Pathophysiology and management of recurrent hypoglycaemia and hypoglycaemia unawareness in diabetes

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A B S T R A C T

Iatrogenic hypoglycaemia is a well-known complication of insulin therapy in patients with diabetes mellitus and a limiting factor for glycaemic control. In a setting of endogenous insulin deficiency (type 1 and advanced type 2 diabetes), one episode of hypoglycaemia reduces both counterregulatory hormone responses to and subjective awareness of subsequent hypoglycaemia, thus impairing physiological defences against hypoglycaemia. This phenomenon may lead to a vicious cycle of recurrent hypoglycaemia and glucose counterregulatory failure, of which hypoglycaemia unawareness (i.e. the inability to perceive symptoms of hypoglycaemia) is the clinical representative. The underlying mechanism of hypoglycaemia-induced counterregulatory failure has not yet been disclosed. Patients with clinical hypoglycaemia unawareness are at high risk of severe hypoglycaemia that requires third-party assistance. Management options include avoidance of hypoglycaemic events and optimisation of insulin therapy to limit deterioration of glycaemic control associated with hypoglycaemia avoidance. Several counterregulatory-stimulating agents have been found to improve hypoglycaemic awareness in small clinical trials, but none have been tested in sufficiently large randomised studies to justify their use in daily practice. More research is required to elucidate the pathogenesis of counterregulatory failure and to develop adequate treatment strategies.

K E Y W O R D S

Diabetes mellitus, glucose counterregulation, hypoglycaemia unawareness, insulin treatment

C A S E R E P O R T

At her three-monthly visit to the outpatient clinic, a 37-year-old woman with type 1 diabetes reported having had a severe hypoglycaemic incident recently. Her five-year-old daughter found her unconscious on the floor and called the neighbours. Only after administration of glucagon intramuscularly did she regain consciousness. She has a 33-year history of diabetes without microvascular complications and is currently being treated with aspart insulin before meals and one injection of glargine at bedtime. Glycaemic control has always been reasonable (but not optimal), with HbA1c values ranging from 7.2 to 8.5%. Hypoglycaemic events are recognised by loss of concentration, diminishing visual acuity, or not at all. Home blood glucose measurements disclose a high number of biochemical hypoglycaemias, the majority of which – the patient admits – were not perceived. Family members often recognise her hypoglycaemic events before she is aware of them herself. She feels insecure, especially when she is alone with her children. She wants to know why hypoglycaemias are so common, why symptoms are no longer perceived, and what led to the severe episode.

Clinical hypoglycaemia rarely occurs in healthy human beings, but it is a fact of life for people with type 1 diabetes mellitus (T1DM) and (advanced) insulin-treated type 2
Hypoglycaemia is feared by many patients not only because of the associated physical discomfort, but mainly because of the risk of cognitive function deterioration that may lead to loss of personal control and adequate conscious behaviour, and eventually to coma. Iatrogenic hypoglycaemia has been described ever since the introduction of insulin, and especially those patients attempting to optimise glycaemic control may suffer multiple episodes a week. Numerous studies, including the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS), have established the inverse relationship between HbA1c and risk for hypoglycaemic events. Despite recent advances in insulin treatment, however, iatrogenic hypoglycaemia remains the principal barrier to obtaining true glycaemic control, i.e. blood glucose values that remain within normoglycaemic limits for an indefinite period of time.

Thus, microvascular and macrovascular complications of diabetes associated with chronic hyperglycaemia are to a certain extent the consequence of (the risk for) hypoglycaemia. By far not all hypoglycaemic events are recognised, which leads to underreporting of events and increases the risk of hypoglycaemia complicated by coma or epileptic seizures, as the current case exemplifies. In this article, we discuss the pathophysiology of hypoglycaemia in diabetes, its potential to cause harm, and the implications of hypoglycaemia in daily clinical practice, including tactics to reduce its frequency.

