The Challenge of Hypoglycaemia in Diabetes: Risks, Consequences and Management

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OUTLINE

- Definition
- Frequency
- Causes
- Consequences
- Management
WHAT IS HYPOGLYCAEMIA?

- Low plasma glucose causing neuroglycopenia

- Clinical definition of hypoglycaemia:
  - Mild: self-treated
  - Severe: requiring help for recovery

- Biochemical definition of low plasma glucose:
  - ≤70 mg/dL (3.9 mmol/L) (previously ≤56 mg/dL [3.1 mmol/L]) (European Medicines Agency)\(^1\)
  - ≤70 mg/dL (3.9 mmol/L) (American Diabetes Association)\(^2\)
  - <72 mg/dL (4.0 mmol/L) for clinical use in patients treated with insulin or an insulin secretagogue (Canadian Diabetes Association)\(^3\)

1. EMA. CPMP/EWP/1080/00. Rev. 1 2012
FREQUENCY OF SEVERE HYPOGLYCAEMIA in adults with type 1 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Follow-up</th>
<th>Frequency (episodes/person/year)</th>
<th>Proportion affected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacLeod, 1993 (Scotland)</td>
<td>600</td>
<td>41 (14-79)</td>
<td>12 months (R)</td>
<td>1.6</td>
<td>29</td>
</tr>
<tr>
<td>ter Braak, 2000 (The Netherlands)</td>
<td>195</td>
<td>41±14</td>
<td>12 months (R)</td>
<td>1.5</td>
<td>41</td>
</tr>
<tr>
<td>Pedersen Bjergaard, 2004 (Denmark)</td>
<td>1076</td>
<td>40 (18-81)</td>
<td>12 months (R)</td>
<td>1.3</td>
<td>37</td>
</tr>
<tr>
<td>Leiter, 2005 (Canada)</td>
<td>202</td>
<td>44±12</td>
<td>12 months (R)</td>
<td>2.6</td>
<td>27</td>
</tr>
<tr>
<td>UK Hypoglycaemia Study Group, 2007 (United Kingdom)</td>
<td>100 (46 &lt;5 years; 54 &gt;15 years)</td>
<td>&lt;5y: 41±13 &gt;15y: 53±10</td>
<td>9–12 months (P)</td>
<td>1.1 3.2</td>
<td>22 46</td>
</tr>
<tr>
<td>Kristensen, 2012 (Denmark)</td>
<td>3813</td>
<td>48±15</td>
<td>12 months (R)</td>
<td>1.2</td>
<td>31</td>
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</tbody>
</table>

DCCT 1993 n=1600 0.6 (intensive) vs 0.19 (std) episodes/person/year
POLLING QUESTION

True or False:

With increasing insulin therapy and duration in T2D, hypoglycaemia becomes comparable to that in T1D?

A. True
B. False
ANNUAL INCIDENCE OF REPORTED severe hypoglycaemia in a population-based survey in Dundee

Prospective recording over 1 month: Type 1 diabetes n=94; Type 2 diabetes on insulin n=173
WITH INCREASING INSULIN THERAPY and duration in T2D, hypoglycaemia becomes comparable to that in T1D.

Severe hypoglycaemia

Non-severe hypoglycaemia

Proportion reporting at least one hypoglycaemic episode (%)

SU, sulphonylurea; T1D, type 1 diabetes; T2D, type 2 diabetes; yr, year

NORMAL PHYSIOLOGICAL RESPONSES
preventing hypoglycaemia

Inhibition of endogenous insulin secretion
- Counterregulatory hormones: Glucagon, Adrenaline
- Symptom onset: Autonomic, Neuroglycopenic

Counterregulatory hormones: Glucagon, Adrenaline
- Symptom onset: Autonomic, Neuroglycopenic

Neurophysiological dysfunction: Evoked responses
- Inability to perform complex tasks
- Widespread EEG changes
- 55 mg/dL

Cognitive dysfunction
- Inability to perform complex tasks
- Widespread EEG changes
- 3.0 mmol/L

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

Protective hypoglycaemic responses
- Prevents hypoglycaemia in the non-diabetic

Arterialised venous blood glucose concentration (mmol/L)

PHYSIOLOGICAL PROTECTION
in patients with insulin treated diabetes shortly after diagnosis

Arterialised venous blood glucose concentration (mmol/L)

70 mg/dl 4 mmol/L

- Counterregulatory hormones
  - Glucagon
  - Adrenaline

70 mg/dl 4 mmol/L

Symptom onset
- Autonomic
- Neuroglycopenic

55 mg/dl 3.0–2.5 mmol/L

Neurophysiological dysfunction
- Evoked responses

3.0 mmol/L

Widespread EEG changes

3.0 mmol/L

Cognitive dysfunction
- Inability to perform complex tasks

<1.5 mmol/L

Severe neuroglycopenia
- Reduced conscious level
- Convulsions
- Coma

IMPAIRED RESPONSE
(hypoglycaemia unawareness) in patients with increasing duration of insulin therapy (+ tight control)

Arterialised venous blood glucose concentration (mmol/L)

45 mg/dl 2.5 mmol/L

Counterregulatory hormones
• Glucagon
• Adrenaline

Symptom onset
• Autonomic
• Neuroglycopenic

55 mg/dl 3.0–2.5 mmol/L

Neurophysiological dysfunction
• Evoked responses

3.0 mmol/L

Widespread EEG changes

3.0 mmol/L

Cognitive dysfunction
• Inability to perform complex tasks

<1.5 mmol/L

Severe neuroglycopenia
• Reduced conscious level
• Convulsions
• Coma

POLLING QUESTION

All of the following are causes of impaired counterregulation in hypoglycaemia except?

