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Clinical approaches to treat impaired awareness of hypoglycaemia

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***Abstract*:** Impaired awareness of hypoglycaemia (IAH) affects between 25% and 30% of all people with type 1 diabetes (T1D) and markedly increases risk of severe hypoglycaemia. This greatly feared complication of T1D impairs quality of life and has a recognised morbidity. People with T1D have an increased propensity to hypoglycaemia as a result of fundamental physiological defects in their ability to respond appropriately to a fall in blood glucose levels. With repeated exposure to low glucose, many then develop a condition referred to as IAH, where there is a reduced ability to perceive the onset of hypoglycaemia and take appropriate corrective action. The management of individuals with IAH relies initially on its identification in the clinic through a detailed exploration of the frequency of hypoglycaemia and an assessment of the individual's ability to recognise these episodes. In this review article, we will address the clinical strategies that may help in the management of the patient with IAH once identified, who may or may not also suffer from problematic hypoglycaemia. The initial focus is on how to identify such patients and then on the variety of approaches involving educational programmes and technological approaches that may be taken to minimise hypoglycaemia risk. No single approach can be advocated for all patients, and it is the role of the health care professional to identify the clinical strategy that best enables their patient to achieve this goal.

Keywords: continuous insulin infusion, hypoglycaemia, impaired awareness of hypoglycaemia, real-time continuous glucose monitoring, sensor augmented pumps, structured education, type 1 diabetes

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Introduction

Since the discovery of insulin in the 1920s there have been many advances in the treatment of diabetes. In particular, improved formulations of insulin as well as better insulin delivery systems have meant that our ability to manage diabetes is considerably enhanced. Yet, despite these innovations, hypoglycaemia resulting from excess exogenous insulin remains an all too common metabolic adverse effect of insulin therapy. Hypoglycaemia is greatly feared and is a barrier to achieving near-normoglycaemia.[1] Hypoglycaemia in people with type 1 and longer duration type 2 diabetes results from a variety of factors, some dependent on the individual with diabetes and some a result of the pathophysiological consequences of beta-cell destruction. Errors in self-management can and do lead to hypoglycaemia and are perhaps to be expected given the burden of managing a chronic disease with its significant demands on the individual. However, underlying abnormalities in the normal counter-regulatory response that are present in nearly all people with type 1 and longer-duration insulin-treated type 2 diabetes also markedly increase the propensity to hypoglycaemia.[2]

In people with type 1 diabetes (T1D), autoimmune destruction of the pancreatic beta cells leads to absolute insulin deficiency and the need for insulin replacement therapy. Insulin delivered exogenously is not under normal physiological feedback and therefore may lead to the development of hypoglycaemia even in the presence of intact counter-regulatory responses. The risk of hypoglycaemia is also increased markedly

with increasing disease duration and strict glycaemic control.[2] This is because, over time, the hormonal counter-regulatory response to hypoglycaemia in T1D is suppressed. This relates to two additional physiological defects. Firstly, the glucagon response to hypoglycaemia is lost in the first few years following diagnosis. Secondly, the catecholamine response to hypoglycaemia is also impaired, both as an effect of disease duration and exposure to recurrent hypoglycaemia.[2] These pathophysiological changes lead to a diminished counter-regulatory response with reduced endogenous glucose production during hypoglycaemia, which is also associated with a reduced symptomatic response. In combination, they markedly increase the propensity of progressive and severe hypoglycaemia in T1D.

