Netherlands
The Journal of Medicine

REVIEW

Pathophysiology and management of recurrent hypoglycaemia and hypoglycaemia unawareness in diabetes

B.E. de Galan[1*], B.J.J.W. Schouwenberg[1,2], C.J. Tack[1], P. Smits[1,2 **]

Departments of [1]Medicine and [2]Pharmacology-Toxicology, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB, Nijmegen, the Netherlands, [*]corresponding author: tel.: +31 (0)24-361 88 19/ +31 (0)24-361 32 86, fax: +31 (0)24-354 17 34, e-mail: b.degalan@aig.umcn.nl

ABSTRACT

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.

KEYWORDS

Diabetes mellitus, glucose counterregulation, hypoglycaemia unawareness, insulin treatment

CASE REPORT

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 HbA_{1c} 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

[**]P. Smits was not involved in the handling and review process of this paper.

diabetes (T2DM). 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,[1] and especially those patients attempting to optimise glycaemic control may suffer multiple episodes a week.[2] Numerous studies, including the Diabetes Control and Complications Trial (DCCT)[3] and United Kingdom Prospective Diabetes Study (UKPDS),[4] have established the inverse relationship between HbA_{1c} 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.[5] 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.

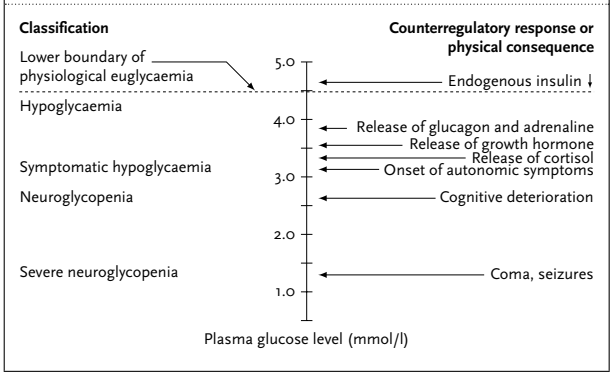
Role of insulin in risk for hypoglycaemia

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%,[6,7] 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.[8]

Normal glucose counterregulation

In the nondiabetic individual, declining blood glucose levels trigger a characteristic and hierarchically organised sequence of responses (*figure 1*).[9,10] 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.[11-13] 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

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[14] or to lower glucose levels following repeated hypoglycaemia.[15-17] The magnitude of counterregulatory function as a whole tends to decrease with age[18] and is more prominent in men than in (premenopausal) women.[19]

Table 1. *Symptoms of hypoglycaemia*

Autonomic symptoms	Neuroglycopenic symptoms
Sweating	Blurred vision
Tingling	Difficulty speaking
Trembling	Feeling faint
Feeling shaky	Difficulty thinking
Feeling hungry	Confusion
Palpitations	Dizziness
Anxiety	Feeling drowsy
	Irritability

