

Hypoglycaemia in type 2 diabetes – perceptions and management

Jiten Vora

Article points

1. The clinical, economic and personal burden of severe hypoglycaemia in people with type 2 diabetes is under-recognised.
2. Education that teaches people how to avoid, recognise and act on their individual hypoglycaemic symptoms is essential.
3. Thiazolidinediones, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists and long-acting insulin analogues offer the option of good glycaemic control with a reduced risk of hypoglycaemia.

Key words

- Cost
- Hypoglycaemia
- Quality of life
- Risk factors

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Achieving optimal glycaemic control helps people with diabetes improve their quality of life and minimise the risk of long-term complications. However, aiming for a low target HbA_{1c} may also increase the incidence of hypoglycaemia. In people with type 2 diabetes the significant incidence of hypoglycaemia is becoming more recognised, as is its impact as a barrier to successful blood glucose control. This article highlights the potential risks associated with hypoglycaemia in these individuals and offers strategies to minimise the risk, including education and optimising the use of treatments for type 2 diabetes.

Until recently, hypoglycaemia was considered a minor problem in the treatment of type 2 diabetes. However, it is becoming increasingly clear that the frequency of hypoglycaemic events in people with type 2 diabetes may have been underestimated and that hypoglycaemia presents a substantial barrier to achieving and maintaining optimal glycaemic control in many people with the condition. Minimising the risk of hypoglycaemia is, therefore, an important consideration in the treatment of type 2 diabetes and strategies for achieving this include education and optimisation of currently available treatments.

Definitions of hypoglycaemia

Clinical and biochemical definition

The biochemical definition of hypoglycaemia varies and continues to be a subject of debate

(Frier, 2009). Definitions of hypoglycaemia have been provided by both the European Medicines Agency (EMA; *Table 1*) and the American Diabetes Association (ADA). The latter define hypoglycaemia as a measured plasma glucose concentration of <3.9 mmol/L, whether or not symptoms are present (ADA Workgroup on Hypoglycaemia, 2005). However, many clinicians would regard this blood glucose concentration in an adult without diabetes as being within the normal fasting range, and not an indication of significant hypoglycaemia.

Symptoms

The profile of hypoglycaemic symptoms is unique to the individual and varies in character, pattern and intensity (Frier, 2005). In order to self-manage hypoglycaemia, people with type 2 diabetes should be familiar with its early

symptoms and know the appropriate action to take (Cefalu and Cefalu, 2005).

Symptoms are rated using scales such as the Edinburgh Hypoglycaemia Scale (Deary et al, 1993) and HYPO score – a composite hypoglycaemic score based on frequency, severity, and degree of unawareness of the hypoglycaemia (Table 2) (Ryan et al, 2004) – but diagnosis in real life relies on patient reporting, which can be unreliable (Heller et al, 1995; Amiel et al, 2008).

Causes and risk factors

The primary cause of hypoglycaemia in people taking medication for type 2 diabetes is missed meals. In the DOVES (Diabetes Outcomes in Veterans; Murata et al, 2005) study of insulin-treated people with type 2 diabetes, more than half (53%) of the reported causes of hypoglycaemic episodes were “skipping a meal”. A secondary cause is the incorrect use of blood glucose-lowering treatments. Hypoglycaemia is a known side-effect of treatment with two diabetes drug classes in particular: insulin and sulphonylureas (SUs), such as glibenclamide (Holstein and Egberts, 2003). In the UKPDS (UK Prospective Diabetes Study; UKPDS Group, 1998) an average of 18% of people treated with glibenclamide reported hypoglycaemic episodes every year over the 10-year study period.

The potential increase in hypoglycaemia with SUs is a consequence of their mode of action, which increases intrinsic insulin production regardless of ambient glucose levels. However, rates of hypoglycaemia vary between individual SUs (Tayek, 2008). Amiel et al (2008) calculated that although rates of hypoglycaemia with SUs are relatively low, around 636 000 people with type 2 diabetes in the UK receive SU therapy, either alone or in combination therapy. At rates of 0.8% per annum for severe events, this equates to >5000 people experiencing a severe event each year (Amiel et al, 2008).

