Hypoglycaemia: the major hazard of insulin treatment

Peter Watkins

Introduction

Hypoglycaemia is a serious and potentially life-threatening effect of insulin use. Most patients experience warning signs and are able to take corrective action, but some patients develop loss of warning and are thus prevented from taking such action. Loss of awareness of hypoglycaemia is thought to be provoked by recurrent hypoglycaemia, and is dreaded by all insulin-treated patients. Avoidance of hypoglycaemia throughout life is therefore crucial. Much of the skill in managing insulin-treated patients is devoted to achieving optimal diabetic control while avoiding hypoglycaemia.

Hypoglycaemia is the major hazard of insulin use and is feared by all insulin-treated patients. It presents an immediate impediment to achieving optimal diabetic control and poses significant risks in many industrial and social situations; as a result, insulin-treated diabetics are barred from various occupations.

Almost all patients treated with insulin will experience hypoglycaemia at some time: at its mildest it is no more than a slight inconvenience, but at its severest it is both a serious risk to life and, at the very least, an embarrassment. Manipulative patients can use hypoglycaemia to threaten family and friends. The threat of hypo- glycaemia is ever present once insulin treatment has started, and its avoidance requires lifelong vigilance.

Although this gloomy description is no exaggeration, most of the time the majority of patients receive adequate warning of impending hypoglycaemia, enabling them to take the necessary preventive measures. These warning symptoms are well known (Table 1). Tremulousness and sweating are by far the most common, while circumoral paraesthesiae are the most specific. Many patients have highly individual symptoms of hypoglycaemia, ranging from quite inexplicable sensations to peripheral paraesthesiae; I have three patients whose carpal tunnel symptoms, causing tingling in the fingers, were the sole warning.

If corrective action is not taken, the brain becomes starved of glucose (neuroglycopenia) and cognitive function declines, with progressive confusion and eventually unconsciousness and even convulsions.

The risks of hypoglycaemia result from the confused state, which leads to accidents of many kinds in both the home and in industry. It is, however, reassuring for people to know that even protracted hypoglycaemia is not normally a cause of death or brain damage, that people do not normally die from hypoglycaemia at night and that complete recovery can be expected, even after the most severe episodes.

There is prolonged debate, with conflicting evidence, as to whether recurrent hypo- glycaemia causes long-term intellectual decline, although it may occur to some extent following major hypoglycaemic problems in childhood. The cause of the small number of deaths at night ('dead-in-bed' syndrome) described each year in young insulin-dependent diabetic patients is still under scrutiny.

When does hypoglycaemia occur?

Patients may experience symptoms when the blood glucose falls below 3.0 mmol/litre; when warning has been lost, symptoms do not occur until lower levels are reached

ARTICLE POINTS

1 Hypoglycaemia is the major hazard of insulin use.

2 If not corrected, it can lead to unconsciousness and eventually coma.

3 At the onset, most people experience warning signs and are able to take corrective action.

4 It is essential that patients know what causes hypoglycaemia, how to prevent it, and what action to take when it occurs.

5 Management of insulin-treated patients is aimed at achieving optimal diabetic control while avoiding hypoglycaemia.

KEY WORDS

- **Hypoglycaemia**
- **Insulin treatment**
- **Loss of hypoglycaemic awareness**
- **Glucagon**

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Table 1. Clinical features of hypoglycaemia

Early warning signs	Shaking, trembling Sweating Paraesthesiae (pins and needles) in lips and tongue Hunger Palpitations Headache (occasionally)
Neuroglycopenia:	
Mild	Double vision Difficulty in concentrating Slurring of speech
More advanced	Confusion Change of behaviour Truculence Naughtiness in children
Unconsciousness	Restlessness with sweating Epileptic fits, especially in children Hemiplegia, especially in elderly people (but rare)

PAGE POINTS

1 Hypoglycaemic symptoms usually occur when blood glucose falls below 3.0 mmol/litre.

2 It most commonly occurs at times of peak insulin action, i.e. during the late morning and at night.

3 Inappropriate alcohol consumption and increased physical activity are well-known precipitants of hypoglycaemia.

4 Other precipitating factors include omission of food and errors of insulin dosage.

(*Figure 1*); while in those who always have poor control, symptoms may occur at slightly higher levels.