As a result of these changes, the average person with T1D experiences approximately two episodes of hypoglycaemia a week,[3,4] a figure that has not changed significantly over the past 20 years despite improvements in insulin preparations. The incidence of asymptomatic hypoglycaemia is even greater, with the average person with T1D experiencing, on average, four episodes per week.[5] It is now well established that exposure to recurrent hypoglycaemia leads to the development of impaired awareness of hypoglycaemia (IAH), defined as 'a diminished ability to perceive the onset of acute hypoglycaemia'.[6] This complication affects approximately a quarter of all people with T1D and, notably, the incidence of IAH has not changed in the last 2–3 decades despite the introduction of insulin analogues and improved insulin delivery systems.[7] The risk of severe hypoglycaemia, where there is a need for external assistance for recovery, is increased sixfold in people with IAH.[8]

In this review article, we will address the clinical strategies that may help in the management of the patient with IAH with or without problematic hypoglycaemia, with a focus initially on how to identify such patients and then on the variety of approaches that may be taken to minimise hypoglycaemia risk. No single approach can be advocated for all patients, and it is the role of the healthcare professional to identify the clinical strategy that best enables their patient to achieve this goal.

Identifying those at risk

Before putting strategies in place to assist with improving awareness of hypoglycaemia, it is key that those at risk of severe hypoglycaemia and/or who have IAH are identified in the clinic. Severe hypoglycaemia risk is highest in those who have already experienced an episode of severe hypoglycaemia in the past or who have IAH.[8,9] It is also increased in young children and the elderly, those with comorbidities such as renal or hepatic disease, gastroparesis or coeliac disease, or with other endocrine disorders that increase the risk of hypoglycaemia (e.g. Addison's Disease), as well as with certain behaviours (alcohol excess, unplanned exercise, multiple self-correction insulin dosing) and with poor insulin management. Longer disease duration is also associated with lower intensity autonomic symptoms and a higher prevalence of IAH, suggesting that subjective symptoms change over time.[10] Interestingly, HbA1c is not in itself a good predictor of severe hypoglycaemia in people with T1D.[11]

A careful clinical history, when combined with a validated objective questionnaires of hypoglycaemia awareness such as those developed by Gold,[8] Clarke,[12] Pedersen-Bjergaard,[13] and the HypoCOMPaSS study group,[14] are useful in establishing a diagnosis of IAH. However, these questionnaires do not fully account for the impact of asymptomatic hypoglycaemia. Recently, using blinded continuous glucose monitoring (CGM) in 153 unselected patients with T1D, it was reported that those experiencing more frequent episodes of asymptomatic hypoglycaemia had reduced awareness of hypoglycaemia, longer duration of diabetes and tighter glycaemic control with lower HbA1c.[15] Therefore, while objective questionnaires are useful, they will not identify those with recurrent asymptomatic hypoglycaemia or those who test infrequently. In this context, continuous or Flash glucose monitoring (GM) may help identify those with recurrent asymptomatic hypoglycaemia.

Education

For individuals with IAH or who have experienced severe hypoglycaemia, education, both hypoglycaemia-specific as well as around insulin and carbohydrate management, remains the cornerstone of any therapeutic intervention. Low numeracy skills have been shown to be adversely associated with diabetes control,[16] and while self-monitoring of blood glucose is associated with improved glycaemic control it remains infrequent.[17] There are a number of structured education programmes focussing on the clinical

management of hypoglycaemia and improving hypoglycaemia awareness.

Education focusing on the clinical management of hypoglycaemia

The Diabetes Teaching and Treatment programme (DTTP), designed in Germany, was one of the first educational programmes designed to optimise insulin management in T1D. The DTTP was a 5-day in-patient course for T1D with a structured written curriculum taught by trained educators. The programme focussed on separating basal and meal-time bolus insulin doses, intensive self-monitoring blood glucose (SMBG) and carbohydrate counting to allow a flexible diet.[18] Hypoglycaemia was not addressed specifically. The DTTP educational intervention was shown to result in a sustained improvement in HbA1c and a reduction in the incidence of severe hypoglycaemia over 12 years of follow up.[19,20] However, as these were follow-up observational studies there was no control group for comparison.