Role of insulin in risk for hypoglycaemia

When discussing potential causes of a hypoglycaemic event with a diabetic patient, it is common to search primarily for the classical risk factors for hypoglycaemia such as missed meals, excess insulin administration, alcohol consumption, and physical activity or sport. However appropriate this may be, many instances of hypoglycaemia are not the result of patient mistakes, but relate to imperfections in therapeutic insulin as opposed to endogenous insulin. In the nondiabetic individual, endogenous insulin release is instantaneous and tailor-made to the amount of carbohydrates that enter the circulation or to any other increase in the blood glucose level. Moreover, after its release by the pancreatic β-cell, insulin first reaches the liver via the portal vein to stimulate hepatic glycogen synthesis and to inhibit hepatic gluconeogenesis. Within the liver, insulin is degraded by approximately 50%, so that only half of the insulin released reaches the periphery to stimulate skeletal muscle glucose disposal or to inhibit lipolysis in adipose tissue. With therapeutic insulin, insulin levels are unregulated and do not decrease until the subcutaneous depot is depleted, even though the plasma glucose level may have started to fall (too low). In addition, insulin injected subcutaneously enters the circulation much slower and follows the reverse route, so that elevated insulin levels persist considerably longer. Variations in insulin absorption may explain why a dose of insulin sufficient to maintain normoglycaemia at one time may be too much at other times. All these factors may lead to inappropriate hyperinsulinaemia, i.e. despite corrected hyperglycaemia, hence creating a risk for hypoglycaemia.

Normal glucose counterregulation

In the nondiabetic individual, declining blood glucose levels trigger a characteristic and hierarchically organised sequence of responses (figure 1). First and foremost, insulin secretion is suppressed when blood glucose levels fall within the physiological range (below 4.5 mmol/l). The resultant reduction in peripheral glucose uptake and increase in hepatic glucose production usually terminates the decline in blood glucose and prevents true hypoglycaemia almost without exception. In addition, the fall in intra-islet insulin appears to have a signalling role for the glucagon response to hypoglycaemia by alleviating its suppressive effect on pancreatic α-cells, thus permitting glucagon release. The release of both glucagon and adrenaline is triggered when plasma glucose values fall below 3.8 mmol/l. They promote hepatic glucose production by stimulation of glycogenolysis and gluconeogenesis. In addition, adrenaline inhibits peripheral glucose uptake, thus contributing to mobilisation of gluconeogenic precursors. Yet adrenaline is normally not critical, provided the glucagon response is intact. Cortisol and growth are released in response to prolonged hypoglycaemia, but have a low significance for acute glucose counterregulation. Plasma glucose values of 3.0 to 3.5 mmol/l trigger central nervous system (CNS) mediated onset of autonomic warning symptoms such as hunger, sweating and palpitations, all of which are fundamental for subjective awareness of hypoglycaemia. These symptoms are aimed to provoke eating behaviour and can be seen as the lower boundary of physiological euglycaemia.


Figure 1. Schematic presentation of physiological glycaemic threshold values for counterregulatory responses to and physical consequences of insulin-induced hypoglycaemia.
a last resort before neuroglycopenia develops and cognitive function declines, both of which reflect CNS glucose deprivation (table 1). The glucose levels at which these counterregulatory responses to hypoglycaemia occur, also referred to as glycaemic thresholds, are reproducible in healthy subjects, yet they can be altered to higher glucose levels following chronic hyperglycaemia or to lower glucose levels following repeated hypoglycaemia. The magnitude of counterregulatory function as a whole tends to decrease with age and is more prominent in men than in (premenopausal) women.

<table>
<thead>
<tr>
<th>Table 1. Symptoms of hypoglycaemia</th>
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<tr>
<td><strong>Autonomic symptoms</strong></td>
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<tr>
<td>Sweating</td>
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<tr>
<td>Tingling</td>
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<td>Trembling</td>
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<td>Feeling shaky</td>
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<td>Palpitations</td>
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<td>Anxiety</td>
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Glucose counterregulation in diabetes

