

Management of hypoglycaemia unawareness in type 1 diabetes: A review

Mary Hayes

Article points

1. Hypoglycaemia unawareness is common in type 1 diabetes and often goes unrecognised and may lead to severe hypoglycaemia and even death.
2. The goal of management is to prevent hypoglycaemia while maintaining normoglycaemia.
3. Blood glucose monitoring, individualised targets and educational programmes are important in prevention and management.
4. A multifaceted intervention of clinical care and education by the diabetes team is required to prevent and manage hypoglycaemia unawareness.

Key words

- Hypoglycaemia unawareness
- Type 1 diabetes
- Educational programmes

Mary Hayes is a Diabetes Specialist Nurse, Tower Hamlets Primary Care Trust, London.

Hypoglycaemia unawareness is defined as the onset of neuroglycopenia before the appearance of autonomic warning symptoms (De Galan et al, 2006). Clinically it manifests as the inability to recognise impending hypoglycaemia by symptoms. This article reviews the pathophysiology of hypoglycaemia, hypoglycaemia unawareness, severe hypoglycaemia and the consequences in adults with type 1 diabetes. It examines the evidence for prevention and management of hypoglycaemia unawareness and concludes that prevention and management of hypoglycaemia unawareness is complex, and can only be achieved by a multifaceted intervention of clinical care and structured patient education by the diabetes team.

Hypoglycaemia is a well-known acute complication of insulin treatment in type 1 diabetes, yet the inability to recognise impending hypoglycaemia (hypoglycaemia unawareness) is common and often not recognised (Heller, 2001). Multiple daily injections (MDI) of insulin or continuous subcutaneous insulin infusion (CSII) are essential for people with type 1 diabetes as their pancreas is no longer able to produce insulin owing to destruction of the pancreatic beta-cells by the body's immune system. Also, glucose counter-regulation is typically impaired in people with type 1 diabetes (Williams and Pickup, 2004).

In order to prevent hypo- or hyperglycaemia, people with diabetes need to maintain their blood glucose within tight limits, which requires adjustment of their insulin, diet and lifestyle. It is crucial that they do this, as prolonged exposure to raised blood glucose leads to the development of macro- and microvascular complications of

diabetes (Diabetes Control and Complications Trial Research Group, 1993). The goal of diabetes treatment is therefore maintenance of normoglycaemia. This requires intensive self-management, which is demanding and requires effort, discipline, skill and knowledge (Shillitoe, 1994), and even then hypoglycaemia can be a regular occurrence (Egger et al, 1997).

Recurrent hypoglycaemic episodes induce hypoglycaemia unawareness and impair glucose counter-regulation. This in turn predisposes to severe hypoglycaemia (Bolli et al, 2002), which can result in permanent neurological damage. Hypoglycaemia can be fatal if untreated or has the potential to cause a fatal accident to the person or others if the individual has a hypoglycaemic episode while driving, for example (Cox et al, 2000). Fear of hypoglycaemia may prevent people with diabetes achieving normoglycaemia, as well as deterring clinicians from optimising insulin therapy.

Homeostasis

In healthy humans, the glucose supply to the brain is maintained by an efficient homeostatic system, which keeps blood glucose levels within a narrow range that is sufficient to support normal brain function. When blood glucose levels rise, insulin is released by the pancreatic beta-cells and travels to the liver via the portal vein to stimulate hepatic glycogen synthesis and inhibit hepatic gluconeogenesis (synthesis of glucose from non-carbohydrate sources, such as amino acids). Within the liver, approximately 50% of the insulin is degraded; as a result, only half of the insulin released reaches the peripheral tissues to stimulate skeletal muscle glucose disposal or inhibit lipolysis in adipose tissue (De Galan et al, 2006).

Glucose is an essential metabolic fuel for the brain, which cannot synthesise glucose or store it as glycogen. The brain is therefore critically dependent on a continuous supply of glucose from the circulation for normal functioning. At normal (or elevated) arterial glucose concentrations, the rate of blood to brain glucose transport exceeds the rate of brain glucose metabolism (Bingham et al, 2005). Other hormones (such as glucagon, adrenaline, corticosteroid hormones and growth hormone) are also involved in maintaining normoglycaemia (MacLeod, 2000).

