Hypoglycaemia unawareness: causes, consequences and treatment

Kenneth M MacLeod MD MRCP, Senior Lecturer in Medicine and Consultant Physician, Royal Devon and Exeter NHS Trust, and Postgraduate Medical School, University of Exeter

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Hypoglycaemia: a limiting factor in the pursuit of normoglycaemia

Fear of hypoglycaemia is a powerful emotion among patients treated with insulin, and hypoglycaemia remains the major factor limiting attempts to achieve and sustain normoglycaemia with intensive insulin therapy. The Diabetes Control and Complications Trial (DCCT) reported a threefold greater risk of severe hypoglycaemia in those randomised to intensive insulin therapy1,2, with most of the episodes occurring during sleep (Table 1). The DCCT feasibility study had previously identified a history of severe hypoglycaemia before study entry and longer duration of diabetes to be predictive of severe hypoglycaemia; patients with these characteristics were excluded from the major prospective randomisation. The risk of severe hypoglycaemia which accompanies attempts to tighten glycaemic control in a less highly selected patient population may therefore be even greater.

In a four-year prospective study of a large clinic population of children with type 1 diabetes, tight glycaemic control, as evidenced by a reduction in the mean glycosylated haemoglobin from 10.2% to 8.8%, was associated with a dramatic increase in the rate of hypoglycaemia-related coma or convolution from 4.8 to 15.6 episodes/100 patient-years. The increase was particularly marked in children below the age of six years, in whom the rate increased from 14.9 to 42.1 episodes/100 patient-years3. Although the absolute frequency of hypoglycaemia is considerably lower in patients with type 2 diabetes, even in this group efforts to intensify glycaemic control have been associated with a significantly increased prevalence of hypoglycaemia, particularly in those treated with insulin.

It is self-evident that the risks of hypoglycaemia will be increased in patients achieving blood glucose concentrations close to normality. In contrast to those with poorer glycaemic control in whom the margins for error are proportionately greater, in tightly controlled patients even a modest mismatch in insulin dose, energy expenditure and carbohydrate consumption will risk hypoglycaemia. The degree of increased risk is, however, unexpected and occurs because hypoglycaemia begets hypoglycaemia in IDDM4; in other words, preceding hypoglycaemia promotes reduced symptomatic awareness and neuroendocrine responsiveness to subsequent hypoglycaemia, resulting in a progressive reduction in awareness of hypoglycaemia and an increase in hypoglycaemic risk. Impaired awareness of hypoglycaemia is a critical acquired defect in the defences against hypoglycaemia for patients with diabetes.

Hypoglycaemia (un)awareness

Loss of awareness of hypoglycaemia is not a new clinical entity. RD Lawrence described it clearly in 1941:

as years of insulin life go on, ... I find it almost the rule that the type of insulin reaction changes, the premonitory autonomic symptoms are missed out and the patients proceed directly to the more serious manifestations affecting the central nervous system ... insulin reactions may differ so much from the original ones that patients are dangerously unaware of their onset.

Approximately one-third of patients with diabetes of more than 15 years' duration experience loss of warning of hypoglycaemia. More recently, it has been appreciated that loss of warning of hypoglycaemia can also be an acute phenomenon associated with intensification of glucose control.

Hypoglycaemia elicits a characteristic sequence of responses in healthy humans which, together with their arteriatised venous glycaemic thresholds, include:

• decreased insulin secretion (at blood glucose ca 4.5 mmol/l)
• increased glucose counterregulatory hormone secretion (at blood glucose ca 3.6–3.8 mmol/l)
• symptoms of hypoglycaemia (at blood glucose ca 3.0 mmol/l)
• cognitive dysfunction (at blood glucose ca 2.6 mmol/l).

These glycaemic thresholds are dynamic rather than static, and they vary in relation to recent antecedent hypoglycaemia. In patients with well-controlled type 1 diabetes, lower plasma glucose concentrations are required to elicit autonomic activation, including adrenaline secretion, and to generate symptoms5. Amiel and co-workers' compared symptomatic and neuroendocrine responses to defined degrees of hypoglycaemia in young people with poorly controlled type 1 diabetes.