Glucose counterregulation in patients with T1DM is typically impaired. The loss of insulin-producing capacity disrupts the first-line defence against falling blood glucose levels and the consequent lack of paracrine control of the pancreatic a-cell precludes an adequate glucagon response. Therefore, hypoglycaemia usually fails to trigger glucagon responses in T1DM within years after diagnosis. When glucagon responses to hypoglycaemia are deficient, adrenaline and autonomic warning symptoms become critical for the integrity of glucose counterregulation. Iatrogenic hypoglycaemia, however, attenuates the magnitude of adrenaline and autonomic symptom responses to a subsequent hypoglycaemic episode, shifts the glycaemic threshold for these responses to lower levels of glycaemia, and impairs hypoglycaemic perceptibility clinically, and possibly reduces β-adrenergic sensitivity. Any hypoglycaemia, whether mild, asymptomatic, or brief, can provoke this phenomenon. Consequently, a downward vicious cycle of worsening counterregulation and recurrent hypoglycaemia may ultimately lead to hypoglycaemia unawareness. Hypoglycaemia unawareness is defined as onset of neuroglycopenia before the appearance of autonomic warning symptoms, and typified clinically by the inability to perceive hypoglycaemia by symptoms (figure 2). Patients with hypoglycaemia unawareness are unable to manifest an adequate behavioural response to avert hypoglycaemia and are at a specifically high risk for severe, disabling hypoglycaemia (e.g. complicated by coma or seizures) that requires external assistance. Various terms are used for the combination of defective hormonal counterregulation and hypoglycaemia unawareness, such as counterregulatory failure, hypoglycaemia-associated autonomic failure (HAAF) and hypoglycaemia unawareness syndrome. Risk factors other than recent antecedent or recurrent hypoglycaemia include good glycaemic control (which by inference is also an index of hypoglycaemic incidence), C-peptide negativity, male sex, and advanced diabetes duration. Diabetic autonomic neuropathy causes many of the counterregulatory defects that are found in patients with hypoglycaemia unawareness. However, most patients with hypoglycaemia unawareness have no signs of autonomic neuropathy or microangiopathy. In cross-sectional studies, classical diabetic autonomic neuropathy was not associated to counterregulatory failure or hypoglycaemic incidence. In T2DM, residual β-cell function largely preserves the first-line defence against hypoglycaemia. Consequently, the glucagon response is retained, hypoglycaemic risk is limited and further counterregulatory defects are prevented. Indeed, hypoglycaemic rates are 15-fold lower in orally treated and still approximately sixfold lower in insulin-treated T2DM patients than in patients with T1DM. Insulin resistance and – possibly – increased sensitivity to plasma catecholamines may contribute to prevention of iatrogenic hypoglycaemia and preservation of glucose counterregulation. However, the concept of hypoglycaemia-induced diminution in counterregulatory function also applies to T2DM. Moreover, insulin deficiency in T2DM causes an absent glucagon response to hypoglycaemia and a steep rise in the risk for hypoglycaemia that approaches that of T1DM. T2DM patients who approach the insulin-deficient state are prone to the same counterregulatory defects as patients with T1DM, including hypoglycaemia unawareness. Recent data indicate that 8 to 31% of insulin-treated T2DM patients report having trouble in correctly identifying hypoglycaemic events and that these patients have a ninefold higher risk for severe iatrogenic hypoglycaemia than patients with normal hypoglycaemic awareness.

Pathogenesis of counterregulatory failure

Although the role of antecedent hypoglycaemia in the development of counterregulatory failure is undisputed, the underlying mechanism has yet to be determined. It has been hypothesised that increased cortisol levels during antecedent hypoglycaemia could act as mediator to reduce counterregulatory responses to subsequent hypoglycaemia. This hypothesis was based on the finding...
that prior supraphysiological elevation of plasma cortisol was able to mimic some of the – primarily metabolic – effects of antecedent hypoglycaemia\textsuperscript{41,42} and that failure to secrete cortisol could prevent the phenomenon.\textsuperscript{43} Prior cortisol elevation did not affect symptomatic awareness of subsequent hypoglycaemia, and lower cortisol levels comparable with those elicited by hypoglycaemia could not reproduce the phenomenon.\textsuperscript{44,46} Thus, the cortisol hypothesis provides no explanation for clinical hypoglycaemia unawareness.

