Title: Managing Hypoglycaemia

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Abstract (No. words = 147)

Intensive glycaemic control reduces the diabetic microvascular disease burden but iatrogenic hypoglycaemia is a major barrier preventing tight glycaemic control because of the limitations of subcutaneous insulin preparations and insulin secretagogues. Severe hypoglycaemia is uncommon early in the disease as robust physiological defences, particularly glucagon and adrenaline release, limit falls in blood glucose whilst associated autonomic symptoms drive patients to take action by ingesting oral carbohydrate. With increasing diabetes duration, glucagon release is progressively impaired and sympatho-adrenal responses are activated at lower glucose levels. Repeated hypoglycaemic episodes contribute to impaired defences, increasing the risk of severe hypoglycaemia in a vicious downward spiral. Managing hypoglycaemia requires a systematic clinical approach with structured insulin self-management training and support of experienced diabetes educators. Judicious use of technologies includes insulin analogues, insulin pump therapy, continuous glucose monitoring, and in a few cases islet cell transplantation. Some individuals require specialist psychological support.

Keywords: Hypoglycaemia, counter-regulation, impaired hypoglycaemia awareness, adrenaline, cardiovascular risk

Introduction

Since the earliest description by Banting, the clinical challenges of hypoglycaemia have been recognised as a major side effect of insulin treatment (1). More precise analyses of the pathophysiology did not emerge until around 20 years later in R D Lawrence's account of symptoms of iatrogenic hypoglycaemia as "being akin to a dose of adrenaline" (2). A more detailed understanding of why individuals with insulin treated diabetes are so vulnerable to hypoglycaemia had to await accurate measurements of both blood glucose and the relevant endocrine responses in the 1980s. These insights have been followed by the development of experimental human and animal models. Studies have continued to the present day, although to date there have been few specific treatments which can prevent hypoglycaemia. The key to managing and preventing hypoglycaemia requires a good understanding of both the pathophysiology and insulin therapeutics. In this review we will consider the epidemiology, pathophysiology and consequences of hypoglycaemia, but concentrate on its practical management.

Definition and Epidemiology

The precise definition of hypoglycaemia continues to be debated. An American Diabetes Association (ADA) working party has attempted a comprehensive definition (3). They have defined "severe hypoglycaemia" as an episode requiring the assistance of another person to administer treatment, "documented symptomatic hypoglycaemia" as the presence of common symptoms of hypoglycaemia with a measured plasma glucose <3.9 mmol/L, "probable symptomatic hypoglycaemia" as self-reported symptoms

not verified by a glucose measurement and “relative hypoglycaemia” as the presence of symptoms with a plasma glucose >3.9 mmol/L.

It is clear that a single definition cannot encompass all types of hypoglycaemia. Indeed, even within these categories there continues to be no consensus. For example, the definition of severe hypoglycaemia does not apply to children who rely on their parents or other adults for recovery even from relatively mild episodes. Thus, paediatricians define severe hypoglycaemia as coma or needing parenteral treatment.

Furthermore, in clinical trials, organisations, both commercial and academic, frequently use different definitions. It is therefore often difficult to compare directly, epidemiological studies and clinical trial data. This also means that meta-analyses often exclude detailed discussion of even severe hypoglycaemia due to the observed ‘heterogeneity’ between studies.

It is important to note that data from clinical trials report rates of hypoglycaemia, including severe, which are many times lower than rates collected from observational data. In the Diabetes Control and Complications Trial (DCCT), which is considered to have resulted in an epidemic of severe hypoglycaemia in the intensive arm, reported rates expressed in episodes per patient year were considerably lower than rates from observational studies. More recent clinical trials have reported even lower rates of severe hypoglycaemia (4) . In contrast, data reported in observational studies have shown virtually no reduction in rates of severe hypoglycaemia over the last 20 years, despite the introduction of analogue insulins and continuous subcutaneous insulin infusion (CSII) (Table 1) (5)(6)(7)(8)(9). These data

suggest that clinicians are either failing to exploit technological developments or that other factors often determine hypoglycaemic risk. Prospective population based studies which have examined hypoglycaemic rates indicate that rates of severe hypoglycaemia in insulin treated patients with type 2 diabetes mellitus (T2DM) are generally around a third of those with type 1 diabetes mellitus (T1DM) (10). Interestingly, comparable rates of hypoglycaemia have been reported in T1DM and T2DM once patients were matched for duration of insulin treatment (11). Data from another prospective study also showed that severe hypoglycaemia rates rise in both T1DM and T2DM with increasing duration of treatment (8). These findings may be explained by a progressive decline in endogenous insulin production leading to both diminished physiological protection from glucagon release and more variable free insulin levels. Finally, as T2DM is much more common than T1DM with an increasing incidence predicted in the coming years (12), management of hypoglycaemia in T2DM in terms of numbers of cases is at least as important as in T1DM.