Table 1. Frequency of severe hypoglycaemia (all episodes requiring external help to promote recovery) and hypoglycaemia-induced convulsion or coma related to glycaemic control1.

| Episodes per 100 patient-years | Intensive treatment group | Conventional treatment group |
|-------------------------------|---------------------------|-----------------------------|
| Severe hypoglycaemia          | 62                        | 19                          |
| Hypoglycaemia-seizure or coma | 16                        | 5                           |
diabetes. Following a period of intensive glycaemic control, the counterregulatory responses to equivalent degrees of hypoglycaemia were markedly reduced, and the blood glucose concentration triggering a significant adrenaline response fell from 3.7 mmol/l to 2.6 mmol/l.

A single episode of hypoglycaemia blunts symptomatic and counterregulatory responses to subsequent hypoglycaemia in normal individuals, and Widom and Simonson replicated these findings in patients with type 1 diabetes. Twice weekly brief episodes of hypoglycaemia (i.e. a doubling of the average frequency of hypoglycaemia) reduces the adrenaline response and increases the proportion of undetected biochemical hypoglycaemia by 33% (Fig 1).

**Adrenaline response**

The defective counterregulation associated with hypoglycaemia unawareness is largely due to a reversible deficiency of adrenaline. Loss of the glucagon response is a ubiquitous defect which occurs early in the natural history of type 1 diabetes and is irreversible. Additional deficiency of adrenaline is seen in many patients with longer-term type 1 diabetes and further weakens defences against hypoglycaemia. Impaired adrenaline secretion is variable and inconsistent. It can occur acutely in the context of short duration diabetes following intensification of control. Even in young children this acquired adrenaline deficiency may contribute significantly to severe hypoglycaemia.

**Autonomic nervous system**

Hypoglycaemic unawareness, defective glucose counterregulation and elevated glycaemic thresholds for symptoms have been described as clinical syndromes which occur as dangerous iatrogenic sequelae of hypoglycaemia. These syndromes are best considered examples of hypoglycaemia-associated autonomic failure, distinct from classical diabetic autonomic neuropathy. The stimulus is specifically hypoglycaemia and not simply prior autonomic activation.

Hypoglycaemia stimulates both the sympathetic neural and adrenomedullary responses of the autonomic nervous system, but it is specifically the former that is reduced after antecedent hypoglycaemia. Beta-adrenergic sensitivity is reduced by antecedent hypoglycaemia in patients with type 1 diabetes; this reduction in tissue sensitivity to catecholamines contributes to the development of hypoglycaemia unawareness.

Hypoglycaemia unawareness is thus the product of a 'vicious circle' of preceding hypoglycaemia resulting in reduced autonomic symptom generation and reduced counterregulatory hormonal responses to subsequent hypoglycaemia, culminating in a significantly increased risk of future severe hypoglycaemia (Fig 2). Hypoglycaemia unawareness appears to result from a maladaptation of the cerebral glucose sensor which allows it to maintain its function during subsequent hypoglycaemia. The reduced response to hypoglycaemia is achieved by an increase in cerebral glucose utilisation, measured as an increased arteriovenous glucose difference. Animal work has suggested that this may result from increased expression of glucose transporters.

**Consequences of hypoglycaemia unawareness**

Patients with hypoglycaemia unawareness are at significantly increased risk of severe hypoglycaemia. Episodes of
severe hypoglycaemia can destroy confidence, relationships and livelihoods — if not lives. A full discussion of the myriad manifestations of acute hypoglycaemia is outwith the scope of this article, but can be found in Fri and Fisher's textbook, *Hypoglycaemia and diabetes: clinical and physiological aspects*. Suffice it to say that acute hypoglycaemia has been associated with a range of transient physical, cognitive and behavioural consequences. These include automatism, seizure disorder, stroke-like episodes, acute cognitive impairment, impaired driving performance and mood disturbance.

