Hypoglycemia in 2016: Detection, Consequences and Prevention

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3:35-4:45 pm

Description given

• Title: Hypoglycemia in 2016: Detection, Consequences and Prevention.
• This talk examines insights from hypoglycemia studies showing how both the young and elderly are particularly at risk of severe hypoglycemia.
• Diagnostically hypoglycemia may be elusive, but clues are illustrated, such as patterns of glycemia and insulin use that underlie hypoglycemia risk.
• Reversible adaptations like impaired hypoglycemia awareness prevent safe achievement of tight glucose control.
• Hypoglycemia’s dangers are caused mostly by its impact on the brain and heart.
• Specific tactics to improve the safety of insulin use are presented.
• Hypoglycemia prevention is critical. We will discuss how new technologies (pumps, CGM, and artificial pancreas) may help reduce hypoglycemia risk.

Disclosures

• Consultant to Sanofi regarding new insulin studies
• Endocrine Society VP Clinical Science- views presented do not necessarily represent those of the Endocrine Society

Learning Objectives

• To understand and be able to describe important aspects of the epidemiology of hypoglycemia
• To be able to describe issues related to the dangers associated with hypoglycemia including heart and brain
• To describe patterns of glycemia and insulin use underlying hypoglycemia and strategies and technologies to prevent hypoglycemia

Outline

• Overview
  — Hypoglycemia is common and feared.
  — Hypoglycemia leads to Impaired Hypoglycemia Awareness (IHA) and Hypoglycemia Associated Autonomic Failure (HAAF)
• Hypoglycemia is dangerous
  — It can cause brain dysfunction and damage
  — It may lead to arrhythmias and death
  — New data suggest hypoglycemia may pro-atherogenic
• Recognition
  — Half of severe hypoglycemia is nocturnal and under diagnosed
  — Detection is critical to prevention, but remains problematic.
  — Patterns of glycemia or insulin use that are recognizable may precede it and can be altered to reduce risk.
• Remedies
  — Adjustment of insulin and the tactics to adjust insulin may reduce its frequency.
  — New technologies may aid in prevention of hypoglycemia.
ADA/Endocrine Society
Hypoglycemia: Definition

- All episodes of an abnormally low plasma glucose concentration that expose an individual with diabetes to potential harm
  - A single threshold plasma glucose value cannot define hypoglycemia
- Glycemic thresholds for symptoms shift to:
  - Lower plasma glucose concentrations after recent antecedent hypoglycemia
  - Higher plasma glucose concentrations in patients with poorly controlled diabetes and infrequent hypoglycemia
- Alert value for an individual with diabetes at risk for hypoglycemia (treated with insulin, a sulfonylurea, or glinide):
  - Blood glucose ≤70 mg/dL (≤3.9 mmol/L)


Why a Blood Glucose (BG) of ≤70 mg/dl to Define Hypoglycemia?

- Approximates the lower limit of normal postabsorptive plasma glucose concentrations
  - Glycemia thresholds for activation of glucose counterregulatory systems in those without diabetes
  - The upper limit of plasma glucose levels reported to reduce counterregulatory responses to subsequent hypoglycemia
- Higher than the glycemic threshold for symptoms for individuals without diabetes or those with well-controlled diabetes
  - Allows time to prevent a clinical hypoglycemic episode
  - Provides a margin of safety because of the limited accuracy of some monitoring devices at low BG levels


ADA/Endocrine Society Classification of Hypoglycemia in Diabetes

- Severe Hypoglycemia: event requiring assistance of another to take corrective action, such as actively administering carbohydrates, glucagon, or take other corrective actions
- Documented Symptomatic Hypoglycemia: event during which typical symptoms of hypoglycemia are accompanied by a measured blood glucose (BG) ≤70 mg/dl (3.9 mmol/L)
- Asymptomatic Hypoglycemia: event not accompanied by typical symptoms but with a measured BG ≤70 mg/dl (3.9 mmol/L)
- Probable Symptomatic Hypoglycemia: event during which symptoms typical of hypoglycemia are not accompanied by a BG but that was presumably caused by a value ≤70 mg/dl (3.9 mmol/L)
- Pseudo-hypoglycemia: event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured BG concentration ≤70 mg/dl (3.9 mmol/L) but is approaching that level


Hypoglycemia: How common – how worrisome?

