



In the consultation room

Tackling hypoglycaemia in type 2 diabetes

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About this series

The aim of the “In the consultation room” series is to provide readers with brief, practical reviews of key aspects of diabetes care that should be covered in the clinic setting. A short set of questions at the end allows readers to test their knowledge.

Author’s introduction

In this short article I highlight the main causes of hypoglycaemia in people with type 2 diabetes and factors that can increase the risk. The consequences are discussed along with practical tips on detection, advice on treatment and useful strategies for minimising risk.

Diabetes medications are the primary cause of hypoglycaemia, in particular those which raise insulin levels in a non-glucose-dependent fashion (i.e. insulin, sulphonylureas and glinides). Hypoglycaemia is a well-recognised side effect of insulin treatment and while the risk may be greater than in those taking sulphonylurea therapy, in particular those using insulin for longer periods of time, the risk with sulphonylureas should not be underestimated. Hypoglycaemia can have significant and lasting clinical, economic and social implications for people with diabetes and their families, as well as for the NHS. Even mild episodes have been shown to negatively impact a person’s quality of life (Alvarez-Guisasola et al, 2010), with more severe hypoglycaemia precipitating major cardiovascular and cerebrovascular events in some individuals (Frier, 2009).

Looking at hypoglycaemia in more detail

The American Diabetes Association Workgroup on Hypoglycemia (2005) defined hypoglycaemia as: “any abnormally low plasma glucose concentration” that exposed the individual “to potential harm,” with a proposed value of <3.9 mmol/L.

The severity is not determined by the presence or absence of symptoms but by an individual’s ability to self-treat. A mild episode can be self-treated but a severe episode requires third-party assistance for recovery.

When blood glucose levels rise the beta-cells in the pancreas secrete insulin, which facilitates the movement of glucose from the blood into the cells. At the same time the alpha-cells in the pancreas switch off, suppressing glucagon

production, and the liver holds on to its glucose store. The reverse happens when blood glucose levels fall. Below a certain threshold the counter-regulatory system is activated, triggering the release of catecholamines (including adrenaline) and giving rise to the initial symptoms we associate with hypoglycaemia (see *Table 1*). This mechanism provides individuals with an early warning of an impending hypo so that they can take remedial action (consume some quick-acting glucose), to ensure sufficient delivery of glucose to the brain.

Neuroglycopenic symptoms occur when there is an insufficient supply of glucose to the brain, causing the signs we associate with cognitive dysfunction (*Table 1*).

The glycaemic threshold for the onset of symptoms varies and may be affected by age, duration of diabetes and exposure to hypoglycaemia (Matyka et al, 1997; Cryer, 2004; Mathieu et al, 2010). With insufficient warning an individual is at greater risk because there is little if any time to take corrective action.

How common is hypoglycaemia?

It is estimated that around one-third of people with type 2 diabetes experience severe hypoglycaemia in a year (Bailey et al, 2010), and while the overall frequency is lower than in those with type 1 diabetes (Abaira et al 1995), the UK Hypoglycaemia Study revealed an annual rate of 7% for those on sulphonylurea therapy – the same as for those using insulin for up to 2 years (UK Hypoglycaemia Study Group, 2007). Sulphonylurea therapy remains a common second-line choice after metformin, and because of the large numbers of individuals involved it is

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a significant problem and one that should not be ignored. It has been suggested that at least 5000 people on sulphonylureas experience a severe episode of hypoglycaemia requiring emergency intervention each year (Amiel et al, 2008).

Also of relevance is that diagnoses of type 2 diabetes are occurring in more people, at an earlier age, and in a population that is living longer – thus there is an increasing likelihood of progression to a requirement for insulin therapy to maintain optimum glycaemic control.

Worryingly, the true incidence of hypoglycaemia is unknown as many episodes may go unnoticed by the individual, while others people may decide not to reveal they are experiencing them for fear of losing their job or driving licence. Detection of hypoglycaemia is vital and there are some useful prompts that may be used in a consultation, including questions that explore the understanding of hypoglycaemia, the perceived causes, how to treat it and also the wider implications for employment and for driving (see TREND-UK [2011]).