Hypoglycaemia is most common during the late morning and at night. These are times of peak insulin action, which is exacerbated at night by lack of food. This vulnerability can be expected from the pattern of blood glucose profiles (*Figure 2*) that most insulin-treated patients demonstrate, with nadirs of blood glucose at these times. Insulin-treated diabetics must therefore be especially vigilant at these times, e.g. when driving in the late morning.

Many other situations are well known to precipitate hypoglycaemia, notably increased physical activity and inappropriate alcohol consumption. Errors of treatment also contribute to the development of hypoglycaemia —- most commonly omission of food (especially the mid-morning snack, which should always be taken, regardless of insulin type) or errors of insulin dosage which may be accidental or, occasionally, deliberate.

In the longer term, rarer causes may predispose to hypoglycaemia. Examples include endocrine disorders such as Addison's disease, or hypopituitarism in which there is a decrease in the level of hormones that antagonise the action of insulin.

Loss of warning of hypoglycaemia

This is the problem that all insulin-treated patients dread. It occurs when patients do not experience the early warning symptoms and directly develop diminished cognitive function, which prevents them taking the required corrective action. In this situation, help is required from a third party.

This commonly occurs in the home when friends and relations observe the affected person to be slow-witted with a vacant expression and perspiring face. He/she may be taciturn, truculent or even obstructive, sometimes refusing to take sugar when advised, although many learn to accept this advice. This state of cognitive impairment can persist for a considerable time — long enough for abnormal behaviour to be noticed during driving, sometimes for several miles, or simply in shoppers in the high street. If corrective action is not taken, loss of consciousness can occur.

Night-time hypoglycaemia is very common, usually occurring between 3 and 6 o'clock in the morning. The blood glucose often falls below the hypoglycaemic threshold: levels as low as 1 mmol/litre are not rare, and are known to cause electroencephalographic (EEG) abnormalities, even in the absence of symptoms. Many people become very restless when hypoglycaemic: this is recognised most frequently by the spouse who takes the necessary remedial action. Profound sweating is common, sometimes necessitating a change of nightclothes or bedclothes and may be the only indication that hypoglycaemia has occurred. Convulsions are not rare, and some patients wake in the morning with a bitten tongue as the only indication that this has occurred.

What causes loss of warning of hypoglycaemia?

Recurrent hypoglycaemia is the principal cause of loss of warning of hypoglycaemia, and dangerous impairment of cognitive function is its chief manifestation (*Figure 1*).

Loss of warning of hypoglycaemia is therefore most likely to occur in those whose diabetes is most tightly controlled.

It was manifest in the Diabetes Control and Complications Trial where severe hylpoglycaemia occurred three times more often in the better controlled group of patients. This mechanism outweighs all others, although the use of beta-blocking drugs also causes loss of warning of hypoglycaemia in a small number of patients.

Autonomic neuropathy is not normally the cause of loss of warning, and the contentious issue regarding human insulin has, quite rightly, led some patients to change back to animal insulins, although scientific evidence of harm is still lacking.

Why does recurrent hypoglycaemia lead to loss of warning? The answer probably lies in the readjustment of the threshold of sensitivity of a glucose sensor in the central nervous system. This alters the hierarchy of response to hypoglycaemia shown in *Figure 1*. Thus, the hypoglycaemic symptoms and counter-regulatory responses, instead of occurring at a blood glucose concentration just above 3 mmol/litre, develop at a lower level — rather less than 2 mmol/litre. Since, in either case, loss of cognitive function occurs at around 2.8 mmol/litre, it is clear that this develops before hypoglycaemic symptoms where awareness has been lost.

Recent research has shown that by eliminating hypoglycaemia it is possible to restore the normal sequence of events during hypoglycaemia, thereby also restoring proper warning (*Figure 1*).

