Hypoglycaemia in diabetes

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Abstract

Hypoglycaemia is a feared and common unwanted effect of diabetes treated with insulin or sulfonylureas, and is the main reason why insulin-treated individuals often fail to achieve the levels of glycaemic control necessary to prevent diabetic complications. Normal brain function depends upon a continuous supply of glucose. If blood glucose falls below normal, interruption of this supply leads to cerebral dysfunction and, if it is not corrected, confusion and coma. Hypoglycaemia results chiefly from the inability of current glucose-lowering therapies to reproduce the physiology of the pancreatic β-cell, leading to inappropriately high insulin concentrations between meals and at night. Early after diagnosis, patients are partly protected by 'physiological' defences to hypoglycaemia that ensure release of adrenaline and glucagon as glucose falls below normal, and resist the glucose-lowering effect of insulin. In addition, activation of the sympatho-adrenal system provokes symptoms that patients learn to recognize and treat by eating or drinking. With increasing duration of diabetes, and following episodes of hypoglycaemia, these defences become impaired and patients are increasingly at risk of severe episodes, particularly if they develop 'hypoglycaemia unawareness'. Hypoglycaemia may be reduced through patient education and individualized glycaemic targets. Newer insulin delivery and glucose-sensing technologies offer promise for those in whom this is a recurrent problem.

Keywords Adrenaline; cerebral dysfunction; glucagon; hypoglycaemia; hypoglycaemia unawareness; sudden death; type 1 diabetes; type 2 diabetes

What's new?

- Hypoglycaemia is associated with adverse cardiovascular outcomes and sudden death in clinical trials, highlighting the possibility that hypoglycaemia may be dangerous in patients with pre-existing ischaemic heart disease
- Glycaemic therapies should be individualized to minimize the risk of hypoglycaemia. Glycaemic targets should be less stringent in vulnerable populations such as the elderly and cognitively impaired. An increasing range of glucose-lowering agents is available, including incretin-based therapies and analogue insulins associated with a lower risk of hypoglycaemia
- Insulin pumps and continuous interstitial glucose monitoring systems are therapeutic options in patients with recurrent hypoglycaemia. The latest systems that are able to automatically suspend insulin at low blood glucose concentrations are effective in reducing nocturnal hypoglycaemia. 'Closed loop devices' that can detect blood glucose concentration and automatically adjust insulin infusion rates are in clinical trials. When combined with patient education, they have the potential to reduce the risk of hypoglycaemia without compromising glucose control

Hypoglycaemia is a major factor preventing patients with diabetes mellitus from achieving the glucose targets needed to prevent diabetic complications. The incidence of hypoglycaemia reflects the limitations of current glucose-lowering therapies, which leads to inappropriately high insulin concentrations, particularly some hours after eating and at night.

Physiological defences against hypoglycaemia

Hypoglycaemia is a problem because the brain depends on a constant supply of glucose to maintain its function. Alternative fuels (e.g. lactate, ketones) can be utilized by the central nervous system (CNS), but during acute insulin-induced hypoglycaemia there is insufficient time for this switch to occur. Thus, as glucose concentration decreases below 3.5 mmol/L, the reduction in the delivery of glucose to cerebral neurones provokes a CNS response. Hypoglycaemia is sensed in the hypothalamus and other areas of the brain, initiating activation of the autonomic nervous system. In those with diabetes, this can limit the severity of an episode, not only by releasing hormones that oppose the action of insulin but by generating symptoms that alert the individual to an impending episode. The sympathetic nervous system is normally activated at a glucose concentration of about 3.7 mmol/L – above the threshold (3.0 mmol/L) at which cognitive function starts to decline (Figure 1).

Hypoglycaemia also leads to the release of glucagon and adrenaline, which limit the fall in glucose by stimulating hepatic glucose release, and reducing glucose uptake into fat and muscle. Other hormones, including growth hormone and cortisol, are also released during hypoglycaemia but have a relatively minor role in combating hypoglycaemia induced by insulin.

The glucagon response to hypoglycaemia begins to fail within 1–2 years of diagnosis in type 1 diabetes, and within 5 years an impaired or absent response is almost universal. A reduced adrenaline response is also common. Both defects represent failure of the body to sense hypoglycaemia; responses to other stimuli are normal. Patients who acquire reduced glucagon and adrenaline responses are particularly susceptible to hypoglycaemia during treatment. This is partly because of their inability to mount an endocrine defence against the glucose-lowering effect of insulin, but also because impaired sympatho-adrenal defences against hypoglycaemia are associated with hypoglycaemia unawareness.