Physiological consequences of hypoglycaemia

The reliance of the brain on glucose as an obligate fuel explains both the vulnerability of patients to hypoglycaemia and the array of defences that have evolved as stress responses. These physiological responses are termed counter-regulatory (opposing the regulatory effect of insulin) (Figure 1). Two key responses are triggered by hypoglycaemia: 1) Increased endogenous glucose production via glycogenolysis and gluconeogenesis; 2) A behavioural response, prompting the individual to consume food. In non-diabetic

individuals, the initial response to glucose values falling below 4.6 mmol/L is a reduction in endogenous insulin secretion (13). Since individuals with T1DM and insulin treated T2DM depend on injected insulin boluses in the absence of endogenous insulin secretion, their ability to defend themselves against hypoglycaemia requires additional mechanisms. Initially, as glucose concentrations fall below 3.8 mmol/L, endogenous glucagon secretion from pancreatic alpha cells induces both glycogenolysis and gluconeogenesis (14). As blood glucose falls further, the adrenal medulla secretes adrenaline which promotes hepatic glucose release through similar mechanisms. Raised cortisol and growth hormone concentrations stimulate gluconeogenesis but since subsequent increases in blood glucose are not observed for some hours, these responses are not relevant in the acute setting (15).

Symptoms of hypoglycaemia

Our knowledge of the symptomatic response to hypoglycaemia is largely based on clinical observations, but Frier and colleagues have used factor analysis to refine our understanding (16). By exploring statistical associations of symptoms reported by two cohorts of adults with insulin treated diabetes, they were able to demonstrate that hypoglycaemia symptoms could be divided into three categories, namely autonomic activation, neuroglycopenia and malaise (nausea and headache) (Table 2). Symptoms vary between individuals, and also by age and type of diabetes. For example, children exhibit emotional and behavioural changes in response to hypoglycaemia as well as autonomic and classical neuroglycopenic symptoms (17). Older patients with T2DM report neurological symptoms which are different when compared to a younger cohort of diabetes patients on insulin (18). This

classification can help patients (and their families) to identify symptoms indicating hypoglycaemia at an early stage and take corrective action before a falling glucose value impairs their cognitive ability.

Counter-regulatory defences in diabetes

Counter-regulatory responses oppose the effects of exogenous insulin on blood glucose concentrations whilst the associated sympatho-adrenal activation also contributes to autonomic symptoms such as sweating, tremor and palpitations. Experimental data indicate that counter-regulatory responses to hypoglycaemia whilst intact at diagnosis of diabetes, are gradually lost with increasing disease duration (19). In T1DM, impaired glucagon responses to hypoglycaemia are apparent by 2 years, and are established in most individuals within 5 years after diagnosis (19). The diminished glucagon response is thought to occur due to a failure of paracrine 'cross-talk' between pancreatic α-cells and β-cells, as the latter are destroyed progressively by the autoimmune process (20).

Sympatho-adrenal responses to hypoglycaemia are also progressively impaired, although the mechanisms are different (19). Impaired adrenaline responses appear to be due to a shifting of the glycaemic threshold for activation to lower glucose values, whilst the secretory capacity of the adrenal glands remain intact to other stimuli (21). Thus, a combined diminution in glucagon and adrenaline responses to hypoglycaemia progressively increases vulnerability to hypoglycaemia in T1DM (22). A diminished adrenaline response reflects an attenuated autonomic response to

hypoglycaemia, as the autonomic nervous system is key to the activation of the neuro-endocrine response to hypoglycaemia. It also appears that the mechanism underlying the diminished sympatho-adrenal response to hypoglycaemia may be distinct from that driving impaired glucagon responses (see below).