Glucose counterregulation in diabetes

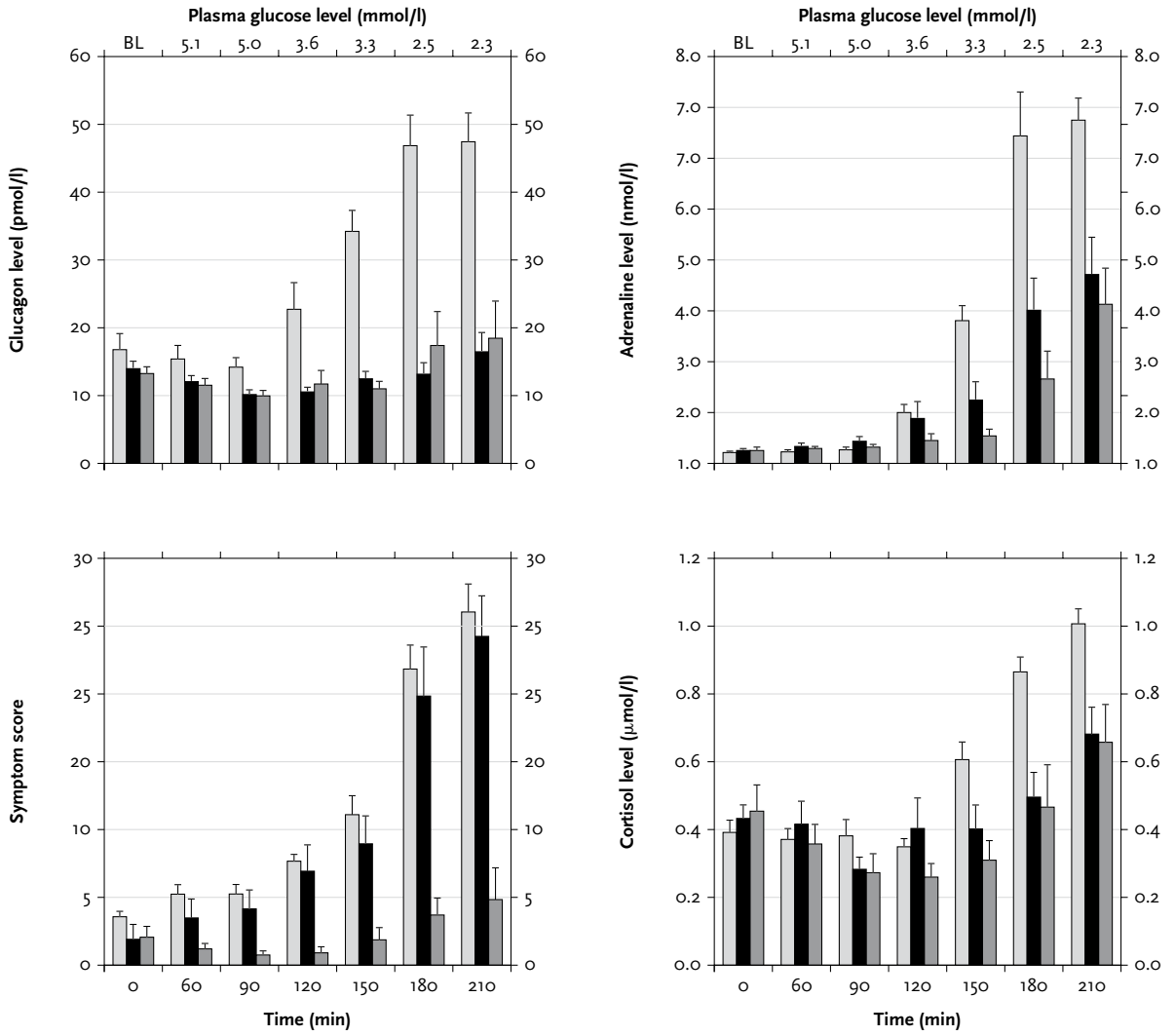
Glucose counterregulation in patients with T1DM is typically impaired. The loss of insulin-producing capacity disrupts the first-line defence against falling blood glucose levels and the consequent lack of paracrine control of the pancreatic α-cell precludes an adequate glucagon response. Therefore, hypoglycaemia usually fails to trigger glucagon responses in TIDM 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,[20,21] impairs hypoglycaemic perceptibility clinically,[22] and possibly reduces β-adrenergic sensitivity.[23,24] Any hypoglycaemia, whether mild, asymptomatic,[17] nocturnal,[25] or brief,[26] 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.[27] Various terms are used for the combination of defective hormonal counterregulation and hypoglycaemia unawareness, such as counterregulatory failure, hypoglycaemia-associated autonomic failure (HAAF)[28] 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.[29-31] 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.[32,33]

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.[34] Indeed, hypoglycaemic rates are >15-fold lower in orally treated and still approximately sixfold lower in insulin-treated T2DM patients [4] than in patients with T1DM.[3] Insulin resistance and – possibly – increased sensitivity to plasma catecholamines[35] 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.[36] Moreover, insulin deficiency in T2DM causes an absent glucagon response to hypoglycaemia[37] and a steep rise in the risk for hypoglycaemia that approaches that of T1DM.[38] T2DM patients who approach the insulin-deficient state are prone to the same counterregulatory defects as patients with T1DM, including hypoglycaemia unawareness.[37] Recent data indicate that 8 to 31% of insulin-treated T2DM patients report having trouble in correctly identifying hypoglycaemic events,[39,40] and that these patients have a ninefold higher risk for severe iatrogenic hypoglycaemia than patients with normal hypoglycaemic awareness.[39]

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

Figure 2. *Responses of glucagon, adrenaline and cortisol to insulin-induced hypoglycaemia in nondiabetic control subjects (light grey bars), T1DM patients with intact hypoglycaemic awareness (black bars) and T1DM patients with hypoglycaemia unawareness (dark grey bars)*[121,122]



Compared with control subjects, both T1DM groups exhibit absent glucagon responses and reduced adrenaline and cortisol responses to hypoglycaemia. In T1DM patients with hypoglycaemia unawareness, the onset of the adrenaline response is shifted to a lower glucose level and hypoglycaemic symptoms are largely absent during hypoglycaemia. BL denotes baseline.

that prior supraphysiological elevation of plasma cortisol was able to mimic some of the – primarily metabolic – effects of antecedent hypoglycaemia[41,42] and that failure to secrete cortisol could prevent the phenomenon.[43] However, 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.[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,[47,48] possibly mediated through increased expression of cerebral GLUT-1 and GLUT-3 glucose transporters.[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.[51-53] Observations of increased cerebral glucose content in T1DM patients with near-normal HbA_{1c} values,[54] or with hypoglycaemia unawareness[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[56] nor in animals.[57,58] Moreover, no differences in blood-to-brain glucose transport were found using positron emission tomography between hypoglycaemia aware and hypoglycaemia unaware T1DM patients.[59]

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,[60] K_{ATP} channel closure,[61] decreased AMP-activated protein kinase activity,[62] and reduced insulin signalling[63] 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.[64] Conversely, administration of nonglucose substrates for metabolism, such as β-hydroxybutyrate or lactate, during hypoglycaemia suppress counterregulatory responses.[65-67] Recent data indicate that hypoglycaemia causes twofold higher increases in brain acetate in T1DM patients than in healthy controls[68] without affecting brain energy metabolism,[69] 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 ^{13}C 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 ^{13}C NMR spectroscopy in humans under hypoglycaemic conditions.[70]

