

Hypoglycemia unawareness and autonomic dysfunction in diabetes: Lessons learned and roles of diabetes technologies

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ABSTRACT

Impaired awareness of hypoglycemia (IAH) is a reduction in the ability to recognize low blood glucose levels that would otherwise prompt an appropriate corrective therapy. Identified in approximately 25% of patients with type 1 diabetes, IAH has complex pathophysiology, and might lead to serious and potentially lethal consequences in patients with diabetes, particularly in those with more advanced disease and comorbidities. Continuous glucose monitoring systems can provide real-time glucose information and generate timely alerts on rapidly falling or low blood glucose levels. Given their improvements in accuracy, affordability and integration with insulin pump technology, continuous glucose monitoring systems are emerging as critical tools to help prevent serious hypoglycemia and mitigate its consequences in patients with diabetes. This review discusses the current knowledge on IAH and effective diagnostic methods, the relationship between hypoglycemia and cardiovascular autonomic neuropathy, a practical approach to evaluating cardiovascular autonomic neuropathy for clinicians, and recent evidence from clinical trials assessing the effects of the use of CGM technologies in patients with type 1 diabetes with IAH.

INTRODUCTION

For almost 100 years, insulin has been the fundamental therapy for type 1 diabetes¹. By suppressing ketogenesis, insulin mitigates the risk for the development of diabetic ketoacidosis, a life-threatening acute complication of diabetes. The Diabetes Control and Complications Trial² and Epidemiology of Diabetes Interventions and Complications study³ further established the use of intensive insulin therapy to prevent or delay the development of chronic microvascular and macrovascular complications. Based on recent updates, the impacts of this relatively short-term glucose control appear to confer durable metabolic benefits for at least 30 years^{4–8}. However, intensive insulin therapy comes at a price. Intensive insulin treatment almost invariably increases the incidence of severe hypoglycemia^{9,10}, which is associated with altered mental state, seizures, cardiac arrhythmias and even death^{11–14}.

Hypoglycemia has traditionally been defined by blood glucose levels of <70 mg/dL (recently termed level 1 hypoglycemia^{15,16}), as these levels trigger the normal physiology of counterregulatory responses to hypoglycemia¹⁷. Recent revisions

of hypoglycemia definitions also include glucose levels <54 mg/dL (i.e., level 2 hypoglycemia¹⁶) for its associations with major comorbidities, such as increased mortality, cognitive dysfunction and the development of impaired awareness of hypoglycemia (IAH)¹⁸, a condition in which patients have diminished or lost ability to perceive the onset of hypoglycemia¹⁹. The Diabetes Control and Complications Trial study defined severe hypoglycemia as hypoglycemic episodes requiring assistance of another person for recovery⁹. This definition was subsequently adopted as the universal definition of severe (or level 3) hypoglycemia^{11,15,16}.

Iatrogenic hypoglycemia is not restricted to type 1 diabetes patients. Both sulfonylurea use and insulin therapy in patients with type 2 diabetes result in increased risks for hypoglycemia^{20,21}. Interestingly, there has been intensive debate as to whether severe hypoglycemic events in type 2 diabetes patients is merely a marker of, or indeed causal of, the well-documented increased risk of cardiovascular events and mortality after hypoglycemia^{22–25}.

Continuous glucose monitoring systems (CGMs, or real-time CGMs) are devices that measure subcutaneous interstitial glucose to estimate blood glucose levels, and report the glucose

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levels and trends to patients in real time²⁶. CGMs can also generate audible or vibrating alarms for low/high glucose levels, based on the settings customized by patients or healthcare providers, to alert the patients to hypo/hyperglycemic events. Based on their capability to (i) improve hemoglobin A1C (HbA1c) and average glucose levels; (ii) reduce the risk for serious hypoglycemic complications^{27–29}; and (iii) reduce the burden of repetitive fingerstick glucose monitoring³⁰, CGMs are now considered the standard of care for type 1 diabetes patients^{31–33}. CGM use has also been further established with improvements in accuracy³⁴, feasibility for patients of various ages^{35,36} and diabetes duration³⁷, and the standardization of metrics for quantifying hypoglycemia^{18,38}. The interest and availability of CGMs that are integrated to sensor-augmented insulin pumps is also rapidly expanding³⁹. For patients with type 2 diabetes, data showing the beneficial roles of CGM technology for glucose control⁴⁰, weight control and lifestyle adherence⁴¹ are also emerging.

The current review gives a brief overview of the current knowledge of the IAH, and its assessment methods, the relationships between hypoglycemia and cardiovascular autonomic neuropathy (CAN), a practical approach on CAN evaluations in clinical care, and the recent clinical trial evidence on the role of CGMs use in the IAH population.