Counter-regulatory responses to hypoglycaemia have been less extensively studied in individuals with T2DM, but the limited evidence available suggests that early in the course of the disease physiological protection to hypoglycaemia is intact with glucagon responses which are normal or modestly reduced (23). As disease duration increases and endogenous insulin production falls, both glucagon and sympathoadrenal responses to hypoglycaemia become impaired (24). Thus the same drivers which increase vulnerability in T1DM may operate in longstanding T2DM. However, the experimental data are somewhat inconsistent and some studies suggest that, particularly in poorly controlled patients, the threshold for the activation of counter-regulatory responses to hypoglycaemia may occur at normal glucose values (25).

Impaired awareness of hypoglycaemia

The impaired sympatho-adrenal response to hypoglycaemia is a consequence, at least in part, of repeated episodes of iatrogenic hypoglycaemia which attenuate the autonomic response to subsequent hypoglycaemia (26). This process resets the glycaemic threshold for the activation of symptoms to a lower glucose level. The phenomenon was first

described in non-diabetic individuals (26) and subsequently in both T1DM (27) and T2DM (28), and reduces an individual's ability to perceive the onset of hypoglycaemic symptoms (28). Whether the progressive impairment in sympatho-adrenal responses which occurs with increasing duration of diabetes is entirely due to repeated hypoglycaemic episodes remains unclear.

Clinical experience indicates that many individuals with longstanding insulin treated diabetes have a diminished ability to perceive acute hypoglycaemia. To date, no satisfactory comprehensive definition of impaired hypoglycaemia awareness has been suggested, although the term "hypoglycaemia unawareness" has largely been replaced by "impaired hypoglycaemia awareness" since complete unawareness is rare. Gold (29) and Clarke (30) have proposed scales which can be used to identify impaired awareness of hypoglycaemia in T1DM. Recent studies have used a Gold score of 4 or above to denote impaired hypoglycaemia awareness (31)(32). The prevalence of impaired hypoglycaemia awareness is difficult to compare across studies and populations given the use of different definitions and treatment durations. Impaired hypoglycaemia awareness represents a progression along a continuum from normal responses to hypoglycaemia, including an altered symptom profile (with early loss of autonomic symptoms), reduced number or intensity of symptoms and, rarely, an absence of symptoms altogether. Impaired hypoglycaemia awareness is more common in those with T1DM but can occur in insulin-treated T2DM (11).

The reported prevalence of impaired hypoglycaemia awareness in T1DM is around 20-25%, rising to around 50% after 25 years or more of treatment (33)(34)(35). In those with T2DM, prevalence has been estimated at between 8-10% (36)(37). It is unclear if impaired hypoglycaemia awareness also develops in those with T2DM taking oral hypoglycaemic agents. Those with impaired hypoglycaemia awareness are at particular risk of severe episodes of hypoglycaemia, with severe hypoglycaemia rates up to seven times as common compare with those who retain hypoglycaemia awareness in prospective observational studies (29).

Factors contributing to impaired awareness of hypoglycaemia

Several factors contribute to impaired hypoglycaemia awareness.

Antecedent or recurrent hypoglycaemia and tight glycaemic control

In addition to the seminal studies conducted in the early 1990s described above, further studies have demonstrated that an episode of antecedent hypoglycaemia can diminish normal counter-regulatory responses to further episodes of hypoglycaemia for up to a week later (38). Twice weekly episodes of mild hypoglycaemia have a similar effect (39), and antecedent hypoglycaemia also impairs counterregulatory responses to subsequent exercise (40). This mechanism appears to explain why tight glycaemic control with intensive insulin therapy can lead to a resetting of the glucose threshold values at which the normal counter-regulatory mechanisms are activated (29). Whilst tight glucose control and episodes of antecedent hypoglycaemia may

induce transient impaired hypoglycaemia awareness, it remains unclear how these factors lead to chronic impaired awareness.

Recurrent, episodic hypoglycaemic events of sufficient depth and duration, however, progressively blunt and impair normal counter-regulatory responses to hypoglycaemia predisposing patients to a vicious cycle of ever more frequent hypoglycaemic episodes with a falling glucose threshold to trigger counter-regulation (41). Cryer has termed this sequence of events, hypoglycaemia-associated autonomic failure (HAAF)(42). It is important to note that the term denotes a condition which is entirely separate from classical autonomic dysfunction, a common neuropathic complication of diabetes.