A. Increasing age
B. Short duration of diabetes
C. Sleep
D. Exercise
WHAT CAUSES IMPAIRED COUNTERREGULATORY DEFENSES AND UNAWARENESS?

- A long duration of diabetes
- Tight glycaemic control (due to repeated episodes of hypoglycaemia)
- Increasing age
- Sleep
- Exercise
- (Drugs – nonselective β-blockers, alcohol)
VICIOUS CIRCLE OF REPEATED HYPOGLYCAEMIA

Hypoglycaemia

Increased vulnerability to further episodes

Impaired physiological responses to hypoglycaemia

Reduced awareness of hypoglycaemia
FEAR OF HYPOGLYCAEMIA IN TYPES 1 AND 2

<table>
<thead>
<tr>
<th></th>
<th>Not worried</th>
<th>Very worried</th>
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<tbody>
<tr>
<td>Blindness</td>
<td></td>
<td></td>
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<tr>
<td>Kidney complications</td>
<td></td>
<td></td>
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<tr>
<td>Mild hypoglycaemia</td>
<td></td>
<td></td>
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<tr>
<td>Severe hypoglycaemia</td>
<td></td>
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</tbody>
</table>

Type 1 diabetes 1991 (n=411) | Type 1 diabetes 2007 (n=223) | Type 2 diabetes + insulin 2007 (n=104)

FEAR OF HYPOGLYCAEMIA
reduces patient adherence and may affect glycaemic control

- Fear of hypoglycaemia can have a behavioural impact on diabetes management.
- Patients may reduce or omit their insulin dose, which may result in suboptimal glucose control and increase the risk of long-term complications.

CONSEQUENCES OF HYPOGLYCAEMIA

- Seizures
- Coma
- Cognitive dysfunction
- Accidents
- Employment
- Fear
- Quality of life
- Prevents desirable glucose targets
- Cardiovascular Risk?
MANAGING HYPOGLYCAEMIA:
Reducing absolute or relative insulin excess, technology, training, psychology

- Insulin analogues produce more physiological insulin profiles

- Clinical trials report little or no fall in HbA1c and slight reductions in symptomatic (nocturnal) hypoglycaemia

- Continuous subcutaneous insulin infusion (CSII), modest differences in HbA1c, combined analyses of all trials show little or no fall in hypoglycaemia

- Trials generally exclude those with a history of severe hypoglycaemia
THE ABILITY OF INSULIN ANALOGUES to reduce severe hypoglycaemia

HypoAna: a cross-over trial involving adults with hypoglycaemic problems
30\% relative risk reduction, p=0.012 Absolute risk reduction, 0.5 severe episodes/patient/year

Per protocol population (n=114)
Severe hypoglycaemia requiring 3rd-party assistance and assessed according to Whipples triad (symptoms, recovery, plasma glucose ≤3.9 mmol/L)
Pedersen-Bjergaard et al. Lancet Diabetes Endocrinol 2014;2:553–61
CSII in people experiencing severe hypoglycaemia

Study

- Bode (poor control)
- Bode (good control)
- Kaderman
- Maniatis
- Rizvi
- Litton
- Linkeschova
- Bruttoessno
- Rudolph, Hirsch
- Plotnick
- Cohen
- Hunger-Dathe
- Weintrob
- Weinzimer
- McMahon
- Siegel-Czarkowski
- Alemzadeh
- Mack-Fogg
- Scialfani
- Rodrigues
- Lepore
- Hoogma

Overall ($I^2 = 84.2\%$, $P = 0.00$)

Meta-analysis comparing CSII vs multiple daily injections (MDI) in those with high frequency of hypoglycaemia (>10 episodes a year)

Pickup et al, Diabet Med 2008
TRAINING PEOPLE WITH TYPE 1 DIABETES

to use insulin flexibly and safely

• Flexible intensive insulin therapy pioneered by Assal and implemented by Berger and Mühlhauser in the early 1980s
  • Separation of basal/meal insulin, CHO counting and appropriate corrective doses

• Blood glucose awareness training (BGAT) developed by Cox et al, early 1990s
  • Estimation of blood glucose (with feedback)
  • Recognition of external cues and changes due to hypoglycaemia, feedback on glucose
OBSERVATIONAL DATA
(n=>600) following 5 days inpatient training