It is therefore necessary to eliminate, as far as possible, all hypoglycaemic episodes, including those occurring quietly at night. This can often be avoided simply by reducing the insulin dose, ensuring adequate carbohydrate intake and, to some extent, relaxing overall diabetic control in the interest of safety. It is wise to try to avoid blood glucose levels of less than around 4 mmol/l.

However, it is much more difficult to eliminate hypoglycaemia while retaining optimal control of diabetes. This requires the acquired skill of the diabetes team and cooperation of patients, as well as considerable time and resources. The introduction of blood glucose awareness training (BGAT) programmes may help and these are under evaluation, but it is not the purpose of this review to explain in detail how this is done.

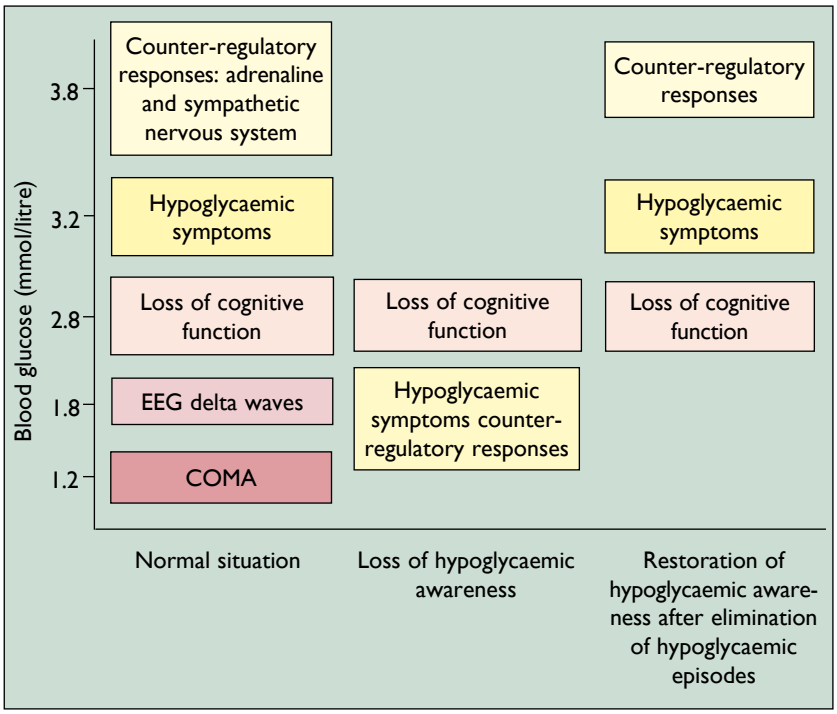

Figure 1. Hierarchy of symptoms and counter-regulatory responses in normal subjects and those who have lost awareness of hypoglycaemia.

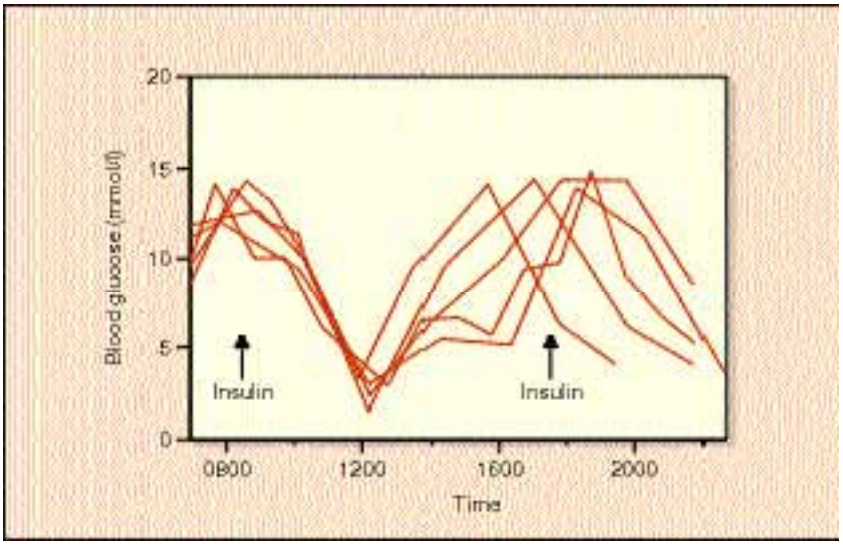

Figure 2. Typical blood glucose profiles of an insulin-dependent diabetic, showing characteristic troughs and peaks of hypoglycaemia.