IMPAIRED AWARENESS OF HYPOGLYCEMIA AS A BARRIER FOR GLUCOSE CONTROL

Patients with IAH develop unrecognized hypoglycemic events and thereby can often miss the opportunity to treat their hypoglycemia in a timely manner¹⁹. Commonly co-existing with IAH is the attenuation or loss of sympathoadrenal mechanisms, which limits the endogenous glucoregulatory recovery from hypoglycemia (specifically, catecholaminergic stimulation of hepatic glucose output and restraint of muscle glucose uptake)⁴². Thus, for people with type 1 diabetes, who have already lost the ability to decrease endogenous insulin secretion and increase glucagon production as counterregulatory mechanisms, IAH and impaired adrenomedullary responses result in a further significant loss of defense mechanisms to avoid severe hypoglycemia (Figure 1)¹⁹. Indeed, IAH is associated with an approximately sixfold increased risk of developing severe hypoglycemia^{43,44}. Clinically, because of the risk of developing dangerously low glucose levels, patients and healthcare providers alike are often reluctant to practise/advocate tight glucose control to achieve proposed glycemic targets⁴⁵.

Approximately 25–40% of type 1 diabetes patients were found to have IAH, with a stable prevalence over the past two decades^{43,44,46,47}. This value is most certainly an underestimation, as even patients who report having intact hypoglycemia awareness are indeed unaware of CGM-confirmed hypoglycemia⁴⁸. In the type 2 diabetes population, the IAH prevalence ranges from approximately 6 to 17% in those using insulin injection programs, and the IAH status is associated with 9–17-fold increased risk for severe hypoglycemia^{49–51}.

A major cause of IAH and impaired adrenomedullary responses to hypoglycemia is recurrent episodes of hypoglycemia, which (as part of a vicious cycle) perpetuate these conditions^{52–54}. There is also evidence that IAH can be induced by sleep^{55,56}, psychological stress⁵⁷ and alcohol⁵⁸, yet there are still controversies as to whether exercise^{59,60} and beta-adrenergic blockers^{61,62} have detrimental or beneficial effects on hypoglycemia awareness status.

The mechanisms for the development of IAH remain to be elucidated⁶³. Earlier studies evaluated the relationships between this condition and adrenal medulla destruction⁶⁴, cortisol (as a systemic mediator)⁶⁵ or CAN⁶⁶. Some studies focused on the glucose sensing in the brain and how it is altered with antecedent hypoglycemia. Consistent with this central nervous system-impaired glucose sensing, recent studies have implicated the use of alternative fuels (e.g., lactate⁶⁷ or monocarboxylic acids⁶⁸) and changes in the neurotransmitter signaling in the brain (e.g., GABAergic⁶⁹, glutaminergic and opioidergic⁷⁰ signaling) as likely causes for IAH and the impaired sympathoadrenal response to hypoglycemia.

As these impaired responses are purported to be caused by recurrent antecedent hypoglycemia, it is logical that a reduction in the incidence of hypoglycemia would be expected to improve hypoglycemia awareness and adrenomedullary responses. In support of this notion, studies have shown that strict hypoglycemia avoidance with rigorous monitoring and behavioral modifications can help improve hypoglycemia awareness in as little as 2 weeks^{71–74}. Additionally, blood glucose awareness training⁷⁵, education to optimize insulin dosing⁷⁶ and hypoglycemia avoidance motivational programs⁷⁷ have also been shown to improve hypoglycemia awareness.

HYPOGLYCEMIA AND CARDIOVASCULAR AUTONOMIC NEUROPATHY

Diabetic CAN, defined as the impairment of autonomic control of the cardiovascular system in the setting of diabetes after exclusion of other causes⁷⁸, is a major diabetic comorbidity that has been associated with a significant increase in mortality in both patients with type 1 diabetes^{79–81} and type 2 diabetes^{82–84}. Despite the association between CAN and increased mortality, currently there is no effective therapy to prevent or reverse this condition beyond glycemic control^{6,85,86} and symptomatic management⁸⁷. The role of autonomic dysfunction as a risk factor for IAH had been studied quite extensively. Particularly as a hallmark of IAH is the loss of sympathetic symptoms (e.g., palpitation, tremor and anxiety) and the epinephrine responses to hypoglycemia, it was postulated that autonomic dysfunction including CAN might directly contribute to the development of IAH⁸⁸. However, more recent evidence showed that in some patients IAH can be induced by a single episode of hypoglycemia⁵³. This suggests that although autonomic dysfunction and CAN might further impact IAH risk and consequences^{89,90}, it is unlikely to be the main mechanism involving its development^{66,91,92}. Furthermore, it appears that self-reported IAH does

