Hypoglycaemia unawareness: (Impaired awareness of hypoglycaemia)

Philip Home
Newcastle University
Manufacturers of glucose-lowering agents including insulin and sulfonylureas, and of devices for monitoring glucose levels and delivering insulin, provide funding to myself or to institutions with which I am associated for educational, advisory and research activities.
Impaired awareness of hypoglycaemia: topics

- What it is and how defined
- Physiological and pathophysiological development
- Measuring impaired awareness
- Improving impaired awareness
Physiological responses to hypoglycaemia

Arterialized glucose (mmol/l)

4.6 mmol/L
Inhibition of endogenous insulin secretion

3.8 mmol/L
Counter-regulatory hormone release
- Glucagon
- Adrenaline

3.2 - 2.8 mmol/L
Symptom onset
- Autonomic
- Neuroglycopenic

3.0 - 2.8 mmol/L
Cognitive dysfunction
- Inability to perform complex tasks

< 1.5 mmol/L
Severe neuroglycopenia
- Reduced conscious level
- Convulsions
- Coma

Frier, in Hypoglycaemia in Clinical Diabetes (ed Frier et al), 2014
Impaired awareness of hypoglycaemia

Arterialized glucose (mmol/l)

- Recurrent hypoglycaemia
- Antecedent hypoglycaemia
- Strict glycaemic control

3.8 mmol/L
- Counter-regulatory hormone release
  - Glucagon
  - Adrenaline

3.2 - 2.8 mmol/L
- Symptom onset
  - Autonomic
  - Neuroglycopenic

2.8 mmol/L
- Cognitive dysfunction
  - Inability to perform complex tasks

Frier, in Hypoglycaemia in Clinical Diabetes (ed Frier et al), 2014
Impaired awareness of hypoglycaemia

- Affects 20–25% of adults with type 1 diabetes and <10% of adults with insulin-treated type 2 diabetes
- Risk of severe hypoglycaemia is up to 6-fold greater
- Spectrum of severity – may be reversible
- No international consensus on definition

Incidence of severe hypoglycaemia in individuals with impaired awareness of hypoglycaemia

Impaired awareness of hypoglycaemia: topics

• What it is and how defined
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• Improving impaired awareness
Thresholds for hypoglycaemia symptoms in non-diabetic men by age group

**age 23 ± 2 yr (n=7)**

<table>
<thead>
<tr>
<th>Blood glucose (mg/dl)</th>
<th>Hypoglycaemic awareness</th>
<th>Onset of cognitive dysfunction</th>
</tr>
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<tbody>
<tr>
<td>72</td>
<td></td>
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<td>63</td>
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<td>36</td>
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**age 65 ± 3 yr (n=7)**

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<th>Blood glucose (mg/dl)</th>
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<td>36</td>
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Zammitt et al, Diabetes Care, 2005
Matyka et al, Diabetes Care, 1997
Sleep blunts the counter-regulatory catecholamine response to hypoglycaemia

Adolescent people with T1DM (n=8)

Adolescent non-diabetic people (n=6)

Hidden nocturnal hypoglycaemia in Type 1 diabetes

- **1980’s**: series of studies (x7) suggest overall incidence 10-50 % of nights
- **Current**: still true with insulin analogues
- **Future**: may be further reduced with more physiological nocturnal insulin profiles

Effect of prior hypoglycaemia on the counter-regulatory response to hypoglycaemia

Hyperinsulinaemic stepped hypoglycaemic glucose clamps

Mornings after afternoon hyperglycemia or after afternoon hypoglycaemia

Dagogo-Jack et al, J Clin Invest, 1993
Impaired awareness of hypoglycaemia: topics

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Awareness of hypoglycaemia: clinical assessment

- Clinical history from patient
- History from observers (especially relatives)
- Blood glucose monitoring data (look for frequent asymptomatic biochemical hypoglycaemia)
- **Validated scoring systems** *(Gold AE et al, Diabetes Care, 1994; Clarke et al, Diabetes Care, 1995)*
Existing questionnaires for hypoglycaemia unawareness

**Gold Score (Gold et al 1994)**
- “Do you know when your hypos are commencing?”
- 7 point Likert scale (1: always aware – 7: never aware)
- Single item lacks some sensitivity

**Clarke questionnaire (Clarke et al 1995)**
- “I always / sometimes / no longer have symptoms when my blood sugar is low”
- Sensitive / specific but how sensitive to change?