Prevention of hypoglycaemia

Much of the skill required to manage insulin-treated patients is therefore devoted to achieving adequate control of diabetes, while avoiding hypoglycaemia. There are also straightforward measures that patients often neglect. They must:

- At all times, carry a supply of glucose, both on their person *and* in their cars,

Publisher's note: Figure 2 is not available full resolution in the online version.

Table 2. Glucose-containing liquids and solids suitable for correcting hypoglycaemia

Lucozade	60 ml (2 fl oz)
Ribena	15 ml (0.5 fl oz)
Coca-cola (not Diet)	80 ml (3 fl oz)
Sugar	2 teaspoonsful
Sugar lumps	3 small
Dextrasol	3 tablets
Hypostop gel	

Each item contains 10 g of carbohydrate

and take 10–20 g at the first warning symptoms. This can take many forms, as shown in *Table 2*.

- Take ample carbohydrate at all times when blood glucose troughs occur, notably mid-morning and bedtime.
- Take additional carbohydrate before and during vigorous exercise.

Careful blood glucose monitoring is crucial in avoiding hypoglycaemic episodes.

Glucagon

Glucagon is a hormone produced by the alpha cells of the pancreatic islets. It raises the blood glucose by mobilising the glycogen stores in the liver (and therefore will not work after prolonged starvation).

It is given in a 1 mg dose by injection, most conveniently intramuscularly, but can also be used subcutaneously or intravenously. It is therefore of great value for bystanders of severely hypoglycaemic patients who are unable to take oral glucose, and can be injected by family members, nurses or doctors. It is valuable in relieving stress in the home setting where a diabetic, often a child, is prone to recurrent, disabling attacks of hypoglycaemia.

Unconsciousness

The patient who has lapsed into severe unconsciousness requires urgent treatment in hospital. Blood should be taken for blood glucose analysis and the sample should be kept in case the patient fails to respond to treatment, since it is always possible that the coma may have another cause.

The unconscious patient should be placed in the recovery position, with airway maintained, and be given intravenous glucose, commonly 20–50 ml of 50% glucose. This hypertonic solution is very irritant and must be given carefully into the vein. The response is usually immediate; if it is not, a further dose should be given after 5–10 minutes, followed by an infusion of 10% glucose. Once full consciousness is restored, a history can be taken and the patient should be fed longer-acting carbohydrate to prevent recurrence.

If recovery does not occur rapidly, another cause for the coma must be sought. If hypoglycaemia has been profound, cerebral oedema can occur and may require treatment with dexamethasone or mannitol.

Conclusions

Any serious hypoglycaemic episode can, to some extent, be regarded as a failure of doctor, patient or the treatment regimen itself. It should provoke serious enquiry to establish the cause and to ascertain whether it is likely to recur.

The opportunity for necessary education should be taken, and patients should be encouraged to carry a diabetic identification card.

Finally, the professional attending the patient, whether doctor or nurse, has a duty to advise people who have had such an episode from loss of warning of hypoglycaemia to stop driving and to avoid any other potentially dangerous activity. The endeavour to avoid hypoglycaemia needs to be maintained and patients need our considerable support to achieve this at almost every diabetic consultation throughout life. ■

PAGE POINTS

1 Simple measures such as always carrying a supply of glucose and taking 10-20 g at the first warning signs will help to prevent hypoglycaemia.

2 Glucagon is produced by the alpha cells of the pancreatic islets and raises blood glucose by mobilising the glycogen stores in the liver.

3 Patients who are unable to take oral glucose or are severely hypoglycaemic should be given 1mg of glucagon by injection.

4 Severely unconscious patients require urgent treatment in hospital.

Further reading

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