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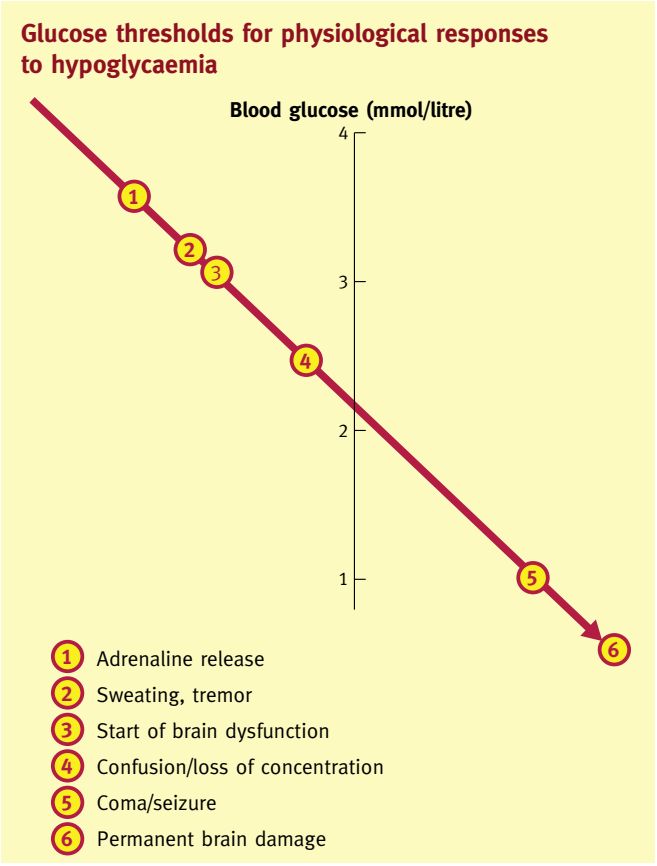
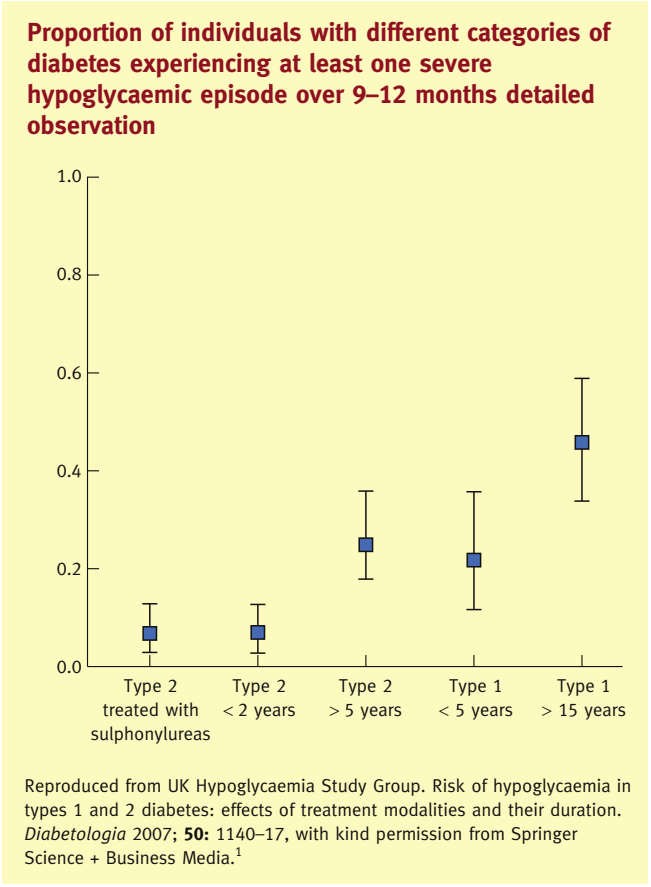


Figure 1



Reproduced from UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007; **50:** 1140–17, with kind permission from Springer Science + Business Media.[1]

Figure 2

Epidemiology

The incidence of severe hypoglycaemia is about 20% per year of patients with type 1 diabetes within a few years of diagnosis but increases to as much as 50% per year in those with longstanding disease.[1] The risk is lower in those with type 2 diabetes but still common; recent estimates suggest severe events are experienced by around 7% a year in those taking sulfonylureas, comparable to those who have recently started using insulin (Figure 2). However, because type 2 diabetes is ten times more common than type 1, severe hypoglycaemia is actually a bigger clinical problem in people with type 2 diabetes and increases with the duration of insulin treatment. Prolonged and occasionally fatal hypoglycaemia can occur in those taking sulfonylureas, particularly in the elderly, patients with renal impairment, and those taking long-acting preparations such as glibenclamide.[2]

Clinical features

The clinical features of hypoglycaemia reflect activation of the autonomic nervous system and include sweating, tremor and palpitations. Other symptoms (e.g. loss of concentration, confusion) are caused by cerebral dysfunction, as a consequence of reduced glucose availability (neuroglycopenia) (Table 1). More rarely, hypoglycaemia leads to abnormal behaviour such as aggression and fugue states. Hemiplegia with a normal conscious level is well described. Severe and prolonged hypoglycaemia causes coma and seizures (focal or generalized). Profound hypoglycaemia can cause irreversible brain damage and even death, but this is rare and most cases are associated with alcohol or suicidal overdose.

The possibility that hypoglycaemia may increase cardiac mortality was raised by the premature termination of a North American trial of intensive glucose control in individuals with type 2 diabetes.[3] Hypoglycaemia could also explain increased mortality associated with trials of intensive insulin therapy in critical care settings.[4] Catecholamine release during hypoglycaemia may provoke cardiac arrhythmias through altered sympathovagal balance and abnormal cardiac repolarization.[5] Hypoglycaemia increases the tendency to thrombosis and can provoke myocardial ischaemia by increasing myocardial oxygen

Symptoms of hypoglycaemia

Autonomic

- Sweating
- Palpitations
- Shaking
- Hunger

Neuroglycopenic

- Confusion
- Speech difficulty
- Drowsiness
- Odd behaviour
- Incoordination

Table 1

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