**Ryan HYPO score (Ryan EA et al 2004)**
- Composite score: frequency, severity, unawareness

**The Pedersen-Bjergaard et al questionnaire**
- Less selective, less sensitive to clinical issues of importance

**The Hypoglycaemia Awareness Questionnaire: HypoA-Q**
- Research tool, building on earlier measures (Speight et al 2014)

*Geddes et al, Diabetes Care, 2007*
Impaired awareness of hypoglycaemia: topics

- What it is and how defined
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- Improving impaired awareness
Effect of avoidance of hypoglycaemia on adrenaline responses to hypoglycaemia in type 1 diabetes

n=7; duration of diabetes 7 yr
Hypoglycaemia reduced from 0.49 ± 0.05 to 0.045 ± 0.03 episodes/person-day
HbA₁c increased from 5.8 ± 0.3 to 6.9 ± 0.2 %

Fanelli et al, Diabetes, 1993
Effect of avoidance of hypoglycaemia on symptom responses to hypoglycaemia in type 1 diabetes

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$\text{HbA}_1\text{c}$ increased from $5.8 \pm 0.3$ to $6.9 \pm 0.2\%$

Fanelli et al, Diabetes, 1993

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<th>Autonomic symptoms (score)</th>
<th>Neuroglycopenic symptom (score)</th>
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<tr>
<td>Time (minutes)</td>
<td>Time (minutes)</td>
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<tr>
<td>non-diabetic people</td>
<td>non-diabetic people</td>
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<tr>
<td>T1DM 3 months</td>
<td>T1DM 3 months</td>
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<td>T1DM 2 weeks</td>
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<td>T1DM baseline</td>
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Fanelli et al, Diabetes, 1993
Effect of avoidance of hypoglycaemia on symptom responses to hypoglycaemia in type 1 diabetes

Cranston et al, Lancet, 1993

n=12; duration of diabetes 11-32 yr
Hypoglycaemia (<3.0 mmol/l) reduced from 17.5 per month to 3 weeks of none before repeat study at an average of 4.1 months
HbA$_{1c}$ increased from 7.4 to 7.8 % (NS)
Studies of effect of patient education on impaired awareness of hypoglycaemia

- BGAT (Cox et al, 1995)
  - 8 weekly group sessions
  - Improved awareness & reduction in SH (6 & 12 months)
- HyPOS (Hermanns et al, 2010)
  - 5 weekly group sessions
  - Improved awareness & reduction in SH (31 months)
  - No difference in overall glycaemic control
- DAFNE (Hopkins et al, 2012)
  - 5 day group education; 40% IAH at entry
  - Restored hypoglycaemia awareness 50%
  - SH pre: $1.7 \pm 8.5$ vs post: $0.6 \pm 3.7$ events per person year
The HypoCOMPaSS study

- Test the hypothesis that in the majority with C-peptide –ve type 1 diabetes and impaired awareness rigorous biochemical hypoglycaemia avoidance will restore awareness and prevent recurrent severe hypoglycaemia
- If provided with adequate / equivalent education, support and treatment goals:
  - Comparable benefits will be obtained with:
    - multiple insulin injections vs CSII and monitoring vs Real Time CGM
- Definitive 24 week 5-centre RCT (2-yr follow-up) 2x2 design
  - CSII vs MDI, and RT-CGM vs none – n=96
  - Diabetes centres providing structured education: Newcastle, Sheffield, Cambridge, Bournemouth, Plymouth

Leelarathna et al, Diabetes Care, 2013; Little et al, Diabetes Care, 2014
Blinded CGM time below <3.0 mmol/l in the HypoCOMPaSS RCT