Peripheral autonomic neuropathy

Traditionally, peripheral autonomic neuropathy was thought to play a role in impaired hypoglycaemia awareness (43) by impeding the secretory capacity of adrenaline in response to hypoglycaemia, thus attenuating classical autonomic symptoms of hypoglycaemia (44). Circulating adrenaline, however, plays a marginal role in the generation of autonomic symptoms which are primarily generated by activation of the sympathetic nervous system (45). Moreover, Hilsted *et al*. have shown that in the presence of autonomic neuropathy, there is an increase in peripheral β-adrenoreceptor sensitivity which may offset any deficit due to reduced secretion of adrenaline (45). Furthermore, a normal sympatho-adrenal response to hypoglycaemia has been demonstrated in subjects with T1DM despite the presence of concomitant cardiovascular autonomic neuropathy (46). Although the

experimental and observational data are inconsistent, peripheral autonomic neuropathy associates with impaired awareness of hypoglycaemia, probably as a consequence of long-standing diabetes, and appears to play only a minor role as a cause of impaired hypoglycaemia awareness.

Mechanistic insights into impaired hypoglycaemia awareness

Precisely how tight glycaemic control and antecedent hypoglycaemia contribute to the development of impaired awareness of low glucose levels remains unclear. Since the demonstration that repeated episodes of hypoglycaemia led to an alteration in the threshold for activation of the neuro-endocrine response, experimental work in both humans and animal models has centred on the central nervous system (CNS). The reader is directed to a recent comprehensive review (47) since a detailed discussion of these studies and their interpretation is beyond the scope of this article. Figure 2 summarises some of the putative mechanisms leading to impaired hypoglycaemia awareness which have been identified as potentially relevant.

Morbidity and mortality associated with hypoglycaemia

Biological consequences of hypoglycaemia

Cardiovascular effects

Whilst the role of tight glycaemic control in reducing microvascular complications is well established (48) , the contribution of tight glucose control in reducing macrovascular complication remains less certain. Three large randomised controlled trials have recently tested this hypothesis by measuring the accumulation of hard cardiovascular (CV) end-points in patients randomised to either intensive glucose or standard glucose control(49)(50)(51). In none of the trials was there a reduction in overall CV risk in those randomised to intensive glucose control, although a patient-level meta-analysis that included data from the first five years of the UK Prospective Diabetes study showed that the risk of major cardiovascular events was reduced by 9% (52). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, however, a significant excess CV mortality was noted in the intensive glucose arm (257 deaths) compared with the standard treatment arm (203 deaths) resulting in early trial closure. Possible explanations for this result include chance, specific medications and weight gain. It is noteworthy that severe hypoglycaemia rates were more common in in ACCORD in those treated intensively, and far higher than in the ADVANCE trial which reported no such increase. Nevertheless, the hypothesis that hypoglycaemia may contribute to increased mortality (and thus negate the potential macrovascular benefit of improved glucose control) continues to be the subject of intense debate.

It is extremely challenging to confirm or refute a causal link between hypoglycaemia and observed CV mortality. One reason is that these trials were not designed originally to examine the relationship between hypoglycaemia and CV outcomes. The ACCORD investigators have argued that there is scant evidence linking severe hypoglycaemia to increased CV mortality in the intensive glycaemic control arm of their trial, since they observed no direct relationship between severe hypoglycaemic episodes and subsequent deaths (53). Nevertheless, the potential role of hypoglycaemia in exacerbating CV risk in patients randomised to intensive glucose control in ACCORD was underestimated (54). Hypoglycaemia may have been underreported in in the intensive treatment arm since repeated episodes of hypoglycaemia leads to reduced awareness. Furthermore, a causal hypoglycaemic event may have lead to pathophysiological changes, leading to increased mortality downstream of the event. Indeed, it is striking that in all three of these major CV outcome trials, a severe hypoglycaemic event predicted mortality, not at the time but weeks or months after the event. (49)(50)(51)(54)(55).

Furthermore, some excess deaths in the intensive treatment arm may have been erroneously coded as being due to coronary events with no possibility of glucose measurement post-mortem (54).

