

Hypoglycaemia in diabetes

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Why is hypoglycaemia important?

The achievement and maintenance of blood glucose concentrations as near normal as possible are major targets of modern diabetes care.^{1,2} Unfortunately, this increases the frequency of hypoglycaemia, so people with diabetes are all too familiar with insulin acting at the wrong time or intensity.³ Hypoglycaemia, the most common acute complication of type 1 diabetes, usually develops rapidly. Its effects range from mild symptoms to brain damage or death.⁴ Alarming, severe hypoglycaemia may occur with no perceived symptoms. In elderly people, it can mimic stroke. A young person with type 1 diabetes presenting with a seizure has a hypoglycaemia-induced convulsion unless proven otherwise.

Hypoglycaemia is important because it limits therapeutic efforts to attain normoglycaemia and protect against long-term complications. It embarrasses, frightens and injures people with diabetes so that fear of hypoglycaemia can dominate their own and their families' lives.

How common is hypoglycaemia?

Major hypoglycaemia was experienced by 27% of patients with intensively treated type 1 diabetes in the Diabetes Control and Complications Trial (DCCT) but by only 2% of those in the UK Prospective Diabetes Study (UKPDS) of type 2 diabetes despite broadly similar levels of glycaemic control.^{1,5} Thus, the rates of severe hypoglycaemia in type 2 diabetes are substantially lower than those seen in type 1 diabetes (of the order of 10% lower).⁶

When it does occur, however, severe hypoglycaemia may have more serious consequences than in type 1 diabetes because older people have more comorbidities (Table 1). In the UKPDS study over the first 10 years, major hypoglycaemia rates varied with treatment modality:²

- diet treated patients: 0.5%
- chlorpropamide: 0.4%
- glibenclamide: 0.6%
- insulin: 2.3%.

Hypoglycaemia-associated autonomic failure

The pursuit of normoglycaemia in diabetes is bedevilled because 'hypoglycaemia begets hypoglycaemia'.⁸ Indeed, the single most significant risk factor for severe hypoglycaemia is previous severe hypoglycaemia. In insulin deficient dia-

betes, (exogenous) insulin-levels do not decrease as glucose levels fall so the integrity of counter-regulatory hormonal responses assumes greater significance. The glucagon response to hypoglycaemia is blunted with increasing duration of type 1 diabetes so the catecholamine response becomes the critical defence mechanism. The epinephrine response is itself progressively blunted by antecedent hypoglycaemia, as is awareness of hypoglycaemia. The coexistence of deficient glucagon and epinephrine responses constitutes a major breach in counter-regulatory defence. The combination of defective glucose counter-regulation and impaired awareness of hypoglycaemia due to antecedent hypoglycaemia is termed hypoglycaemia associated autonomic-failure (HAAF) (Fig 1). By shifting glucose thresholds for the symptomatic, autonomic and neuroendocrine (sympathoadrenal)

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

Episodes per 100 patient-years	Treatment group	
	Intensive	Conventional
Severe hypoglycaemia	62	19
Hypoglycaemia seizure or coma	16	5

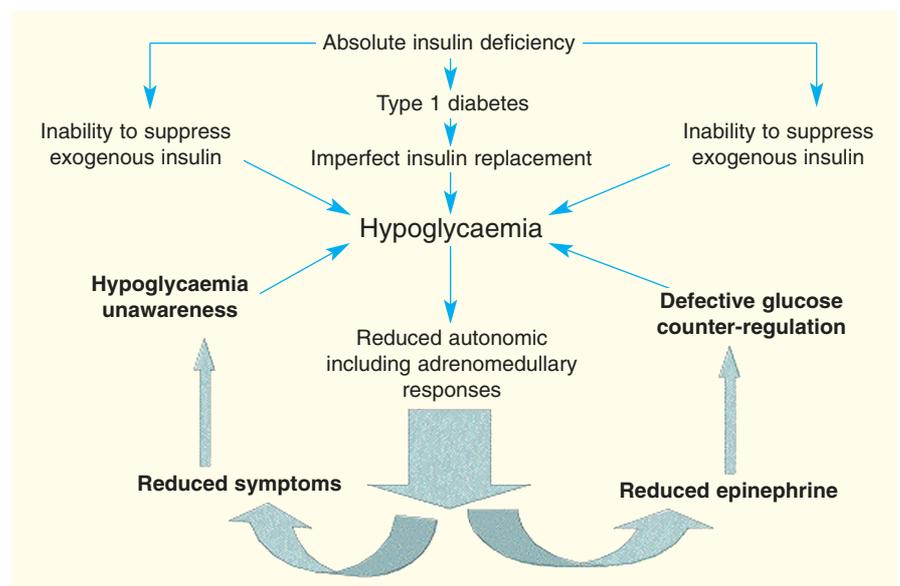


Fig 1. Hypoglycaemia-associated autonomic failure in diabetes (modified, with permission, from Ref 6).