Other oral antidiabetes drugs (OADs), such as metformin and thiazolidinediones (TZDs), decrease insulin resistance or postprandial glucose absorption and are associated with a lower risk of hypoglycaemia.

Table 1. Definitions of hypoglycaemia (Committee for Proprietary Medicinal Products, 2002).

Type of hypoglycaemia	Definition
Major hypoglycaemia	Symptomatic episode requiring external assistance with blood glucose levels <3.0 mmol/L and prompt recovery after glucose or glucagon administration.
Minor hypoglycaemia	Symptomatic episode with a blood glucose level <3.0 mmol/L and no need for external assistance.
Asymptomatic	Blood glucose measurement <3.0 mmol/L.

Newer drugs that act on the incretin system, such as the dipeptidyl peptidase-4 (DPP-4) inhibitors and the glucagon-like peptide-1 (GLP-1) receptor agonists are also associated with a low risk of hypoglycaemia, except when administered in combination with SUs (Buse et al, 2004; Kendall et al, 2005; Amiel et al, 2008; Marre et al, 2009).

Glycaemic control reflects the balance between blood glucose-lowering medication, exercise and food intake (Boyle and Zrebiec, 2008). Strenuous or prolonged exercise and alcohol consumption can also have a huge influence on the risk of hypoglycaemia (Holstein and Egberts, 2003; Frier, 2005; Amiel et al, 2008). To minimise this risk, people with type 2 diabetes should be advised of the increased risk of delayed onset and nocturnal hypoglycaemia following exercise and alcohol consumption.

Another known significant risk factor for hypoglycaemia is increasing age (Ben-Ami et al, 1999). Blood glucose concentration thresholds for the glucagon and adrenaline counterregulatory responses decrease with age (Marker et al, 1992; Meneilly et al, 1994), which can limit the interval between sensing hypoglycaemia and the onset of symptoms such as cognitive dysfunction, thus increasing the risk of severe hypoglycaemia (Frier, 2002).

Although the adrenaline counterregulatory response threshold may be higher in the early stages of type 2 diabetes than in type 1 diabetes (Levy et al, 1998), with increasing duration of insulin therapy, type 2 diabetes more closely resembles type 1 diabetes, and the incidence

Table 2. Common symptoms of hypoglycaemia (Deary et al, 1993; Ryan et al, 2004).

Autonomic
● Hunger
● Palpitation
● Shaking
● Sweating
Neuroglycopenic
● Confusion
● Drowsiness
● Lack of coordination
● Odd behaviour
● Speech difficulty
● Problems with vision
● Light-headedness/dizziness
● Stress/irritability
● Slow/delayed responses
General malaise
● Headache
● Nausea

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1. The authors of the UK Hypoglycaemia Study reported that the proportion of participants with type 2 diabetes treated with SUs self-reporting mild and severe hypoglycaemic episodes was 39% and 7%, respectively.
2. Estimating the number of hypoglycaemic events in people with type 2 diabetes is complex. Symptom recognition, especially in older people, is limited, while variations in treatment regimen, symptom threshold and clinical trial reporting preclude interstudy or patient group comparisons.

of severe hypoglycaemia increases (UK Hypoglycaemia Study Group, 2007). This, combined with the effects of age, suggests that severe hypoglycaemia is a profound risk for people with type 2 diabetes.

Prevalence of hypoglycaemia

In type 2 diabetes the incidence of hypoglycaemic events is lower than in type 1 diabetes. The authors of the UK Hypoglycaemia Study reported that the proportion of participants with type 2 diabetes treated with SUs self-reporting mild and severe hypoglycaemic episodes was 39% and 7%, respectively. However, over time an increase in the number of hypoglycaemic episodes was observed in people with type 2 diabetes taking insulin (*Figure 1*) (UK Hypoglycaemia Study Group, 2007).

Estimating the number of hypoglycaemic events in people with type 2 diabetes is complex. Symptom recognition, especially in older people, is limited, while variations in treatment regimen, symptom threshold and clinical trial reporting preclude interstudy or patient group comparisons (Frier, 2002; Boyle and Zrebiec, 2008).