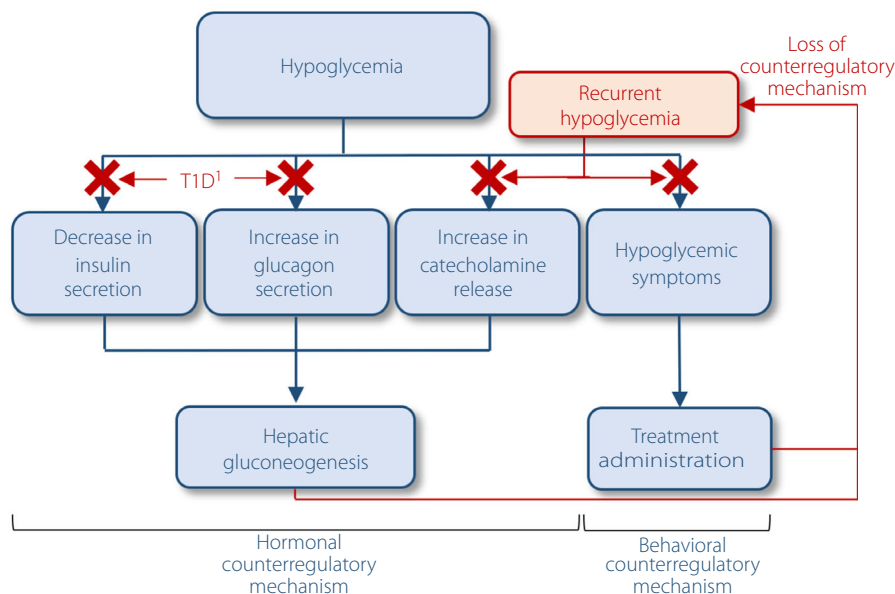


Figure 1 | Hypoglycemia counterregulatory mechanisms and the impacts of type 1 diabetes (T1D) and recurrent hypoglycemia on these mechanisms. ¹Or advanced type 2 diabetes.

not predict CAN⁹³. Yet, the associations between hypoglycemia and CAN in particular are quite complex, and remain to be further elucidated. There is ample evidence that CAN is independently associated with hypoglycemia in patients with diabetes^{25,94,95}. Several studies have also shown that hypoglycemia can promote reductions in heart rate variability and the baroreflex sensitivity in both patients with diabetes^{96,97} and healthy controls⁹⁸ that might last for many hours after euglycemia is restored⁹⁷. In addition, our group has reported that increased glucose variability, particularly with a predominance of hypoglycemic stress measures, was associated with blunting in measures of heart rate variability in type 1 diabetes patients⁹⁴. These data lend support to a potential role of hypoglycemia in the development of CAN and the loss of the protective cardio-vagal mechanisms, which might directly impact cardiac electrical activities and thus eventually increase the risk of cardiac arrhythmias in these patients^{94,97,99–101}. Experimental evidence reported that hypoglycemia might lead to peripheral nerve axonal degeneration, possibly through alterations in the glucose uptake, depletion of energy substrates and changes in Schwann cell metabolism affecting particularly the large myelinated fibers^{102,103}, although the exact mechanisms and whether these hypoglycemia-associated changes are functional^{104,105}, reversible¹⁰⁶ or permanent are still unclear^{107,108}. An additional example of the complex interactions between hypoglycemia, CAN and neuropathy is treatment-induced neuropathy. Treatment-induced neuropathy is a condition described in patients who have experienced a rapid decline in blood glucose levels after the use of insulin, oral hypoglycemic medications, or even diet only to control hyperglycemia, and often manifests as a painful

sensory and autonomic neuropathy, often with a dramatic onset and course^{109,110}.

ASSESSMENT OF IMPAIRED AWARENESS OF HYPOGLYCEMIA AND IMPAIRED ADRENOMEDULLARY RESPONSES TO HYPOGLYCEMIA

The hyperinsulinemic hypoglycemic clamp technique is the gold standard of assessing hypoglycemia awareness and hormonal responses to hypoglycemia^{17,111}. This validated tool assesses the hypoglycemia awareness status by collecting hypoglycemic symptoms during the clamp procedure at specified intervals to determine at what level of glucose hypoglycemic symptoms are experienced^{112,113}. Information is captured on several domains that include: difficulty thinking/confused, warm, shaky/tremulous, nausea, tired/drowsy, hungry, weak, sweaty, headache, heart-pounding, difficulty speaking, nervous/anxious, dizzy, faint, tingling and blurred vision¹¹². In general, it is accepted that individuals who do not develop significant hypoglycemic symptoms around glucose levels of 50–54 mg/dL are considered to have IAH¹¹⁴. Additional methods include the assessment of epinephrine levels and other counterregulatory hormones (norepinephrine, glucagon, cortisol, growth hormone, pancreatic polypeptide) during the various stages of hypoglycemia¹⁷. Techniques in measuring the endogenous glucose production for the assessment of hepatic glucose output can also be incorporated into hypoglycemic clamps¹¹⁵. Both single-step¹¹⁶ (from baseline to one single hypoglycemia glucose level target) or step-wise¹¹⁷ (from baseline to sequentially lower hypoglycemic level targets) clamps are commonly used. Some studies also carry out additional hyperinsulinemic-euglycemic

clamps¹¹⁷, in randomized orders with the hypoglycemic clamps, to blind the participants, so that the participants' hypoglycemic symptoms and hormonal measures would not be confounded by the knowledge of an anticipated hypoglycemic event or insulin administration. Although the hypoglycemic clamp is a well-established method to objectively measure the status of counter-regulatory mechanisms, the pitfalls of clamp studies are the invasiveness, expense and the significant time commitment from the patients, and thus these studies are often restricted to a small patient cohort. The interlaboratory variabilities in epinephrine assays also prohibit the comparison among studies (Table 1)¹¹⁸.

