Hypoglycaemia in diabetes

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Abstract

Hypoglycaemia is a feared and common unwanted effect of diabetes mellitus treated with insulin or sulfonylureas; it is the main reason insulin-treated individuals often fail to achieve the levels of glycaemic control necessary to prevent diabetic complications. Normal brain function depends on a continuous supply of glucose. If blood glucose falls below normal, interruption of this supply leads to cerebral dysfunction and, if not corrected, confusion and coma. Hypoglycaemia results chiefly from the inability of current glucose-lowering therapies to reproduce pancreatic β-cell physiology, 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 (epinephrine) 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 after episodes of hypoglycaemia, these defences become impaired, and patients are increasingly at risk of severe episodes, particularly if they develop 'hypoglycaemia unawareness'. Hypoglycaemia can be reduced through patient education and individualized glycaemic targets. Newer insulin delivery and glucose-sensing technologies offer promise if this is a recurrent problem.

Keywords Adrenaline (epinephrine); cerebral dysfunction; glucagon; hypoglycaemia; hypoglycaemia unawareness; MRCP; sudden death; type 1 diabetes; type 2 diabetes

Introduction

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.

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Key points

- Mild hypoglycaemia is an inevitable part of insulin treatment in individuals whose diabetes is well controlled, particularly in type 1 diabetes
- Severe episodes may not have an obvious cause and can occur without warning, even in individuals with above-target glycaemic control
- Hypoglycaemic episodes contribute to progressive impairment of the physiological defences and reduced awareness and can be partly reversed by scrupulous avoidance of hypoglycaemic episodes
- Prolonged severe, occasionally fatal, hypoglycaemia can be precipitated by sulfonylureas, particularly in individuals who are elderly or have renal impairment
- Patient education and individualization of therapy are key to reducing the burden of hypoglycaemia. Technology (insulin pumps, continuous interstitial glucose monitoring systems) is an important therapeutic option in patients with problematic hypoglycaemia. When combined with patient education, this has the potential to reduce risk of hypoglycaemia without compromising glucose control

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 used 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 to <3.5 mmol/litre, the reduction in delivery of glucose to cerebral neurons provokes a CNS response.

Hypoglycaemia is sensed in the hypothalamus and other areas of the brain, initiating activation of the autonomic nervous system. In individuals with diabetes, this can limit the severity of an episode, not only by releasing hormones that oppose the action of insulin, but also by generating symptoms that alert the individual to an impending episode. The sympathetic nervous system is usually activated at a glucose concentration of about 3.7 mmol/litre – above the threshold (3.0 mmol/litre) at which cognitive function starts to decline (Figure 1).

Hypoglycaemia also leads to the release of glucagon and adrenaline (epinephrine), 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 mellitus, and within 5 years an impaired or absent response is almost universal. A reduced adrenaline response is also common. Both defects

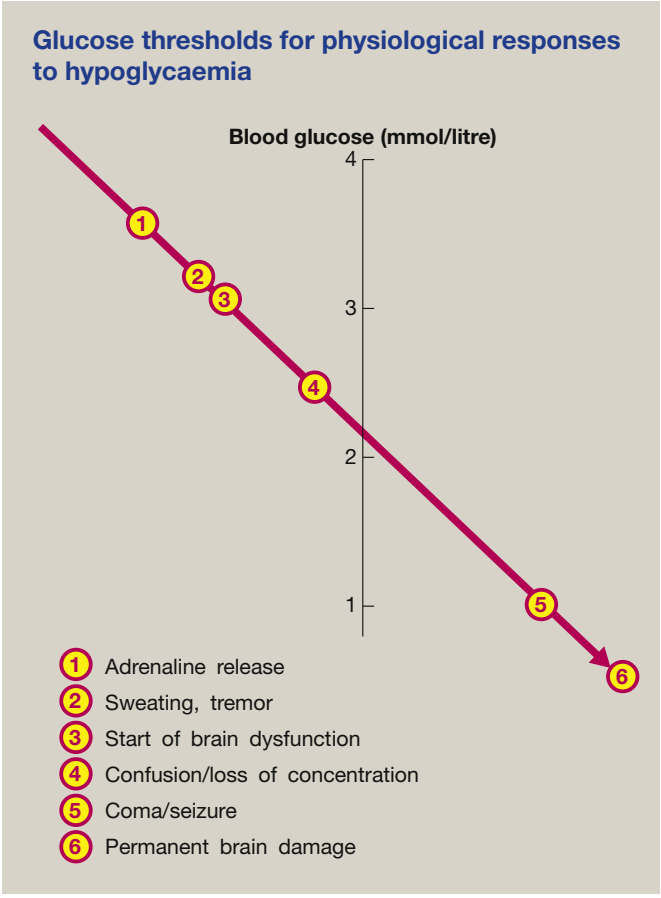

Figure 1

represent a 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 impaired awareness of hypoglycaemia.