Since the CNS plays such a pivotal role in the sensing of hypoglycaemia and the activation of counterregulation, many studies on the pathogenesis of counterregulatory failure have focussed on the brain. In humans and rodents, prolonged (days to weeks) hypoglycaemia was found to increase cerebral glucose uptake,\textsuperscript{47,48} possibly mediated through increased expression of cerebral GLUT-1 and GLUT-3 glucose transporters.\textsuperscript{49,50} These data led to the suggestion that recurrent hypoglycaemic events preserved or increased brain glucose uptake, thereby shifting hypoglycaemic symptom perception and onset of counterregulatory responses to lower levels of (systemic) hypoglycaemia.\textsuperscript{51,52} Observations of increased cerebral glucose content in T1DM patients with near-normal HbA\textsubscript{1c} values,\textsuperscript{54} or with hypoglycaemia unawareness\textsuperscript{55} compared with controls seem to support this hypothesis. However, the induction of hypoglycaemia
unawareness was not accompanied by alterations in global blood-to-brain glucose transport when shorter periods of antecedent hypoglycaemia were used, neither in humans nor in animals. Moreover, no differences in blood-to-brain glucose transport were found using positron emission tomography between hypoglycaemia aware and hypoglycaemia unaware T1DM patients. Another possibility is that recent antecedent hypoglycaemia causes alterations in the brain’s glucose-sensing neurons in the ventromedial hypothalamus (VMH) that initiate the glucose counterregulatory response (except glucagon). As a result, the onset of counterregulatory responses would then shift to deeper levels of hypoglycaemia. Increased glucokinase activity, decreased AMP-activated protein kinase activity, and reduced insulin signalling have all been suggested as underlying mechanism, but none have been universally established. Finally, hypoglycaemia-induced alteration of brain (glucose) metabolism may be involved in the pathogenesis of counterregulatory defects. Administration of 2-deoxyglucose, a glucose compound that cannot be metabolised, leads to stimulation of glucose counterregulation and hyperglycaemia. Conversely, administration of nonglucose substrates for metabolism, such as β-hydroxybutyrate or lactate, during hypoglycaemia suppress counterregulatory responses. Recent data indicate that hypoglycaemia causes twofold higher increases in brain acetate in T1DM patients than in healthy controls without affecting brain energy metabolism, suggesting that increased blood-to-brain transport of alternative metabolic substrates could be the mechanism underlying counterregulatory failure. How hypoglycaemia affects brain glucose metabolism and if alterations therein occur after repeated hypoglycaemia is still unknown. Localised 1³C nuclear magnetic resonance (NMR) spectroscopy, provides a novel highly sophisticated tool to study brain glucose metabolism in vivo. Under optimal conditions, it has become feasible to use 1³C NMR spectroscopy in humans under hypoglycaemic conditions.

Morbidity and mortality of severe hypoglycaemia

Severe decrements in blood glucose levels that interfere with the individual’s ability for self-management have the potential to cause significant physical harm. It has been estimated that 2 to 4% of all deaths in T1DM occur under hypoglycaemic conditions. In most instances, death cannot be attributed directly to hypoglycaemia, but relates to the circumstances under which the hypoglycaemic event evolved, e.g. in traffic, during swimming or scuba diving, at heights, etc. To avoid hypoglycaemia while driving, it is recommended to test blood glucose before and at regular intervals during driving, to ingest prophylactic carbohydrates when blood glucose is below 5 mmol/l, and to keep an emergency supply of carbohydrates for treatment purposes and to cope with unexpected delays, such as traffic jams. A direct relation between hypoglycaemia and death has been proposed in the dead in bed syndrome, a rare disorder characterised by an unexpected death in a young, previously healthy, tightly controlled T1DM patient, often with a history of recurrent (nocturnal) hypoglycaemia. Death in this syndrome is thought to be the result of a fatal ventricular arrhythmia caused by hypoglycaemia-induced lengthening of the QT interval. It is not yet known to what extent hypoglycaemia contributes to mortality in T2DM, yet the fact that hypoglycaemia can induce arrhythmia may be clinically relevant in a population prone to cardiovascular disease (such as T2DM). Moreover, hypoglycaemia as a cause of out-of-hospital mortality may be easily missed in the elderly T2DM population. It is unclear whether severe hypoglycaemia constitutes a risk factor for persistent loss of cognitive function. There are occasional case reports of serious brain damage induced by severe hypoglycaemia and a recent study reporting altered brain structure after severe hypoglycaemia. In addition, insulin-treated diabetic patients with a history of repeated severe hypoglycaemia were found to perform slightly worse on an IQ test than patients without such a history. Prospective studies and a recent cross-sectional study, however, have been unable to establish an association between severe hypoglycaemia and cognitive decline. On the contrary, cognitive dysfunction and structural abnormalities on brain MRI scans appeared to be more prevalent in patients with microvascular complications such as diabetic retinopathy than in those with a history of severe hypoglycaemia. Indeed, evidence is accumulating that loss of cognitive function may result from hyperglycaemia or hypoglycaemia-induced micro- or macroangiopathy, a condition for which the term ‘diabetic encephalopathy’ has been proposed. As a corollary, cognitive function may benefit more from strict glycaemic control and prevention of hyperglycaemia than from meticulous avoidance of (severe) hypoglycaemia. Studies with extended follow-up, preferably 30 years or longer, are needed to identify whether or not diabetic patients with diabetic encephalopathy are at increased risk of hypoglycaemia-induced brain damage.