In the outpatient setting, methods to assess hypoglycemia awareness based on questionnaires (i.e., "self-reported hypoglycemia awareness") have also been developed and widely utilized, particularly for studies requiring larger sample sizes. The Gold questionnaire⁴³ contains a single question (besides two questionnaire-validation questions) asking individuals to report their experience in detecting hypoglycemic events with scores ranging from 1 (always aware) to 7 (never aware) on a Likert-type scale. In contrast, the Clarke questionnaire⁴⁴ is comprised of eight questions evaluating participants' prior hypoglycemia experiences, such as the history of severe hypoglycemia developments and the glucose levels at which patients start to detect hypoglycemic symptoms, and generates a score (0–7) based on the responses. Scores ≥ 4 are indicative of IAH, and ≤ 2 indicates normal awareness for both the Gold and Clark questionnaires. The Pedersen-Bjergaard questionnaire⁴⁶ asks individuals to report whether they recognize symptoms during hypoglycemic events and, based on the answer, the hypoglycemia awareness status is categorized as "normal," "impaired awareness," "unawareness" and "undetermined." All of these questionnaires have been previously validated based on their associations with severe hypoglycemia. The Clarke questionnaire has also been validated with hypoglycemic clamps¹¹⁴. HypoA-Q¹¹⁹ is a 33-item questionnaire assessing hypoglycemia awareness when

awake/sleep, and the hypoglycemia frequency, severity and impacts on patients. This questionnaire was validated with strong correlations with the Gold and Clarke questionnaires, together with weak correlations with diabetes-related distress and HbA1c. Other than wide usability with their non-invasiveness and no/minimal cost, self-reported hypoglycemia awareness assessments might also benefit from the direct reporting of patients' experiences in real life¹²⁰, rather than in highly controlled inpatient settings of hypoglycemic clamps. In contrast, the subjectivity of the experience (e.g., possibly influenced more by the recent events) or lack of a controlled environment might generate biases for the awareness reporting.

DIAGNOSIS OF DIABETIC CARDIOVASCULAR AUTONOMIC NEUROPATHY IN CLINICAL CARE

The American Diabetes Association recommends that screening for CAN should be carried out for patients with evidence of other chronic complications, such as nephropathy, peripheral neuropathy, retinopathy and cardiovascular disease, as well as for patients with IAH¹²¹, with high glucose variability, before insulin dose adjustments and/or perioperatively⁷⁹. The symptoms of CAN are less prevalent in contemporary cohorts of patients with diabetes, and most patients with CAN are completely asymptomatic^{101,121}. Weakness, lightheadedness, palpitations, syncope with standing or exercise intolerance are usually associated with advanced CAN^{6,85,122}.

Clinical signs, such as resting tachycardia (>100 b.p.m.) and orthostatic hypotension (a fall in systolic or diastolic blood pressure by >20 mmHg or >10 mmHg, respectively, on standing without an appropriate increase in heart rate) are both easy to document in an office^{78,123}, but in general present in later stages of CAN^{121,124}. A decrease in heart rate variability is the earliest sign of CAN^{78,125,126}, and can be assessed in an office by obtaining an electrocardiogram during 1–2 min of deep breathing and calculating indices of heart rate variability^{127,128}. However, given that both the symptoms and signs described

Table 1 | Current measures for assessing hypoglycemia awareness

	Measurements	Advantages	Disadvantages
Outpatient	Questionnaires: <ul style="list-style-type: none"> • Gold⁴³ • Clark⁴⁴ • Pedersen-Bjergaard⁴⁶ • HypoA-Q¹¹⁹ 	<ul style="list-style-type: none"> • Non-invasive • No/minimal cost • Reporting of experience from real-life hypoglycemic episodes • Amenable to use in large patient cohorts • Feasible for clinical use 	<ul style="list-style-type: none"> • Subjectivity bias • Recall bias • Uncontrolled environment • Lack of sensitivity to detect/quantify changes in awareness with short-term interventions
Inpatient	Edinburgh Hypoglycemia Scores ¹¹² determined during the hyperinsulinemic hypoglycemic clamp.	<ul style="list-style-type: none"> • Controlled environment, including reproducible hypoglycemic levels 	<ul style="list-style-type: none"> • Invasiveness • Expense • Patient time commitment • Small patient cohorts

are non-specific, a careful differential diagnosis is required to exclude other common medical causes (e.g., hyperthyroidism, anemia, dehydration, adrenal insufficiency, arrhythmic disorders), prescription medications effects (e.g., antihypertensive agents, antimuscarinic agents, diuretics), over-the-counter supplements and recreational agents¹²¹.

The cardiovascular reflex tests that assess changes in heart rate and blood pressure in response to several simple physiological maneuvers, such as deep breathing, standing or Valsalva, remain the gold standard diagnostic for autonomic testing in both clinical care and research settings, although these are more expensive and add burden for both clinicians and patients¹²¹.

CLINICAL TRIALS TESTING THE USE OF CONTINUOUS GLUCOSE MONITORING SYSTEMS IN TYPE 1 DIABETES PATIENTS WITH IMPAIRED AWARENESS OF HYPOGLYCEMIA

Early CGM clinical trials primarily focused on the CGMs' impact on glucose control, hypoglycemia reduction and quality of life¹²⁹. Additional questions were raised regarding the potential benefits of the CGM technology in improving the hypoglycemia awareness and epinephrine responses in patients with IAH. Below we summarize some of the most relevant trials that have addressed these questions.

