Hypoglycemia in diabetes: Risks and Practical Prevention Strategies

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Disclosures

- American Board of Internal Medicine Exam Committee (Advisor)
Inez P.

78 year old woman with 30 year history of type 2 DM. Brought in by her daughter because of concerns about hypoglycemia. She stopped by to visit at 2 pm and found her mother unresponsive on the couch. Paramedics were called and BG was found to be 32. Inez doesn’t know what happened but remembers sitting down to watch TV at 9:30 am.

Inez P.

PMH significant for ASCVD with stent placement 3 years ago. Current meds are clopidogrel, atorvastatin, lisinopril, glyburide 5 mg bid, metformin 2000 mg qd, sitagliptin 100 mg qd

Eats breakfast at 8 am, eats lunch with friends at a restaurant 3-4 times/wk but doesn’t always eat lunch when home, dinner is at 5:30 pm. Frequently snacks during the day on fruit, cookies, chips. Walks about 2 mi twice a week for exercise

HbA1c was 7.2 % at her last visit with her doctor 3 mo ago
Outline

I. What is hypoglycemia and how common is it in patients with diabetes?

II. What are the risks of hypoglycemia and how might it lead to adverse outcomes?

III. How can we help patients avoid/treat hypoglycemia and hypoglycemia associated adverse events?

How is hypoglycemia in diabetes defined?

Joint position statement of ADA and EASD supported new definitions created by International Hypoglycemia Study Group

(Diabetes Care and Diabetologia Jan 2017)

- Definitions are evidenced based and designed to identify levels of hypoglycemia that have serious clinical and health economic consequences
- Intention is to guide diabetes and regulatory communities as new therapies to prevent and treat hypoglycemia are developed

Consensus report to identify and define clinically meaningful T1D outcomes beyond A1c also supported the new definitions

(Agiostratidou et al. Diabetes Care Dec 2017)

- AACE, AADE, ADA, Endocrine Society, JDRF International, Helmsley Charitable Trust, Pediatric Endocrine Society, and T1D Exchange
Classifying Hypoglycemia in Clinical Trials

<table>
<thead>
<tr>
<th>Level</th>
<th>Glycemic Criteria/Description</th>
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<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td>Glucose &lt; 70 mg/dL (3.9 mmol/L) and ≥ 54 mg/dL (3.0 mmol/L)</td>
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<tr>
<td><strong>Level 2</strong></td>
<td>Glucose &lt; 54 mg/dL (&lt;3.0 mmol/L)</td>
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<tr>
<td><strong>Level 3</strong></td>
<td>A severe event characterized by altered mental and/or physical status requiring assistance</td>
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</tbody>
</table>

Conversion: \(\text{mg/dL} \times 0.0555 = \text{mmol/L}\).


Hypoglycemia in diabetes

- The limiting factor in the management of diabetes
- Fear of hypoglycemia prevents patients from obtaining the reduction in microvascular risk associated with good glycemic control
- Impact can range from inconvenience, to coma, seizures, and death
How common is hypoglycemia in clinical practice?

- Hypoglycemia Assessment Tool (HAT) study led by Kamlesh Khunti in UK
- Global study of 27,585 insulin treated patients from 24 countries
- Online tool designed to collect patient reported information about HG frequency and severity both in retrospect and prospectively


Data collected prospectively over 1 month

**Type 1 Diabetes**
- 14% had severe HG
- 83% had any HG

**Type 2 Diabetes**
- 9% had severe HG
- 47% had any HG

Verify this citation is correct. Previous citation was "Diabetes Research and Clinical Practice 11(2015): 229."
Editor, 2/11/2018
T1D Exchange Clinic Registry

- 4973 patients (26–93 yrs of age, >2 yrs from dx) from 70 US-based endocrine practices provided information about severe hypoglycemia (SH)
- 11.8% reported SH (coma or seizure) in previous 12 months
- Multivariate analysis found significant relationships between SH and lower educational levels, lower household income, and absence of private insurance

Weinstock et al. JCEM 2013.
II. What are the risks of hypoglycemia and how might it lead to adverse outcomes?

