose Counterregulation in Long-Standing Type 1 Diabetes.
PMID: 29190340  Free PMC Article
Similar articles

Restoration of self-awareness of hypoglycemia in adults with long-standing type 1 diabetes: hyperinsulinemic-hypoglycemic clamp substudy results from the HypoCOMPaSS trial.
PMID: 24130355  Free PMC Article
Similar articles
• Outcomes depend on comparator but greatest benefits seen when compare HCL with standard CSII without CGM

• 60 adults with type 1 diabetes who received, in a crossover randomized design, day-and-night hybrid closed-loop insulin delivery and insulin pump therapy, the latter with or without real-time continuous glucose monitoring.

• 377 hypoglycemic episodes with HCL vs 662 in controls (P < 0.001), mostly nocturnal hypoglycemia.

• HCL also demonstrated earlier recovery from hypoglycemia leading to higher 2-hour post-hypoglycaemia glucose levels and reduced duration of hypoglycemia

• Many adults achieve HbA1c <7.5% at expense of increased hypoglycemia. When change to HCL maintain same HbA1c or slight increase but significant reduction in hypoglycemia
Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial


• 86 eligible patients (age >6) were randomly assigned to receive hybrid closed-loop therapy (n=46) or sensor-augmented pump therapy (n=40; control group)

• Time in target was significantly higher with HCL (65%) compared with controls (54%); mean difference 10·8 %, 95% CI 8·2 to 13·5%; p<0·0001

• The time spent with glucose concentrations below 3·9 mmol/L (difference -0·83 %, -1·40 to -0·16; p=0·0013

• Reductions in HbA₁c percentages were significantly greater with HCL vs control group (mean difference 0·36%, 95% CI 0·19 to 0·53; p<0·0001)

• HCL reduction from 8.3% to 7.4% at 12 weeks
Islet cell transplantation

Reversal of hypoglycemia unawareness and protection from severe hypoglycemia events are two of the main benefits of islet transplantation and they persist for the duration of graft function.

Hypoglycemic score (Clarke score; 4) (A) and proportion of subjects with hypoglycemia unawareness (hypoglycemic score ≥ 4) (B) preand post-ITx, according to islet function. *P 0.007 for comparison of posttransplant hypoglycemic score between off-insulin and graft failure groups. *P value is not applicable, since no hypoglycemia was reported posttransplant.

Diabetes Care 2008; 31:2113-2115. Restoration of hypoglycemia awareness after islet transplantation
Paired CSII and islet transplant

**A**

![Graph showing Beta-score over time](image)

- Pre-Tx
- 3 months
- 12 months

**B**

![Graph showing HypoScore over time](image)

- Pre-Tx
- 3 months
- 12 months

**C**

![Graph showing SD glucose (mmol/L) over time](image)

- Pre-Tx
- 3 months
- 12 months

**D**

![Graph showing CONGA4 over time](image)

- Pre-Tx
- 3 months
- 12 months
Summary- Hypoglycemia in T1D and T2D

**T1D**
- High incidence which increases with duration diabetes
- IAH not directly predictive of CV mortality
- CGM use with CSII and with MDI reduces frequency of hypoglycemia
- CGM use with CSII may improve IAH but does not restore to normal
- Islet transplantation (without insulin independence) restores hypoglycemia awareness in those with IAH

**T2D**
- Less of a problem than in T1D and highest in those with T2D on MDI
- Higher CV mortality in those with IAH
- CGM use does not reduce frequency of hypoglycemia but insufficient data on impact in T2D treated with MDI
- GLP1 analogues may be of benefit over other agents when used with insulin
Honey, I think your blood sugar is a bit out of balance!