In 2011, Ly *et al.*¹³⁰ carried out a small group randomized clinical trial study to evaluate whether the use of CGMs versus self-monitoring of blood glucose (SMBG) might improve epinephrine responses during hypoglycemic clamps in adolescents with type 1 diabetes and IAH (Table 2). The target glucose levels were 108–180 mg/dL in both groups, and the CGM group had the hypoglycemia alarm thresholds set at 108 mg/dL. Although after 4 weeks the CGM group had greater epinephrine responses during the hypoglycemic clamps (Table 3), suggesting a potential benefit of CGMs in improving hypoglycemia awareness, these findings were limited by the small sample size and to a group with relatively short diabetes duration.

Subsequently, the comparison of optimised MDI versus pumps with or without sensors in severe hypoglycaemia group¹³¹ carried out a 2 × 2 factorial (SMBG vs CGM; multiple daily injections, MDI vs continuous subcutaneous insulin infusion) randomized trial to assess whether hypoglycemia avoidance with intensive education could improve hypoglycemia awareness regardless of the glucose monitoring and insulin delivery models. At the study end, the incidence of hypoglycemia was reduced in all study arms, and the degree of hypoglycemia awareness improvements was similar between the CGM and SMBG groups, including the hypoglycemia symptoms scores during the hypoglycemic clamps in a subcohort study¹³². However, the low CGM use time (<50%) in approximately 40% of the participants could have significantly confounded the results.

The effects of RT-CGM on glycemia and QoL in patients with T1DM and IAH study group¹³³ evaluated glucose control (CGM vs SMBG) in IAH patients with a cross-over trial. The CGM phase was related to 15% more time-in-range (72–

180 mg/dL), and 41% and 55% reduction of the time in hypoglycemia and the number of patients who developed severe hypoglycemia, respectively. The Gold scores at the end of the CGM phase were lower, and tended to be lower compared with the end of the SMBG phase and to the baseline, respectively. Similar findings, however, were not observed in the Clarke scores. Although the cross-over design allows more “individualized” comparisons to evaluate CGMs' impact, it was unclear if a 16-week CGM intervention was long enough to significantly improve self-reported hypoglycemia awareness, and whether the 12-week washout period could sufficiently “reset” the hypoglycemia awareness to the baseline.

In 2018, Rickels *et al.*¹³⁴ carried out a small cohort, 18-month pre-post trial evaluating the changes in the endogenous glucose production and epinephrine responses with CGM interventions. In this IAH population with severely problematic hypoglycemia, the incidence of severe hypoglycemia decreased nearly 60% during the intervention. The hypoglycemic clamps also showed a doubled endogenous glucose production at 18 months, with no statistically significant improvements in epinephrine responses. Improvements in autonomic symptom scores and self-reported hypoglycemia awareness were also observed.

The HypoDE (or “Hypoglycemia in Deutschland”) study¹³⁵ is the largest randomized trial (CGM vs SMBG) to date testing CGMs' effects in patients with IAH or severe hypoglycemia history. The CGM group showed 72% fewer hypoglycemic episodes with glucose ≤54 mg/dL, along with 64% fewer severe hypoglycemic episodes. The entire cohort also had a 40% improvement in hypoglycemia awareness scores, although no difference was found between the CGM and SMBG groups.

Flash glucose monitoring systems (e.g., FreeStyle LibreTM), like CGMs, can provide glucose levels and trends, but without the feature of automated low/high glucose alarms¹³⁶. Flash glucose monitoring systems have been documented to reduce the time in hypoglycemia¹³⁷ and severe hypoglycemia¹³⁸ for type 1 diabetes patients, and reduce hypoglycemia¹³⁹ and improve HbA1c¹⁴⁰ in the type 2 diabetes population. Reddy *et al.* compared the efficacy of CGMs versus Flash glucose monitoring systems in reducing hypoglycemia in type 1 diabetes patients with IAH or severe hypoglycemia history¹⁴¹. The CGM group showed greater hypoglycemia reduction, particularly at night, attributed to the low glucose alarm systems. However, the improvements in hypoglycemia awareness in these two groups were statistically indistinguishable. Potential confounders include flash glucose monitoring systems' lower glucose accuracy in the low glucose range^{136,142,143} that might have falsely reported more hypoglycemia.

Although CGMs have clearly shown the benefit of hypoglycemia reduction without compromising the overall glycemic control, the extent to which CGMs can help improve hypoglycemia awareness and epinephrine responses remains unclear. Although meticulous avoidance of hypoglycemia has been shown to improve hypoglycemia awareness within 2–16 weeks^{71–74}, none of the aforementioned studies showed an absolute avoidance of hypoglycemia, which could explain this

Table 2 | Clinical trials evaluating continuous glucose monitoring use in type 1 diabetes patients with impaired awareness of hypoglycemia