- Multiple studies show a high frequency in type 1 diabetes—children and adults
- In the DCCT half the severe hypos were during sleep
- Precise estimation is hard—often asymptomatic
- In T1DM, studies show avg. 36% have night BG of < 54 mg/dl (long observation CGM shows most): avg. 32 % ≤ 45; avg 17% ≤ 36 mg/dl
- 62% avg. (9-100%) are without symptoms (large confidence intervals)
- Recent studies show fewer severe hypos
- CDC—Hypoglycemia: In 2011, about 282,000 emergency room visits for adults aged 18 years or older had hypoglycemia a condition that occurs when one’s blood glucose is lower than normal, usually less than 70 mg/dL.

Hypoglycemia in Clinical Diabetes, 3rd edition 2014 p 98 table 5.1
Estimated Rates of Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009

Data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (2007 through 2009) to estimate the frequency and rates of hospitalization after emergency department visits for adverse drug events in older.


Severe hypoglycemia is a SERIOUS and costly problem in both type 1 and type 2 diabetes in the US

- 80,993 annual hypoglycemia hospitalizations in T1D in 2009
- 466,442 annual hypoglycemia hospitalizations in T2D in 2009

- $417,541 per hospitalization
- $376,654 per hospitalization

- ~$368 million annually in T1D
- ~$4.4 billion annually in T2D


National Surveilance of Hypoglycemia

- National Electronic Injury Surveillance System (NEISS) – Cooperative Adverse Drug Event Surveillance (CADES) project.
  - 63 hospitals
  - Ascertainment of insulin-related hypoglycemia and errors.
  - Adjudication of preceding events, physician diagnoses, clinical and laboratory testing, treatment administered, discharge diagnosis.

- Nationwide Emergency Department Sample (NEISS):
  - 20% Stratified sample of EDs affiliated with community hospitals.
  - Largest payer ED database in the U.S.
  - Validated algorithm based on diagnostic codes for hypoglycemia as primary cause of admission.

- Health and Retirement Survey (HRS):
  - National probability sample of adults age > 50.
  - Self-reported frequency of hypoglycemic symptoms.

Age-adjusted Emergency Department Visit Rates for Hypoglycemia Crisis Among Adults with Diabetes, United States 2006-2011

*Data source: Nationwide Emergency Department Sample, NHIS, National Health Interview Survey, CDC, 2010*.

Background Context

- Large reductions in rates of diabetes-related complications over the past 15 years (Gregg et al., 2014).
  - MI, Stroke, Amputation, ESRD.
  - Hyperglycemic death and hyperglycemic crisis.

- Reductions in CVD risk factors, A1c levels, processes of care, over the past 10 years (Ali et al., 2012).

- Rates, trends, and effects of hypoglycemia are less clear.

Edward Gregg, CDC data

Emergency Department Visit Rates for Hypoglycemia and Hyperglycemic Crisis in the United States, 2011

*Data source: National Emergency Department Sample
Age-adjusted to diabetic population in 2010 based on NHIS using age groups 18-44 years, 45-64 years, 65-74 years, and 75+ years*
Insulin hypoglycemia and errors (IHE) lead to ED visits and admissions
- 97,648 (95%CI, 64,410-130,887) ED visits for IHEs occurred annually
- Almost one-third (29.3%; 95%CI, 21.8%-36.8%) resulted in hospitalization.
- Severe neurologic sequelae were documented in an estimated 60.6% (95% CI, 51.3%-69.9%) of ED visits for IHEs, and blood glucose levels of 50 mg/dL or less were recorded in more than half of cases (53.4%).
- Insulin-treated patients 80 years or older were more than twice as likely to visit the ED (rate ratio, 2.5; 95%CI, 1.5-4.3) and nearly 5 times as likely to be subsequently hospitalized (rate ratio, 4.9; 95%CI, 2.6-9.1) for IHEs than those 45 to 64 years.
- The most commonly identified IHE precipitants were:
  - reduced food intake 45.9% (38.2-53.6)
  - administration of the wrong insulin product. 22.1% (17.2-26.9)

Altered recognition and counterregulation with night hypos
- Prolonged overnight lows do not provoke adequate epinephrine counterregulation and poor counterregulation generally (glucagon already lost)
- Those undergoing hypoglycemia do not necessarily wake in a timely fashion
- Inadequate detection may further compromise counterregulation and lead to HAAF syndrome or IHA—a vicious cycle

Detection of nighttime lows
- Routine monitoring and reliance on symptoms in type 1 DM is not trustworthy
- Bed partners may note restlessness, altered breathing patterns, sweating, pet dogs may detect lows
- If symptoms occur they are often delayed by 1-2 hours
- CGM studies detect apparent lows frequently but the accuracy is estimated to be as low as ~50% (misdiagnosing lows and underestimating them as well)
- CGM “Alarm fatigue” lead some to turn off or leave in next room
- Many patients treat without testing and may not appear on routine meters or pump downloads

