Hypoglycaemia

Key messages
All of us will remember a case of hypoglycaemia!!

- The frequency and severity of hypoglycaemia is commonly underestimated and often mis-attributed to other conditions.
  - The symptoms of hypoglycaemia are different in the elderly compared with younger people, partly as a function of age.

- Risk increases with duration of diabetes.

- The increasingly stringent glycaemic targets inherent in modern diabetes care demands that patients, and their relatives and carers, are fully informed about the symptoms and effects of hypoglycaemia and its emergency management.
Risk factors for hypoglycaemia in patients with type 2 diabetes mellitus

- Age (not dose of drug)
- Impaired renal function
- Poor nutrition or fasting
- Intercurrent illness
- Duration of diabetes > 10 years
- Alcohol ingestion
- Polypharmacy
- Use of long-acting sulphonylureas or insulin
- Recent hospital admission
- Endocrine deficiency (pituitary, thyroid, adrenal)
- Deficient counter-regulatory hormonal responses
- Impaired awareness of hypoglycaemia
Question

• Is major hypoglycaemia as common in T2DM on SUs for more than 5yrs as T1DM on insulin in the first 5 years?

• YES

• NO
Epidemiology of hypoglycaemia in UK

Proportion reporting at least one hypoglycaemic episode

Major hypoglycaemia

Mild hypoglycaemia

SU, sulphonylurea

Question

• Does hypoglycaemia occur more commonly during sleep than during waking hours?

• YES

• NO
Major hypoglycaemia occurs more frequently during sleep

- 36% of major episodes that occurred while awake had no warning signs
- 43% of all major episodes occurred between midnight and 08:00 am

216 participants with T1DM reported 714 episodes of major hypoglycaemia, the majority of which occurred during sleep. Major hypoglycaemia was defined as blood glucose <2.8 mmol/L requiring third-party assistance.

DCCT, Diabetes Control and Complications Trial

Hypoglycaemic episodes often go unrecognised by patients

• Many patients are asymptomatic and CGMS data show that unrecognised hypoglycaemia is common in patients with diabetes
  – In one study, 63% of patients with T1DM and 47% of patients with T2DM had unrecognised hypoglycaemia as measured by CGMS
  – In another study, 83% of hypoglycaemic episodes detected by CGMS were unnoticed by patients with T2DM

CGMS, continuous glucose monitoring system
Causes and risk factors for hypoglycaemia

- **Common causes of hypoglycaemia**¹,²
  - Delayed or missed meal
  - Consuming a smaller meal than planned
  - Increased level of physical activity
  - Drug/alcohol consumption

- **Common risk factors for major hypoglycaemia**³,⁴
  - Age/duration of diabetes treatment
  - Strict glycaemic control
  - Impaired hypoglycaemia awareness
  - History of major hypoglycaemia

## Common symptoms of hypoglycaemia

<table>
<thead>
<tr>
<th>Autonomic</th>
<th>Neuroglycopenic</th>
<th>General malaise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweating</td>
<td>Confusion</td>
<td>Headache</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Drowsiness</td>
<td>Nausea</td>
</tr>
<tr>
<td>Shaking</td>
<td>Odd behaviour</td>
<td></td>
</tr>
<tr>
<td>Hunger</td>
<td>Speech difficulty</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Incoordination</td>
<td></td>
</tr>
</tbody>
</table>

Edinburgh Hypoglycaemia Scale in which the 11 most commonly reported symptoms were incorporated

Mild hypoglycaemia while driving

• **STOP !** But
• How long to wait before going on?
  • 10-15 mins
  • 15-30 mins
  • 30-45 mins
  • 45- 60 mins
  • 60-90 mins
  • 2 hours
Pathophysiological cardiovascular consequences of hypoglycaemia

CRP, C-reactive protein; IL-6, interleukin 6; VEGF, vascular endothelial growth factor
Desouza et al. Diabetes Care 2010;33:1389–94
Cardiovascular effects of hypoglycaemia

Dead in bed syndrome!!