Authors (year)	Main objective	Trial design and targeted population	Primary outcome(s)	Baseline population characteristics	CGM models (active usage time)
Ly <i>et al.</i> (2011) ¹³⁰	Assess if the use of CGMs with preset hypo alarms (at glucose 108 mg/dL) improves counterregulatory response to hypoglycemia.	Randomized, controlled. Two arms (CGM vs SMBG). Duration: 4 weeks. Adolescents (aged 12–18 years) with IAH defined per modified Clarke (<i>n</i> = 11).	Epinephrine response to hypoglycemia measured during hypoglycemia clamp study.	CGM <i>n</i> = 6; SMBG <i>n</i> = 5 Female: Not reported Age: CGM: 13.7 ± 0.7 years Standard: 15 ± 0.8 years DoD: 15 ± 0.8 years CGM: 5.2 ± 1.4 years Standard: 6.5 ± 1.2 years HbA1c: CGM: 7.7 ± 0.2% Standard: 7.9 ± 0.3% MDI: Not reported	Medtronic Minimed paradigm real-time system (not reported)
Little <i>et al.</i> (HypoCOMPaSS; 2014) ¹³¹ ; Leelarathna <i>et al.</i> (HypoCOMPaSS clamp sub-cohort study; 2013) ¹³²	Determine if rigorous hypoglycemia prevention improves hypoglycemia awareness and prevents SH development in patients with IAH, independent of insulin delivery and glucose monitoring modalities.	Randomized, controlled. 2 × 2 factorial (CGM vs SMBG, CSII vs MDI). Duration: 24 weeks. Patients with IAH defined per Gold. (<i>n</i> = 96)	Difference in hypoglycemia awareness (assessed with Gold) between the CGM and SMBG groups, and between the MDI and CSII groups. Clamp sub-cohort study: the glucose concentration at which participants felt hypoglycemic during progressive hypoglycemia.	83 patients completed study; CGM <i>n</i> = 42 and SMBG <i>n</i> = 41 Female: 64% Age: 48.6 ± 12.2 years DoD: 28.9 ± 12.3 years HbA1c: 8.2 ± 1.2% MDI: 97% Clamp Subcohort <i>n</i> = 18 (CGM <i>n</i> = 11, SMBG <i>n</i> = 7) Female: 66.7% Age: 50 ± 9 years DoD: 35 ± 10 years HbA1c: 8.1 ± 1% MDI: 50%	Medtronic (median 57%)
van Beers <i>et al.</i> (IN CONTROL; 2016) ¹³³	Assess whether CGM use improves glycemia control and prevents severe hypoglycemia in patients with IAH.	Randomized, cross-over. Two arms (CGM vs SMBG). Duration: 16-week intervention with 12-week washout. Patients with IAH defined per Gold, either on CSII or MDI. (<i>n</i> = 52)	Mean difference in the percentages of time in normoglycemia.	CGM <i>n</i> = 26, SMBG <i>n</i> = 26 Female: 46% Age: 48.6 ± 11.6 years DoD: 30.5 ± 40.8 years HbA1c: 7.5 ± 0.8% MDI: 56%	Medtronic Enlite glucose sensor (median 89.4; IQR 80.8–95.5);
Rickels <i>et al.</i> (2018) ¹³⁴	Assess if hypoglycemia avoidance with CGMs improves glucose counterregulation in patients	Single arm (CGM). Duration: 18 months.	Difference in the endogenous glucose production response during stepped-	Female: 55% Age: 44 ± 4 years DoD: 31 ± 4 years HbA1c: 7.2 ± 0.2%	Dexcom seven plus/G4 or Medtronic Sof-Sensor (<i>n</i> = 7/4)

Table 2 (Continued)

Authors (year)	Main objective	Trial design and targeted population	Primary outcome(s)	Baseline population characteristics	CGM models (active usage time)
Heinemann <i>et al.</i> (HypoDE; 2018) ¹³⁵	with long-standing diabetes and IAH. Ascertain whether the incidence and severity of hypoglycemia can be reduced through CGM use in patients on MDI and with high risk for developing SH.	Patients with IAH defined per Clarke and other criteria. [†] (n = 11) Randomized, controlled. Two arms (CGM vs SMBG). Duration: 22-week intervention and 4-week follow up. Patients on MDI with SH within the last year or IAH defined per Clarke. (n = 149)	hypoglycemic and euglycemic clamps. The mean difference in the number of hypoglycemic events (defined as CGM glucose ≤ 54 mg/dL for ≥ 20 min) between baseline and the follow up phase.	MDI: 27% 141 patients in final analysis; CGM n = 75, SMBG n = 66 Female: CGM: 47% Control: 34% Age: CGM: 45.8 \pm 12.0 years Control: 47.3 \pm 11.7 years DoD: CGM: 21.6 \pm 13.9 years Control: 20.9 \pm 14.0 years HbA1c: CGM: 7.6 \pm 1.0% Control: 7.3 \pm 1.0% MDI: 100%	Dexcom G5 (mean 90.7%) (median 100%)
Reddy <i>et al.</i> (H-HART; 2018) ¹⁴¹	Assess the impacts of CGMs and FGMs on hypoglycemia reduction in patients on MDI with high risk for developing SH.	Randomized. Two arms (CGM vs FGM). Duration: 8 weeks. Patients on MDI with SH within the last year or IAH defined per Gold (n = 40)	The median difference between the change of time in hypoglycemia (<59 mg/dL) from baseline to endpoint.	CGM n = 20, SMBG n = 20 Female: 40% Age: 49.5 years (37.5–63.5) DoD: 30.0 years (21.0–36.5) HbA1c: 7.3% (6.5–7.8) MDI: Not reported [‡]	Dexcom G5 (not reported)

Data presented in mean \pm standard deviation or median (interquartile range [IQR]). AUC, area under the curve; CSII, continuous subcutaneous insulin infusion; DoD, duration of diabetes; HbA1c, hemoglobin A1c; IAH, impaired awareness of hypoglycemia; SH, severe hypoglycemia; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes. [†]Severely problematic hypoglycemia (hypoglycemia [hypo] score ≥ 1.047), marked glycemic lability (glycemic lability index ≥ 433 mmol/L²/h/week or a composite of HYPO score ≥ 423 and glycemic lability index ≥ 329 mmol/L²/h/week, and either at least one episode of severe hypoglycemia in the past 12 months or the presence of >5% of time spent at <60 mg/dL by 72-h blinded continuous glucose monitoring (CGM). [‡]The study aimed to assess the CGM effects on multiple daily injection (MDI)-using population; actual percentage not reported.