Diagnosis of clinical hypoglycaemia unawareness

There are no tests available to definitively establish the presence of hypoglycaemia unawareness or defects in hormonal glucose counterregulation in daily practice. Diagnosis of hypoglycaemia unawareness is subject to clinical judgment, the assessment of which is clinically relevant because of its predictive value for the frequency of severe hypoglycaemic episodes. Self-reported failure to perceive hypoglycaemic symptoms is associated with a ninefold higher risk of severe hypoglycaemic events, underscoring patients’ capability for reliable self-diagnosis. Clinical signs suggestive of hypoglycaemia unawareness include self-reporting of biochemical


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hypoglycaemia unaccompanied by symptoms, loss of autonomic symptoms as initial sign of hypoglycaemia, a (recent) history of severe hypoglycaemia (e.g. coma), or the reporting that lower blood glucose levels are required to elicit symptoms. Nocturnal hypoglycaemias should be specifically addressed as they are more frequent then previously acknowledged and go typically unnoticed.\textsuperscript{89} Continuous glucose monitoring (CGMS) may help to detect nocturnal or otherwise asymptomatic hypoglycaemia, but its tendency to overestimate the time spent under hypoglycaemic conditions and its relatively low accuracy during hypoglycaemia should be taken into account.\textsuperscript{89,90} It may prove valuable to interview spouses and family members, as they often recognise (the neuroglycopenic symptoms of) hypoglycaemic events before the patient with hypoglycaemia unawareness perceives them. As irritability or even frank aggression may be a consequence of neuroglycopenia,\textsuperscript{92} such instances can be disturbing for both patients and their relatives, especially when the patient denies being hypoglycaemic and refuses to take appropriate action. A peculiar observation concerns the expression of odd behaviour by dogs whose owners are in a hypoglycaemic state,\textsuperscript{93,94} a phenomenon that might be utilised for hypoglycaemia alerting.\textsuperscript{94}

\textbf{TREATMENT OF HYPOGLYCAEMIA UNAWARENESS AND COUNTERREGULATORY DEFECTS}

Table 2 shows all the treatment options for the management of hypoglycaemia unawareness and the counterregulatory defects.

\begin{table}[h]
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\begin{tabular}{|l|l|l|}
\hline
\textbf{Options} & \textbf{Mechanism} & \textbf{Comment} \\
\hline
Reducing hypoglycaemia risk & Avoidance of hypoglycaemia & Two to three weeks is sufficient to improve hypoglycaemia unawareness clinically \\
Optimising insulin treatment & Idem & Effect on counterregulation depends on effectiveness of hypoglycaemia avoidance \\
Pharmacological therapy & Stimulation of glucagon response & Not tested in clinical trials \\
- Alanine & Enhancement of adrenaline effect & Not tested in clinical trials \\
- \(\beta\)-adrenergic agents & CNS stimulation & May be efficacious, but emergence of tolerance may limit effect of long-term use \\
- Methylxanthine derivatives & Modulation of hypoglycaemia sensing & Not effective in humans, possibly due to inability to cross blood-brain barrier \\
- K\textsubscript{ATP} channel modulators & Idem & Promising, but not tested in clinical trial \\
- Fructose & Improving accuracy of hypoglycaemia detection & Intensive programme that has only been found effective at the hands of its founders \\
Miscellaneous & Prevention of exercise-induced hypoglycaemia & Single observation in a limited number of subjects \\
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\textbf{Hypoglycaemic risk reduction}

Several studies have found that hypoglycaemia unawareness is reversible, at least in part, when hypoglycaemic events are meticulously avoided. Avoidance of hypoglycaemia for two to three weeks appears sufficient to restore symptomatic awareness of hypoglycaemia, to improve the adrenaline response to hypoglycaemia, to shift the glycaemic thresholds for these responses to higher plasma glucose levels,\textsuperscript{95-97} and to normalise \(\beta\)-adrenergic sensitivity.\textsuperscript{98} Not all counterregulatory defects respond to this strategy: glucagon responses typically remain unaffected, whereas adrenaline responses improve but usually do not normalise, possibly reflecting more or less permanent loss of adrenaline-releasing capacity.\textsuperscript{99} By close monitoring of blood glucose excursions (including at night) and intensifying patient-doctor contacts, it has been reported feasible to limit deterioration of glycaemic control to <1\% increase in Hb\textsubscript{A1c}.\textsuperscript{100} However, in daily practice the associated worsening of glycaemic control is often much greater, constituting a significant drawback to the strict hypoglycaemia avoidance approach. Therefore, this strategy should be reserved for patients for whom the benefit of avoiding hypoglycaemias clearly outweighs the long-term harm of poorer metabolic control. For example, patients with a history of severe, complicated hypoglycaemia, patients who run the risk that hypoglycaemias result in potentially fatal (traffic) accidents and perhaps patients – or whose relatives – who cannot cope mentally with the burden of recurrent hypoglycaemias.\textsuperscript{8,101} Preferably, tight glycaemic control should be gradually re-introduced once hypoglycaemic awareness has returned.
Optimisation of insulin treatment: insulin analogues and CSII