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.[71] 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, et cetera. 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.[72]

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.[73,74] Death in this syndrome is thought to be the result of a fatal ventricular arrhythmia caused by hypoglycaemia-induced lengthening of the QT interval.[75] 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).[76] 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,[77-80] and a recent study reporting altered brain structure after severe hypoglycaemia.[81] 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.[82] Prospective studies[83-85] and a recent cross-sectional study,[86] 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.[86] Indeed, evidence is accumulating that loss of cognitive function may result from hyperglycaemia or hyperglycaemia-induced micro- or macroangiopathy, a condition for which the term 'diabetic encephalopathy' has been proposed.[87] 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.[39,88] Self-reported failure to perceive hypoglycaemic symptoms is associated with a ninefold higher risk of severe hypoglycaemic events,[88] underscoring patients' capability for reliable self-diagnosis. Clinical signs suggestive of hypoglycaemia unawareness include self-reporting of biochemical

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.[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.[90,91] 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,[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,[93,94] a phenomenon that might be utilised for hypoglycaemia alerting.[94]

TREATMENT OF HYPOGLYCAEMIA UNAWARENESS AND COUNTERREGULATORY DEFECTS

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

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,[95-97] and to normalise β-adrenergic sensitivity.[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.[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 HbA_{1c}.[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.[101] Preferably, tight glycaemic control should be gradually re-introduced once hypoglycaemic awareness has returned.

Table 2. *Treatment options for the management of hypoglycaemia unawareness*

Options	Mechanism	Comment
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		
• Alanine	Stimulation of glucagon response	Not tested in clinical trials
• β_2-adrenergic agents	Enhancement of adrenaline effect	Not tested in clinical trials
• Methylxanthine derivatives	CNS stimulation	May be efficacious, but emergence of tolerance may limit effect of long-term use
• K_{ATP} channel modulators	Modulation of hypoglycaemia sensing	Not effective in humans, possibly due to inability to cross blood-brain barrier
• Fructose	Idem	Promising, but not tested in clinical trial
Miscellaneous		
• Blood glucose awareness training	Improving accuracy of hypoglycaemia detection	Intensive programme that has only been found effective at the hands of its founders
• High-intensity exercise	Prevention of exercise-induced hypoglycaemia	Single observation in a limited number of subjects

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,[102-104] and preserve counterregulatory function better[105] than regular insulin. Basal insulin is best replaced by a long-acting insulin analogue.[103,106-109] 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,[110-113] 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.[114] 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[115] and to prevent nocturnal hypoglycaemia somewhat better than a bedtime snack.[116] 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.[117] Analogously, the β_2-adrenergic agonist terbutaline provides similar clinical effects by enhancing the glucose-stimulating action of adrenaline.[115,116] Theoretically, reduced β-adrenergic sensitivity may limit its usefulness in patients with hypoglycaemia unawareness,[23,24] but recent evidence indicates that responsiveness to β_2-adrenergic agonists is unaltered in these patients.[118] 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[119,120] and in T1DM patients with hypoglycaemia unawareness.[121] 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.[122] 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.[123] 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 sensing, for instance by agents that alter glucokinase activity or K_{ATP} 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.[124,125] 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 K_{ATP} channel blocker) nor diazoxide (a K_{ATP} channel opener) have been found to affect counterregulatory responses to hypoglycaemia,[126] 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.[127] 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

detection and to decrease the number of asymptomatic hypoglycaemia without compromising glycaemic control,[128] even in the long term.[129] Counterregulatory function may benefit from this reduction in hypoglycaemic incidence – and the detection of falling blood glucose levels at earlier stages – in that a near-normal adrenaline response to insulin-induced hypoglycaemia can be retained.[130] Attempts to translate BGAT into a Dutch version have only been partially successful, as its effect on hypoglycaemia detection was far less evident.[131,132]

Patients who experience hypoglycaemia during or shortly following low- or intermediate-intensity exercise may benefit from a brief period of high-intensity exercise to revert the fall in blood glucose. In seven T1DM patients who exercised for 20 minutes at 40% of maximal capacity, 10 seconds of sprinting on a cycle ergometer was sufficient to stabilise glucose levels and to prevent hypoglycaemia without reductions in insulin use.[133] Interval training, in which low- and high-intensity exercise is alternated, may be equally effective to avoid exercise-induced hypoglycaemia.[134]

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 glycaemic 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.