responses, antecedent hypoglycaemia leads to a vicious cycle of recurrent hypoglycaemia and further impairment of glucose counter-regulation. HAAF is reversible with perhaps as little as three weeks of scrupulous avoidance of hypoglycaemia; this can restore hypoglycaemia awareness and improve the reduced epinephrine (but not the glucagon) response.⁶

Prediction and prevention

The symptoms of hypoglycaemia are idiosyncratic, non-specific and variable, even within an individual. The most important aspect of prevention is for patients to have a low threshold for considering hypoglycaemia the cause of any unusual symptoms or signs, and treating it. Among the most consistent predictors of severe hypoglycaemia are:

- previous severe hypoglycaemia
- recurrent asymptomatic hypoglycaemia (especially nocturnal)
- impaired awareness, long duration of diabetes
- intensified insulin therapy.^{9,10}

In a five-year prospective study of young people with type 1 diabetes⁴ the risk of severe hypoglycaemia increased 1.5-fold per 2% reduction in haemo-

globin A1c (HbA1c). Hypoglycaemia is also particularly prevalent and problematic in the first trimester of pregnancy.¹⁰ The risk factors and appropriate remedies are summarised in Table 2, with the most important factors considered in more detail below.

Nocturnal hypoglycaemia

Nocturnal hypoglycaemia affects over 50% of insulin users, particularly children, and is often unrecognised. It can predispose to both asymptomatic and potentially severe hypoglycaemia on the next day. Eliminating nocturnal hypoglycaemia by more physiological insulin replacement and more carefully matching it to carbohydrate intake has therefore gained an entirely appropriate momentum.³

Symptomatic awareness

Assessment of a patient's symptomatic awareness of hypoglycaemia and risk of severe hypoglycaemia should be a routine part of diabetes care. Awareness changes with recent glycaemic targets and hypoglycaemic experience. In clinical practice, a useful question is 'What symptoms tell you that your blood glucose is too low?'. Patients who report autonomic symptoms (sweating, shaking

and palpitations) as their 'early warning' symptoms are likely to have adequate awareness; those who rely on neuroglycopenic symptoms (confusion, slurred speech, unsteadiness) are likely to have impaired awareness.

An often informative subsidiary question is 'Are you usually able to detect hypoglycaemia before your partner, or are they usually the first to realise you are hypo and draw your attention to it?'. Where possible, the answer should be corroborated by the partner.

More objective assessment comes from the patient's diary or a download of meter results. A diary that shows repeated asymptomatic biochemical hypoglycaemia strongly suggests impaired hypoglycaemia awareness. An HbA1c in the normal (non-diabetic range) should alert the physician to the possibility of unrecognised hypoglycaemia.

Awareness of hypoglycaemia is impaired in about 25% of people with type 1 diabetes, increasing sixfold the risk of severe hypoglycaemia; the comparable figures for type 2 diabetes are 8% and ninefold.¹¹

Genetic predisposition

Recent evidence suggests that angiotensin-converting enzyme (ACE) genotype and serum ACE concentrations may provide useful markers for risk of severe hypoglycaemia in adults and children.¹² Further study is required to determine whether these can be added to other hypoglycaemic risk factors better to identify patients at risk of severe hypoglycaemia and whether they can be modified by ACE inhibition.

Recognition and treatment

It is possible to lessen the daily burden of hypoglycaemia without compromising glycaemic targets by heightening awareness (patient and professional), better education and skills training, and more physiological and lifestyle sensitive insulin replacement. New technologies include:

- continuous glucose sensors
- ultra quick-acting and basal analogue insulin

Table 2. Risk factors and remedies for hypoglycaemia (adapted, with permission, from Ref 3).

Risk factor	Remedy
Non-physiological insulin profiles or failure to anticipate them	Between meal and pre-bed snacking Bedtime isophane insulin Consider newer analogue insulin
Prolonged hypoglycaemia after vigorous or sustained exercise	Reduce overnight insulin after unusually active day
Delayed action of alcohol	Avoid alcohol excess Reduce overnight insulin if intake associated with exertion
Hypoglycaemia unawareness	Aim to restore awareness by: <ul style="list-style-type: none"> ● scrupulous avoidance of hypoglycaemia ● relaxation of glycaemic targets (pre-meal 4 mmol/l, pre-bed 7 mmol/l) ● more physiological insulin replacement
Limited knowledge and skills about: <ul style="list-style-type: none"> ● hypoglycaemia recognition ● treatment ● prevention 	Education for both patient and healthcare professional

- continuous subcutaneous insulin infusion
- education: blood glucose awareness training.