Whilst it is challenging to establish causation rather than association, due to potential confounding, hypoglycaemia is probably associated with excess CV mortality, at least in part, by being more prevalent in those with concomitant liver disease and kidney disease, comorbidities which may independently increase the risk of CV mortality. Hence, hypoglycaemia might merely be a

physiological marker for susceptibility, as opposed to being a direct cause of mortality. Nevertheless, a recent large systematic review and meta-analysis using specific statistical adjustment, concluded that it was unlikely that comorbidities alone explained the relationship between hypoglycaemia and CV disease (57). The authors studied the relationship in studies involving nearly a million participants and demonstrated that severe hypoglycaemia was strongly associated with CV disease (relative risk 2.05, 95% confidence interval 1.74 to 2.42; P<0.001). In this systematic review and meta-analysis, Goto *et al*. highlighted the many plausible mechanisms whereby hypoglycaemia might increase CV risk. These included the haemodynamic consequences of the counter-regulatory response (particularly sympatho-adrenal activation), which might precipitate CV events such as angina or myocardial infarction. Indeed, electrocardiographic features of cardiac ischemia have been noted in a patient with hypoglycaemic coma (58). Others have reported iatrogenic hypoglycaemia inducing angina pectoris in a patient with diabetes and concomitant coronary artery disease (59). Hypoglycaemia can be pro-arrhythmogenic via a number of mechanisms. Tattersall and Gill in 1991, described the phenomenon of unexplained nocturnal sudden death in young patients with T1DM (60), termed the “dead-in-bed syndrome” in an accompanying editorial (61). One hypothesis is that nocturnal hypoglycaemia generates arrhythmias leading to the dead-in-bed syndrome (62)(63)(64). Hypoglycaemia also might increase the propensity to tachyarrhythmias consequent on an increase in the QT interval (QTc) (65) and QT dispersion (66). An increase in catecholamine levels generated during the sympatho-adrenal response to hypoglycaemia has been shown to contribute to QTc

prolongation (65)(67). The adrenergic response to hypoglycaemia may also precipitate ventricular tachycardia by increasing myocardial calcium concentrations (68), and hypoglycaemia has been associated with bradyarrhythmias (69)(70). A recent study has proposed that an increase in vagal tone resulting from the counter-regulatory response to hypoglycaemia may underlie the onset of bradyarrhythmias during hypoglycaemia (71). These events appeared to be precipitated by nocturnal hypoglycaemic episodes with bradycardia, atrial and ventricular ectopics occurring more frequently at night (71). Sleep modulates the counter-regulatory response to hypoglycaemia with the glucose threshold for initiation of counter-regulation falling in early sleep, and late sleep reducing the induction of counter-regulatory hormones (72).

Acute and recurrent hypoglycaemia exert a plethora of effects on thrombosis and inflammation, thus potentially increasing cardiovascular risk. Hypoglycaemia can cause both platelet activation and aggregation (73)(74), probably mediated by the adrenergic response to hypoglycaemia (74). Hypoglycaemia promotes a pro-inflammatory state by increasing levels of factor VIII, von Willebrand factor, and through the inhibition of thrombolysis (75)(76)(77). The latter changes appear to be mediated by increased circulating adrenaline (78) as are increased levels of IL-6 and TNF-α (77)(79)(80) and rises in cell adhesion molecules, ICAM-1, VCAM-1 and E-selectin (77). Repeated episodes of hypoglycaemia may also damage the vascular endothelium by reducing endogenous and exogenous nitric oxide mediated endothelial function (81). Studies in rodents have shown that

repetitive hypoglycaemia can increase monocyte adherence to the aorta, and that monocyte-endothelial interactions are catecholamine driven (82).

CNS effects

Cognitive function

Hypoglycaemia, and in particular impaired hypoglycaemia awareness, have been linked to cognitive dysfunction (83). In addition, a decline in intellectual capacity has been noted with progressive loss of hypoglycaemia awareness (84). However, the data are inconsistent with other studies suggesting cognitive function maybe preserved in those with impaired hypoglycaemia awareness (85).

Psycho-social consequences of hypoglycaemia

Hypoglycaemia carries a significant economic burden in terms of health care costs and lost productivity at work (86)(87), although these indirect costs are rarely acknowledged when therapy costs are calculated. In addition, there are important psychological consequences with hypoglycaemia associated with a poor quality of life in both T1DM and T2DM (88)(89). Episodes of hypoglycaemia lead to fear of further episodes and consequent negative behaviour such as more lax glycaemic control (90)(91). Patients that suffer recurrent hypoglycaemia and have hypoglycaemia unawareness are more likely to be anxious and depressed. Negative psychological consequences of hypoglycaemia may present a cognitive barrier to the treatment of further episodes and thus hinder effective treatment of impaired hypoglycaemia awareness. (31)