Recurrent hypoglycemia leads to impaired awareness of hypoglycemia

- Shift in glucose threshold that elicits counterregulatory response (i.e. lower and lower blood sugars required to elicit response)
- Reduction in magnitude of counterregulatory hormone response
- Neuroglycopenia often first symptom of hypoglycemia
- Estimated to occur in 20–25% of patients with T1D and increase risk of severe hypoglycemia by 3-6x (Geddes. Diab Med 2008)
Hypoglycemia is associated with increased risk of mortality

- In clinical trials: history of severe hypoglycemia nearly doubled risk of mortality in both ACCORD and ADVANCE

- In observational studies: Prospective clinical based study of 1000+ showed that those those with history of severe hypoglycemia at baseline had OR for mortality of 3.38 at 5 years (95% CI: 1.55-7.38, p <0.005) (McCoy DC 2012)

Confirmation of hypoglycemia in the "dead-in-bed" syndrome, as captured by a retrospective continuous glucose monitoring system

Robert Tanenberg, Christopher Newton, Almond Drake, III
Endocr Pract. 2010 Mar-Apr;16(2):244-8.

- 23-year-old man with 12 yrs of T1D
- Complicated by frequent and severe hypoglycemia
- Wore pump and CGM
- Found dead in undisturbed one morning
How might hypoglycemia cause death?

- Acute hypoglycemia increases QTC interval (Robinson et al. Diabetes 2003)
- Acute hypoglycemia increases platelet activation (Joy et al. Diabetes 2010)
- Acute hypoglycemia decreases systemic fibrinolytic balance by increasing in PAI-1 (Joy et al. Diabetes 2010)

Confirming the Bidirectional Nature of the Association Between Severe Hypoglycemic and Cardiovascular Events in Type 2 Diabetes: Insights From EXSCEL

- Post hoc analysis of 14,572 participants of Exenatide Study Cardiovascular Event Lowering study
- Subjects were adults with type 2 diabetes with baseline A1c 6.5-10%. 70% had previous CVD events
- SHE defined as episode where subject was incapacitated and required the assistance of another to treat low sugar and data collected at each visit
- Examined time dependent relationships between severe hypoglycemia and subsequent major cardiac events and between non fatal CV events and subsequent severe hypoglycemia
Bidirectional association between SHE and CVD.

- Adjusted for age, sex, ethnicity, weight smoking, treatment assignment
- Association between SHE and subsequent CVD
- Adjusted for age, gender, ethnicity, A1c, comorbidities, meds, insulin use
- Association between nonfatal CVD and subsequent SHE
Hypoglycemia and cognitive function

- Hypoglycemia was not associated with accelerating cognitive decline in DCCT cohort (Jacobson et al. NEJM 2007)
- Experimentally induced nocturnal hypoglycemia reduced sleep associated consolidation of declarative memory in adults with and without diabetes (Jauch-Chara et al. Diabetes Care 2007)

Effects of glycemia on cognition in school age children

- Examined 61 children with mean age of 9 yrs
- Children did tests on PDA just prior to pre-meal glucose testing for 4-6 weeks

Gonder-Frederick et al. Diabetes Care 2009
Hypoglycemia and dementia risk on older patients with type 2 DM  
(Whitmer et al. JAMA 2009)

• Study included 16,667 individuals in Kaiser diabetes registry who were >55 years of age on 1/1/2003 with diagnosis of T2DM and no diagnosis of dementia or mild cognitive impairment

• Examined relationship between hypoglycemia episodes required hospitalization or ED visit between 1/1/1980-12/31/2002 and 1822 incident cases of dementia identified after 1/1/2003

### Table 3. Hypoglycemia and Risk of Incident Dementia

<table>
<thead>
<tr>
<th>No. of Hypoglycemic Episodes</th>
<th>No. of Dementia Cases</th>
<th>Adjusted for Age (as Time Scale), BMI, Race/Ethnicity, Education, Sex, and Duration of Diabetes</th>
<th>Additionally Adjusted for Comorbidities</th>
<th>Additionally Adjusted for 7-Year Mean HbA1c Level, Diabetes Treatment, and Years of Insulin Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or more</td>
<td>250</td>
<td>1.08 (1.47-1.93)</td>
<td>1.48 (1.29-1.70)</td>
<td>1.44 (1.25-1.66)</td>
</tr>
<tr>
<td>1</td>
<td>150</td>
<td>1.46 (1.23-1.72)</td>
<td>1.29 (1.10-1.59)</td>
<td>1.26 (1.10-1.49)</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>2.15 (1.84-2.81)</td>
<td>1.86 (1.42-2.43)</td>
<td>1.80 (1.37-2.36)</td>
</tr>
<tr>
<td>3 or more</td>
<td>43</td>
<td>2.80 (1.78-3.76)</td>
<td>2.10 (1.48-2.73)</td>
<td>1.94 (1.42-2.64)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin.