Hypoglycaemia

Hypoglycaemia occurs when the blood glucose concentration drops below 3.6–3.8 mmol/L. Autonomic symptoms (sweating, pounding heart, shaking and hunger) develop at approximately 3.2 mmol/L and neuroglycopenic symptoms (confusion, drowsiness, speech difficulty, incoordination, visual disturbances, atypical behaviour and circumoral paresthesia) starts to occur at approximately 3 mmol/L (Williams and Pickup, 2004). These glycaemic thresholds are dynamic rather than static, and vary according to recent hypoglycaemic events (MacLeod, 2000).

Once injected, therapeutic insulin levels are unregulated and do not decrease until the subcutaneous depot is depleted, even though the blood glucose level may have started to fall too low. Insulin injected subcutaneously enters the circulation at a much slower rate than it does when released into the blood in people without

diabetes, and so high insulin levels persist considerably longer. In addition, variations in insulin absorption may vary, increasing the risk of hypoglycaemia (De Galan et al, 2006).

Hypoglycaemia unawareness

Hypoglycaemia unawareness is defined as ‘the onset of neuroglycopenia before the appearance of autonomic warning symptoms’ (De Galan et al, 2006). Clinically, this manifests as the inability to perceive hypoglycaemia by symptoms.

The mechanisms of hypoglycaemia unawareness are not fully understood (Fanelli et al, 2004), although there is evidence that hypoglycaemia (that is brief, mild, symptomatic or nocturnal – which is often unrecognised) contributes to unawareness (Cryer, 1993). It is thought that the neurones that initiate the autonomic response adapt to chronic hypoglycaemia by increasing glucose transporter expression and glucose uptake; subsequently, hypoglycaemia fails to produce sufficient intercellular glycopenia and so no longer elicits a response (Williams and Pickup, 2004).

The inability to produce insulin disrupts the first line of defence against hypoglycaemia, and the consequence of this is a lack of pancreatic control of pancreatic beta-cells, which precludes an adequate glucagon response. It is thought that hypoglycaemia fails to trigger glucagon responses within 1–2 years of diagnosis (De Galan, 2006). The combination of a reduction in awareness of symptoms and defective counter-regulation results in a vicious circle of recurrent hypoglycaemia, which has been termed ‘hypoglycaemia begetting hypoglycaemia’ (Cryer, 1993).

There are no tests available to definitively establish the presence of hypoglycaemia unawareness or defects in hormonal glucose counter-regulation in daily practice. The diagnosis of these conditions is made by clinical judgement; nevertheless, assessment of hypoglycaemia unawareness and defects in hormonal glucose counter-regulation is clinically relevant because of their predictive value for the frequency of severe hypoglycaemia episodes.

Nocturnal hypoglycaemia results from diminished awareness while sleeping and decreased adrenaline responses during sleep. In addition to the classic autonomic and

Page points

1. Hypoglycaemia occurs when the blood glucose concentration falls below 3.6–3.8 mmol/L.
2. Autonomic symptoms develop at approximately 3.2 mmol/L and neuroglycopenic symptoms at approximately 3 mmol/L.
3. These glycaemic thresholds are dynamic rather than static, and vary according to recent hypoglycaemic events.
4. Hypoglycaemia unawareness is defined as ‘the onset of neuroglycopenia before the appearance of autonomic warning symptoms’.

Page points

1. Nocturnal hypoglycaemia results from diminished awareness while sleeping and decreased adrenaline responses during sleep.
2. Hypoglycaemia unawareness is much feared because it leads to severe hypoglycaemia, which has multiple negative consequences, including cognitive impairment, social embarrassment, accidents and even death.
3. The extreme fear of hypoglycaemia can lead to inappropriate self-management, such as keeping the blood glucose level raised in an attempt to avoid hypoglycaemia.
4. Fear of hypoglycaemia affects both people with diabetes and clinicians, who are deterred from optimizing blood glucose levels.

neuroglycopenic symptoms, night sweats and morning headaches are also associated with nocturnal hypoglycaemia (DeVries et al, 2004).

Severe hypoglycaemia is not defined in terms of a specific blood glucose level, but by symptoms, that is when the blood glucose concentration becomes so low that neuroglycopenia leaves the person unable to administer treatment him or herself because of increasing mental confusion and lethargy as unconsciousness approaches (Gonder-Frederick et al, 1997).

Effects of hypoglycaemia unawareness

The acute effects of hypoglycaemia range from transient discomfort, through embarrassment resulting from the effects of neuroglycopenia on behaviour, to emergencies when hypoglycaemia becomes profound (Rubin, 2005). Because hypoglycaemia unawareness leads to severe hypoglycaemia, which has multiple negative consequences, including cognitive impairment, social embarrassment, accidents and even death, it is of great significance and is much feared.