Because of its pivotal role in counterregulatory impairments, any reduction in the rate of iatrogenic hypoglycaemia will automatically support the integrity of counterregulatory function and contribute to prevention of subsequent episodes. Practising hypoglycaemia risk reduction within the boundaries of glycaemic control can be attained by selecting insulin preparations that best mimic the physiological profile of rapid bursts of insulin secretion at mealtimes and stable, peak-less insulin levels between meals and overnight. In general, short-acting insulin analogues, such as lispro or aspart, are associated with a lower rate of hypoglycaemia, especially in the postabsorptive state, and preserve counterregulatory function better than regular insulin. Basal insulin is best replaced by a long-acting insulin analogue. These agents produce a lower peak concentration and have a more predictable pharmacokinetic profile than NPH insulin, which may specifically reduce the risk of nocturnal hypoglycaemia. Finally, continuous subcutaneous insulin infusion (CSII), preferably with a short-acting insulin analogue, is viewed as the best method to match insulin administration to daily fluctuating requirements, for which clinical hypoglycaemia unawareness is an accepted indication. Conceptually, use of CGMS may be of adjunctive value to optimise insulin therapy, yet studies addressing this issue are few and have produced conflicting results. An extensive discussion on treatment optimisation, however, is beyond the scope of this review.

Pharmacological management of hypoglycaemia unawareness

Although providing therapeutic insulin in a more physiological fashion can minimise the risk of iatrogenic hypoglycaemia, this alone is often insufficient to normalise hypoglycaemic awareness or hormonal glucose counterregulation. From a pharmacological point of view, several agents have the potential to stimulate or support glucose counterregulation more directly. A number of approaches have been tested. A first approach is to stimulate hormonal counterregulation directly in order to prevent the occurrence of or promote recovery from hypoglycaemic events. Alanine can enhance the glucagon response to hypoglycaemia and has been found to support recovery from experimental hypoglycaemia and to prevent nocturnal hypoglycaemia somewhat better than a bedtime snack. The remarkable finding of a discernible glucagon response to hypoglycaemia in patients with long-term T1DM in the postprandial period has been attributed to alanine in the meal. Analogously, the β2-adrenergic agonist terbutaline provides similar clinical effects by enhancing the glucose-stimulating action of adrenaline. Theoretically, reduced β-adrenergic sensitivity may limit its usefulness in patients with hypoglycaemia unawareness, but recent evidence indicates that responsiveness to β2-adrenergic agonists is unaltered in these patients. Neither alanine nor terbutaline have been studied in a clinical trial.

A second approach to enhance glucose counterregulation is by CNS stimulation. Several studies have examined the central stimulant effects of the methylxanthine derivatives theophylline and caffeine for their capacity to ameliorate hypoglycaemia unawareness. Both agents have been found to enhance counterregulatory hormone (except glucagon) responses to, the perception of, and recovery from hypoglycaemia in uncomplicated T1DM patients and in T1DM patients with hypoglycaemia unawareness. Despite the well-known emergence of tolerance associated with prolonged use of methylxanthines under nonhypoglycaemic conditions, some of the glucose counterregulation enhancing effects are retained during hypoglycaemia. In a clinical setting, three months of caffeine use in a group of nonselected T1DM patients resulted in increased reporting of symptomatic hypoglycaemia and a reduction in biochemical (i.e. asymptomatic) hypoglycaemia, whereas glycaemic control remained unaffected. These promising data need confirmation by larger controlled studies of longer duration before use of caffeine or theophylline can be recommended for the management of hypoglycaemia unawareness. A final approach is to manipulate cerebral hypoglycaemia by agents that alter glucokinase activity or KATP channel opening. Fructose, which may enhance cerebral hypoglycaemia sensing by modulation of glucokinase activity, has been found to stimulate glucagon and adrenaline responses to hypoglycaemia, to stimulate hepatic glucose production and to inhibit peripheral glucose uptake. Whether fructose ameliorates hypoglycaemia unawareness and if so, whether the effects of fructose are sustained with long-term use has, however, not been studied so far. In nondiabetic subjects, neither glibenclamide (a KATP channel blocker) nor diazoxide (a KATP channel opener) have been found to affect counterregulatory responses to hypoglycaemia, possibly because the agents were unable to cross the blood-brain barrier.