a Analyzes combined using Cox proportional hazard models.

b The 1 or more group was compared to 0 and 1, 2, and 3 or more groups were simultaneously compared to 0.

c Adjustment made using a comorbidity composite scale.
Examined relationship between score on DSST and hypoglycemia risk in 2956 ACCORD-MIND participants over 20 months
The Dangers and Fears of Hypoglycemia

Hypoglycemia has enormous physical, financial, and emotional burdens for patients and practices

- Best studied in type 1 diabetes where fear can result in increased vigilance and immobilizing distress (Martin-Nemeth, J Diab Comp 2015)
- Patients with greatest fear of hypoglycemia usually have history of severe hypoglycemia and are more anxious than patients with a lower fear of hypoglycemia
- Fear of hypoglycemia negatively impacts quality of life measures
- Fear is greatest at night and may impact sleep
- In Japan 27% of type 2 DM surveyed had high measures of fear of hypoglycemia (Sakane, J Diab Invest. 2015)

Costs of hypoglycemia

- Between 2007 -2011, nearly 100,000 persons with diabetes were treated in emergency rooms for hypoglycemia each year at a cost exceeding $100 million per year (Geller et al. JAMA Intern Med. 2014)
III. How can we help patients avoid/treat hypoglycemia and hypoglycemia associated adverse events?

Conventional risk factors for hypoglycemia – relative or absolute insulin excess
- Insulin or insulin secretagogue doses are excessive, ill-timed, or of the wrong type
- Exogenous glucose delivery is decreased (e.g. after missed meals and during the overnight fast)
- Glucose utilization is increased (e.g. during exercise)
- Endogenous glucose production is decreased (e.g. after alcohol indigestion)
- Sensitivity to insulin is increased (e.g. after weight loss, an increase in regular exercise or improved glycemic control, and in the middle of the night)
- Insulin clearance is decreased (e.g. renal failure)

Cryer PE et al. J Clin Endo Metab 2009;94:709-728

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**Treatment for hypoglycemia**

1. Recognize symptoms so they can be treated as soon as they occur
2. Confirm the need for treatment if possible (blood glucose <3.9 mmol/L (70 mg/dL) is the alert value)
3. Treat with 15 g fast-acting carbohydrate to relieve symptoms
4. Retest in 15 minutes to ensure blood glucose > 4.0 mmol/L (72 mg/dL) and re-treat (see above) if needed
5. Eat a long-acting carbohydrate to prevent recurrence of symptoms

Glucagon should be used to treat hypoglycemia when someone is unconscious
Steps to reduce hypoglycemia

- Re-evaluate glycemic goals
- Educate patient on when to anticipate, how to recognize hypoglycemia, how to avoid hypoglycemia, and appropriate treatment of hypoglycemia
- Review insulin/secretagogue regimen, especially with respect to timing of administration and selection of dose

Evidence based methods to reduce hypoglycemia in patients with diabetes

- Structured education program like 5 day DAFNE (Dose Adjusted for Normal Eating) course in UK (Hopkins. DC 2012)
- Threshold suspend (Bergenstal. NEJM 2013) or hybrid closed loop (Bergenstal. JAMA 2016) pumps
- Addition of continuous glucose monitor to existing regimen (Beck. JAMA 2017)
- Use degludec instead of lantus U100 as basal insulin (Lane. JAMA 2017)
- Islet transplantation (Rickels. JCEM 2016)
Technology to reduce hypoglycemia

- Hybrid closed loop system
- Automates rate of basal infusion
- Requires manual food and correction boluses

124 T1DM adults with history of pump use

Study consisted of 2 week run in period and 3 month treatment period where the first 6 days were used to collect data for the algorithm

System adjusted algorithm every midnight based on data collected

System was in closed loop mode for 87.2% of study period

A1c changed from 7.4% to 6.9%
Randomized trial done 2014-16 in 24 endocrine practices in US

Tested the impact of CGM use vs usual care on change in A1c at 24 weeks.