Causes and risks

Any blood glucose-lowering therapy that stimulates insulin production regardless of the ambient glucose concentration has the potential to cause hypoglycaemia, but there are additional factors which may predispose an individual to increased risk, as detailed in *Table 2*.

Impacts and consequences

Mild episodes of hypoglycaemia can cause unpleasant short-term symptoms and disruption to a person's daily activities, but there is evidence to suggest that more severe episodes can cause permanent damage. The profound autonomic stimulation that is triggered during hypoglycaemia increases the heart rate, blood pressure and overall workload of the heart, causing myocardial and cerebral ischaemia and possibly even precipitating myocardial infarction or stroke (Frier, 2009). Desouza et al (2010) describe some of the mechanisms by which hypoglycaemia contributes to this increased cardiovascular risk, including blood coagulation abnormalities, arrhythmias, and inflammatory responses and endothelial damage.

Table 1. Signs and symptoms of hypoglycaemia (Cryer et al, 2003; Cryer, 2007).

Autonomic	Neuroglycopenic	Severe neuroglycopenic
Hunger	Confusion	Headache
Palpitations	Drowsiness	Malaise
Sweating	Lack of co-ordination	Nausea
Shaking	Speech difficulties (slurring)	Reduced consciousness
Dizziness	Atypical behaviour	Coma
Tachycardia	Aggression	Convulsions

Large clinical trials investigating the impact of intensive glycaemic management – including the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (ACCORD Study Group, 2010) – have shown increased all-cause mortality in the intensively treated group and identified hypoglycaemia as a predictor of cardiovascular events, but a causal relationship has not been firmly established (Desouza et al, 2010). The factor appears to be the susceptibility of an individual to the effects of hypoglycaemia rather than the intensity of the treatment strategy *per se*.

Other important considerations about the consequences of hypoglycaemia include the following:

- Older people are more susceptible to cognitive dysfunction and an increased risk of dementia, especially when they are exposed to recurrent

Table 2. Factors that may predispose an individual to an increased risk of hypoglycaemia (Choudhary and Amiel, 2011; TREND-UK, 2011; Kalra et al, 2013).

Factor	Example
Insufficient carbohydrate intake	Missing or delaying a meal, variable meal patterns, consuming less carbohydrate than usual and fasting
Increased carbohydrate utilisation	Increased physical activity
Increased insulin sensitivity	Weight loss
Decreased endogenous glucose production (from liver)	Excessive alcohol consumption
Cumulative blood glucose-lowering effect of several drugs	Addition of another blood glucose-lowering agent that enhances the action of insulin, sulphonylureas or glinides
Renal or hepatic impairment	Affecting the clearance of blood glucose-lowering drugs causing increased concentrations
Incorrect timing or doses of drugs	Miscalculation of doses of insulin or oral hypoglycaemic agents
Incorrect administration of insulin	Due to poor injection technique
Impaired hypoglycaemia awareness	May be associated with repeated exposure to hypoglycaemia, longer duration of diabetes and being older
Autonomic neuropathy	Reduced hypoglycaemia awareness and gastroparesis
Rarer causes and endocrine disorders	Addison's disease, hypothyroidism, hypopituitarism and growth hormone deficiency

Questions to test your knowledge

The answers are not necessarily found in this article.

1. Severe hypoglycaemia is always preceded by autonomic symptoms. Is this true or false?
2. The glycaemic threshold for activation of the counter-regulatory mechanism varies between individuals. Is this true or false?
3. Poor injection technique in people using insulin can cause hypoglycaemia. Is this true or false?
4. According to NICE (2009; 2013; 2014), pioglitazone, dipeptidyl peptidase-4 inhibitors and sodium–glucose cotransporter 2 inhibitors may be considered second line (after metformin) when a person is at significant risk of hypoglycaemia or its consequences. Is this true or false?
5. Group 1 licence holders whose diabetes is treated by a sulphonylurea must notify the Driver and Vehicle Licensing Agency of this by law. Is this true or false?