Intensifying Rx T2DM & Hypoglycemia

Failure of epinephrine response to hypoglycemia sleep vs. awake T1DM
- Jones TW et al 1998 NEJM 338;1657-1662
- Banarer S & Cryer PE 2003; Diabetes 52: 1195-1203

Sleep and hypoglycemia awareness

**Time asleep similar early night**
**Progressive lack of arousal**

**Prediction of nocturnal hypos (CGM)**

**Factors contributing to risk of nighttime hypoglycemia**
- Basal insulin overtreatment
- Long period between meals
- Inconsistent injection absorption → nocturnal hyperinsulinemia
- Delayed effects of exercise from the prior day
- Bedtime correction dosing & overcorrection (targets, ISF)
- Enhanced insulin sensitivity overnight
- Poor epinephrine counterregulation with sleep
- Impaired hypoglycemia awareness at night (sleep HAAF)
- Impairment of counterregulation & symptoms in supine posture
- Repeated nocturnal hypoglycemia sets up the HAAF syndrome making symptom detection of overnight lows difficult for patients and care givers.

**Adverse impact of nocturnal hypoglycemia**
- Impaired counterregulation (sleep HAAF) with more rapid descent into more severe hypoglycemia
- Impaired recognition—60s unrecognized twice a week may lead to full blown HAAF syndrome
- Impaired sleep quality, daytime drowsiness, mood changes
- Risk for nocturnal falls
- Cognitive dysfunction—especially children with seizures
- Neurological dysfunction—temporary and rarely permanent neurological impairment
- Lengthening of Q-T interval—predispose to arrhythmias
- Possible causative agent in “dead in bed” syndrome

**Remedies for insulin hypoglycemia overnight**
- Caffeine has been shown to improve recognition of lows but appears to decrease cerebral blood flow
- Terbutaline (beta agonist) when it works it tends to result in hyperglycemia
- Snacks (including alanine, uncooked corn starch) are notoriously insufficient in protecting against overnight lows but may be used in susceptible individuals
- If hypoglycemia is occurring usually the insulin dose needs to be reduced! (most common is basal insulin)
- Severe imbalance of basal/bolus in either direction increases the risk of hypoglycemia

**Impaired Hypoglycemia awareness: Clinical Issues & Solutions**
- Change from Sliding Scale Insulin to Pattern Management
- Avoid fixed ratio insulins
- Earlier use of more complex (physiological) regimens
- Use of analog insulins (LisPro, Aspart, Glulisine-future use of extra rapid analogs?) for meals combined with CHO counting, and for basal insulin (Glargine, Detemir, Degludec, U-300 glargine); increased use of insulin pumps
- Adequate and prompt hypoglycemia treatment– the 15/15 rule, not food, have glucagon & training
- Strict avoidance of hypoglycemia-days, weeks, months
- Specific interventions based on understanding pathophysiology?
Brain Areas Susceptible/Spared Damage from Hypoglycemia

- Cortex
- Caudate/Putamen
- Hippocampus
- Cerebellum especially Purkinje cells
- Globus Pallidus
- White matter
- Brain stem
- Spinal cord

Hypoglycemia and Developing Brain

- Neonatal hypoglycemia associated with low IQ (Pildes et al, 1974)
- Diabetes before age 5 associated with a 10 pt lower IQ (Ack et al. 1961)
- Diabetic adolescents have lower verbal intelligence, visuomotor coordination (Ryan et al. 1984)
- Onset of IDDM before 4 associated with lower IQ performance than siblings (Rovet 1987,1988)

Neurologic Manifestations of Hypoglycemia

- Decortication
- Decerebration
- Hemiplegia (transient)
- Choreaathetosis
- Ataxia
- Convulsion (general or focal)
- Locked in Syndrome
- Amnesia
- Stroke
- Cortical Atrophy
- Peripheral neuropathy
- Other focal abnormalities (pons, visual pathways)