REFERENCES

1. Lawrence RD. Insulin hypoglycaemia. Changes in nervous manifestations. Lancet 1941;ii:602-4.
2. Gross TM, Mastrototaro JJ, Fredrickson LP. Detection of unseen hypoglycemia using continuous glucose monitoring. Diabetologia 2003;43(suppl 1):A5-19.
3. The diabetes control and complications trial research group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977-86.
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
5. Cryer PE. Hypoglycaemia: The limiting factor in the glycaemic management of Type I and Type II Diabetes*. Diabetologia 2002;45:937-48.
6. Eaton RP, Allen RC, Schade DS. Hepatic removal of insulin in normal man: dose response to endogenous insulin secretion. J Clin Endocrinol Metab 1983;56:1294-300.
7. Porksen N. The in vivo regulation of pulsatile insulin secretion. Diabetologia 2002;45:3-20.
8. Heller SR. Diabetic hypoglycaemia. Baillieres Best Pract Res Clin Endocrinol Metab 1999;13:279-94.
9. The DCCT Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med 1991;90:450-9.
10. Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. J Clin Invest 1987;79:777-81.
11. Mitrakou A, Ryan C, Veneman T, et al. Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. Am J Physiol 1991;260:E67-74.
12. Unger RH. The Berson memorial lecture. Insulin-glucagon relationships in the defense against hypoglycemia. Diabetes 1983;32:575-83.
13. Ter Braak E, Appelman A, Erkelens D, van Haeften T. Glibenclamide decreases glucagon release during mild hypoglycaemia. Diabetologia 1998;41(suppl 1):A68.
14. Banarer S, McGregor VP, Cryer PE. Intraislet hyperinsulinemia prevents the glucagon response to hypoglycemia despite an intact autonomic response. Diabetes 2002;51:958-65.
15. Boyle PJ, Schwartz NS, Shah SD, Clutter WE, Cryer PE. Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. N Engl J Med 1988;318:1487-92.
16. Heller SR, Cryer PE. Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. Diabetes 1991;40:223-6.
17. Davis MR, Shamoon H. Counterregulatory adaptation to recurrent hypoglycemia in normal humans. J Clin Endocrinol Metab 1991;73:995-1001.
18. Davis SN, Shavers C, Mosqueda Garcia R, Costa F. Effects of differing antecedent hypoglycemia on subsequent counterregulation in normal humans. Diabetes 1997;48:1328-35.
19. Davis SN, Fowler S, Costa F. Hypoglycemic counterregulatory responses differ between men and women with type 1 diabetes. Diabetes 2000;49:65-72.
20. Meneilly GS, Cheung E, Tuokko H. Altered responses to hypoglycemia of healthy elderly people. J Clin Endocrinol Metab 1994;78:1341-8.
21. Mei Q, Mundinger TO, Lernmark A, Taborsky GJ Jr. Early, selective, and marked loss of sympathetic nerves from the islets of BioBreeder diabetic rats. Diabetes 2002;51:2997-3002.

22. Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV. Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. Diabetes 1988;37:901-7.

23. Dagogo Jack SE, Craft S, Cryer PE. Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. J Clin Invest 1993;91:819-28.

24. De Galan BE, Tack CJ, Willemsen JJ, Sweep CG, Smits P, Lenders JW. Plasma metanephrine levels are decreased in type 1 diabetic patients with a severely impaired epinephrine response to hypoglycemia, indicating reduced adrenomedullary stores of epinephrine. J Clin Endocrinol Metab 2004;89:2057-61.

25. White NH, Skor DA, Cryer PE, Levandoski LA, Bier DM, Santiago JV. Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy. N Engl J Med 1983;308:485-91.

26. Bolli GB, De Feo P, De Cosmo S, et al. A reliable and reproducible test for adequate glucose counterregulation in type I diabetes mellitus. Diabetes 1984;33:732-7.

27. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care 1994;17:697-703.

28. Trovik TS, Jaeger R, Jorde R, Sager G. Reduced sensitivity to beta-adrenoceptor stimulation and blockade in insulin dependent diabetic patients with hypoglycaemia unawareness. Br J Clin Pharmacol 1994;38:427-32.

29. Korytkowski MT, Mokan M, Veneman TF, Mitrakou A, Cryer PE, Gerich JE. Reduced beta-adrenergic sensitivity in patients with type 1 diabetes and hypoglycemia unawareness. Diabetes Care 1998;21:1939-43.

30. Enoksson S, Caprio SK, Rife F, Shulman GI, Tamborlane WV, Sherwin RS. Defective activation of skeletal muscle and adipose tissue lipolysis in type 1 diabetes mellitus during hypoglycemia. J Clin Endocrinol Metab 2003;88:1503-11.

31. Cryer PE. Hypoglycemia-associated autonomic failure in diabetes. Am J Physiol Endocrinol Metab 2001;281:E1115-21.

32. Davis SN, Mann S, Galassetti P, et al. Effects of differing durations of antecedent hypoglycemia on counterregulatory responses to subsequent hypoglycemia in normal humans. Diabetes 2000;49:1897-903.

33. Davis SN, Tate D. Effects of morning hypoglycemia on neuroendocrine and metabolic responses to subsequent afternoon hypoglycemia in normal man. J Clin Endocrinol Metab 2001;86:2043-50.

34. Veneman T, Mitrakou A, Mokan M, Cryer P, Gerich J. Induction of hypoglycemia unawareness by asymptomatic nocturnal hypoglycemia. Diabetes 1993;42:1233-7.