This has led to suggestions that the current estimate of approximately 2.5% of people with

type 2 diabetes per year experiencing a grade 2–4 hypoglycaemic event (i.e. the person was temporarily incapacitated by hypoglycaemia and remedial medical action was taken) may be an underestimate (Frier, 2002; Wright et al, 2006). Indeed, hypoglycaemia as assessed by continuous blood glucose monitoring in the UK Hypoglycaemia Study suggests a “real” prevalence of twice that self-reported in the early stages of type 2 diabetes (UK Hypoglycaemia Study Group, 2007).

The incidence of hypoglycaemia increases with intensive glucose-lowering therapy. In the VADT (Veterans Affairs Diabetes Trial) the number of symptomatic hypoglycaemia episodes was 383 per patient-year with standard therapy and 1333 per patient-year for intensive therapy (Duckworth et al, 2009), while in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation) trial 150 people (2.7%) undergoing intensive treatment had at least one severe hypoglycaemic episode, compared with 81 people (1.5%) undergoing standard treatment ($P<0.001$). Minor hypoglycaemia also occurred more frequently in people treated intensively (ADVANCE Collaborative Group et al, 2008).

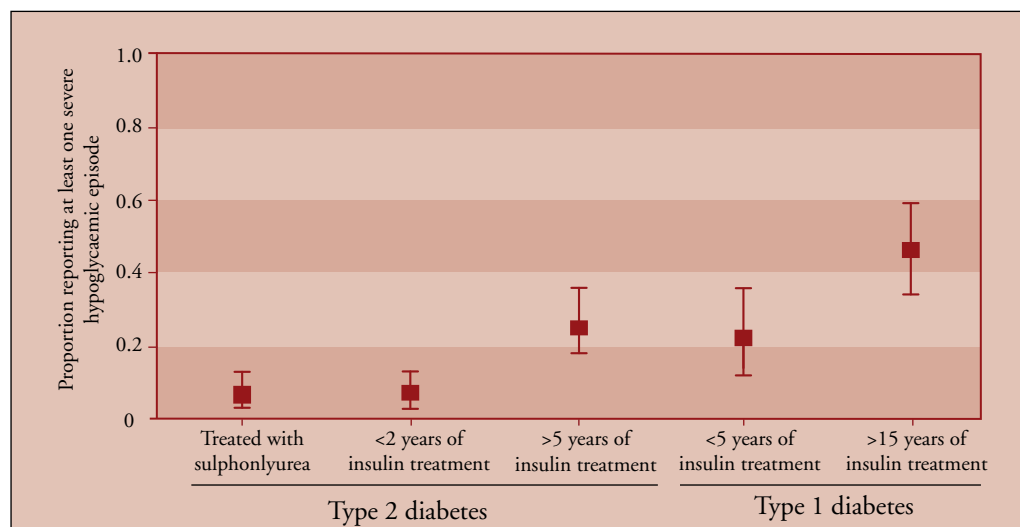


Figure 1. The proportion of people with type 1 and type 2 diabetes experiencing at least one self-reported hypoglycaemic episode during 9–12 months of follow-up. The vertical bars represent a 95% confidence interval. Reproduced with kind permission of the UK Hypoglycaemia Group (2007) and Springer Publishers.

A recent analysis of the ADVANCE study suggested that although severe hypoglycaemia was clearly associated with increased risks of macrovascular events, microvascular events and death, the risk of these events was similar between standard and intensive glycaemic control treatment groups (Zoungas et al, 2010). Similarly, in the ACCORD (Action to Control Cardiovascular Risk in Diabetes; ACCORD Study Group et al, 2008) trial the incidence of hypoglycaemia requiring any assistance was 16.2% with intensive therapy and 5.1% with standard therapy ($P<0.001$). However, symptomatic, severe hypoglycaemia was associated with an increased risk of death with both intensive and standard treatments, and the risk of death was lower among those who experienced at least one episode of hypoglycaemia in the intensive arm than in the standard arm, suggesting that symptomatic, severe hypoglycaemia does not account for the difference in mortality between intensive and standard treatment seen in this trial (Bonds et al, 2010).