ACCORD and Hypoglycemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive Therapy (N=5128)</th>
<th>Standard Therapy (N=5123)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia, no. (%)</td>
<td>538 (10.5)</td>
<td>179 (3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Requiring medical assistance</td>
<td>538 (10.5)</td>
<td>179 (3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Requiring any assistance</td>
<td>830 (16.2)</td>
<td>261 (5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fainting or near-fainting heart failure, no. (%)</td>
<td>132 (3.0)</td>
<td>134 (2.4)</td>
<td>0.70</td>
</tr>
<tr>
<td>Motor vehicle accident in which patient was driver, no. (%)</td>
<td>9/5503 (0.2)</td>
<td>14/5518 (0.3)</td>
<td>0.40</td>
</tr>
<tr>
<td>Any nonhypoglycemic serious adverse event, no. (%)</td>
<td>113 (2.2)</td>
<td>82 (1.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Fluid retention, no./total no. (%)†</td>
<td>384/5053 (7.1)</td>
<td>337/5054 (6.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Calculated with the use of Fisher’s exact test or a two-sample t-test.
†Of the patients with fluid retention, 89% had pretibial edema or ankle swelling, 30% had shortness of breath, 12% had chest pain, 9% had orthopnea, and 12% had bilateral pulmonary rales.

No clear evidence that hypoglycemia explains the 22% increased mortality seen in the ACCORD trial.
No clear exoneration of hypoglycemia either.


Proportion of participants with at least one episode of hypoglycemia requiring medical assistance: Accord Trial


Relationship Between Hypoglycemia and Mortality for Patients with Type 2 Diabetes

Relationship Between Severe Hypoglycemia and Adverse Events: ADVANCE


Severe Hypoglycemia May Cause a Prolongation of QT Interval in Patients With Type 2 Diabetes

- Significant prolongation of QT interval after hypoglycemic clamps
  - Increased risk of arrhythmias

Hypoglycemia May Be Associated With Increased Rates of Chest Pain and ECG Abnormalities

Hypoglycemia and Cardiovascular risk
VADT: serious hypoglycemia and atherosclerosis progression

A. Saremi, G.D. Bahn, P. D. Reaven, on behalf of the Veterans Affairs Diabetes Trial (VADT)

Diabetes Care published online January 19, 2016

Traditional risk factors better

Fig. 3 Glucose staircase with overnight cliff: signature of basal→meal imbalance

Fig. 7 Treat-to-Target Trial: Timing and Frequency of Hypoglycemia

Table 3—Baseline characteristics of participants by serious hypoglycemia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No ≤ 0 5%</th>
<th>No ≤ 0 1%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
<td>104 ± 20</td>
<td>101 ± 20</td>
<td>0.99</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>140 ± 50</td>
<td>135 ± 50</td>
<td>0.99</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>50 ± 10</td>
<td>48 ± 10</td>
<td>0.99</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>90 ± 10</td>
<td>89 ± 10</td>
<td>0.99</td>
</tr>
<tr>
<td>systolic blood pressure</td>
<td>120 ± 10</td>
<td>120 ± 10</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Hypoglycemia by Time of Day

Hypoglycemia episodes

Insulin levels throughout the day

Basal Overdose

Bolus Underdose

Progressive daytime increases in basal insulin rate of insulin pump create a dangerous basal insulin excess that may cause hypoglycemia

Pumps: Insulin staircase & cliff

Adapted from McCullough, Hypoglycemia, Therapy for diabetes and related disorders, 6th edition, 2014 American Diabetes Association, Umpierrez G (editor)
Low blood glucose index & BG variability in relation to severe hypos

Kovatchev BP et al. J Clin Endocrinol Metab 2000; 85:4287-4292

Risk starts with near miss
Worse highs & lows!
Hypos create instability
As do hyperglycemia

Risk starts with near miss
Worse highs & lows!
Hypos create instability
As do hyperglycemia

Solutions for nocturnal hypos

- Many drugs and nutrition interventions have been used for treatment of impaired hypoglycemia awareness
- Their success is modest and inconsistent
- Caffeine, terbutaline, amino acid cocktails, bedtime snacks, uncooked cornstarch are among the many
- If they work, often they cause too much hyperglycemia.
- Because they are not very practical they are not often used reliably

Does RT-CGM reduce hypo risk?