Continuous glucose monitoring

Asymptomatic nocturnal hypoglycaemia and postprandial hyperglycaemia not evident from routine fasting and pre-meal blood glucose monitoring can be detected with continuous glucose monitoring (CGM) devices. In one recent study, unrecognised hypoglycaemia was detected by CGM in 62.5% and 42.5% of type 1 and type 2 patients, respectively. This information can help adjust insulin replacement to optimise glycaemic control with minimal hypoglycaemia.^{13,14}

Ultra quick-acting and basal analogue insulins

Insulin lispro and insulin aspart are more rapidly absorbed from subcutaneous tissue and have a quicker and shorter action than human soluble insulin. Substituting a rapid acting analogue has been reported to reduce the incidence of hypoglycaemia in intensively treated patients at high risk of nocturnal hypoglycaemia.¹⁵

The ideal basal insulin should have a prolonged activity profile following a single daily dose, no pronounced peaks in activity and reproducible absorption when injected subcutaneously. The search for such an insulin has yielded insulin glargine (LANTUS®). Evidence to date suggests it can reduce fasting glucose more effectively than previous retarded formulations of soluble insulin (NPH and ultralente) with less nocturnal hypoglycaemia, particularly in type 2 diabetes.¹⁶ Insulin detemir may offer similar advantages.

Continuous subcutaneous insulin infusion

Some studies have shown that continuous subcutaneous insulin infusions can achieve better and more stable glycaemic control than multiple injection therapy without increased hypoglycaemia, though others have not. A recent review has suggested that short-acting insulin

Table 3. The most important benefits of blood glucose awareness education and training.

- Improved detection of hypoglycaemia and hyperglycaemia
- Improved judgment regarding when to reduce high glucose, raise low glucose and not drive while hypoglycaemic
- A lower incidence of ketoacidosis, severe hypoglycaemia and road traffic accidents
- Better mood, quality of life and diabetes knowledge
- Less worry about hypoglycaemia.

analogues delivered via pumps can achieve good glycaemic control with reduced hypoglycaemia in carefully selected patients.¹⁷

Education: blood glucose awareness training

Increasingly robust evidence shows that targeted intervention for patients with type 1 diabetes using a programme of educational and psychological initiatives, together providing 'blood glucose awareness training', have sustained and broad-ranging positive effects.¹⁸ The main benefits found in the study are listed in Table 3. Importantly, the incidence of hypoglycaemia was reduced without any worsening of metabolic control and the programme was most effective in those with reduced hypoglycaemia awareness.

Table 4. Employment standards for patients with diabetes being considered for potentially hazardous occupations (reproduced, with permission, from Diabetes UK).

- Patient should be physically and mentally fit in accordance with non-diabetic standards
- Their diabetes should be under regular (at least annual) specialist review
- Their diabetes should be under stable control
- They should be regularly self-monitoring their blood glucose and be motivated and well educated in diabetes self-care
- There should be no disabling hypoglycaemia
- There should be normal awareness of individual hypoglycaemic symptoms
- There should be no advanced retinopathy or nephropathy and no severe peripheral neuropathy or autonomic neuropathy
- There should be no significant coronary heart disease, peripheral vascular disease or cerebrovascular disease
- Suitability for employment should be reassessed annually by both an occupational and a diabetes specialist physician

Driving and employment issues

Acute hypoglycaemia impairs cognitive and psychomotor skills. Despite this, most studies suggest hypoglycaemia-related road traffic accidents are rare events.¹⁹ A responsible, collaborative approach between patients, healthcare professionals and licensing authorities is needed to make decisions appropriate to an individual's risk of hypoglycaemia and type of driving (long-distance, shift, night-time etc).

Diabetes consultations, particularly with patients on insulin, should emphasise that the privilege of driving goes hand-in-hand with the responsibility of appropriate self-management. Similarly, there should be individual assessment of the risk of work in hazardous roles or environments. Diabetes UK has produced guidelines for assessment for people with insulin-treated diabetes and their suitability for hazardous employment (Table 4). While deliberately non-prescriptive, the guidelines detail key factors that may be helpful when completing employment medicals.

Good glycaemic control – what is it? Towards a patient centred-definition

The above discussion means that any therapeutic targets based solely on rigid metabolic or cardiovascular risk indicators must be jettisoned. Instead, 'good glycaemic control' should be considered the level most closely approximating

Key Points

Susceptibility to hypoglycaemia limits attempts to achieve normoglycaemia in diabetes

The rate of severe hypoglycaemia is tenfold lower in type 2 than in type 1 diabetes but it may have serious consequences, particularly in old people with comorbidities

Assessment of a patient with diabetes should include assessment of their symptomatic awareness of hypoglycaemia and risk of severe hypoglycaemia

Hypoglycaemia unawareness increases the risk of severe hypoglycaemia six-to ninefold

New technologies to reduce hypoglycaemia include continuous glucose sensors, short- and long-acting insulin analogues, pump treatment and blood glucose awareness training

Hypoglycaemia has major implications for driving and employment, requiring knowledgeable, sensitive and individualised management

KEY WORDS: autonomic failure, diabetes, driving, education, employment, hypoglycaemia, type 1 diabetes, type 2 diabetes

normal without troublesome side effects, particularly hypoglycaemia, since any individual event is unpleasant and predisposes to further, potentially more serious, events.³

Conflict of interest

None.

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