Nonpharmacological interventions

Focusing primarily on the clinical problem of hypoglycaemia unawareness, Cox and co-workers developed what is known as blood glucose awareness training (BGAT), a specific training programme to improve the accuracy of blood glucose level estimation. The BGAT programme involves instruction on (discrete) physical symptoms as internal cues and on the effect of diet, physical exercise, insulin pharmacology, and last blood glucose reading as external cues to allow more adequate assessment of blood glucose level. Although originally developed to improve detection of hyperglycaemia, BGAT has been found to support the accuracy of hypoglycaemia...
support glucose counterregulation and – consequently – thoroughly, in order to develop targeted strategies that impairments and hypoglycaemia unawareness more understand the pathophysiology of counterregulatory insulin treatment. More effort should be exercised to regulated insulin replacement), iatrogenic hypoglycaemia insulin in a much more physiological way (e.g. by glucose-the imperfections of therapeutic insulin by providing control to a certain extent. Unless we learn to overcome risk-reducing strategies without compromising glycaemic prove difficult, if not impossible, to apply hypoglycaemia of increased hypoglycaemic incidence. Conversely, it may control can at some point only be achieved at the expense self-monitoring are optimised, improvement of glycaemic and insulin pumps may help to limit hypoglycaemic risk. Use of insulin analogues, both short- and long-acting, limiting factor in the glycaemic management of diabetes. For patients with T1DM or advanced T2DM, and is the iatrogenic hypoglycaemia constitutes an important burden for patients with T1DM or advanced T2DM, and is the limiting factor in the glycemic management of diabetes. Use of insulin analogues, both short- and long-acting, and insulin pumps may help to limit hypoglycaemic risk. However, provided that insulin treatment and blood glucose self-monitoring are optimised, improvement of glycaemic control can at some point only be achieved at the expense of increased hypoglycaemic incidence. Conversely, it may prove difficult, if not impossible, to apply hypoglycaemia risk-reducing strategies without compromising glycaemic control to a certain extent. Unless we learn to overcome the imperfections of therapeutic insulin by providing insulin in a much more physiological way (e.g. by glucose-regulated insulin replacement), iatrogenic hypoglycaemia will remain a daily issue for all diabetic patients requiring insulin treatment. More effort should be exercised to understand the pathophysiology of counterregulatory impairments and hypoglycaemia unawareness more thoroughly, in order to develop targeted strategies that support glucose counterregulation and – consequently – reduce hypoglycaemic incidence.

**CONCLUSION**

In insulin-treated diabetic patients, iatrogenic hypoglycaemia is typically the result of the interplay of insulin excess on the one hand and counterregulatory failure, as reflected by defective hormonal counterregulation and hypoglycaemia unawareness, on the other. Although rarely causing direct physical harm, iatrogenic hypoglycaemia constitutes an important burden for patients with T1DM or advanced T2DM, and is the limiting factor in the glycemic management of diabetes. Use of insulin analogues, both short- and long-acting, and insulin pumps may help to limit hypoglycaemic risk. However, provided that insulin treatment and blood glucose self-monitoring are optimised, improvement of glycaemic control can at some point only be achieved at the expense of increased hypoglycaemic incidence. Conversely, it may prove difficult, if not impossible, to apply hypoglycaemia risk-reducing strategies without compromising glycaemic control to a certain extent. Unless we learn to overcome the imperfections of therapeutic insulin by providing insulin in a much more physiological way (e.g. by glucose-regulated insulin replacement), iatrogenic hypoglycaemia will remain a daily issue for all diabetic patients requiring insulin treatment. More effort should be exercised to understand the pathophysiology of counterregulatory impairments and hypoglycaemia unawareness more thoroughly, in order to develop targeted strategies that support glucose counterregulation and – consequently – reduce hypoglycaemic incidence.

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