Answers: 1 – false; 2 – true; 3 – true; 4 – true; 5 – false.

hypoglycaemia (Whitmer et al, 2009). This may also make them more vulnerable to falls and put them at an increased risk of bone fractures (Frier, 2009; Malabu et al, 2014).

- Road traffic accidents and road fatalities caused by hypoglycaemia while driving have been reported (Hitchen, 2006; personal communication from the Driver and Vehicle Licensing Agency, October 2014).
- People with diabetes may fear hypoglycaemia as much as serious complications such as amputation and blindness (Pramong et al, 1991). The psychological impact may be immense, leading to feelings of anxiety, loss of control and even depression (Alvarez-Guisasola et al, 2010).
- Even mild episodes of hypoglycaemia may be sufficient to inhibit medication concordance (Amiel et al, 2008) and may be a major obstacle to achieving optimum glycaemic control (Wild et al, 2007; Alvarez-Guisasola et al, 2010), and some individuals will snack throughout the day to avoid hypoglycaemia, with resulting weight gain and prolonged periods of hyperglycaemia (Russell-Jones and Khan, 2006).
- From an economic perspective, hypoglycaemia is the most common diabetes-related reason for paramedics being called (Brackenridge et al, 2006) and the cost of call-outs linked to hypoglycaemia in 2009–10 was around £17 million (National Audit Office, 2012). It is estimated that each hospital admission for severe hypoglycaemia costs the NHS at least £1000 (Amiel et al, 2008).

Treatment

People with type 2 diabetes and their families need to know how to recognise and treat mild hypoglycaemia. In adults who are conscious, orientated and able to swallow, 15–20 g of quick-acting carbohydrate should be given. Examples include:

- 100 mL of Lucozade™.
- 150 mL (a small can) of non-diet fizzy drink.
- 200 mL (a small carton) of smooth orange juice.
- Five or six dextrose tablets.
- Four large jelly babies.
- Seven large jelly beans.
- Two tubes of glucose gel.

This should be repeated after 5–10 minutes if the person does not feel better (or the blood glucose level is still <4 mmol/L). When the person starts to feel better, this should be followed by a meal or some starchy food, such as a sandwich, to prevent recurrence (TREND-UK, 2011).

GlucaGen® injections act by mobilising glucose stores from the liver and are generally reserved as a treatment for those on insulin and must only be administered by someone who is trained to do so.

Strategies to minimise risk

Arguably a great deal more could be done following an episode of severe hypoglycaemia, and indeed during routine diabetes consultations, to identify causes and implement strategies to minimise future risk. Here are some suggestions:

- 1 Consider prescribing therapies with a reduced risk of hypoglycaemia. According to NICE (2009; 2013; 2014), pioglitazone, dipeptidyl peptidase-4 inhibitors and sodium–glucose cotransporter 2 inhibitors may be considered second line (after metformin) when: “the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [e.g. those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone].”
- 2 Review and reduce drug doses appropriately (e.g. with declining renal function and following weight loss).
- 3 Regularly assess injection technique in those on insulin.
- 4 Individualise blood glucose targets, aiming for tighter control early on but exercising caution later and in those with comorbidities and a longer duration of diabetes.
- 5 Consider appropriate use of exception reporting within the Quality and Outcomes Framework.
- 6 Identify those at increased risk (e.g. drivers, those working at heights or with machinery, and those living alone or in residential homes [adjusting the timing of medication or meal-times, if appropriate]).
- 7 Use structured self-monitoring to identify blood glucose trends and to identify asymptomatic hypoglycaemia.

- 8 Discuss hypoglycaemia with individuals using terms they understand, as part of routine review.
- 9 Offer patient education on recognising, preventing and treating hypos, and discuss and document the implications for employment and driving.

In addition, it is good practice to follow up all episodes of severe hypoglycaemia to identify the cause and agree a strategy to minimise future risk. ■

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Author's conclusion

A key objective of diabetes management is the avoidance of hyperglycaemia and its associated symptoms and the prevention of long-term vascular complications. However, in our efforts to improve glycaemic control we must always remember the potential risk of hypoglycaemia.