Costs of hypoglycaemia

In a study analysing the DARTS MEMO (Diabetes Audit and Research in Tayside Scotland Medicines Monitoring Unit) database, the incidence of severe hypoglycaemia requiring emergency assistance was the same in people with type 2 diabetes taking insulin (7.3%) as in those with type 1 diabetes taking insulin (7.1%) (Leese et al, 2003). Severe hypoglycaemia was observed in 0.8% of people taking SUs, in whom the mean HbA_{1c} level was 8.0% (64 mmol/mol).

The cost of severe hypoglycaemia in the total population of people who experienced hypoglycaemia ($n=160$) was estimated as ≤£92 078 in 1 year, of which hospital care accounted for ≤£50 140 (Table 3). Extrapolating these data to the whole of the UK and applying the Hospital and Community Health Services Inflation Index gives an estimated annual direct cost for treating severe hypoglycaemia of approximately £15.6 million (Leese et al, 2003; Curtis, 2010).

A study assessing the costs of severe hypoglycaemic events in people with diabetes

in Germany, Spain and the UK showed that hospital treatment was a major cost in all countries (Hammer et al, 2009). Average treatment costs were higher for people with type 2 diabetes (Germany, €533; Spain, €691; UK, €537) than in those with type 1 diabetes (€441, €577 and €236, respectively). Telephone calls, visits to doctors, blood glucose monitoring and patient education contributed substantially to costs for non-hospitalised people.

Resource use in primary care due to hypoglycaemia has also been estimated in 861 people with diabetes in Cardiff using a postal questionnaire (Davis et al, 2005). During the 3-month survey period, the mean total number of contacts with primary care for respondents with type 2 diabetes was 11.8, with 11.5 contacts following mild-to-moderate hypoglycaemic episodes and 13.2 contacts following severe episodes.

An increased risk of fractures (Monami et al, 2008a) and cardiovascular events, including cardiac ischaemia and acquired long QT syndrome (DeSouza et al, 2003; Robinson et al, 2003), may indirectly contribute to the costs of hypoglycaemia. Accidents associated with hypoglycaemia while driving can also have severe consequences (Levy et al, 2008). In the UK it has been estimated that five fatal crashes per year and 45 serious events per month are related to hypoglycaemia (Hitchen, 2006).

Impact on quality of life

Episodes of hypoglycaemia and fear of hypoglycaemia can have a serious impact on both the short- and long-term quality of life of people with type 2 diabetes (Levy et al, 2008). The UKPDS found that people who reported

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Table 3. Cost estimate of hypoglycaemia in people with type 1 and type 2 diabetes in Tayside per year.

	Ambulance	A&E	Ward
Number of episodes	223	153	52
Tayside (case per day)	£127	£89	£218
Cost of hypoglycaemia	£28 321	£13 167	£50 140

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Page points

1. As well as hypoglycaemia itself, other psychological factors associated with hypoglycaemia include fear of hypoglycaemia, guilt related to that fear, uncertainty, high levels of anxiety and low levels of overall happiness.
2. Two diabetes education programmes, which include information on hypoglycaemia, have been developed for people with type 2 diabetes in the UK: DESMOND (Diabetes Education and Self Management for Ongoing and Newly Diagnosed) and X-PERT (Expert Patient Education versus Routine Treatment).

more frequent hypoglycaemia also reported increased tension, overall mood disturbance and less work satisfaction (UKPDS Group, 1999).