35. Ovalle F, Fanelli CG, Paramore DS, Hershey T, Craft S, Cryer PE. Brief twice-weekly episodes of hypoglycemia reduce detection of clinical hypoglycemia in type 1 diabetes mellitus. Diabetes 1998;47:1472-9.

36. Cryer PE. Banting Lecture. Hypoglycemia: the limiting factor in the management of IDDM. Diabetes 1994;43:1378-89.

37. Polinsky RJ, Kopin IJ, Ebert MH, Weise V. The adrenal medullary response to hypoglycemia in patients with orthostatic hypotension. J Clin Endocrinol Metab 1980;51:1401-6.

38. Hoeldtke RD, Boden G, Shuman CR, Owen OE. Reduced epinephrine secretion and hypoglycemia unawareness in diabetic autonomic neuropathy. Ann Intern Med 1982;96:459-62.

39. Bottini P, Boschetti E, Pampanelli S, et al. Contribution of autonomic neuropathy to reduced plasma adrenaline responses to hypoglycemia in IDDM: evidence for a nonselective defect. Diabetes 1997;46:814-23.

40. Hepburn DA, Patrick AW, Eadington DW, Ewing DJ, Frier BM. Unawareness of hypoglycaemia in insulin-treated diabetic patients: prevalence and relationship to autonomic neuropathy. Diabet Med 1990;7:711-7.

41. Stephenson JM, Kempler P, Perin PC, Fuller JH. Is autonomic neuropathy a risk factor for severe hypoglycaemia? The EURODIAB IDDM Complications Study. Diabetologia 1996;39:1372-6.

42. de Galan BE, Hoekstra JB. Glucose counterregulation in Type 2 diabetes mellitus. Diabet Med 2001;18:519-27.

43. Shamoon H, Friedman S, Canton C, Zacharowicz L, Hu M, Rossetti L. Increased epinephrine and skeletal muscle responses to hypoglycemia in non-insulin-dependent diabetes mellitus. J Clin Invest 1994;93:2562-71.

44. Levy CJ, Kinsley BT, Bajaj M, Simonson DC. Effect of glycemic control on glucose counterregulation during hypoglycemia in NIDDM. Diabetes Care 1998;21:1330-8.

45. Meneilly GS, Cheung E, Tuokko H. Counterregulatory hormone responses to hypoglycemia in the elderly patient with diabetes. Diabetes 1994;43:403-10.

46. Spyer G, Hattersley AT, MacDonald IA, Amiel S, MacLeod KM. Hypoglycaemic counter-regulation at normal blood glucose concentrations in patients with well controlled type-2 diabetes. Lancet 2000;356:1970-4.

47. Korzon Burakowska A, Hopkins D, et al. Effects of glycemic control on protective responses against hypoglycemia in type 2 diabetes. Diabetes Care 1998;21:283-90.

48. Ortiz Alonso FJ, Herman WH, Zobel DL, Perry TJ, Smith MJ, Halter JB. Effect of epinephrine on pancreatic beta-cell and alpha-cell function in patients with NIDDM. Diabetes 1991;40:1194-202.

49. Leese GP, Wang J, Broomhall J, et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. Diabetes Care 2003;26:1176-80.

50. Segel SA, Paramore DS, Cryer PE. Hypoglycemia-associated autonomic failure in advanced type 2 diabetes. Diabetes 2002;51:724-33.

51. Henderson JN, Allen KV, Deary IJ, Frier BM. Hypoglycaemia in insulin-treated Type 2 diabetes: frequency, symptoms and impaired awareness. Diabet Med 2003;20:1016-21.

52. Akram K, Pedersen-Bjergaard U, Borch-Johnsen K, Thorsteinsson B. Recall of severe hypoglycaemic episodes and course of hypoglycaemia awareness in insulin-treated Type 2 diabetes in one year follow-up. Diabetologia 2003;46:A304.

53. Davis SN, Shavers C, Costa F, Mosqueda Garcia R. Role of cortisol in the pathogenesis of deficient counterregulation after antecedent hypoglycemia in normal humans. J Clin Invest 1996;98:680-91.

54. McGregor VP, Banarer S, Cryer PE. Elevated endogenous cortisol reduces autonomic neuroendocrine and symptom responses to subsequent hypoglycemia. Am J Physiol Endocrinol Metab 2002;282:E770-7.

55. Davis SN, Shavers C, Davis B, Costa F. Prevention of an increase in plasma cortisol during hypoglycemia preserves subsequent counterregulatory responses. J Clin Invest 1997;100:429-38.

56. Raju B, McGregor VP, Cryer PE. Cortisol elevations comparable to those that occur during hypoglycemia do not cause hypoglycemia-associated autonomic failure. Diabetes 2003;52:2083-9.

57. Galassetti P, Mann S, Tate D, et al. Effects of antecedent prolonged exercise on subsequent counterregulatory responses to hypoglycemia. Am J Physiol Endocrinol Metab 2001;280:E908-17.

58. McGregor VP, Greiwe JS, Banarer S, Cryer PE. Limited impact of vigorous exercise on defenses against hypoglycemia: relevance to hypoglycemia-associated autonomic failure. Diabetes 2002;51:1485-92.