**Long-term sequelae**

What are the long-term sequelae of the recurrent severe hypoglycaemia to which patients with impaired awareness are clearly exposed? In a two-year retrospective review of young people with type 1 diabetes, severe hypoglycaemic reactions were more common in infants (55%) and children aged 2–5 years old (45%), than in children aged 5–9 years (13%)14. This is significant because the developing brain is particularly susceptible to hypoglycaemic injury. Children with insulin-dependent diabetes who have experienced hypoglycaemic seizures show long-term deficits in perceptual, motor, memory and attention tasks15. Data pertaining to the long-term consequences of recurrent severe hypoglycaemia in adults are less clear-cut. Some authors report a positive correlation between the frequency of severe hypoglycaemia and estimated IQ decrement in insulin-treated patients16 while others fail to find any such association17. This discrepancy may be because the subjects in the latter studies were young, of high mean intelligence, had diabetes of fairly short duration, and had experienced severe hypoglycaemia relatively infrequently. Case histories suggest that frequent severe hypoglycaemia and hypoglycaemia unawareness are associates of severe cognitive impairment and personality dysfunction in some patients with long-standing diabetes18.

**Key Points**

- Impaired awareness of hypoglycaemia is a critical acquired defect in defences against hypoglycaemia in patients with diabetes
- Hypoglycaemia unawareness results from a vicious circle of preceding hypoglycaemia which reduces the autonomic, symptomatic and counterregulatory hormonal response to subsequent hypoglycaemia
- Patients with hypoglycaemia unawareness are at significantly increased risk of severe hypoglycaemia
- Nocturnal hypoglycaemia can be considered ‘the submerged part of the hypoglycaemia iceberg’
- In all patients with type 1 diabetes, but particularly those with risk factors for severe hypoglycaemia, adjustments in insulin therapy should be directed at achieving safe glycaemic targets
- Avoiding hypoglycaemia and maintaining hypoglycaemic awareness must remain critical goals for patients with diabetes

**Fig 2. Vicious circle in which recurrent hypoglycaemia during intensive treatment of type 1 diabetes causes hypoglycaemia unawareness and impaired counterregulation, ultimately increasing the risk for severe hypoglycaemia** (adapted from Ref 11, with permission).

**Nocturnal hypoglycaemia**

Nocturnal hypoglycaemia has been described as the submerged part of the hypoglycaemia iceberg. Early studies suggested it occurred in 50% of insulin users, with 50% of episodes recognised by the patient. Even with modern insulin regimens, the frequency, severity and duration of nocturnal hypoglycaemia are significantly underestimated. Overnight glucose profiles in the home environment in 29 prepubertal patients with type 1 diabetes
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(median age 9.4 years) revealed asymptomatic hypoglycaemia (glucose <3.5 mmol/l) in 13 of 29 patients studied; four of these 13, together with a further seven, were hypoglycaemic on the second night. Median glucose was 1.9 mmol/l and median duration of hypoglycaemia was 270 minutes. These studies highlight the fact that young children using conventional insulin regimens are at high risk of profound asymptomatic nocturnal hypoglycaemia which is difficult to predict.

Unrecognised hypoglycaemia has also been implicated in the so-called ‘dead-in-bed’ syndrome which describes sudden death in young diabetic patients with uncomplicated disease. Autopsy in these patients is typically negative. Northern European studies have suggested that such deaths account for 6% of all deaths in diabetic patients under the age of 40 years. Tattersall and Gill reported 22 patients aged 12–43 years who were found ‘dead-in-bed’ in the UK in 1989; 19 of them were sleeping alone at the time of death, 20 were found lying in an undisturbed bed, and a history of nocturnal hypoglycaemia was noted in 14. The cause of premature death in these young people is not proven, but a plausible theory is death in hypoglycaemia. Attempts to normalise blood glucose should therefore proceed cautiously, particularly in those with a history of hypoglycaemia, and especially if they live alone.

Restoring awareness, reducing hypoglycaemia

If loss of awareness of hypoglycaemia occurs as a maladaptive response to preceding hypoglycaemic experience, it should be possible to prevent – and perhaps reverse – it by strict hypoglycaemia avoidance.

The first suggestion that restoration of hypoglycaemia awareness is possible came from observations in patients following curative treatment of insulinoma. Subsequent studies confirmed that hypoglycaemia awareness can be restored, and counterregulatory hormonal secretion (particularly adrenaline) recovered, following meticulous avoidance of hypoglycaemia in type 1 diabetes of both short and long duration.