Recent qualitative work has highlighted both the psychological barriers and consequences of reduced hypoglycaemia awareness. Rogers *et al*. found that attitudes to impaired awareness in a group of their patients fell into two broad categories. The first described severe hypoglycaemia as aversive and were keen to regain awareness. The second expressed what the authors described as ‘unhelpful attitudes’ which included normalizing the presence of hypoglycaemia unawareness, underestimating its consequences; wanting to avoiding the 'sick role'; and overestimating the consequences of high glucose values (92). Reduced hypoglycaemia awareness also has a major impact on people's confidence their careers and personal relationships (93). These adverse consequences are not confined to patients but also apply to their families. In a recent powerful account, Lawton *et al*. describe the fear that family members experience due to aggressive and argumentative behaviour. Repeated episodes of coma led to feelings of anxiety about leaving their partners unsupervised. Resentment could build up over time, and family members highlighted extensive unmet needs for information and emotional support (94).

Internationally, various regulations exist to regulate driving in those that suffer from episodes of hypoglycaemia and indeed hypoglycaemia unawareness. The loss of a driving licence, especially if use of a motor vehicle is key to employment, can further precipitate and perpetuate feelings of depression and anxiety. The European Driving regulations have recently been updated and made more stringent, presumably on the basis that a strong predictor of a severe hypoglycaemic event is a previous episode. Individuals now stand to

lose their license if they experience more than one severe episode in a calendar year even if an episode occurs at a time unrelated to driving, such as at night. Ironically, these new rules may have actually made it more difficult for professionals to support people with these problems. A recent paper suggests that reported rates of severe hypoglycemia in individuals with T1DM have suddenly reduced markedly following implementation of EU driver's licensing legislation (95). The authors make a strong case that this is due to concealed severe hypoglycemia and highlight the paradox that this might actually reduce driving safety if patients fail to report problems with hypoglycaemia.

Risk reduction in hypoglycaemia

Treatment of acute hypoglycaemia

Acute hypoglycaemia warrants expeditious action. Whilst the definition of hypoglycaemia is debated, a capillary blood glucose threshold of 3.5 mmol/L has been suggested as acceptable clinically for initiation of treatment of hypoglycaemia (96). The Joint British Societies have provided comprehensive guidance on emergency management of hypoglycaemia (97). Figure 3 summarises the key points for the inpatient management of acute hypoglycaemia in adults, with treatment needed for patients that have a capillary blood glucose <4.0 mmol/L.

Strategies for recurrent hypoglycaemia and hypoglycaemia unawareness

Various strategies have been proposed for managing patients that are prone to recurrent hypoglycaemia, and patients that have established impaired hypoglycaemia awareness.

Programmes aimed at reversing impaired hypoglycaemia awareness

The original observation that a few hours of antecedent hypoglycaemia fundamentally impairs physiological responses to hypoglycaemia indicated that these defects were functional, rather than structural, and as such might be reversible (26). A number of subsequent clinical studies showed that even prolonged hypoglycaemia unawareness can be reversed in part, with restoration of hypoglycaemic symptoms and resetting of glycaemic thresholds for adrenaline release, hypoglycaemic symptoms and cognitive function (98) (99). Interestingly this was not always associated with a restoration of counter-regulatory hormone release (100) . Nevertheless, these studies have highlighted an important clinical approach to the problem of impaired awareness. Programmes to reverse impaired hypoglycaemia awareness, whereby patients work to avoid all episodes of hypoglycaemia for a few weeks without running their blood glucose high, can be effective. The important features appear to include intensive blood glucose monitoring, including measurements at night, frequent contact with the doctor or nurse and a willingness of the patient to adopt a more relaxed view about the occasional high blood glucose value. Importantly, these studies showed that it was possible to eliminate hypoglycaemia without significant deterioration in glycaemic control although HbA_{1C} inevitably drifted upwards.

The importance of structured training to ensure that patients have the skills to use insulin appropriately in T1DM was recognised in a few European countries as far back as the 1980s (101). However, it is only recently been more widely adopted despite early publications reporting improved glycaemic control and marked reductions in severe hypoglycaemia rates. More recent reports both from this group and others who have translated the approach to other countries, continue to report falls in severe hypoglycaemia rates of around 50% following the attendance at training courses teaching self-management skills. One observational study involving over 9,000 individuals also demonstrated that the exponential relationship between severe hypoglycaemia and HbA_{1C} first demonstrated in the DCCT could also be abolished in those who underwent structured training (102). Similar falls in severe hypoglycaemia rates have also been reported following participation in a UK adaptation of a similar skills based training course (Dose Adjustment for Normal Eating (DAFNE) course (103), suggesting that structured training courses teaching people to use insulin safely leads to clinically relevant reductions in the risk of severe hypoglycaemia (104). Following structured training, however, a significant minority of patients continue to experience or develop reduced hypoglycaemia awareness, with an associated high risk of hypoglycaemia. Those affected often have psychological barriers and programmes which target these issues have reported some success. The most longstanding is the “Blood glucose awareness training” (BGAT), which has been developed by Cox and colleagues at the University of Virginia (105). BGAT, which teaches individuals to recognise and respond to symptoms of a low blood glucose is taught to groups of individuals in an outpatient setting,