59. McCall AL, Fixman LB, Fleming N, Tornheim K, Chick W, Ruderman NB. Chronic hypoglycemia increases brain glucose transport. Am J Physiol 1986;251:E442-7.

60. Uehara Y, Nipper V, McCall AL. Chronic insulin hypoglycemia induces GLUT-3 protein in rat brain neurons. Am J Physiol 1997;272:E716-9.

61. Kumagai AK, Kang YS, Boado RJ, Pardridge WM. Upregulation of blood-brain barrier GLUT1 glucose transporter protein and mRNA in experimental chronic hypoglycemia. Diabetes 1995;44:1399-404.

62. Boyle PJ, Nagy RJ, O'Connor AM, Kempers SF, Yeo RA, Qualls C. Adaptation in brain glucose uptake following recurrent hypoglycemia. Proc Natl Acad Sci U S A 1994;91:9352-6.

63. Boyle PJ, Kempers SF, O'Connor AM, Nagy RJ. Brain glucose uptake and unawareness of hypoglycemia in patients with insulin-dependent diabetes mellitus [see comments]. N Engl J Med 1995;333:1726-31.

64. Benzo CA. Minireview. The hypothalamus and blood glucose regulation. Life Sci 1983;32:2509-15.

65. Biggers DW, Myers SR, Neal D, et al. Role of brain in counterregulation of insulin-induced hypoglycemia in dogs. Diabetes 1989;38:7-16.

66. Frizzell RT, Jones EM, Davis SN, et al. Counterregulation during hypoglycemia is directed by widespread brain regions. Diabetes 1993;42:1253-61.

67. McCrimmon RJ, Jacob RJ, Fan X, McNay EC, Sherwin RS. Effects of recurrent antecedent hypoglycaemia and chronic hyperglycaemia on brainstem extra-cellular glucose concentrations during acute hypoglycaemia in conscious diabetic BB rats. Diabetologia 2003;46:1658-61.

68. McNay EC, Sherwin RS. Effect of recurrent hypoglycemia on spatial cognition and cognitive metabolism in normal and diabetic rats. Diabetes 2004;53:418-25.

69. Segel SA, Fanelli CG, Dence CS, et al. Blood-to-brain glucose transport, cerebral glucose metabolism, and cerebral blood flow are not increased after hypoglycemia. Diabetes 2001;50:1911-7.

70. Bingham EM, Dunn JT, Smith D, et al. Differential changes in brain glucose metabolism during hypoglycaemia accompany loss of hypoglycaemia awareness in men with type 1 diabetes mellitus. An ^{11C}-3-O-methyl-D-glucose PET study. Diabetologia 2005;48:2080-9.

71. Fagius J, Berne C. Changes of sympathetic nerve activity induced by 2-deoxy-D- glucose infusion in humans. Am J Physiol 1989;256:E714-20.

72. Amiel SA, Archibald HR, Chusney G, Williams AJ, Gale EA. Ketone infusion lowers hormonal responses to hypoglycaemia: evidence for acute cerebral utilization of a non-glucose fuel. Clin Sci Colch 1991;81:189-94.

73. Maran A, Cranston I, Lomas J, Macdonald I, Amiel SA. Protection by lactate of cerebral function during hypoglycaemia [see comments]. Lancet 1994;343:16-20.

74. Veneman T, Mitrakou A, Mokan M, Cryer P, Gerich J. Effect of hyperketonemia and hyperlacticacidemia on symptoms, cognitive dysfunction, and counterregulatory hormone responses during hypoglycemia in normal humans. Diabetes 1994;43:1311-7.

75. Bischof MG, Mlynarik V, Brehm A, et al. Brain energy metabolism during hypoglycaemia in healthy and type 1 diabetic subjects. Diabetologia 2004;47:648-51.

76. De Galan BE, Van der Graaf M, Klomp D, Parkes LM, Heerschap A, Tack CJ. Feasibility study on the use of MRS to investigate human brain metabolism in vivo during hypoglycemia. Diabetes 2005;54:A155.

77. Cryer PE. Hypoglycaemia: The limiting factor in the glycaemic management of Type I and Type II Diabetes*. Diabetologia 2002;45:937-48.

78. Tattersall RB, Gill GV. Unexplained deaths of type 1 diabetic patients. Diabet Med 1991;8:49-58.

79. Campbell I. Dead in Bed Syndrome – A New Manifestation of Nocturnal Hypoglycemia. Diabet Med 1991;8:3-4.

80. Robinson RT, Harris ND, Ireland RH, MacDonald IA, Heller SR. Changes in cardiac repolarization during clinical episodes of nocturnal hypoglycaemia in adults with Type 1 diabetes. Diabetologia 2004;47:312-5.

81. Lindstrom T, Jorfeldt L, Tegler L, Arnqvist HJ. Hypoglycaemia and cardiac arrhythmias in patients with type 2 diabetes mellitus. Diabet Med 1992;9:536-41.

82. Agardh CD, Rosen I, Ryding E. Persistent vegetative state with high cerebral blood flow following profound hypoglycemia. Ann Neurol 1983;14:482-6.