Avoiding hypoglycaemia is the key to maintaining hypoglycaemia awareness and reducing the long-term risk of hypoglycaemia, so it is important that insulin therapy regimens for type 1 diabetes are designed not only to maintain near normoglycaemia but also to minimise hypoglycaemia. Such a goal is feasible provided that:

- a rational plan of insulin therapy is adopted, including the appropriate use of the short-acting insulin analogues
- blood glucose is properly monitored
- blood glucose targets are individualised
- education programmes are widely implemented

The induction of hypoglycaemia unawareness is not the inevitable consequence of intensifying glycaemic control. However, there are many economic, cultural and organisational barriers which make the long-term achievement of an HbA1c less than 7% without hypoglycaemia an elusive goal for many patients with type 1 diabetes. Scrupulous measures to minimise the risk of hypoglycaemia are essential for those at greatest risk of hypoglycaemia. The most consistently reliable predictors of future severe hypoglycaemia are a history of severe hypoglycaemia, hypoglycaemic injury and coma. In a prospective study, frequency of severe hypoglycaemia correlated significantly with duration of diabetes, awareness of hypoglycaemia, age, history of previous severe hypoglycaemia, and autonomic function scores.

Risk indicators

A critical review of home blood glucose monitoring data can help predict those at risk of severe hypoglycaemia. Patients with variable and frequently very low blood glucose readings during routine self-blood glucose monitoring are at increased risk for subsequent severe hypoglycaemia, whereas patients with lower glycosylated haemoglobin levels do not all show this increased risk. Recently, data generated from intensive self-blood glucose monitoring and stored on memory meters were mathematically modelled and a low blood glucose index (LBGI) computed for each patient. The clinical utility of LBGI was established over the following six months when low, moderate and high risk patients reported a frequency of severe hypoglycaemia of 0.4, 2.3 and 5.2 episodes, respectively (p = 0.001). While critical scrutiny of home blood glucose testing is perhaps the most valuable indicator of risk, hypoglycaemia unawareness should be considered in those with very low HbA1c readings (eg <6.0%; upper limit of normal 5.5%).

Modification of treatment strategies

Some studies have suggested that the majority of patients make clinically serious errors in glucose estimation, and use symptoms that do not discriminate between hyperglycaemia and hypoglycaemia. Individualised training to increase awareness of glucose-related symptoms has been advocated. Intensive education programmes such as blood glucose awareness training (BGAT) enhance the patients’ ability to estimate their blood glucose concentrations correctly and to detect hypoglycaemia at an early stage. Preliminary studies suggest that after BGAT the incidence of hypoglycaemia decreases, the blunting of adrenaline responses is attenuated, and the severity of hypoglycaemia reduced. There has even been a report that such patients are less frequently involved in road traffic accidents.

A review of other lifestyle factors is also worthy of consideration. Avoidance or moderation of alcohol is clearly important since alcohol reduces symptomatic awareness of developing hypoglycaemia and impairs the counterregulatory hormonal responses, particularly adrenaline and growth hormone.
Modification of insulin therapy

In all patients with type 1 diabetes, but particularly those with risk factors for severe hypoglycaemia, adjustments in insulin therapy should be directed at achieving safe glycaemic targets. This should include a more conservative definition of hypoglycaemia as a plasma glucose concentration less than 4.0 mmol/l, a message which found popular expression in the British Diabetic Association’s ‘Make Four the Floor’ campaign. Continuous subcutaneous insulin therapy has been recommended as the most physiological way of replacing insulin, but in most centres multiple daily insulin injections are the most practical alternative. Avoiding fixed mixtures of soluble and isophane insulin before the evening meal is an important strategy, allowing appropriate adjustment of insulin to control the fasting blood glucose concentration without increasing the risk of nocturnal hypoglycaemia.

Some studies have suggested that the use of rapid acting insulin analogues, which allow more immediate preprandial insulin substitution, are associated with significant reductions in hypoglycaemia. In an early report of 199 tightly controlled patients with type 1 diabetes, the frequency of hypoglycaemic coma was reduced during treatment with Lispro from 36 to three episodes in a six-month period, and the frequency of severe hypoglycaemia was reduced from 58 to 36 episodes. A recent review of all the data available on hypoglycaemic events from 24 controlled clinical trials was, however, more guarded. A significant reduction in mild hypoglycaemia was reported in five of 22 studies, no change in the frequency of severe hypoglycaemia in 10/12 studies and a reduction in nocturnal hypoglycaemia in only 6/22. Thus, while any reduction of hypoglycaemia is welcome, the benefits of a switch to an analogue insulin may not be as significant as initially hoped.