although an online version is also available. Randomised controlled trials have demonstrated reductions in time spent at low glucose levels and improved increases in adrenaline. Observational studies have shown falls in impaired hypoglycaemia awareness and rates of severe hypoglycaemia (106)(105)(107).

Within the DAFNE programme a course has also been developed with a psychological underpinning for individuals who experience impaired awareness following DAFNE training. This course, developed primarily by clinical psychologists, is delivered by diabetes educators, initially in groups but then 1:1. In a pilot study involving 23 T1DM adults, de Zoysa *et al*. have demonstrated that a pilot psychoeducational programme improved both awareness of hypoglycaemia and reduced severe hypoglycaemia at 12 months (31). Importantly both approaches reduced hypoglycaemic problems without a deterioration in glycaemic control. However, more studies are needed to establish whether these results can be achieved in standard secondary care diabetes centres as opposed to centres with a specialist interest in hypoglycaemia.

Insulin regimens, technology and pancreatic transplantation

Differences between human and animal insulin in generating varying degrees of hypoglycaemia have been an area of controversy in the past. Current scientific evidence does not support the notion of an increased frequency of severe hypoglycaemia, or impaired hypoglycaemia awareness, with human insulin preparations (108).

Choice of insulin therapy may also dictate therapeutic benefits in treatment of recurrent severe hypoglycaemia and impaired hypoglycaemia awareness.

Basal insulin analogues are potentially effective in reducing nocturnal hypoglycaemia when compared to Neutral Protamine Hagedron (NPH) insulin in T1DM (109). Furthermore, in those with T1DM complicated by recurrent severe hypoglycaemia, recent trial data suggests that the use of insulin analogues (detemir and aspart) can result in a clinically significant reduction in severe hypoglycaemia rates compared with human insulin (110). CSII has previously been shown to improve hypoglycaemia symptom awareness in those with impaired hypoglycaemia awareness (111). A recent meta-analysis suggests, however, that CSII confers no additional benefit versus multiple daily injections (MDI) in reducing the frequency of severe hypoglycaemia (112). An earlier meta-analysis by Pickup *et al*., comparing CSII with MDI, only examined studies in those prone to multiple episodes of severe hypoglycaemia per year (>10 episodes per 100 patient years on MDI) (113). Pickup *et al*., reported that the rate of severe hypoglycaemia in T1DM was significantly reduced during CSII compared with MDI, and that those with the longest duration of disease and most severe hypoglycaemia benefitted most. Furthermore, the HypoCOMPaSS trial has recently reported that hypoglycaemia awareness can be improved in those with long-standing T1DM, and severe hypoglycaemia reduced equally using conventional MDI and SMBG compared with CSII and continuous glucose monitoring (CGM), although patient satisfaction was higher with CSII (32). The factors common to all treatment groups were a brief education followed by intensive weekly support from a healthcare professional.

Intense research is currently focussing on the artificial pancreas which employs wireless technology communication between a CGM device and an insulin pump. Real time data on interstitial glucose levels are communicated to the insulin pump, which then delivers an appropriate dose of insulin. Results using the closed-loop system have recently been reported from two multi-centre, crossover, randomised controlled trials showing improved HbA_{1C} levels and less time spent at hypoglycaemic levels, although Thabit *et al*. did report three severe hypoglycaemic episodes during the closed-loop phase (114). Closed-loop technology is on the verge of moving from the research arena to a clinical tool, and it is likely that this technology will become clinically available in the next 5 to 10 years. In some individuals with severe recurrent hypoglycaemia and impaired hypoglycaemia awareness, referral for either islet cell or whole pancreatic transplantation may restore hypoglycaemia awareness (115).