How is hypoglycaemia defined?

The glycaemic thresholds for symptoms of hypoglycaemia and for counter-regulatory responses are not fixed among individuals with diabetes, and can also vary in the same person with time. Defining hypoglycaemia in clinical practice and clinical trials is therefore challenging. The classification of hypoglycaemia has recently been revised, published as a position statement and widely adopted across the diabetes community:[1]

- **Level 1** – a glucose concentration of <3.9–3.0 mmol/litre (<70–54 mg/dl) with or without symptoms. Readings at this value are an alert to both patient and professional that the individual is at risk of clinically important hypoglycaemia. These values need rechecking, and treating if still low. Repeated episodes require adjustment of therapy.
- **Level 2** – a glucose concentration of <3.0 mmol/litre (<54 mg/dl) with or without symptoms. This should be considered clinically significant hypoglycaemia associated with impaired awareness, cardiac arrhythmias plus an increased risk of severe episodes. It requires adjustment of therapy and specific attention.
- **Level 3** – severe hypoglycaemia, defined as severe cognitive impairment requiring external assistance for recovery, or causing coma or seizure. It is not defined by a specific blood glucose value, but concentrations are likely to be 2 mmol/litre (36 mg/dl) or below.

Epidemiology

The incidence of severe hypoglycaemia is about 20% per year in individuals with type 1 diabetes mellitus within a few years of diagnosis, but increases to as much as 50% per year in those with long-standing disease. The risk is lower in patients with type 2 diabetes but it is still common: recent estimates suggest severe events are annually experienced by around 7% of those taking sulfonylureas, comparable to those who have recently started using insulin (Figure 2). However, because type 2 diabetes is 10 times more common than type 1, severe hypoglycaemia is numerically, 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 individuals who are elderly, have renal impairment or are taking long-acting sulfonylurea preparations such as glibenclamide.

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 can increase cardiac mortality was raised by the premature termination of a North American trial of intensive glucose control in individuals with type 2 diabetes.[2] Hypoglycaemia could also explain the increased mortality associated with trials of intensive insulin therapy in critical care settings. Catecholamine release during hypoglycaemia may provoke cardiac arrhythmias through altered sympatho-vagal balance and abnormal cardiac repolarization. Hypoglycaemia increases the tendency to thrombosis and can provoke myocardial ischaemia by increasing myocardial oxygen demand. These mechanisms may increase the risk of cardiovascular death in individuals with pre-existing ischaemic heart disease.

Hypoglycaemia unawareness

Difficulty recognizing impending hypoglycaemia is a problem for about one-quarter of all patients with type 1 diabetes and almost 50% of those who have had diabetes for >20 years. Impaired

Proportion of individuals with different categories of diabetes experiencing at least one severe hypoglycaemic episode over 9–12 months detailed observation