Fear is a powerful emotion and the extreme fear of hypoglycaemia can lead to inappropriate self-management, such as keeping the blood glucose level raised in an attempt to avoid hypoglycaemia (Clark and Asimakopoulou, 2005; Rubin, 2005). Family members and carers can also be affected and develop their own fears, leading to tension and conflict in relationships and overprotective, hypervigilant behaviours, which may be resented by the person with diabetes (Clark and Asimakopoulou, 2005).

Such fear is heightened by the proposal of a direct relationship between hypoglycaemia and death, resulting from the dead-in-bed syndrome: a rare disorder characterised by unexpected death in a previously healthy, tightly controlled young person with type 1 diabetes, often with a history of recurrent nocturnal hypoglycaemia. The syndrome is thought to result from a fatal ventricular arrhythmia caused by hypoglycaemia-induced lengthening of the QT interval (DeGalan et al, 2006).

Such is the fear of hypoglycaemia, it affects not only those with diabetes but also clinicians, who may be reluctant to optimise insulin therapy by imposing tight blood glucose control for fear of

inducing hypoglycaemia (Gonder-Frederick et al, 1997).

Prevention

Prevention is preferable to treatment, and as hypoglycaemia unawareness is thought to be caused by 'hypoglycaemia begetting hypoglycaemia', then hypoglycaemia needs to be avoided.

It is common for clinicians to search for primary risk factors as a cause of hypoglycaemia; these would include missed meals, excessive insulin administration, alcohol consumption and physical activity or sports. Alcohol consumption reduces symptomatic awareness of developing hypoglycaemia and further impairs the counter-regulatory hormonal response, particularly to adrenaline and growth hormone (MacLeod, 2000). Changes in medication (such as addition of an insulin sensitiser), or renal deterioration (where insulin clearance is decreased) contribute to hypoglycaemia and increase the risk of hypoglycaemia unawareness (Cryer et al, 2003).

While assessment of the risk factors is appropriate in many cases, hypoglycaemia is also related to imperfections in therapeutic insulin delivery, as opposed to endogenous insulin release, which is instant and matched to the amount of carbohydrate entering the circulation or to any other increase in the blood glucose level (De Galan et al, 2006). For these reasons, hypoglycaemia can never be completely eliminated, but people with diabetes and diabetes teams must make every effort, by both educational and clinical means, to support this aim.

Management of hypoglycaemia unawareness

Clinical

The most effective way of reducing the risk of hypoglycaemia unawareness is to undertake proactive methods as discussed above. To prevent hypoglycaemia unawareness, the goal must be to prevent hypoglycaemia (Fanelli et al, 1993) while still aiming to retain normoglycaemia (MacLeod, 2000). Blood glucose monitoring, individualised targets and educational programmes are important in the bid to prevent and manage hypoglycaemia.

Blood glucose monitoring is essential as people with hypoglycaemic unawareness are less accurate at detecting blood glucose levels below 3.9mmol/L (Clarke et al, 1995). Continuous glucose monitoring (CGM) systems that can detect hypoglycaemia are welcome to both patients and clinicians, as their use could improve blood glucose control and reduce hypoglycaemia, especially at night (Fanelli et al, 2004).

It is easier to prevent hypoglycaemia if insulin is delivered to mimic the physiology of endogenous insulin secretion in people without diabetes. Recombinant DNA technology has enabled the design of insulin with improved pharmacokinetics and dynamic characteristics to provide prandial and basal insulins that more accurately mimic the physiological insulin dynamics of people without diabetes (Owens et al, 2001).

CSII therapy has been shown to reduce hypoglycaemia (Bode et al, 1996) and severe hypoglycaemia, without an increase in HbA_{1c}. Other studies (Chantelau et al, 1989; Boland et al, 1999; Fanelli et al, 2004) have also shown a reduction in hypoglycaemia with CSII. The decrease is partly due to better pharmacokinetic delivery of insulin and a 15–20% reduction in insulin requirements compared with MDI (Bode et al, 1996). Clearly, therefore, although all types of intensive therapy increase the risk of hypoglycaemia from non-optimised regimens, in many patients the frequency of severe hypoglycaemia is significantly reduced during CSII treatment, particularly when a short-acting insulin analogue is used (De Galan et al, 2006).