Potential therapeutic targets

A number of potential pharmacological agents under development for the treatment of impaired hypoglycaemia awareness and reducing recurrent hypoglycaemia are summarised in Table 3. Whilst these potential therapies have shown promising results in animal studies and small scale Phase 2 human studies, no large scale clinical trials appear to have been undertaken (116)(117)(118)(119) (120).

A Care pathway for individuals

Figure 4 shows a care pathway which reflects our own clinical approach in a clinic we run for individuals with hypoglycaemia problems, many of whom have reduced hypoglycaemia awareness. Probably the most important question is to ask an individual, is at what blood glucose level they experience hypoglycaemic symptoms. A blood glucose level consistently below 3 mmol/L indicates reduced hypoglycaemia awareness and increased risk of hypoglycaemia. This information needs to be supplemented by a detailed history of the course and frequency of episodes of hypoglycaemia, particularly those that are severe, together with a joint examination of meter downloads of glucose measurements. A joint discussion between patient, diabetes specialist nurse and physician allows the clinicians to establish the psychological and emotional reaction to low blood glucose values. Ideally the consultation should also include an important family member or partner who may corroborate or add to the patient's account, particularly as they are frequently the first person to note the onset of hypoglycaemia. They may also contradict the clinical account and it is often helpful to witness the interchange between partners and family members. CGM monitoring often provides additional useful information, although probably the most important next step is a series of consultations between a diabetes nurse educator/dietician with wide experience of insulin therapy and hypoglycaemia problems. This should be followed by specific skills training, supplemented by the use of technologies such as analogue insulins, CSII/CGM and on occasions insulin

suspend pumps. Our experience is that new technologies are not successful unless those affected are willing to use them and acquire the skills to self manage their diabetes, and that the health care professionals have the experience to use the technology appropriately.

Those who continue to experience problems may benefit from interventions such as BGAT or DAFNE-HART. There are a few individuals (thankfully rare) who fail to improve after those approaches and in these cases, when available, islet transplantation can be transformational. A recent meta-analysis recently endorsed a similar clinical approach pointing out that the steps in this pathway were largely supported by reasonably high quality evidence (121).

Conclusion

The key pathophysiological defects, which explain the vulnerability of individuals with insulin treated diabetes to hypoglycaemia, were described in human studies in the 1980s and 90s. Yet despite nearly 20 years of extensive subsequent research involving both clinical and animal studies, no specific therapeutic interventions have emerged to prevent or treat hypoglycaemia.

Improving technology can now deliver insulin more precisely and flexibly and alert individuals to falling glucose levels before they develop severe cognitive impairment. However, for many the cost of such technology is prohibitive. Although these and other developments, including the artificial pancreas and islet transplantation, have moved or are moving from the research to the

clinical arena, their use will remain beyond the means of most individuals or health care systems for many years.

In the meantime the principles of preventing and managing problematic hypoglycaemia will depend upon training patients to use insulin safely and to take the appropriate action when their blood glucose levels are low. These approaches require a good understanding of the pathophysiology, the limitations of current insulin delivery systems and the psychological barriers that prevent some patients from treating themselves appropriately. Implementing these principles is not expensive and should be available wherever insulin therapy is used to achieve tight glycaemic control.

Practice points

- Hypoglycaemia problems are common in the management of insulin treated diabetes and clinicians responsible for managing individuals with diabetes need to have a good grasp of the pathophysiology and systematic clinical approaches to assist those affected.
- Recurrent hypoglycaemia and impaired hypoglycaemia awareness need to be anticipated recognised and addressed.
- Structured education programmes, insulin analogues and CSII all have a role in management of impaired hypoglycaemia awareness and should be provided if patients are to be encouraged to achieve HbA_{1c} targets <7.5% (<58.5 mmol/mol).

- Scrupulous avoidance of hypoglycaemia and empowering the patient to achieve individualised glycaemic targets is key.

Research agenda

- Future human research is needed to elucidate mechanisms leading to counter-regulatory failure following recurrent hypoglycaemia.
- Further experimental work exploring neuronal pathways involved in hypoglycaemia homeostasis is warranted to understand if specific treatments can be developed for the management of impaired hypoglycaemia awareness.
- Mechanisms whereby hypoglycaemia can precipitate fatal cardiac arrhythmias need to be identified as those at risk could be protected.
- Inflammatory pathways activated following hypoglycaemia that potentially increase CV risk need to be identified as they maybe amenable to therapeutic targeting.

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