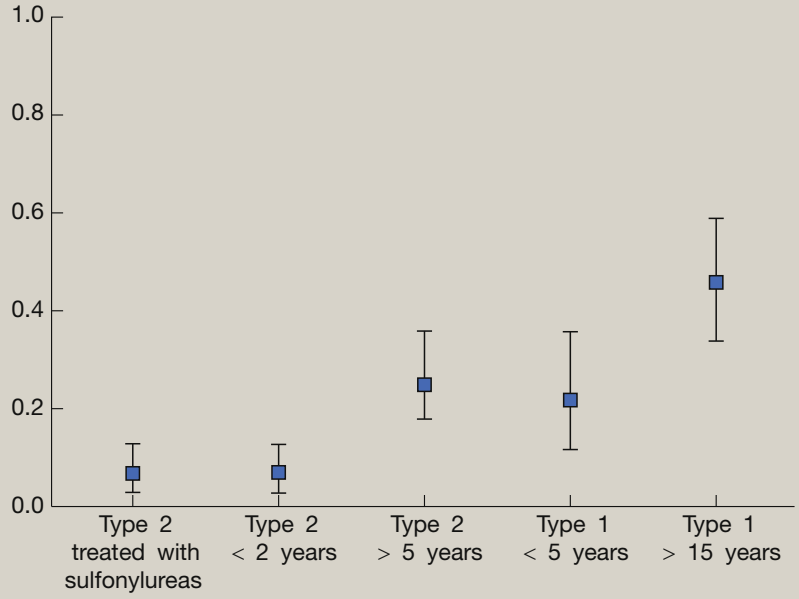

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Figure 2

awareness affects around 10% of individuals with type 2 diabetes treated with insulin.

Reduced awareness results from a change in the glucose threshold for activation of the physiological defences to hypoglycaemia. In individuals with hypoglycaemia unawareness, the threshold for activation of the autonomic nervous system becomes reset to a lower concentration of about 2.5 mmol/litre or less (Figure 3). This means that warning signs, such as sweating and tremor, are often generated at a blood glucose concentration below that for normal brain function, which prevents them being recognized. The extent of impaired perception is variable but some patients lose their ability to detect early warning symptoms and can suddenly lose consciousness unless relatives or friends are present to alert or revive them.

Hypoglycaemia unawareness, when severe, can have a devastating effect on affected individuals and their family. These individuals lose their driving licence, and most forms of employment become impossible. They often need someone to keep a careful watch on them day and night. Despite this some patients are still impelled to maintain blood glucose concentrations at normal levels by taking extra insulin doses and remain at high risk of coma or seizures. Repeated severe episodes can reduce cognitive ability through structural cerebral damage.

Symptoms of hypoglycaemia

Autonomic
- Sweating
- Palpitations
- Shaking
- Hunger

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

Table 1

Factors in hypoglycaemia

The traditional causes of hypoglycaemia are often attributed to relatively minor miscalculations (missed meal, excessive insulin dose, exercise) but there is often no explanation. Hypoglycaemic episodes are particularly common in patients who maintain tight glycaemic control, partly because the glycaemic threshold for physiological responses to a low glucose is so close to normal. Mild hypoglycaemic symptoms are to be expected in individuals who try to maintain tight glucose control. However, periods of hypoglycaemia can impair physiological defences to hypoglycaemia and increase the risk of further episodes (see below). Severe attacks that require the help of others can occur in any patient with type 1 diabetes, particularly at night and even when glycaemic control is not particularly tight.