Bott et al, Diabetologia 1997
EFFECT OF A STRUCTURED TRAINING COURSE on severe hypoglycaemia in type 1 diabetes

- 20 hour inpatient training course
- Patients advised to measure blood glucose before main meals and at bedtime
- Insulin adjusted to actual blood glucose level and intended carbohydrate intake

Sännan et al. Diabetologia 2005
EFFECT OF DURATION OF DIABETES on rates of severe hypoglycaemia pre and post DAFNE training

Elliott et al, Abst Diabetic Med 2012
ALERTING PATIENTS to impending hypoglycaemia

• CGM available for over 10 years
  • Provides readings in real time
  • Indicates direction of glucose travel
  • Provides alarm and interacts with CSII

• In randomized controlled trials HbA1c generally falls but severe hypoglycaemia is unchanged

• A recent trial showed that when combined with an insulin suspend pump, nocturnal hypoglycaemia fell, no change in HbA1c
ESTABLISHING THE BENEFIT
of new technologies in clinical trials: selecting the right population

95 individuals with unawareness studied for 6 months severe hypoglycaemia (coma or seizure)

Ly et al JAMA 2013
HYPO-COMPASS 2x2 RCT, CSII, MDI, RT, SMBG

96 adults with impaired awareness modest improvement in awareness, no diff between groups

Brief education from professional followed by ongoing support

CSII and/or RT

% time / 24 hours <3.0 mmol/L

Episodes per patient year

Little et al Diabetes Care 2014
POLLING QUESTION

True or False:

Hypoglycaemia avoidance programmes can reverse hypoglycaemia unawareness?

A. True
B. False
REVERSING HYPOGLYCAEMIA UNAWARENESS

effect of hypoglycaemia avoidance programme

12 men with unawareness, 3 weeks absence of hypoglycaemia

![Graph showing plasma glucose levels before and after intervention.](image)
Principles

• Preventing all hypoglycaemic episodes for 4-6 weeks while keeping glycaemic control unaltered
• Frequent glucose monitoring (especially at night)
• Insulin adjustment of dose and type
• Labour intensive for patient and clinician
• May take months - many individuals unable or unwilling to alter their approach
• Only one long-term report*, 4/6 individuals with fewer hypoglycaemic problems and reasonably tight control

*Dagogo-Jack et al *Diabetes Care* 2009
DAFNE - HART
a pilot intervention for adults with hypoglycaemia problems

• Curriculum

• Education in hypoglycaemia unawareness; insulin adjustment
  • Motivational interviewing - eliciting and strengthening change talk
  • Cognitive behaviour theory
    Identifying and addressing thoughts that influence behaviour
    Three thinking traps

• Social learning

• Patient empowerment

• 6 week course – 3 full days (group); 2 one-to-one sessions; final group

• Diabetes educators trained in psychological techniques

• 4 courses delivered with 6 patients per course

• Weekly supervision for educators
IMPACT OF DAFNE HART ON GLYCAEMIC CONTROL and hypoglycaemia 12 months post course

24 adults with unawareness, following DAFNE training

**Baseline** vs **12 months post course**

- **HbA1c (mmol/mol)**
  - Baseline: 60
  - 12 months: 57

- **SH /pt year (median)**
  - Baseline: 0-104
  - 12 months: 0-3

- **Moderate hypo per pt / 6 weeks (median)**
  - Baseline: 0-100
  - 12 months: 0-18

*de Soyza et al Diabetes Care 2013*
IMPROVING GLUCOSE COUNTERREGULATION

Indirect

• Caffeine
  • Increases symptoms in experimental/clinical studies, no fall in severe episodes in a clinical trial

• Modafanil, Diazoxide
  • Have effects on $K^+$ channels and modify Gamma-Aminobutyric Acid (GABA). Modest effects on adrenergic symptoms in small studies but no clinical trials

• Selective serotonin reuptake inhibitors (SSRIs)
  • Increased sympathoadrenal effects in experimental hypoglycaemia, but no clinical trials

Direct

• Theophylline
• Terbutaline
IMPROVING GLUCOSE COUNTERREGULATION DIRECTLY

Raju et al, JCEM 2006
RESTORING AWARENESS
with islet cell transplantation

31 subjects, mean duration 30y
A PATHWAY FOR INDIVIDUALS WITH HYPOGLYCAEMIA PROBLEMS?

Review/support from experienced diabetes nurse/dietitian

Structured training in insulin self management
insulin analogues

CGM/CSII

Addressing major psychological issues in individuals with hypoglycaemia unawareness

Islet cell transplantation??
CONCLUSION

• Hypoglycaemia prevents tight glucose control and remains a major burden to those with diabetes

• Technology now has the potential to make a significant difference to those with problems

• Structured training in flexible intensive insulin therapy has major effects in reducing severe hypoglycaemia

• Many with unawareness have significant psychological issues and self-manage their diabetes inappropriately

• Probably the most important intervention is frequent ongoing support from skilled professionals who understand hypoglycaemia and diabetes self-management