As well as hypoglycaemia itself, other psychological factors associated with hypoglycaemia include fear of hypoglycaemia, guilt related to that fear (Cryer and Childs, 2002; Wild et al, 2007), uncertainty, high levels of anxiety and low levels of overall happiness. People who are unable to recognise the early symptoms of hypoglycaemia may feel a loss of control and uncertainty, which can be central to fear of hypoglycaemia and poor glycaemic control (Wild et al, 2007). Evidence from the RECAP-DM (Real-Life Effectiveness and Care Patterns of Diabetes Management; Álvarez Guisasola et al, 2008) study confirms these findings, demonstrating that the severity of hypoglycaemia was associated with people not achieving HbA_{1c} goals. Those with hypoglycaemic symptoms also reported significantly lower scores for treatment effectiveness, side-effects, convenience

and satisfaction, and were more likely to report barriers to adherence.

Minimising the risk of hypoglycaemia Education

Person-centred structured education regarding hypoglycaemia risk, symptom recognition, need for rapid treatment and impact of missed meals and alcohol intake should be provided along with all treatments for diabetes (Boyle and Zrebiec, 2008). The DOVES study showed that people with type 2 diabetes who were better educated about the condition had higher symptom awareness than those who were less well educated (Murata et al, 2004).

Two diabetes education programmes, which include information on hypoglycaemia, have been developed for people with type 2 diabetes in the UK: DESMOND (Diabetes Education and Self Management for Ongoing and Newly Diagnosed; Davies et al, 2008) and X-PERT (Expert Patient Education versus Routine Treatment; Deakin et al, 2006). These initiatives comprise a series of lessons where people discuss problems associated with hypoglycaemia and the appropriate management of their lifestyle and medication to minimise the risk and optimise quality of life and glycaemic control.

People on the DESMOND programme showed improved weight loss, smoking cessation and beliefs about illness, but no improvement in HbA_{1c} levels versus controls (Davies et al, 2008). Participation in the X-PERT programme led to improvements in a number of areas including glycaemic control, reduced total cholesterol, body weight, BMI, waist circumference and self-empowerment (Deakin et al, 2006).

As part of successful diabetes management, healthcare professionals should emphasise the idiosyncratic nature of hypoglycaemic symptoms, ensure that the individual is aware of their own symptom profile (McAulay et al, 2001) and provide strategies for avoiding and addressing hypoglycaemia (Table 4).

Therapeutic options

Both insulin and SUs are associated with a higher risk of hypoglycaemia than other

Table 4. Strategies for avoiding and addressing hypoglycaemia.

Set appropriate expectations regarding likelihood of hypoglycaemia	Mild or moderate hypoglycaemia can be anticipated when trying to attain glycaemic control, but risk of severe events is rare. Severe hypoglycaemia occurs in type 2 diabetes, but risk increases with tighter glycaemic control and certain agents.
Consistency is essential	Consider: <ul style="list-style-type: none"> ● Timing of meals and snacks. ● Carbohydrate intake. ● Exercise. ● Alcohol. ● Travel and holidays.
Self-monitoring of blood glucose	Tailor frequency and timing of self-monitoring based on regimen. Monitor before exercise. Educate on possibility of unrecognised symptoms.
Reinforce hypoglycaemic symptom recognition and self-treatment	Educate family (encourage individual to educate friends). Ask individual about symptoms at each visit. Educate on self-treatment.

Reproduced with permission from: Cefalu and Cefalu (2005) Controlling hypoglycaemia in type 2 diabetes: which agent for which patient? *J Fam Pract* 54: 855–862. Quadrant Healthcom. Supplemented with information from Boyle and Zrebiec (2008) and Frier (2005).

blood glucose lowering drugs (UKPDS Group, 1998; Holstein and Egberts, 2003). Recent developments in diabetes therapy have sought to reduce the risk of hypoglycaemia while allowing people with type 2 diabetes to reach their HbA_{1c} targets. Two of these developments are the long-acting basal insulin analogues and therapeutic molecules targeted at the incretin pathway (Deacon, 2011; Madsbad et al 2011). A new class, the sodium-glucose co-transporter (SGLT)-2 inhibitors, also offer an exciting approach to diabetes management without significant adverse effects (Chao, 2011).