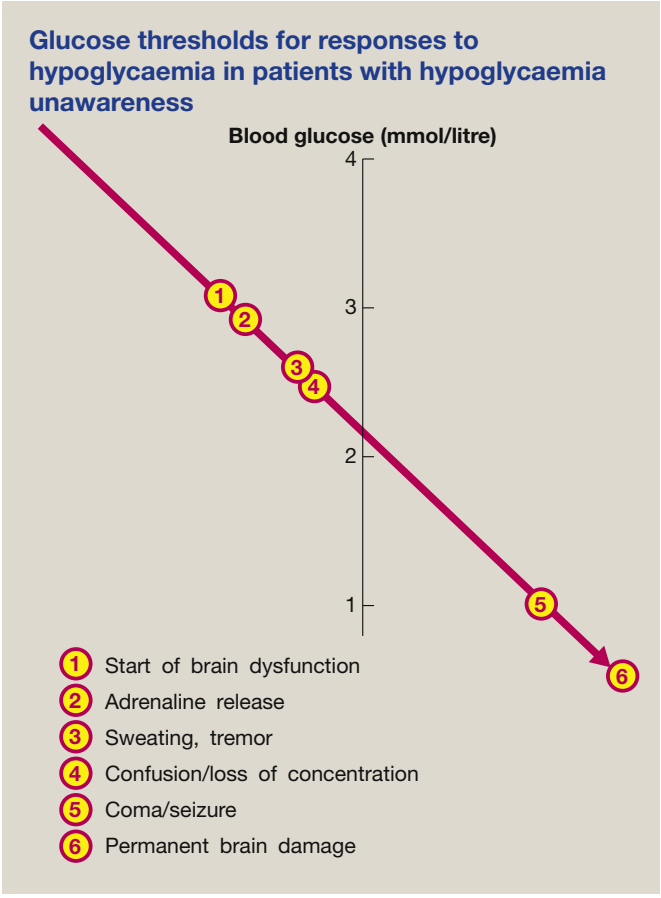

Figure 3

Duration of diabetes

Severe hypoglycaemia seldom occurs within the first few years after diagnosis, but becomes more common with increasing duration of disease in both type 1 and type 2 diabetes (Figure 2). This is partly because individuals who maintain endogenous insulin secretion exhibit smoother insulin concentration profiles. With progressive failure of β-cell secretion (which occurs in both main types of diabetes), there is a greater reliance on injected insulin, and the resulting insulin profiles are more erratic, increasing the risk of hypoglycaemia. Progressive β-cell damage is probably the cause of defects in glucagon response to hypoglycaemia, which is a major protective factor preventing severe episodes. Thus, patients with diabetes of long duration have both particularly erratic insulin profiles and defective physiological protection, which combine to confer a high risk of hypoglycaemia.

Tight glycaemic control and antecedent hypoglycaemia

Tight glycaemic control and intensive insulin therapy result in reduced endocrine and symptomatic responses to hypoglycaemia as a result of resetting of the glucose threshold at which they are activated. Increases in symptoms and adrenaline secretion usually occur at a glucose concentration of about 3.5 mmol/litre, but intensifying control reduces this to about 2.5 mmol/litre. This is below the glucose concentration at which cognitive ability begins to deteriorate, and these patients are at high risk of severe hypoglycaemic episodes.

Resetting of the glucose threshold for protective physiological responses occurs as a result of repeated episodes of hypoglycaemia[3] and maladaptation of cerebral pathways that mediate these responses. This can lead to a 'downward spiral' of progressively impaired physiological responses, increasingly frequent hypoglycaemic episodes and the development of hypoglycaemia unawareness.

The demonstration that just a few hours of antecedent hypoglycaemia could fundamentally alter physiological responses to hypoglycaemia suggested that these defects are functional rather than structural, and might be reversible. There is evidence that impaired hormonal responses and hypoglycaemia unawareness can be at least partly reversed by strict avoidance of hypoglycaemia.

The important principle is to avoid all episodes of hypoglycaemia for at least 4–6 weeks. This requires intensive blood glucose monitoring (including measurements at night), frequent contact with the doctor or nurse, tailored insulin regimens, and willingness of the patient to adopt a more relaxed attitude towards occasional high blood glucose concentrations. It should be possible to achieve this without a major deterioration in glycaemic control.

Alcohol

Patients must be warned of the potential dangers of alcohol. Alcohol increases susceptibility to hypoglycaemia, because it inhibits gluconeogenic pathways (which raise blood glucose during hypoglycaemia) and autonomic warning symptoms such as tremor. Hypoglycaemic episodes among patients with diabetes who drink alcohol are often more prolonged and severe, and the early symptoms can be unrecognized by others, who assume that the affected individual is drunk. When drinking alcohol, patients should ensure that they maintain their blood glucose higher than usual, and that those around them are aware that they have diabetes.

Nocturnal episodes

Hypoglycaemia at night is a particular problem in many patients with diabetes. Some studies have shown that more than one half of those with type 1 diabetes (particularly children) experience a blood glucose concentration <3.5 mmol/litre on any given night, and that episodes can last for hours. Those affected often remain asleep and have no recollection of the event on the following day.

The main reason for the high incidence of nocturnal hypoglycaemia is a lack of an effective basal insulin that can provide effective physiological replacement overnight, combined with long periods between meals. This is a particular problem in children who go to bed in the early evening and do not eat again for >12 hours. However, other factors add to the risk of nocturnal episodes. Physiological defences against hypoglycaemia are reduced by lying flat, and sympatho-adrenal responses to hypoglycaemia are reduced during sleep.

The risk of nocturnal hypoglycaemia can be reduced by monitoring blood glucose before bedtime and by taking a bedtime snack. Taking basal insulin at night rather than before the evening meal can also help. However, this approach can shift the risk to later during the night rather than eliminating it completely. Short-acting prandial and long-acting basal insulin

analogues are associated with a lower risk of nocturnal hypoglycaemia compared with human insulins. Recent studies have shown that the ultra-long-acting analogue insulin degludec (Tresiba) can reduce severe hypoglycaemia in both type 1 and type 2 diabetes, particularly at night. Continuous subcutaneous insulin infusion using insulin pumps can reduce nocturnal hypoglycaemia through more precise adjustments of insulin rates; this is also a useful option in patients who experience this problem.