Table 3 | Reported time in hypoglycemia, hypoglycemia awareness and autonomic response outcomes in clinical trials evaluating continuous glucose monitoring use in type 1 diabetes patients with impaired awareness of hypoglycemia

Author	Time in hypoglycemia at study end [†] (%)	Hypoglycemia awareness outcomes	Endogenous Glucoregulatory Response Outcomes
Ly <i>et al.</i> (2011) ¹³⁰	NA	NA	Changes in epinephrine levels during hypoglycemic clamps compared with euglycemic clamps (%) Baseline: CGM: 214 ± 72% Standard: 288 ± 151% (<i>P</i> = 0.688) Study end (4 weeks): CGM: 604 ± 234% Standard: 114 ± 83% (<i>P</i> = 0.048) [‡] Changes in epinephrine levels during hypoglycemic clamps at baseline vs study end: CGM: <i>P</i> = 0.031 Standard: <i>P</i> = 0.375
Little <i>et al.</i> (HypoCOMPaSS; 2014) ¹³¹ ; Leelarathna, <i>et al.</i> (HypoCOMPaSS clamp subcohort study; 2013) ¹³²	Glucose <72 mg/dL CGM: 6.3 ± 9.1% SMBG: 5.2 ± 4.2% (<i>P</i> = 0.47) Glucose ≤54 mg/dL CGM: 2.1 ± 5.1% SMBG: 1.3 ± 2.1% (<i>P</i> = 0.36) Clamp Study Subcohort – AUC of the % of time spent with glucose <54 mg/dL (mean ± standard error): CGM: 658 ± 223 SMBG: 797 ± 193 (<i>P</i> = 0.64)	Gold scores Baseline: 5.1 ± 1.1 Study end: 4.1 ± 1.4 (<i>P</i> < 0.001) [‡] Clarke scores Baseline: 4.1 ± 1.6 Study end: 3.2 ± 1.7 (<i>P</i> < 0.001) HypoA-Q scores Baseline: 13.4 ± 3.4 Study end: 9.1 ± 4.2 (<i>P</i> < 0.001) No differences in hypoglycemia awareness scores between the CGM vs SMBG and CSII vs MDI models. Clamp Study Subcohort Plasma glucose level of first felt hypoglycemia Baseline: 47 ± 2 mg/dL Study end: 56 ± 4 mg/dL (<i>P</i> = 0.02) [‡] Symptom score AUC Baseline: 500 (364–685) Study end: 650 (365–1,285) (<i>P</i> = 0.02) No differences in the above measures between CGM vs SMBG and CSII vs MDI models.	Clamp Study Subcohort –AUC of incremental metanephrine levels Baseline: 2,412 (–3,026 to 7,279) Study end: 5,180 (–771 to 11,513) (<i>P</i> = 0.02) Glucose thresholds for metanephrine response Baseline: 43 (41–45) mg/dL Study end: 49 (41–58) mg/dL (<i>P</i> = 0.03) No differences in the above measures between the CGM vs SMBG and CSII vs MDI models.
van Beers <i>et al.</i> (IN CONTROL; 2016) ¹³³	Glucose ≤70 mg/dL CGM: 6.8% [5.2–8.3] SMBG: 11.4% [9.9–13.0] (<i>P</i> < 0.0001)	Gold scores End of CGM phase: 4.6 [4.3–5.0] End of SMBG phase: 5.0 [4.6–5.4] (<i>P</i> = 0.035) Change in Gold scores from baseline End of CGM phase: –0.5 [–0.8 to –0.1] End of SMBG phase: –0.1 [–0.4–0.2] (<i>P</i> = 0.076) Clarke scores End of CGM phase: 4.4 [3.9–4.8] End of SMBG phase: 4.4 [3.9–4.8] (<i>P</i> = 0.953) Change in Clarke scores from baseline End of CGM phase: –0.1 [–0.5–0.3] End of SMBG phase: –0.4 [–0.8–0.0] (<i>P</i> = 0.216)	NA

Table 3 (Continued)