In the United Kingdom (UK), Dose Adjusted for Normal Eating (DAFNE) was developed as structured education course based on the DTTP. In a randomised, controlled trial of the DAFNE intervention, participants who had attended the DAFNE course showed significant improvements in HbA_{1c} after 6 months, but no significant reduction in the incidence of severe hypoglycaemia.[21] A subsequent, 1-year follow up of this cohort showed a small but significant reduction in the percentage of individuals reporting IAH.[22] Consistent with these findings, the Tayside Insulin Management (TIM) structured education programme resulted in a significant reduction in HbA_{1c} (mean 0.4%) after 6 months of participation and improved awareness of hypoglycaemia in 25% of participants, as well as reduction in incidence of severe hypoglycaemia.[23]

Structured educational programmes are now advocated for all people with T1D and, at least in the short-term, appear to result in improved control without additional hypoglycaemia risk. It is less clear whether, used alone, they can effectively restore hypoglycaemia awareness and reduce severe hypoglycaemia without more specific education on hypoglycaemia avoidance.[24,25] Hypoglycaemia awareness was not always objectively assessed in these studies and numbers of participants were too small to draw reliable conclusions about frequency of severe hypoglycaemia.

Education and psychological interventions focussing on improving awareness of hypoglycaemia

To compliment the structured educational programmes, a number of groups have combined hypoglycaemia-specific education with psychological training and support. The Recovery of Hypoglycaemia Awareness in Longstanding T1D (HypoCOMPaSS) trial employed a brief educational intervention focussed on detection of hypoglycaemia.[26] This 24-week study randomised people with T1D and IAH, to insulin pumps (CSII) or multiple daily injections (MDI) with or without CGM. All groups underwent the educational intervention. Interestingly, in all groups there was a highly significant (50%) reduction in time in hypoglycaemia (<3.0 mmol/l), and an improvement in hypoglycaemia awareness.[27] Neither CGM nor CSII (or a combination of both) showed any advantage over education and ongoing support.[27] Of note, compliance with CGM was suboptimal, participants wore sensors for a median of 57% of time in the study.[27] It is therefore possible that any additional benefit of CGM was missed. It is also possible, given how brief the initial hypoglycaemia educational programme was, that the main benefit from the interventions came from the weekly contact and review of glucose profiles by the research team.

The Blood Glucose Awareness Training Programme (BGAT) is an 8-week programme that uses weekly skills-based training sessions to improve an individual's ability to focus on internal cues to detect, anticipate, avoid and treat both hyperglycaemia and hypoglycaemia as well as to identify external cues that increase hypoglycaemia risk.[28] BGAT has been shown to improve accuracy of hypoglycaemia testing in those with IAH and to reduce hypoglycaemia events in those with intact awareness,[29,30] with benefits sustained for up to 5 years.[31] Using a similar approach to BGAT, but focussing specifically on hypoglycaemia and those suffering from recurrent hypoglycaemia, Hypoglycaemia Anticipation, Awareness and Treatment Training (HAATT) is a psychoeducational programme that has been shown to reduce rates of both moderate and severe hypoglycaemia in people with T1D without compromising glycaemic control.[32]

HyPOS is another structured education programme (weekly 90-min group education sessions over 5 weeks) for people with T1D and IAH.[33] When compared with standard education,

HyPOS was shown to improve hypoglycaemia awareness after 6 months and to reduce the frequency of severe hypoglycaemia after 31 months in those subjects with T1D and IAH; although there was also a 4-fold reduction in severe hypoglycaemia following standard education in this study.[34]

Most recently, DAFNE-Hypoglycaemia Awareness Restoration Training (DAFNE-HART) has been developed as a psychoeducational training programme designed for people who, despite completing the DAFNE course, continue to experience IAH with high rates of severe hypoglycaemia.[35] The study recruited people with T1D and IAH assessed using the Gold score.[8] DAFNE-HART uses motivational interviewing and cognitive behavioural therapy, and, in a small pilot study, has been shown to reduce severe hypoglycaemia and improve hypoglycaemia awareness.[35] These improvements were achieved without a compromise or deterioration in glycaemic control. This was a small-scale uncontrolled pilot study, but undoubtedly suggests that targeting unhelpful thought processes and beliefs may be effective for some individuals. A larger scaled, adequately powered RCT is underway to test this hypothesis.