83. Chalmers J, Risk MT, Kean DM, Grant R, Ashworth B, Campbell IW. Severe amnesia after hypoglycemia. Clinical, psychometric, and magnetic resonance imaging correlations. Diabetes Care 1991;14:922-5.

84. Perros P, Sellar RJ, Frier BM. Chronic pontine dysfunction following insulin-induced hypoglycemia in an IDDM patient. Diabetes Care 1994;17:725-7.

85. Casey E, Evans A, Krentz A, Watkins P, Hopkins D. Central pontine myelinolysis. An unusual complication of diabetes. Diabetes Care 1999;22:998-1000.

86. Musen G, Lyoo IK, Sparks CR, et al. Effects of type 1 diabetes on gray matter density as measured by voxel-based morphometry. Diabetes 2006;55:326-33.

87. Langan SJ, Deary IJ, Hepburn DA, Frier BM. Cumulative cognitive impairment following recurrent severe hypoglycaemia in adult patients with insulin-treated diabetes mellitus. Diabetologia 1991;34:337-44.

88. Reichard P, Pihl M, Rosenqvist U, Sule J. Complications in IDDM are caused by elevated blood glucose level: the Stockholm Diabetes Intervention Study (SDIS) at 10-year follow up. Diabetologia 1996;39:1483-8.

89. Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. Ann Intern Med 1996;124:379-88.

90. Austin EJ, Deary IJ. Effects of repeated hypoglycemia on cognitive function: a psychometrically validated reanalysis of the Diabetes Control and Complications Trial data. Diabetes Care 1999;22:1273-7.

91. Ferguson SC, Blane A, Perros P, et al. Cognitive ability and brain structure in type 1 diabetes: relation to microangiopathy and preceding severe hypoglycemia. Diabetes 2003;52:149-56.

92. Sima AA, Kamiya H, Li ZG. Insulin, C-peptide, hyperglycemia, and central nervous system complications in diabetes. Eur J Pharmacol 2004;490:187-97.

93. Pedersen-Bjergaard U, Pramming S, Thorsteinsson B. Recall of severe hypoglycaemia and self-estimated state of awareness in type 1 diabetes. Diabetes Metab Res Rev 2003;19:232-40.

94. Banarer S, Cryer PE. Sleep-related hypoglycemia-associated autonomic failure in type 1 diabetes – Reduced awakening from sleep during hypoglycemia. Diabetes 2003;52:1195-203.

95. Chen M, Daly M, Williams N, Williams S, Williams C, Williams G. Non-invasive detection of hypoglycaemia using a novel, fully biocompatible and patient friendly alarm system. BMJ 2000;321:1565-6.

96. Stocks AE. Can dogs help patients with hypoglycaemia? Diabetologia 2002;45:A79.

97. Fanelli CG, Epifano L, Rambotti AM, et al. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. Diabetes 1993;42:1683-9.

98. Dagogo Jack S, Rattarasarn C, Cryer PE. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. Diabetes 1994;43:1426-34.

99. Cranston I, Lomas J, Maran A, Macdonald I, Amiel SA. Restoration of hypoglycaemia awareness in patients with long- duration insulin-dependent diabetes. Lancet 1994;344:283-7.

100. Fritsche A, Stefan N, Haring H, Gerich J, Stumvoll M. Avoidance of hypoglycemia restores hypoglycemia awareness by increasing beta-adrenergic sensitivity in type 1 diabetes. Ann Intern Med 2001;134:729-36.

101. Cryer PE. Hypoglycaemia: The limiting factor in the glycaemic management of Type I and Type II Diabetes*. Diabetologia 2002;45:937-48.

102. Jorgensen HV, Pedersen-Bjergaard U, Rasmussen AK, Borch-Johnsen K. The impact of severe hypoglycemia and impaired awareness of hypoglycemia on relatives of patients with type 1 diabetes. Diabetes Care 2003;26:1106-9.

103. Anderson JH Jr, Brunelle RL, Koivisto VA, Trautmann ME, Vignati L, DiMarchi R. Improved mealtime treatment of diabetes mellitus using an insulin analogue. Multicenter Insulin Lispro Study Group. Clin Ther 1997;19:62-72.

104. Brunelle BL, Llewelyn J, Anderson JH, Jr., Gale EA, Koivisto VA. Meta-analysis of the effect of insulin lispro on severe hypoglycemia in patients with type 1 diabetes. Diabetes Care 1998;21:1726-31.

105. Home PD, Lindholm A, Riis A. Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: a randomized controlled trial. Diabet Med 2000;17:762-70.

106. Lalli C, Ciofetta M, Del Sindaco P, et al. Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. Diabetes Care 1999;22:468-77.

107. Wang F, Carabino JM, Vergara CM. Insulin glargine: a systematic review of a long-acting insulin analogue. Clin Ther 2003;25:1541-77, discussion.

108. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. Diabetes Care 2000;23:639-43.

109. Yki-Jarvinen H, Dressler A, Ziemen M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group. Diabetes Care 2000;23:1130-6.