Author	Time in hypoglycemia at study end [†] (%)	Hypoglycemia awareness outcomes	Endogenous Glucoregulatory Response Outcomes
Rickels <i>et al.</i> (2018) ¹³⁴	Glucose <60 mg/dL Run-in: 6.5 ± 1.6% Study end (18-months): 4.0 ± 0.7% (<i>P</i> = NS)	Clark scores Baseline: 6 (6–7) 6 months: 4 (4–5) 12 months: 3 (2–5) 18 months: 3 (2–5) (<i>P</i> < 0.01)Clamp Study Autonomic symptoms during hypoglycemic vs euglycemic clamps: Baseline: 3.7 ± 0.9 vs 2.5 ± 0.3 (<i>P</i> = NS) 6 months: 5.1 ± 1.0 vs 1.5 ± 0.7 (<i>P</i> < 0.05) 18 months: 5.6 ± 1.2 vs 2.2 ± 0.6 (<i>P</i> < 0.05) No statistical significance when comparing the symptom scores at 6 and 18 months to baseline.	Epinephrine levels during hypoglycemia Baseline: 152 ± 37 pg/mL 6 months: 204 ± 37 pg/mL (<i>P</i> = NS) 18 months: 152 ± 36 pg/mL (<i>P</i> = NS) Norepinephrine levels during hypoglycemia Baseline: 378 ± 44 pg/mL 6 months: 317 ± 38 pg/mL (<i>P</i> = NS) 18 months: 362 ± 60 pg/mL (<i>P</i> = NS) Endogenous glucose production (compared to baseline): [‡] Baseline: 0.42 ± 0.08 mg/kg/min 6 months: 0.54 ± 0.07 mg/kg/min (<i>P</i> = NS) 18 months: 0.84 ± 0.15 mg/kg/min (<i>P</i> < 0.05)
Heinemann <i>et al.</i> (HypoDE; 2018) ¹³⁵	Glucose ≤70 mg/dL CGM: 1.6% (0.9–3.7) Control: 6.4% (3.7–12.0) Adjusted between-group differences: <i>P</i> < 0.0001 Glucose ≤54 mg/dL CGM: 0.3% (0.1–0.9) Control: 2.5% (1.0–6.1) Adjusted between-group differences: <i>P</i> < 0.0001	Clark scores Baseline CGM: 5.0 (4.0–6.0) Control: 5.0 (4.0–6.0)Follow up CGM: 3.0 (1.0–4.0) Control: 3.0 (1.0–5.0)Adjusted between-group differences: <i>P</i> = 0.7662	NA
Reddy <i>et al.</i> (I-HART; 2018) ¹⁴¹	Glucose <70 mg/dL CGM: 6.2% (3.1–10.2) FGM: 11.0% (8.2–17.0) Median change from baseline: <i>P</i> < 0.01 Glucose <50 mg/dL CGM: 0.9% (0.2–1.8) FGM: 3.8% (3.0–6.4) Median change from baseline: <i>P</i> < 0.003	Gold scores Baseline: CGM: 5 (5–6) FGM: 5 (4–5)Study end (8 weeks): CGM: 4.5 (3.0–5.0) FGM: 5.0 (3.5–6.0)Median change from baseline: CGM: 0.0 [–1.0 to 0.0] (<i>P</i> = NS) FGM: 0.0 [–0.8 to 0.0] (<i>P</i> = NS)Differences in median changes from baseline to study end: <i>P</i> = 0.23	NA

Data presented in mean ± standard deviation or median (interquartile range) or mean/median [95% confidence interval], unless noted otherwise. AUC, area under the curve; CSII, continuous subcutaneous insulin infusion; FGM, flash glucose monitoring; HypoCOMPASS, comparison of optimised MDI versus pumps with or without sensors in severe hypoglycaemia; HypoDE, hypoglycemia in Deutschland; IAH, impaired awareness of hypoglycemia; I-HART, impact on hypoglycaemia awareness of real time CGM and intermittent continuous glucose data; IN CONTROL, effects of RT-CGM on glycemia and QoL in patients with T1DM and IHA; MDI, multiple daily injections; NA, not available; NS, not significant; T1D, type 1 diabetes. [†] Variable definitions for hypoglycemia were used. These trials were performed prior to the current continuous glucose monitoring (CGM)/hypoglycemia guidelines. For self-monitoring of blood glucose level (SMBG) groups or run-in phase, time in hypoglycemia were assessed with blinded CGMs. [‡] Primary outcomes of the trials.

finding. Recent observational data^{144–146} show that IAH is still common and problematic in type 1 diabetes patients, despite CGM use, and thus IAH might unfortunately remain an important clinical obstacle in diabetes management for CGM users.

To definitively determine whether CGMs/diabetes technologies could improve hypoglycemia awareness, more optimal trial design that eliminates confounders and provides sufficient intervention duration is important¹³¹. This includes matching individuals for age, duration of diabetes, HbA1c, hypoglycemia awareness scores and hypoglycemia cognition¹⁴⁵ to reduce some effects from the individual variabilities. It would also be of interest whether a treat-to-target approach (e.g., time in hypoglycemia targets of <4%¹⁴⁷ or even <1%¹⁴⁸), with techniques such as more rigorous strategies to engage patients to CGMs¹⁴⁹ or CGM alarm setting adjustments^{150,151}, could improve hypoglycemia awareness or epinephrine responses to hypoglycemia.

CONCLUSION

CGM is an effective tool to help reduce hypoglycemia and severe hypoglycemic episodes in type 1 diabetes patients, including those with IAH. Whether CGMs could help improve hypoglycemia awareness, and how CAN and IAH are interrelated, remain to be determined or further elucidated.

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DISCLOSURE

The authors declare no conflict of interest.

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