Insulin preparations

Since the discovery of insulin in the 1920's there have been significant improvements in the formulations available. Most people with type 1 diabetes have transitioned from animal to human and then to analogue insulins; the latter are usually delivered as a basal–bolus regime. Analogue insulins are molecularly engineered formulations that have been developed to improve the pharmacokinetics, absorption profile and duration of action of human insulin.[36] A detailed review of the application of the various insulin formulations in T1D is beyond the scope of this article so the authors will make the assumption that most readers will accept that optimal insulin replacement uses analogue insulin either as part of a multi-injection regimen or with an insulin pump.

When used in a multi-dose regimen (MDI), it is established that both rapid-acting insulin analogues (e.g. Rys et al.[37]) and first generation basal insulin analogues (e.g. Szypowska et al.[38]) are associated with less hypoglycaemia, especially through the night. More recently, we have seen the development of ultra-long acting analogue preparations; degludec and glargine U300. In the BEGIN Basal–Bolus Type 1 study, nocturnal hypoglycaemia was 25% lower with degludec over glargine U100,[39] while in the SWITCH 1 trial overall rates of symptomatic hypoglycaemia, nocturnal symptomatic hypoglycaemia and severe hypoglycaemia were reduced by degludec compared with glargine U100,[40] although effects on hypoglycaemia awareness were not reported.

Thus, in the management of the individual with T1D who has recurrent hypoglycaemia, optimal insulin replacement when part of a multi-dose regimen, should usually involve the use of rapid acting insulin analogues and if available ultra-long acting basal analogues.

Technology

There have been significant technological advancements in insulin delivery systems and glucose monitoring devices over the last few decades that are having a major effect on the management of people with T1D and are a particularly useful way to manage the individual with IAH.

Insulin pump therapy

Continuous subcutaneous insulin infusion (CSII)[41,42] *via* an insulin pump allows insulin to be delivered at varying rates throughout the day. This should allow more flexibility to the individual and allow dosing that more closely mimics normal glucose homeostasis. However, the evidence that CSII reduces the frequency of severe hypoglycaemia compared with MDI is mixed, with one meta-analysis showing no difference,[43] and another a small benefit.[44] In both meta-analyses the studies included pre-dated the ultra-long basal insulin analogues with their improved pharmacodynamics, and there is little information provided regarding the additional education provided to those using CSII. In the more recent HypoCOMPASS study, which randomised participants to MDI or CSII, no significant differences in robust measures of the hypoglycaemic response and hypoglycaemia awareness were evident between treatment modalities.[26,27] Similarly, in the Relative Effectiveness of Pumps Over MDI and Structured Education (REPOSE) study, 248 people with T1D were randomised to CSII ($n = 132$) or MDI ($n = 128$), following completion of the DAFNE structured education programme and followed for 24 months. No statistically

significant differences in change from baseline in HbA1c or frequency of severe hypoglycaemia were found between groups, although both groups showed an improved HbA1c and reduced severe hypoglycaemia compared with baseline.[45] These results suggest that the CSII offers no additional benefit to MDI in the treatment of those with IAH, so the choice of therapy should be driven by patient preference.