110. Hermansen K, Madsbad S, Perrild H, Kristensen A, Axelsen M. Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: a randomized open crossover trial in type 1 diabetic subjects on basal-bolus therapy. Diabetes Care 2001;24:296-301.

111. Boland EA, Grey M, Oesterle A, Fredrickson L, Tamborlane WV. Continuous subcutaneous insulin infusion. A new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. Diabetes Care 1999;22:1779-84.

112. Bode BW, Steed RD, Davidson PC. Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type I diabetes. Diabetes Care 1996;19:324-7.

113. Linkeschova R, Raoul M, Bott U, Berger M, Spraul M. Less severe hypoglycaemia, better metabolic control, and improved quality of life in Type 1 diabetes mellitus with continuous subcutaneous insulin infusion (CSII) therapy; an observational study of 100 consecutive patients followed for a mean of 2 years. Diabet Med 2002;19:746-51.

114. Kanc K, Janssen MM, Keulen ET, et al. Substitution of night-time continuous subcutaneous insulin infusion therapy for bedtime NPH insulin in a multiple injection regimen improves counterregulatory hormonal responses and warning symptoms of hypoglycaemia in IDDM. Diabetologia 1998;41:322-9.

115. Wiethop BV, Cryer PE. Alanine and terbutaline in treatment of hypoglycemia in IDDM. Diabetes Care 1993;16:1131-6.

116. Saleh TY, Cryer PE. Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. Diabetes Care 1997;20:1231-6.

117. Porcellati F, Pampanelli S, Rossetti P, et al. Counterregulatory hormone and symptom responses to insulin-induced hypoglycemia in the postprandial state in humans. Diabetes 2003;52:2774-83.

118. De Galan BE, de Mol P, Wennekes L, Schouwenberg BJ, Smits P. Preserved sensitivity to beta2-adrenergic receptor agonists in patients with type 1 diabetes mellitus and hypoglycemia unawareness. J Clin Endocrinol Metab 2006;91:2878-81.

119. Hvidberg A, Rasmussen MH, Christensen NJ, Hilsted J. Theophylline enhances glucose recovery after hypoglycemia in healthy man and in type I diabetic patients. Metabolism 1994;43:776-81.

120. Watson JM, Sherwin RS, Deary IJ, Scott L, Kerr D. Dissociation of augmented physiological, hormonal and cognitive responses to hypoglycaemia with sustained caffeine use. Clin Sci (Lond) 2003;104:447-54.

121. De Galan BE, Tack CJ, Lenders JW, et al. Theophylline improves hypoglycemia unawareness in type 1 diabetes. Diabetes 2002;51:790-6.

122. De Galan BE, Tack CJ, Lenders JW, Lutterman JA, Smits P. Effect of 2 weeks of theophylline on glucose counterregulation in patients with type 1 diabetes and unawareness of hypoglycemia. Clin Pharmacol Ther 2003;74:77-84.

123. Watson JM, Jenkins EJ, Hamilton P, Lunt MJ, Kerr D. Influence of caffeine on the frequency and perception of hypoglycemia in free-living patients with type 1 diabetes. Diabetes Care 2000;23:455-9.

124. Bingham E, Hopkins D, Pernet A, Reid H, MacDonald IA, Amiel SA. The effects of KATP channel modulators on counterregulatory responses and cognitive function during acute controlled hypoglycaemia in healthy men: a pilot study. Diabet Med 2003;20:231-7.

125. Gabriely I, Hawkins M, Vilcu C, Rossetti L, Shamoon H. Fructose amplifies counterregulatory responses to hypoglycemia in humans. Diabetes 2002;51:893-900.

126. Gabriely I, Shamoon H. Fructose normalizes specific counterregulatory responses to hypoglycemia in patients with type 1 diabetes. Diabetes 2005;54:609-16.

127. Cox DJ, Clarke WL, Gonder-Frederick L, et al. Accuracy of perceiving blood glucose in IDDM. Diabetes Care 1985;8:529-36.

128. Cox DJ, Gonder Frederick LA, Lee JH, Julian DM, Carter WR, Clarke WL. Effects and correlates of blood glucose awareness training among patients with IDDM. Diabetes Care 1989;12:313-8.

129. Cox DJ, Gonder Frederick L, Julian DM, Clarke W. Long-term follow-up evaluation of blood glucose awareness training. Diabetes Care 1994;17:1-5.

130. Kinsley BT, Weinger K, Bajaj M, et al. Blood glucose awareness training and epinephrine responses to hypoglycemia during intensive treatment in type 1 diabetes. Diabetes Care 1999;22:1022-8.

131. Ter Braak EW, de Valk HW, de la Bije YF, van der Laak MF, van Haeften TW, Erkelens DW. Response to training in blood glucose awareness is related to absence of previous hypoglycemic coma. Diabetes Care 2000;23:1199-200.

132. Broers S, le Cessie S, van Vliet KP, Spinhoven P, van der Ven NC, Radder JK. Blood Glucose Awareness Training in Dutch Type 1 diabetes patients. Short-term evaluation of individual and group training. Diabet Med 2002;19:157-61.