A number of other measures have been suggested as potentially useful, but they require further investigation. Caffeine has been reported to augment the sympatho-adrenal and autonomic symptomatic responses to hypoglycaemia with improved symptomatic awareness. The beta-blocker propranolol may also be useful in restoring autonomic symptoms during hypoglycaemia in diabetic patients without warning symptoms, with the beneficial effect predominantly related to an increase in hypoglycaemia-induced sweating.

An encouraging message from recent clinical trials is that integrating the above strategies can lead to the achievement of excellent glycaemic control without severe hypoglycaemia. Indeed, an Italian group achieved a 60-fold lower frequency of severe hypoglycaemia than in the experimental group of the DCCT despite similar HbA1c levels. Avoiding hypoglycaemia and maintaining hypoglycaemia awareness must remain centre stage as critical therapeutic goals for patients with diabetes.

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Address for correspondence: Dr K M MacLeod, Department of Diabetes and Vascular Medicine, Royal Devon and Exeter NHS Trust and Postgraduate Medical School, University of Exeter, Barrack Road, Exeter EX2 5AX. E-mail: k.m.macleod@exeter.ac.uk

New hypoglycaemic therapies.

Edwin A M Gale FRCP, Professor of Diabetic Medicine, University of Bristol

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Background
Therapeutic options for the treatment of diabetes were for many years limited to diet, metformin, sulphonylureas and insulin. In the 1990s, a number of new agents became available, with many others in development1. At the same time, a new impetus towards improved glucose control was provided by the results of the Diabetes Control and Complications trial in type 1 diabetes2 and of the UK Prospective Diabetes Study in type 2 diabetes3. Both studies showed clear benefits from more aggressive treatment of blood glucose. In the aftermath of these studies insulin monotherapy remains the treatment of choice for type 1 diabetes, but treatment of type 2 diabetes now aims for tight control of hypertension, hyperlipidaemia and other elements of cardiovascular risk in addition to improved blood glucose control. A typical patient with actively treated type 2 diabetes may, for example, be using insulin, metformin, a statin, an angiotensin-converting enzyme inhibitor and aspirin in addition to anti-anginal therapy. Polypharmacy means that issues such as compliance and possible drug interactions become increasingly important.

New therapies for type 1 diabetes
Type 1 diabetes causes pancreatic beta cell failure, and treatment is by hormone replacement. The principle is simple, but in practice it is extremely difficult to imitate the physiological pattern of insulin secretion. The most successful means of doing this — other than by insulin infusion pump therapy — is to inject a quick acting insulin before each main meal, with bedtime insulin to cover basal insulin requirements during the night. New short-acting insulin analogues have been introduced to provide better meal-time insulin replacement, and long-acting analogues will soon be available to cover the overnight period.

Short-acting insulin analogues
Two preparations are now available: insulin lispro and insulin aspart. Lispro is prepared by reversal of proline and lysine on positions 27 and 28 of the insulin B chain, and aspart by substitution of aspartate for proline on position B28. These analogues have receptor binding characteristics similar to human insulin, but dissociate more rapidly from hexameric configuration following injection. Peak action is reached within 30–45 minutes compared with 60–90 minutes with standard soluble insulin preparations. More rapid absorption means shorter duration of action, so comparisons with standard insulin preparations have tended to show lower postprandial but higher preprandial glucose levels, with little or no change in glycated haemoglobin (HbA1c).

Marketing claims that these insulins can be injected immediately before meals and are more convenient should be considered critically. Optimal matching of meals and insulin is achieved if the analogues are given 15–20 minutes before meals, rather than immediately before. Equally, blinded comparisons have shown that HbA1c levels are unaffected if soluble insulin is substituted for a rapid acting analogue injected shortly before a meal. Patients who want the convenience of pre-meal injection will, in general, achieve the same HbA1c if they inject their usual insulin before eating4.

[Note: The text contains references and addresses for correspondence, which are not included in the plain text representation.]