• Hypoglycaemia is known to prolong both the QT interval and cardiac repolarisation – increased risk of ventricular tachyarrhythmia

• EURODIAB IDDM Complications Study (n=3,248 T1) showed that QTc interval prolongation is independently associated with the frequency of severe hypoglycaemia

1. Adapted from: Frier et al. Diabetes Care 2011;34(Suppl. 2):S132–7
Major hypoglycaemia significantly increases the risk for adverse outcomes in patients with T2DM

Hazard ratios for incident vascular outcomes and death among patients who had major hypoglycaemia as compared with those who did not

<table>
<thead>
<tr>
<th>Clinical outcome and interval after hypoglycaemia</th>
<th>No. of events</th>
<th>Hazard ratio adjusted for treatment assignment (95% CI)</th>
<th>p-value</th>
<th>Hazard ratio adjusted for multiple covariates (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrovascular events</td>
<td>1147</td>
<td>4.05 (2.86–5.74)</td>
<td>&lt;0.001</td>
<td>3.45 (2.34–5.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Microvascular events</td>
<td>1131</td>
<td>2.39 (1.60–3.59)</td>
<td>&lt;0.001</td>
<td>2.07 (1.32–3.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>1031</td>
<td>4.86 (3.60–6.57)</td>
<td>&lt;0.001</td>
<td>3.30 (2.31–4.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular cause</td>
<td>542</td>
<td>4.87 (3.17–7.49)</td>
<td>&lt;0.001</td>
<td>3.78 (2.34–6.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from non-cardiovascular cause</td>
<td>489</td>
<td>4.82 (3.16–7.35)</td>
<td>&lt;0.001</td>
<td>2.86 (1.67–4.90)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval
Neurological consequences of hypoglycaemia

• Hypoglycaemia deprives the brain of glucose, promoting an autonomic response (e.g., sweating, trembling, anxiety) and neuroglycopenic-induced behavioural changes and cognitive impairment

• Normal counter-regulatory responses to hypoglycaemia can be impaired following repeated hypoglycaemia

• Chronic cognitive impairment is rare

Vicious cycle of repeated hypoglycaemia

Repeated episodes of hypoglycaemia

Defective counter-regulation

Impaired awareness of hypoglycaemia

Increased vulnerability to further hypoglycaemia
Hypoglycaemia unawareness is associated with a higher rate of major hypoglycaemia.

Major hypoglycaemia was defined as an episode requiring external assistance for recovery. Subjective changes in hypoglycaemia symptom intensity were recorded by the participants based on a hypoglycaemia awareness scale of 1 to 7, where 1 = always aware and 7 = never aware, and a score of 4 or more correlates with impaired awareness.

*Based on data from a retrospective survey of 215 patients with T2DM treated with ≥2 injections of insulin daily for ≥1 year

Socio-economic consequences of major hypoglycaemia in T1D and T2D

Major hypoglycaemic events (UK, Germany and Spain)

**Frequency**

- **T1D:** 1.1–3.2 major hypoglycaemic events/year\(^1\)
- **T2D:** 0.1–0.7 major hypoglycaemic events/year (treatment dependent)\(^1\)

**Increased treatment cost**

- Annual cost of hospitalisation and ambulances for major hypoglycaemia in the UK estimated at **£16.9 million\(^2\)**
- Total cost of a major hypoglycaemic event across the survey: **£364.56 in T2D and £160.22 in T1D\(^3\)**
- Annual cost of admissions with hypoglycaemia in Scotland: £0.9 million T1D, £2.5 million T2D\(^4\)

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Socio-economic consequences of minor hypoglycaemia in T2D

Minor hypoglycaemic events (France, Germany, UK, USA)

Reduced productivity

- Average productivity loss: £9.90–£60.69/event
- Following a daytime event:
  - 18.3% lose an average of 9.9 hours of work time
  - 23.8% miss a meeting/deadline
- Following a nocturnal hypoglycaemic event:
  - 22.7% arrive late/miss work
  - 31.8% miss a meeting/deadline
  - 14.7 hours of work are lost