In the UK, patients need to have suffered episodes of severe hypoglycaemia before gaining funding for CSII (National Institute for Clinical Excellence, 2003). It could be argued that suitable patients should be offered CSII therapy at an earlier stage to pre-empt severe hypoglycaemia and associated fears. If CGM systems were available for suitable patients and able to link directly to CSII, this would further improve control with the possibility of eliminating hypoglycaemia.

Education programmes

Dose Adjustment For Normal Eating (DAFNE) is a structured education programme for people with type 1 diabetes on basal–bolus regimens

(DoH, 2005). Participants are empowered to match insulin doses to their food choices, while keeping their blood glucose level close to normal. The long-term evidence from DAFNE studies in Germany shows improved outcomes, including a reduction in the incidence of hypoglycaemia maintained for up to 6 years following the intervention (Mühlhauster and Berger, 2002).

The Department of Health (2005) recommends structured patient education but acknowledges the lack of structured education for CSII, suggesting that patients attend the DAFNE course before making the decision to commence CSII. However, this course does not cover the response needed for hypoglycaemia or the adjustments to the basal profile required. While it is useful to build upon the knowledge gained from DAFNE, further research is needed to ensure that structured education strategies are appropriate and effective for CSII users to further reduce the risk of hypoglycaemia.

Blood glucose awareness training (BGAT) involves behavioural techniques such as self-monitoring, direct feedback and active homework. Classes deal with recognising the symptoms of high and low blood glucose levels and physiological factors influencing accurate detection and interpretation, such as attention, distraction, completing explanations for hypoglycaemic events and denial. Further sessions provide information on food, exercise and insulin to enable participants to modify treatment decisions that may contribute to irregular blood glucose levels.

BGAT has been shown to improve the detection of hypoglycaemia (Cox et al, 1991). BGAT-2 was most effective in patients with hypoglycaemia unawareness. Participants maintained improved detection of hypoglycaemia and reduced frequency of low blood glucose levels at the 12-month follow-up. BGAT-2 also had beneficial effects on psychological functioning, e.g. improved judgment regarding when to raise low blood glucose and not to drive while hypoglycaemic. Improvement in these areas led to a reduction in concern about hypoglycaemia and an increase in quality of life and diabetes knowledge. The reduction in severe hypoglycaemia was not associated with worsening

Page points

1. Continuous glucose monitoring systems that can detect hypoglycaemia are welcome to both patients and clinicians as they could improve blood glucose control and reduce hypoglycaemia, especially at night.
2. Recombinant DNA technology has enabled the design of insulin that more accurately mimics the physiological insulin dynamics of people without diabetes.
3. CSII has been shown to reduce hypoglycaemia and severe hypoglycaemia without an increase in HbA_{1c}.
4. However, in the UK, patients need to have suffered episodes of severe hypoglycaemia before gaining funding for CSII.

Page points

1. Prevention and management of hypoglycaemia and glycaemic management of diabetes are complex and generally only partly successful.
2. Structured educational programmes have an important role to play in the prevention and management of hypoglycaemia unawareness.
3. Such programmes include DAFNE (dose adjustment for normal eating), blood glucose awareness training (BGAT) and HyPOS.
4. HyPOS is an educational programme from Germany designed specifically for people with type 1 diabetes who have hypoglycaemia problems. It focuses exclusively on low blood glucose values.

of HbA_{1c} (Cox et al, 2001).

HyPOS is an educational programme from Germany that was designed specifically for people with type 1 diabetes who have hypoglycaemia problems. The programme focuses exclusively on low blood glucose values. The efficacy of a newly developed programme to enhance hypoglycaemia awareness in a setting that resembles one commonly found in clinical practice rather than a research setting, which means this programme could easily be adopted by UK diabetes teams (Hermanns et al, 2007).

Clearly, structured education programmes have an important role to play in the prevention and management of hypoglycaemia unawareness.

Conclusion

If it were not for the potentially devastating effects of hypoglycaemia on the brain, the glycaemic management of type 1 diabetes would be straightforward. In reality, however, prevention and management of hypoglycaemia and glycaemic management of diabetes are complex and generally only partly successful. Further research is needed to elucidate the pathophysiology of counter-regulatory impairment and hypoglycaemia unawareness and enable the development of more targeted strategies that support glucose counter-regulation and consequently reduce hypoglycaemia.

CSII therapy has been proven to reduce severe hypoglycaemia, and so the working party review (DoH, 2007) was both timely and much needed. Continuous glucose monitoring systems may contribute to reducing hypoglycaemia, and linking these systems with CSII therapy could help eliminate the symptoms of hypoglycaemia, prevent the acute complications of hyperglycaemia and contribute to the prevention of long-term diabetes complications.