* $p<0.001$ vs baseline

Little et al, Diabetes Care, 2014
Change in rate of severe hypoglycaemia in the HypoCOMPaSS trial

Episodes per patient year

Baseline: 77% affected pre-trial
24 weeks: 19% during trial

Little et al, Diabetes Care, 2014
Improved hypoglycaemia awareness: Clarke

Change in hypoglycaemia awareness in the HypoCOMPaSS trial using the Clarke score

Score

Baseline 24 weeks

7
6
5
4
3
2
1
0

Leelarathna et al, Diabetes Care, 2013
HypoCOMPaSS results: MDI v CSII, biomedical outcomes

Little et al, Diabetes Care, 2014

- **Gold score**
  - MDI: 4.5 ± 1.0
  - CSII: 5.0 ± 1.0

- **HbA₁c (mmol/mol)**
  - MDI: 65 ± 5
  - CSII: 60 ± 5

- **Severe hypoglycaemia (events/person-yr)**
  - MDI: 0.5 ± 0.2
  - CSII: 0.1 ± 0.2

- **Insulin dose (U/kg)**
  - MDI: 0.8 ± 0.4
  - CSII: 0.6 ± 0.4
HypoCOMPaSS results: SMPG vs RT-CGM, biomedical outcomes

Little et al, Diabetes Care, 2014

- **Gold score**
  - SMBG: 4.5 ± 0.5
  - RT: 4.2 ± 0.4

- **HbA₁c (mmol/mol)**
  - SMBG: 60 ± 2
  - RT: 62 ± 3

- **Severe hypoglycaemia (events/person-yr)**
  - SMBG: 0.5 ± 0.2
  - RT: 0.4 ± 0.1

- **Insulin dose (U/kg)**
  - SMBG: 0.6 ± 0.2
  - RT: 0.5 ± 0.1
HypoCOMPaSS primary outcomes: summary

- Equivalent biomedical outcomes with MDI and CSII
  - when provided with equivalent education / support
  - treatment satisfaction highest with pump
- Equivalent biomedical outcomes with RT-CGM and SMBG
  - including weekly 8-point profile
- Symptomatic recognition of hypoglycaemia
  - catecholamine response restored in clamp sub-study
- Characteristics of 20% with continued SH under exploration
  - older age independent of diabetes duration
- Identify those most suitable for:
  - Psychological intervention (HART-D)
  - LGS (Ly / Battelino); closed loop; transplantation

Leelarathna et al, Diabetes Care, 2013; Little et al, Diabetes Care, 2014
Response of severe hypoglycaemia and hypo-glycaemia awareness to islet transplantation

- Clinical Islet Transplantation Consortium: prospective, open label, single arm study
- transplanting a allogeneic Human Pancreatic Islet Product intraportally
- eight centres enrolled 48 adults with T1DM
- reduced awareness of hypoglycaemia, and ≥1 episode of SH in the prior year.
- median daily insulin dose 0.00 (range 0.00 - 0.43) U/kg at 1 year – 94% had a functioning graft
- median Clarke score (decreased recognition of hypoglycaemia), baseline 6, 1-year 0 (p<0.001); Ryan score (inability to self-treat) also decreased (p<0.001)
- SH, one episode in 1 year, glycemic lability index, and mean amplitude of glycemic excursions all decreased (p < 0.001)

Hering et al, ADA Abstract, 2014
Gold score changes in participants in the UK islet transplantation programme

Shaw, ADA presentation, 2014
Impaired awareness of hypoglycaemia: Conclusions

- IAH is a significant problem both in regard of day-to-day functioning and severe hypoglycaemia risk
- Sleep, and older age, are physiological causes of IAH
- Prior hypoglycaemia, including unrecognized biochemical hypoglycaemia, is a pathophysiological cause of IAH
- People with IAH can be detected by simple clinical and monitoring measures
- Avoidance of hypoglycaemia can lead to improvement in IAH
- Patient education is of fundamental importance to this
- Technological approaches may have a role where patient education fails to deliver longer term remission from IAH
Thank you for your attention