CGM and Flash GM

In a meta-analysis of six randomised controlled trials ($n = 892$) real-time CGM (Rt-CGM) was reported to lead to an overall reduction in HbA1c of 0.3%, and a 23% reduction in median exposure to hypoglycaemia, but no reduction in severe hypoglycaemia compared with SMBG.[46] IN CONTROL was a 16-week cross-over study, comparing CGM with SMBG in adults with T1D and IAH, following a 6-week run-in period involving diabetes management re-education.[47] This study reported significantly fewer severe hypoglycaemic episodes with the use of CGM compared with SMBG, but no significant difference were seen in self-reported hypoglycaemia awareness scores.[47] Similar findings have been reported for Flash GM (FGM), where improvements in glycaemic control and reductions in episodes of hypoglycaemia correlated to the frequency of scanning.[48–50] One issue emerging for CGM and FGM is that both devices are less accurate during hypoglycaemia (e.g. Freckmann et al. and Farrell et al.[51,52]), and may therefore not detect all hypoglycaemic events. This may explain why they have not been shown in clinical trials to improve hypoglycaemia awareness. In addition, a recent observational study of people with T1D using CGM found that, while the overall incidence of severe hypoglycaemia declined, those with IAH continued to experience up to a six-fold increased risk for developing severe hypoglycaemia despite the use of CGM.[53] That being said, both FGM and CGM remain very useful tools that aid the management of those with IAH through providing information about blood glucose levels, the direction and rate of change in glucose, and for CGM, alarms that alert the individual to impending hypoglycaemia.

Sensor augmented pumps

Sensor augmented pump (SAP) therapy consists of an integrated system of an insulin pump, providing a continuous subcutaneous insulin infusion (CSII), with a CGM and a transmitter to send glucose readings wirelessly to the pump. The sensors continuously measure interstitial glucose levels providing readings, trends and warnings against pre-set high and low parameters. This information guides the user to make changes to their insulin therapy in 'real time'. There are two types of SAP available: in the first, the insulin dosing software is independent of the CGM and therefore the user adjusts the basal rate manually when required; the second type is a more integrated device that allows for automated suspension of basal insulin delivery in response to a predicted or detected low glucose level. It is worth noting that, for all SAP devices, meal and correction bolus' need to be delivered manually with support from an insulin pump bolus wizard calculator.

There have been two multicentre RCTs comparing SAP treatment with MDI plus SMBG treatment. The STAR 3 trial randomised 329 adults and 156 children with T1D and suboptimal glycaemic control to SAP or MDI. The SAP consisted of a CSII and CGM that were integrated. Significant benefits in favour of SAP were seen in HbA1c after 6 months, but there was no difference between groups in rates of severe hypoglycaemia after 12 months follow up.[54] Similar findings were reported in the Eurhythmic Trial, where the benefit of SAP was primarily a greater HbA1c reduction over MDI.[55] In contrast, using SAP and low glucose suspend (LGS) compared with standard CSII therapy in people with T1D and IAH, Ly *et al.*[56] reported a reduction in severe hypoglycaemia and less time with glucose levels lower that 70 mg/dl (3.9 mmol/l) and 60 mg/dl (3.3 mmol/l) with SAP and LGS.

Closed-loop artificial pancreas

A closed-loop system or artificial pancreas is composed of three components; a continuous glucose monitor, CSII to deliver hormones and a dosing algorithm to control hormone delivery. There are two types of artificial pancreas that have been developed: single-hormone systems that deliver insulin and dual-hormone systems that infuse both insulin and glucagon.

Single-hormone closed-loop systems have been shown to reduce time in hypoglycaemia (usually defined as <3.9 mmol/l in these trials) by approximately 50% compared with standard CSII.[57]

However, many of these studies have been of short duration, often taking place in clinical research facilities, and few have included subjects with IAH. Abitbol *et al*. carried out a randomised cross-over study comparing dual and single hormonal artificial pancreas systems in 35 people with T1D (17 hypoglycaemia aware and 18 hypoglycaemia unaware).[58] Both single and dual hormone systems were reported to reduce hypoglycaemia episodes (<3.0 mmol/l); however, there was no statistical significance between the two systems.

Overall, whilst there have been impressive technological advances over the past two decades in insulin delivery systems and glucose sensors that may certainly lessen the burden of hypoglycaemia and aid management when used appropriately, the technologies do still have some limitations that mean it is yet to be established that technologies *per se* can restore hypoglycaemia awareness. We expect to see a number of clinical trials over the next few years that will better inform clinical decision making.