Enrolled adults with T1D using MDI with A1c 7.5-9.9%
Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial


**Table 3. Continuous Glucose Monitoring Metrics**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Baseline</th>
<th>12 and 24 Weeks (n=102)</th>
<th>Mean Adjusted Difference (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minutes per day &lt;70 mg/dL</td>
<td>68 (36 to 70)</td>
<td>83 (36 to 133)</td>
<td>15 (4 to 22)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Minutes per day &gt;180 mg/dL</td>
<td>101 (30 to 160)</td>
<td>101 (12 to 204)</td>
<td>10 (2 to 12)</td>
<td>.005</td>
</tr>
<tr>
<td>Minutes per day &gt;330 mg/dL</td>
<td>126 (60 to 264)</td>
<td>126 (72 to 264)</td>
<td>0 (6 to 22)</td>
<td>.36</td>
</tr>
<tr>
<td>Hypoglycemic episodes (med/10 h)</td>
<td>157 (27)</td>
<td>157 (39)</td>
<td>0 (2 to 14)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

**Notes:**
- CGM = continuous glucose monitoring
- CI = confidence interval
- p < 0.05 was considered significant to account for multiple comparisons (with Bonferroni correction for the metrics that are approximately normally distributed).
Reducing Hypoglycemia in the Real World: A Retrospective Analysis of Predictive Low-Glucose Suspend Technology in an Ambulatory Insulin-Dependent Cohort

Lars Müller, PhD,1 Steph Habif, EdD, MS,2 Scott Leas, BA,2 and Eliah Aronoff-Spencer, MD, PhD3

- Retrospective analysis of low glucose suspend (Tandem IQ) users who uploaded 21+ days of data between 8/31/18-3/14/19
- Group A were experienced pump users who had CGM data before and after starting low glucose suspend pump
- Group B were new pump users without CGM data before low glucose suspend pump was started

<table>
<thead>
<tr>
<th>TABLE 1. COHORT DEMOGRAPHICS</th>
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<tr>
<td></td>
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<td></td>
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<tr>
<td>n</td>
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<tr>
<td>Mean days of use</td>
</tr>
<tr>
<td>Age, mean, (SD)</td>
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<tr>
<td>Age, range</td>
</tr>
<tr>
<td>Under 18, n (%)</td>
</tr>
<tr>
<td>18–60, n (%)</td>
</tr>
<tr>
<td>Over 60, n (%)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
</tr>
<tr>
<td>Type 1, n (%)</td>
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<tr>
<td>Type 2, n (%)</td>
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</tbody>
</table>

SD, standard deviation.
Use of LGS pump significantly reduced time < 70 mg/dl (3.9 mmol/l) and number of events with BG < 54 mg/dl (3 mmol/l)

### Double blind randomized, cross over non-inferiority trial done at 84 US and 6 Polish centers 2014-2016 designed to examine effect of treatment of hypoglycemia in high risk patients

- Subjects had a 16 weeks titration phase and a 16 weeks maintenance phase for each treatment
- Randomized 1:1 to glargine vs degludec and 1:1 to morning or evening dosing within each treatment sequence
Inez P.

78 year old woman with 30 year history of type 2 DM. Brought in by her daughter because of concerns about hypoglycemia.

Current meds include glyburide 5 mg bid, metformin 2000 mg qd, sitagliptin 100 mg qd.

HbA1c was 7.2 % at her last visit with her doctor 3 mo ago
What should she do to avoid future episodes of severe hypoglycemia?

Food related strategies
- Eat more consistently with respect to timing and portion sizes
- Avoid high carb snacks

Medication related strategies
- Stop the glyburide and replace with insulin. Would start with long acting analog if she agreed to eat more consistently or consider developing a basal/bolus regimen
- Stop the glyburide and change the HbA1c target

Activity related strategies
- Check BG before and after exercise. Eat if BG < 100
Conclusions

• Hypoglycemia is frequent in patients with diabetes and can be fatal
• Recurrent hypoglycemia leads to impaired awareness of hypoglycemia, which can further increase risk of having SH
• SH is associated with increased risk for mortality and incident CVD
• Clinicians must make efforts to reduce hypoglycemia while maintaining optimal control