Extremes of age

Very young and old individuals are especially vulnerable to hypoglycaemia. Infants and young children are unable to recognize or report hypoglycaemic symptoms, and irregular eating habits combined with unpredictable periods of exercise make hypoglycaemia a major problem for the parents of very young children with diabetes. Repeated severe episodes may even impair intellectual ability.

Symptoms of hypoglycaemia can be difficult to recognize in elderly patients, who are more likely to experience 'dizziness' and confusion. Autonomic responses to hypoglycaemia decrease with age, and the ageing brain can be more susceptible to the acute effects of glucose deprivation. Impaired renal function is more common and is a major risk factor in elderly patients with type 2 diabetes treated with sulfonylureas.

In both groups, it is therefore sensible to set less strict glycaemic targets and design insulin regimens accordingly. In elderly patients with multiple co-morbidities or cognitive impairment, a less stringent glycaemic target of HbA_{1c} <64 mmol/mol (<8%) is generally advisable.

Autonomic neuropathy

This has been previously implicated as contributing to the risk of hypoglycaemia but probably has little effect. The fact that hormonal defences to hypoglycaemia become progressively impaired with increasing duration of disease has raised the possibility that these changes result from the development of microvascular damage. Normal sympatho-adrenal activation involves an intact autonomic nervous system, and it has been suggested that hypoglycaemia unawareness is a form of autonomic neuropathy. However, the observation that these defects can be reversed, and the demonstration of normal responses in some patients with autonomic neuropathy, indicates that autonomic neuropathy is not a major cause of hypoglycaemia unawareness. Defects in physiological defences against hypoglycaemia undoubtedly represent autonomic dysfunction (termed by some as 'hypoglycaemia-associated autonomic failure'), but appear largely unrelated to classical autonomic neuropathy of diabetes.

Emergency management of acute hypoglycaemia in patients with diabetes

- Establish the diagnosis using a capillary sample. Immediately give quick-acting oral glucose 15–20 g (such as 150 ml full-sugar cola, 200 ml orange juice, 5–6 dextrose tablets, or oral dextrose gel in uncooperative patients who can still swallow). After recovery, this should be followed by long-acting carbohydrate if a meal is not due within 1 hour. If oral administration is not possible, proceed as follows.
- Give glucose 10% in 50 ml boluses until recovery occurs or 250 ml has been given.
- In the absence of intravenous access, intramuscular glucagon is a useful alternative, because it can be given by nursing staff. Give 0.5–1 mg; the higher doses can cause vomiting, particularly in children. Glucagon is ineffective in alcoholic patients, in whom glycogen stores are depleted. After recovery, ensure that oral carbohydrate is taken.
- Failure to recover consciousness within 60 minutes indicates possible brain damage. Start an intravenous infusion of glucose 10% and maintain blood glucose at about 11 mmol/litre. Consider dexamethasone, 1 mg intravenously. Some patients make a full recovery after periods of coma lasting as long as 48 hours.
- Patients who are alert, oriented and clinically well 1 hour after treatment and whose blood glucose is stable (capillary sample taken 1 hour after arrival) do not require admission to hospital. However, patients who develop severe hypoglycaemia while taking sulfonylureas should have their renal function checked and be admitted for glucose monitoring for 24 hours because of occasional prolonged episodes that cannot be predicted. The local diabetes team should be notified; further follow-up is often helpful, in terms of adjusting insulin regimens or educating and reassuring the patient and family.

Patient education and technology

All patients starting to use insulin (or sulfonylureas) should be taught the symptoms of hypoglycaemia and the action to take when they recognize that they are 'low'. It is inappropriate and potentially dangerous to induce hypoglycaemia in hospital as part of the educational process; such episodes are often completely different from those experienced in everyday life, and have caused permanent brain damage and even death.

Many individuals with diabetes fear the risks and consequences of hypoglycaemia more than diabetic complications. These fears must be anticipated and dealt with in education programmes.[4] Patients need to know that mild episodes are an inevitable consequence of effective treatment, and that even severe episodes seldom have any permanent sequelae. A pilot intervention addressing motivational and cognitive barriers surrounding hypoglycaemia was successful in engaging those with recurrent severe episodes and restoring awareness. The partners of those who maintain tight control need to know how to treat an acute episode, including the use of glucagon.