Increased treatment cost

- 5.6 extra blood glucose tests within 7 days after event
- Risk of suboptimal insulin dose (25% of patients reduce dose)
- 25% contact a healthcare provider after an episode
- Out-of-pocket costs due to extra/special groceries, extra testing supplies and transport: £16.42/month

Brod et al. Value Health 2011;14:665–71
ER visits and hospitalizations due to ADE categorized by therapy category

Number of ER visits due to ADE (in pts >64yrs)

Number of resultant hospitalizations

ADE = Adverse Drug Event

## Diagnoses in endocrine therapy category

<table>
<thead>
<tr>
<th>Diagnose (AE manifestation)</th>
<th>Proportion of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia with loss of consciousness or seizure</td>
<td>26.0%</td>
</tr>
<tr>
<td>Hypoglycemia with altered mental status or other neurologic sequelae</td>
<td>40.7%</td>
</tr>
<tr>
<td>Hypoglycemia with cardiovascular sequelae</td>
<td>8.3%</td>
</tr>
<tr>
<td>Hypoglycemia with weakness, dyspnea, or respiratory distress</td>
<td>5.7%</td>
</tr>
<tr>
<td>Hypoglycemia with other or unspecified sequelae</td>
<td>14.0%</td>
</tr>
<tr>
<td>Other</td>
<td>5.3%</td>
</tr>
</tbody>
</table>

→ 94.7% of all endocrine emergency hospitalizations are due to hypoglycemia

Question
Do you consider

• Hypoglycaemia risk when prescribing antibiotics to patients on SUs?

• YES

• NO
Risk of hypoglycaemia with antimicrobial + sulphonylurea

• Retrospective cohort study conducted between 2006-2009
• Assessed risk of hypoglycaemia with antimicrobial drug prescription in patients using sulphonylureas
• Involved patients ≥66 years who were prescribed glipizide or glyburide

Risk of hypoglycaemia with antimicrobial + sulphonylurea

- The following were associated with higher rates of hypoglycaemia vs a panel of noninteracting antimicrobials:

<table>
<thead>
<tr>
<th>Drug</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>3.96</td>
<td>2.42-6.49</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>2.60</td>
<td>2.18-3.10</td>
</tr>
<tr>
<td>Sulfamethoxazole-trimethoprim</td>
<td>2.56</td>
<td>2.12-3.10</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>2.11</td>
<td>1.28-3.47</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1.62</td>
<td>1.33-1.97</td>
</tr>
</tbody>
</table>

Risk of hypoglycaemia with antimicrobial + sulphonylurea

• Number needed to harm:
  - ranged from 71 for clarithromycin to 334 for ciprofloxacin

• Hypoglycaemia associated with:
  - Older age,
  female sex,
 black/hispanic race,
 higher comorbidity,
 prior hypoglycaemic episode

Risk of hypoglycaemia with antimicrobial + sulphonylurea

• In 2009, in the USA, 28% of patients prescribed a sulphonylurea were also prescribed 1 of these 5 antimicrobials
  - these were associated with 13% of all hypoglycaemic events

• Treatment of subsequent hypoglycaemia adds $30.54 in additional Medicare costs to each of these microbial drug prescriptions

Risk of hypoglycaemia with antimicrobial + sulphonylurea

Conclusions

• The prescription of interacting antimicrobial drugs to patients taking sulphonylureas is very common, but is associated with substantial morbidity and increased healthcare costs

Prevention of hypoglycaemia

1. Identify high-risk patients: advanced age, renal impairment
2. Avoid long-acting sulphonylurea preparations
3. Use short-acting sulphonylurea (e.g. gliclazide)
4. Be aware of drug interactions
5. Educate patients and relatives/carers about hypoglycaemia
6. Consider agents that do not cause hypoglycaemia
7. DPP4s, GLP1 agonists, SGLT2 inhibitors
8. Have a safe journey home!
9. Stay away from