- CGM used with pumps reduces biochemical hypoglycemia or does not increase the risk despite lower average BG.
- The benefit depends on learning how to use this tool
- It must be worn most of the time to achieve benefit
- CGM is clearly not for everyone but it is a very useful tool in motivated and sophisticated users
- The recent DiaMonD study in people with type 1 DM using CGM and basal bolus therapy there was improvement in overall control and a reduction in the risk of hypoglycemia. This occurred in young and older subjects, with or without high education level. (ADA 2016)

Sensor augmented pump with low glucose insulin suspension

<table>
<thead>
<tr>
<th>Table 1: Baseline Characteristics of Study Participants</th>
<th>No. (%) of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study focus—those with IHA</td>
<td></td>
</tr>
<tr>
<td>Insulin Pump (n=44)</td>
<td></td>
</tr>
<tr>
<td>Sensor-Augmented Pump (n=46)</td>
<td></td>
</tr>
<tr>
<td>age, mean (SD) (range), y</td>
<td>19.7 (12.95) (1.48-46.7)</td>
</tr>
<tr>
<td>female</td>
<td>28 (63.3)</td>
</tr>
<tr>
<td>age groups, y</td>
<td>2 (4.5)</td>
</tr>
<tr>
<td>7–12</td>
<td>14 (29.5)</td>
</tr>
<tr>
<td>13–20</td>
<td>16 (36.4)</td>
</tr>
<tr>
<td>21–50</td>
<td>15 (34.0)</td>
</tr>
<tr>
<td>Duration of diabetes, mean (SD), y</td>
<td>12.3 (16.0)</td>
</tr>
<tr>
<td>Duration of pump therapy, mean (SD), y</td>
<td>4.4 (3.4)</td>
</tr>
<tr>
<td>Insulin/kg, mean (SD), kg/l</td>
<td>8.76 (6.23)</td>
</tr>
<tr>
<td>Hypoglycemia awareness score, mean (SD)</td>
<td>6.4 (1.5)</td>
</tr>
</tbody>
</table>

TT Ly et al. JAMA. 2013;310(12):1144-1147
Clinical outcomes

Table 2. Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Insulin Pump (n = 45)</th>
<th>Sensor-Augmented Pump With Low Glucose Alarm (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious and Moderate Hypos</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20.4% (12.8% to 30.1%)</td>
<td>12.4% (11.1% to 15.3%)</td>
</tr>
<tr>
<td>No. of events (total no. of patients)</td>
<td>24 (45)</td>
<td>17% (45)</td>
</tr>
<tr>
<td>End point</td>
<td>6.0% (6.8% to 9.3%)</td>
<td>28.4% (20.9% to 39.0%)</td>
</tr>
<tr>
<td>No. of events (total no. of patients)</td>
<td>12 (45)</td>
<td>35 (42)</td>
</tr>
<tr>
<td>Incidence rate per 100 patient-months (95% CI)</td>
<td>34.2 (22.0% to 55.3%)</td>
<td>9.5 (3.3% to 17.0%)</td>
</tr>
<tr>
<td>Patients randomized</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>Incidence rate per 100 patient-months (95% CI)</td>
<td>3.6% (3.7% to 6.3%)</td>
<td>0.5%</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Questions about this study

- 2 outliers in one group with severe hypos
- Absent those 2 subjects moderate hypos not significantly different although severe hypos were.
- Questions about adequacy of methods
- Important is that this is the only study to seek out IAH patients

Cite editorial and Heinemann et al critique.

Threshold Low glucose suspend pump (ASPIRE)

Figure 2. Primary and Secondary End Points. A, As shown in Figure A, the mean (±SD) changes in cardiopulmonary bypass blood glucose levels during the study phases (the primary safety end point) were similar in the threshold suspend and control groups (−0.66±4.74 vs. −0.68±4.85, diurnal, −0.06±0.72, nocturnal, −0.79±2.72 vs. −1.1±2.2). As shown in Panel B, the mean area under the curve (AUC) for nocturnal hypoglycemic events during the study phases (the primary efficacy end point) was 37.2% lower in the threshold suspend group than in the control group (3.9±5.1 vs. 6.3±7.4; P=0.05). The percentage of serum glucose values that were less than 60 mg/dL was higher in the threshold suspend group than in the control group, with values during nighttime hours (6:00 PM to 7:00 AM) or during daytime and nighttime hours combined (1:30 PM to 7:00 AM). The F value was less than 0.001 for each range in the panel. (See Table S2 in the Supplementary Appendix for the percentages of serum glucose values in all ranges.) B, Pump was able to low glucose suspend and reduce nocturnal hypoglycemia.

Overnight control is safer and as well controlled

Artificial (Bionic) Pancreas

- Model predictive control with new predicted low glucose suspend pumps works with several different algorithms (not yet FDA approved)
- Several groups in Boston, New Haven, Charlottesville, Cambridge England have shown better control and reduced hypoglycemia with differing algorithms and single or dual hormone approaches.
- Commercial applications are expected within the next few years on a number of these.

Questions?

Thank you.