In type 1 diabetes, the problem of hypoglycaemia may be reduced by reliable continuous glucose sensors and new methods of insulin delivery.[5] The latest models of insulin pump, combined with continuous interstitial glucose monitoring systems, can further lower the risk in vulnerable patients. Some devices, which are able automatically to suspend insulin delivery at low blood glucose concentrations, have been shown to reduce severe hypoglycaemia in clinical trials. However, technological solutions alone cannot be effective without high-quality patient education. Islet cell transplantation can restore the automatic inhibition of insulin and pancreatic glucagon release and may be an option in patients with intractable recurrent severe

hypoglycaemia. For most patients, training in diabetes self-management and individualization of glycaemic therapy remain the cornerstone of preventing hypoglycaemia and limiting the burden it imposes. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 53-year-old-woman presented having had an episode of increased sweating and shaking. She had long-standing type 1 diabetes mellitus (T1DM) A capillary blood glucose at the time was 3.5 mmol/litre. Both her symptoms and her blood sugar concentration responded to a sugary drink which raised her blood glucose to 4.2 mmol/litre.

Based on this scenario, which of the following pieces of advice regarding her diabetes management is most useful?

A. She should be reminded how to treat a low blood glucose with oral carbohydrates.
B. She should reduce her bolus insulin to prevent further episodes.
C. She should to monitor her blood glucose regularly before meals and adjust either of her insulins, particularly if she is running low at times without symptoms.
D. She should be reassured that running low 2–3 times a week is to be expected when aiming for tight control and she should ensure she carries the appropriate treatment on her at all times.
E. She should reduce her basal insulin by 10–15% to prevent further hypoglycaemia

Question 2

A 30-year-old teacher was seen for a yearly diabetes check-up. He had type 1 diabetes. His control had always been excellent, with glycated haemoglobin ($HbA1_c$) <48 mmol/mol; <6.5% (20–42; 3.0–6.0). In the past he has reported feeling low 2–3 times a week, but has always been able to treat himself. He tells you that things have not changed and he is happy with his level of glucose control. A routine capillary blood glucose reading in the clinic is 2.9 mmol/litre. He concedes that in recent months, on a number of occasions his wife has suggested he is probably low and persuaded him to check his blood glucose. Although he felt fine each time, he was surprised to find that his glucose was between 2 and 3 mmol/litre.

Which of the suggested approaches to his management is the most appropriate?

A. He should be encouraged to test more often and try to run his blood glucose high between 9 and 15 mmol/litre for a few weeks.
B. Congratulate him on his excellent level of metabolic control but suggest he should consider doing more blood glucose tests to identify when his glucose level is low.
C. He should be advised to consider giving up his job. Explain that because he has developed reduced awareness of hypoglycaemia this puts the pupils he looks after at increased risk should he have a severe episode while at work.
D. He should be strongly encouraged to work with a diabetes nurse to treat his impaired awareness of hypoglycaemia (IAH) by modifying his treatment to avoid all hypoglycaemic episodes for a few weeks.
E. He should be given an insulin pump with a low-glucose suspend (LGS) feature

Question 3

A 76-year-old woman was found unresponsive in her kitchen. She had type 2 diabetes and was taking metformin, gliclazide (a sulfonylurea derivate) and a basal insulin analogue (Lantus) once a day. She had had a recent episode of vomiting and diarrhoea. Paramedics recorded a blood glucose of 2.5 mmol/litre, and she responded to glucagon given intramuscularly. She was taken to hospital.

Investigations

- Urea 13 mmol/litre (2.5–7.0)
- Creatinine 140 micromol/litre (60–110)

What is the most appropriate management decision?

A. Discharge, to drink plenty of fluids and check renal function in 2–3 days. Stop her gliclazide a few days then restart.
B. Admit to hospital, monitor blood glucose for approximately 24 hours, consider changing her medication.

C. Her metabolic control is likely to be good as she has had hypoglycaemia and if she is otherwise well and recovered, there is probably no need to make drastic changes. Her hypoglycaemia was due to an intercurrent illness which is unlikely to recur. She could be discharged with early review in clinic

D. She can be discharged home but ask her relatives to visit her on a daily basis

E. The metformin should be stopped due to her impaired renal function. She could then be discharged home with routine review in clinic