Long-acting basal insulin analogues

The long-acting basal insulin analogues – insulin glargine and insulin detemir – can be added to other (meal-related) insulin analogues to mimic the physiological insulin profile (Boyle and Zrebiec, 2008). Both insulin glargine and insulin detemir are as efficacious as the older basal insulin – neutral protamine Hagedorn (NPH) insulin – but have a reduced risk of nocturnal hypoglycaemia and possibly weight gain (Horvath et al, 2007; Monami et al, 2008b).

One-year results from the 4-T (Treating to Target in Type 2 Diabetes) trial showed that participants receiving insulin detemir experienced a significantly lower incidence of hypoglycaemia (all grades; 73.9%) than those receiving either biphasic insulin aspart (91.9%, $P<0.01$) or prandial insulin aspart (96.2%, $P<0.01$) (Holman et al, 2007). After 3 years, rates of hypoglycaemia (all grades) converged and did not significantly differ between treatment groups (insulin detemir, 44%; biphasic insulin aspart, 49.4%; prandial insulin aspart, 51%; $P=0.67$) (Holman et al, 2009).

Incretin-based treatments

Two types of treatment based on the incretin pathway have been developed: GLP-1 receptor agonists and DPP-4 inhibitors, which inhibit GLP-1 and glucagon inhibitory peptide (GIP) breakdown. The action of GLP-1 is glucose-dependent, reducing glucagon levels and increasing insulin production only during

periods of hyperglycaemia. As the normal fasting glucose range is approached, glucagon level and insulin production return to normal (Nauck et al, 1998; Amiel et al, 2008).

The GLP-1 receptor agonists exenatide and liraglutide improve glycaemic control in people with type 2 diabetes who are inadequately controlled on diet and exercise, or single or multiple oral agents, and provide similar glycaemic control to insulin glargine (Heine et al, 2005; Monami et al, 2009). The frequency of hypoglycaemic episodes with either exenatide or liraglutide is low when these agents are combined with metformin, but increases when they are combined with SUs (Buse et al, 2004; Buse et al, 2009; DeFronzo et al, 2005; Kendall et al, 2005; Marre et al, 2009).

The DPP-4 inhibitors currently licensed in the UK for people with type 2 diabetes are sitagliptin, saxagliptin and vildagliptin, with additional agents undergoing investigation. The mechanism of action of DPP-4 inhibitors is glucose-dependent, with increased insulin production only occurring when ambient blood glucose levels are high. This contributes to the low risk of hypoglycaemia observed with the drug class. Indeed, in separate trials, each of the DPP-4 inhibitors has been compared with a sulphonylurea as add-on therapy to metformin; each DPP-4 inhibitor was shown to offer equivalent glucose lowering efficacy to the comparator sulphonylurea, but was associated with a lower risk of hypoglycaemia and minimal weight gain (Nauck et al, 2007; Ferrannini et al, 2009; Göke et al, 2010).

Conclusion

Hypoglycaemia is increasingly being recognised as a serious and expensive problem in type 2 diabetes, particularly in older people and those treated with insulin and SUs with a prolonged duration of diabetes. The clinical and cost implications are immense as the population ages and the number of people with type 2 diabetes continues to increase.

Person-centred diabetes education is essential to ensure that people with diabetes can recognise and act on their individual symptoms rapidly. The choice of therapy is

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1. Two types of treatment based on the incretin pathway have been developed: glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 inhibitors, which inhibit GLP-1 and glucagon inhibitory peptide breakdown.
2. Person-centred diabetes education is essential to ensure that people with diabetes can recognise and act on their individual symptoms of hypoglycaemia rapidly.

“Hypoglycaemia is increasingly being recognised as a serious and expensive problem in type 2 diabetes, particularly in older people and those treated with insulin and sulphonylureas with a prolonged duration of diabetes.”

also important: recent advances in therapies may improve glycaemic control and reduce the risk of long-term vascular consequences of diabetes, while not increasing the risk of hypoglycaemia. ■

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Conflicts of interest

The author declares that he has received honoraria, travel grants and research funding from pharmaceutical companies involved in diabetes care, including Sanofi, Novo Nordisk, Eli Lilly, MSD, Novartis, Bristol-Myers Squibb, AstraZeneca, GlaxoSmithKline and Takeda.

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