Hypoglycemia in Diabetes: Epidemiology and Clinical Impact

Outline
I. What is hypoglycemia and impaired awareness of hypoglycemia?
II. How common is it in patients with diabetes?
III. How do hypoglycemia and impaired awareness of hypoglycemia impact patients with diabetes?

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

Disclosure to Participants
Consultant: Locemia, Novo Nordisk, Lilly, Zucera
Research Support: NIH, JDRF, Lilly
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I. What is hypoglycemia and impaired awareness of hypoglycemia?
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Impaired awareness of hypoglycemia

- Recurrent hypoglycemia reduces the threshold at which the counterregulatory response is elicited; first symptom may be neuroglycopenia that requires assistance of another to treat
- Occurs in up to 25% of type 1 patients
- Occurs in 9.8% of insulin treated type 2 patients (Schopman, Diab Res Clin Prac 2010)
- Patients over 65 years often do not have typical symptoms of hypoglycemia – lightheadedness and unsteadiness not tremor and palpitations (Jay, Diab Med 2004)

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
- On line 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


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Dead in bed syndrome

- 23 year old man with 12 yrs of T1DM
- Complicated by frequent and severe hypoglycemia
- Wore pump and CGM
- Found dead in undisturbed one morning

Tanenberg et al. Endocr Pract. 2010;16(No. 2) 245
Note to layout: In the legend, please change "unaware" to "awareness impaired"
Gabrielle, 11/17/2015

while this is fine, the effect of impaired awareness on rate of severe episodes is much more important --
6 fold increase:
Gold AE, MacLeod KM, Frier BM: Frequency of severe hypoglycemia in patients with type I (insulin
dependent) diabetes with impaired awareness of hypoglycemia. Diabetes Care 17:697-703, 1994
Simon Heller, 11/27/2015

DEAR REVIEWERS: Kindly provide specific direction: keep this slide as is or replace it with data from the
Gold study?
Gabrielle, 11/27/2015

could slides showing impact on BG during the day and on SH both be shown? It is important
Elizabeth Seaquist, 1/21/2016
Mortality and hypoglycemia in type 1 diabetes

- Cause of death in 2-4% of people with type 1 diabetes (Laing et al. Diabetic Medicine 1999)
- Hypothesized to be cause of death in bed syndrome described by Tattersall and Gill in 1991 where person < 40 years of age with 0-25 years of type 1 diabetes is found dead in undisturbed bed

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 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)

Is hypoglycemia the cause of death in patients with history of severe hypoglycemia?

ADVANCE Trial: Relationship between severe HG and adverse events

- Longitudinal cohort study of 9173 DM patients without CAD before 1/1/2006 in academic primary care practice network
- 3% (285) had hypoglycemic events before 1/1/2006 identified by ICD-9 codes for ED, inpatient and outpatient visits
- Measured incident CAD through 6/30/2012

**Table 1. Baseline Characteristics Stratified by Hypoglycemia**

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>No Hypoglycemia</th>
<th>Hypoglycemia</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;50 yrs, n (%)</td>
<td>738 (57.9)</td>
<td>141 (57.7)</td>
<td>0.83</td>
</tr>
<tr>
<td>Age ≥50 yrs, n (%)</td>
<td>582 (42.1)</td>
<td>81 (42.3)</td>
<td>0.83</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>801 (60.5)</td>
<td>162 (69.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>65 (4.9)</td>
<td>60 (25.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Nonvisual symptoms, n (%)</td>
<td>79 (5.9)</td>
<td>28 (11.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Visual symptoms, n (%)</td>
<td>34 (2.6)</td>
<td>54 (22.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospitalization, n (%)</td>
<td>223 (16.9)</td>
<td>31 (12.7)</td>
<td>0.32</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>25 (1.9)</td>
<td>4 (1.7)</td>
<td>0.82</td>
</tr>
<tr>
<td>Cardiovascular death, n%</td>
<td>5.9 (4.9)</td>
<td>11.6 (5.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>11.6 (5.0)</td>
<td>11.6 (5.0)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

**Figure A. Cumulative Hazards Ratios**

- 8/4/2017
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

Poor Cognitive Function and Risk of Severe Hypoglycemia in Type 2 Diabetes

Examined relationship between score on DSST and hypoglycemia risk in 2956 ACCORD-MIND participants over 20 months

Digital Symbol Substitution Test (scored as # correct in test period)

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)
Fear of Hypoglycemia

- 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)

Conclusions

- Hypoglycemia is common in patients with diabetes
- Hypoglycemia and the fear of hypoglycemia have profound effects on the lives of patients with diabetes