Transplant intervention

For those individuals with severe disabling hypoglycaemia, where education and technological interventions have proven unhelpful, pancreas transplantation either as a whole pancreas or pancreatic islets is a therapeutic option. Patients with T1D who have undergone either islet or pancreas transplantation recover two of the primary physiological defects in T1D , namely endogenous insulin suppression and glucagon secretion during hypoglycaemia.[59,60] Both islet and pancreas transplant recipients also have improved epinephrine and autonomic symptom responses to hypoglycaemia, as well as a normalised endogenous glucose response to insulin-induced hypoglycaemia, which is essential for both prevention and recovery from hypoglycaemia.[59,60] Interestingly, recent work suggest that it may take up to 18 months for the epinephrine and symptom responses to hypoglycaemia to normalise post-transplant, suggesting that the prolonged exposure to recurrent hypoglycaemia prior to transplant resulted in substantial modification of the glucose-sensing network.[61]

Novel therapies

A few experimental therapies may also emerge from our understanding of those mechanisms that lead to the development of IAH in T1D. For example, formoterol fumerate, an inhaled highly selective β_2-adrenoreceptor agonist, was shown to increase the counter regulatory responses to hypoglycaemia in a small study of people with T1D.[62] While infusion with the opiate receptor blocker Naloxone during antecedent hypoglycaemia was shown to prevent experimentally induced defects in epinephrine release during subsequent hypoglycaemia in people with T1D.[63] In another preclinical study, George *et al*. reported a 37% increase in the epinephrine response to hypoglycaemia following oral delivery of the ATP-sensitive potassium channel opener, diazoxide, in a small cohort of people with T1D and IAH.[64] Finally, in a recently published study, a single intervention with high intensity exercise (HIT) was shown to improve hypoglycaemia counter regulation and awareness in a study of 12 subjects with long-standing T1D and IAH.[65] This study was based on the hypothesis that IAH develops as a result of habituation to repeated hypoglycaemia, and that introduction of a novel strong stimulus (e.g. HIT) can dishabituate (restore) the habituated response. An on-going clinical study, HIT4HYPOs, is seeking to determine if the benefits are sustained over 4 weeks of a HIT programme.[66]

Conclusion and management strategies

IAH remains a concern and problem for many people with long duration T1D. While there are an increasing number of technologies in place to aid the management of T1D, few have been robustly demonstrated to restore hypoglycaemia awareness. Management strategies should aim to individualise treatment targets and therapies based on individual abilities and preferences, as well as local resources. The Clinical Practice Recommendation published in *Diabetes Care* in 2015 for people suffering from problematic hypoglycaemia provides a useful framework in this context. In this, Choudhary and colleagues recommended health care professionals adopt a four-stage, tiered algorithm to individualise therapy based on a composite target of optimal glucose control without problematic hypoglycaemia (Figure 1).[67] A detailed enquiry into history of hypoglycaemia and level of hypoglycaemia awareness are central to the assessment of all people with insulin-treated diabetes and, for those with problematic hypoglycaemia, an enquiry into potential causes, risk factors or co-morbidities that may precipitate the events. A robust evidence