Many people with type 1 diabetes are currently treated with MDI with analogue insulins and education; however, with endogenous insulin, coupled with an imbalance of counter-regulatory hormones, hypoglycaemia is inevitable. Structured education highlighting the prevention and management of hypoglycaemia unawareness is clearly needed.

How can nurses recognise hypoglycaemia unawareness?

Studying hypoglycaemia unawareness has caused the author to change her day-to-day practice. In the past she would have offered little but praise for people with type 1 diabetes of long duration who had a good HbA_{1c}, other than enquiring how they were, and offering to check their equipment or examine injection sites. The author has always believed that there was little that the specialist nurse can teach people with diabetes after all of these years of them self-managing their diabetes. The only time she would have enquired about unawareness would be if an ambulance had been called or the patient or their family mentioned it. Now she actively looks out for people who have had diabetes of long duration in order to ask about hypoglycaemia unawareness. Currently, advice tends to be given on an individual basis as people with hypoglycaemia unawareness need to receive immediate education. Group education classes would need to be in addition to immediate individual advice and need to be planned, but are clearly needed in order to attempt to keep our patients, and those around them, safe. ■

Bingham EM et al (2005) *Diabetologia* 48: 2080–9
 Bode BW et al (1996) *Diabetes Care* 19(4): 324–7
 Boland EA et al (1999) *Acta Medica Scandinavica* 223(6): 543–8
 Bolli GB et al (2002) *Diabetes, Nutrition and Metabolism* 15(6): 402–9
 Chantrelau E et al (1989) *Diabetologia* 32(7): 421–6
 Clark M, Asimakopoulou KG (2005) Diabetes in older adults. In: Snoek FJ, Skinner TC (eds) *Psychology in Diabetes Care*. Wiley, Chichester
 Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W (1995) Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care* 18(4): 517–22
 Cox DJ et al (1991) *Psychosomatic Medicine* 53(4): 453–62
 Cox DJ et al (2000) *Diabetes Care* 23(2): 163–70
 Cox DJ et al (2001) *Diabetes Care* 24(4): 637–42
 Cryer PE (1993) *Diabetes Care* 16(Suppl 3): 40–7
 Cryer PE et al (2003) *Diabetes Care* 26(6): 1902–12
 De Galan BE et al (2006) *The Netherlands Journal of Medicine* 64(8): 269–79
 DeVries JH et al (2004). *Diabetes/Metabolism Research and Review* 20: S43–S46
 DCCT Research Group (1993) *NEJM* 329(14): 977–86
 DoH (2005) *Structured Patient Education in Diabetes. Report from the Patient Education Working Group*. DoH, London
 DoH (2007) *Insulin pump services: Report of the Insulin Pumps Working Group*. DoH, London
 Egger M et al (1997) *Diabetic Medicine* 14(11): 919–28
 Fanelli CG et al (1993) *Diabetes* 42(11): 1683–9
 Fanelli CG et al (2004) *Diabetes/Metabolism Research and Reviews* 20(Suppl 2): S32–S42
 Gonder-Frederick L et al (1997) *Diabetes Care* 20(4): 661–9
 Heller SR (2001) How should hypoglycaemia unawareness be managed? In: Gill G, Pickup J, Williams G (eds) *Difficult Diabetes*. Blackwell Science, Oxford
 Hermanns N et al (2007) *Diabetes/Metabolism Research and Reviews* 23(7): 528–38
 MacLeod KM (2000) *Journal of the Royal College of Physicians of London* 34(3): 245–50
 Mühlhauser I, Berger M (2002) *Diabetologia* 45(12): 1723–33
 NICE (2003) *Guidance on the Use of Continuous Subcutaneous Insulin Infusion for Diabetes. Technology Appraisal Guidance – No.57*. NICE, London
 Owens DR et al (2001) *Lancet* 358(9283): 739–46
 Rubin RR (2005) Counselling and psychotherapy in diabetes mellitus. In: Snoek FJ, Skinner TC (eds) *Psychology in Diabetes Care*. Wiley, Chichester
 Shillito R (1994) *Counselling People with Diabetes*. British Psychology Society, Leicester
 Williams G, Pickup JC (2004) *Handbook of Diabetes*. 3rd ed. Blackwell Publishing, Oxford

This article was written as part of a Diabetes and Complications postgraduate module at Brighton University. Dr John Quinn was Module Leader and Carmel Keller was Principal Lecturer.