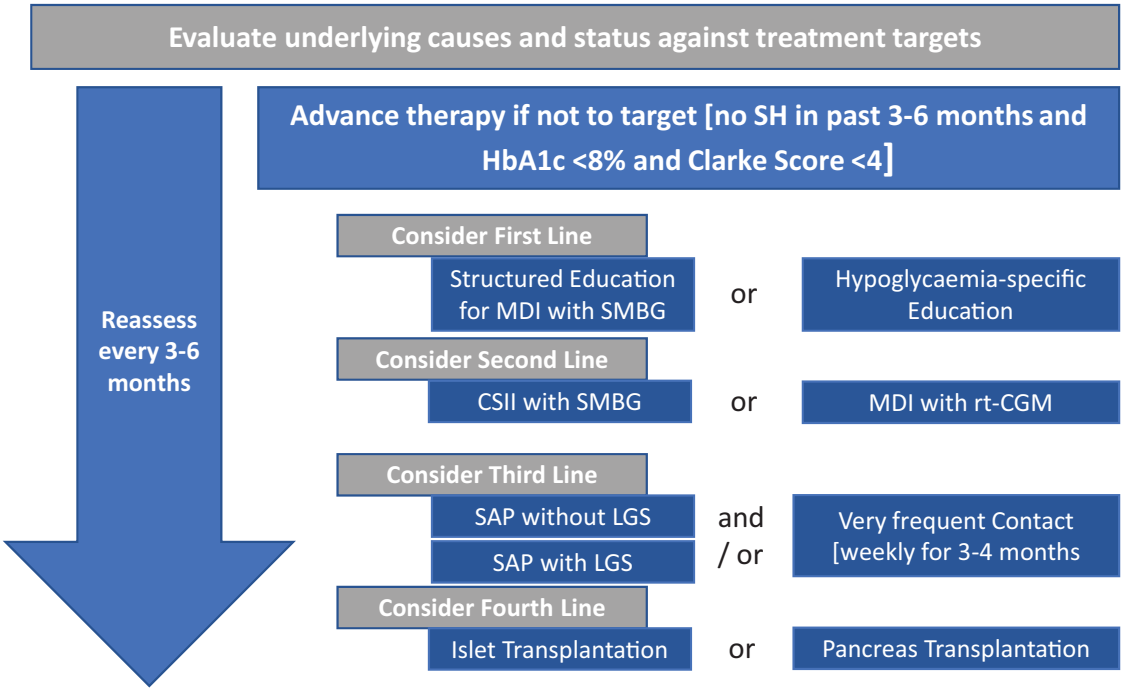

Figure 1. Four-stage, tiered algorithm to individualise therapy based on a composite target of optimal glucose control without problematic hypoglycaemia.
HbA1c, glycated haemoglobin; LGS, low glucose suspend; MDI, multiple daily injections; rt-CGM, real-time continuous glucose monitoring; SAP, sensor augmented pump; SH, severe hypoglycaemia; SMBG, self-monitoring blood glucose.

base also supports the first management step, which is to use a structured education programme or hypoglycaemia-specific education program. The four-stage algorithm recommends MDI with SMBG as part of the first line of therapy with CSII with SMBG or MDI, with rt-CGM as the preferred second stage. However, the increasingly widespread use of FGM and the failure of RCTs to show benefit of CSII over MDI, would suggest that stage 1 and 2 can be more usefully combined and the choice of intervention largely left to patient preference and local resources. One might then consider rt-CGM as the logical next step for the individual who still experiences problematic hypoglycaemia, before progressing to SAP with or without low glucose suspend. Finally, for the individual whose quality of life is severely disrupted by recurrent problematic hypoglycaemia, pancreas or islet transplantation may be required.

While technologies will continue to evolve they are not without limitations and remain largely accessible only in wealthier countries. Therefore, there remains a pressing need to increase our understanding of the underlying mechanisms that lead to the development of IAH so we will be in a better position to consider how to manage this complication. For example, restoration of glucagon secretion during hypoglycaemia would be a major breakthrough, but an appreciation and understanding of why this defect develops in diabetes is first required. If indeed IAH develops as a habituated process, structured education focussing on strict avoidance of hypoglycaemia will be key, along with cognitive behavioural therapy and psychological interventions to support hypoglycaemia avoidance and aid chronic changes in behaviour. Novel strategies such as dishabituation may also be an option to restore hypoglycaemia awareness. Further studies are required focussing on those with IAH with appropriate outcomes to assess restoration of hormonal and symptomatic awareness. In addition, an agreed definition of hypoglycaemia used by all investigators is imperative to allow study outcomes to be compared and analysed. No one insulin preparation, delivery or monitoring system is suitable for every person with T1D, it should to be tailored to the individual. As with the clinical approach to managing IAH, it should be patient centred and focussed on the individuals' requirements, understanding and resources available.

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