# Hypoglycemia Unawareness and Autonomic Dysfunction in Diabetes – Lessons Learned and Roles of Diabetes Technologies

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*Short Running Title: Does CGM improve hypoglycemia awareness?*

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**Words in Abstract**: 166

**Words in Text** (excluding references, figure and table legends): 3434

**Figures**: 1

**Tables**: 3

**References**: 151

**Abbreviations**: IAH, impaired awareness of hypoglycemia; T1D, type 1 diabetes; CGM, continuous glucose monitoring; CAN, cardiovascular autonomic neuropathy; DCCT, Diabetes Control and Complications Trial; T2D, type 2 diabetes; HbA1c, hemoglobin A1C; TIN, treatment-induced neuropathy; EGP, endogenous glucose production; HRV, heart rate variability; EKG, electrocardiogram; SMBG, self-monitoring of blood glucose; MDI, multiple daily injections; CSII, continuous subcutaneous insulin infusion; FGM, flash glucose monitoring.


## 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 about 25% of patients with type 1 diabetes (T1D), IAH has complex pathophysiology and may lead to serious and potentially lethal consequences in patients with diabetes, particularly in those with more advanced disease and comorbidities. Continuous glucose monitoring (CGM) 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, CGMs 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 (CAN), a practical approach to evaluate CAN for clinicians, and recent evidence from clinical trials assessing the effects of the use of CGM technologies in patients with T1D with IAH.



**Keywords**: Hypoglycemia, impaired awareness of hypoglycemia, cardiovascular autonomic neuropathy, continuous glucose monitoring, type 1 diabetes


## Introduction

For almost 100 years, insulin has been the fundamental therapy for type 1 diabetes (T1D)[1]. 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 Trial (DCCT)[2] and Epidemiology of Diabetes Interventions and Complications study[3] 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 status, 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 hypoglycemia[17]. Recent revisions of hypoglycemia definitions also include glucose levels <54 mg/dL (i.e., level 2 hypoglycemia[16]) 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 hypoglycemia[19]. The DCCT study defined severe hypoglycemia as hypoglycemic episodes requiring assistance of another person for recovery[9]. This definition was subsequently adopted as the universal definition of severe (or level 3) hypoglycemia[11, 15, 16].

Iatrogenic hypoglycemia is not restricted to T1D patients. Both sulfonylurea usage and insulin therapy in patients with type 2 diabetes (T2D) result in increased risks for hypoglycemia[20, 21]. Interestingly, there has been intensive debate as to whether severe hypoglycemic events in T2D is merely a marker of, or indeed causal, with regard to the well-documented increased risk of cardiovascular events and mortality following 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 levels and trends to patients in real-time[26]. CGMs can also generate audible or vibrate 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, 1) to improve hemoglobin A1C (HbA1c) and average glucose levels, 2) reduce the risk for serious hypoglycemic complications[27-29], and 3) reduce the burden of repetitive fingerstick glucose monitoring[30]; CGMs are now considered the standard of care for T1D

patients[31-33]. CGM use has also been further established with the improvements in accuracy[34], the feasibility in patients with various ages[35, 36] and diabetes duration[37], 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 expanding[39]. For patients with T2D, data demonstrating the beneficial roles of CGM technology for glucose control[40], weight control and lifestyle adherence[41] 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 timely treat their hypoglycemia[19]. Commonly co-existing with IAH is the attenuation or loss of sympathoadrenal mechanisms, that 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 T1D, 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[19]. (Figure 1) Indeed, IAH is associated with about six-fold increased risk of developing severe hypoglycemia[43, 44]. Clinically, due to 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 targets[45].

Approximately 25-40% of T1D patients were found to have IAH, with a stable prevalence over the last 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 hypoglycemia[48]. In the T2D population, the IAH prevalence ranges from about 6-17% in those using insulin injection programs, and the IAH status is associated with 9-17 folds 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 stress[57] and alcohol[58], 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 elucidated[63]. Earlier studies evaluated the relationships between this condition and adrenal medulla destruction[64], cortisol (as a systemic mediator)[65] or CAN[66]. Some studies have focused on the glucose-sensing in the brain and how it is altered with antecedent hypoglycemia. Consistent with this CNS impaired glucose sensing, recent studies have implicated the use of alternative fuels (e.g., lactate[67] or monocarboxylic acids[68]) and changes in the neurotransmitter signaling in the brain (e.g., GABAergic[69], glutaminergic and opioidergic[70] signaling) as likely causes for IAH and the impaired sympathoadrenal response to hypoglycemia.

Since 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 short as two weeks[71-74]. Additionally, blood glucose awareness training[75], education to optimize insulin dosing[76], and hypoglycemia avoidance motivational program[77] have also been shown to improve hypoglycemia awareness.

**Hypoglycemia and Cardiovascular Autonomic Neuropathy**

Diabetic CAN, defined as the impairment of autonomic control of cardiovascular system in the setting of diabetes after exclusion of other causes[78], is a major diabetic comorbidity that has been associated with a significant increase in mortality in both patients with T1D[79-81] and T2D[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 management[87]. The role of autonomic dysfunction as a risk factor for IAH had been studied quite extensively. Particularly since 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 may directly contribute to the development of IAH[88]. However, more recent evidence demonstrated that in some patients IAH can be induced by a single episode of hypoglycemia[53]. This suggests that although autonomic dysfunction and CAN may 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 not predict CAN[93]. 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 controls[98] that may last for many hours after euglycemia is restored[97]. 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 T1D patients[94]. These data lend support to a potential role of hypoglycemia in the development of CAN and the loss of the protective cardiovagal mechanisms, that may 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 may lead to peripheral nerve axonal degeneration possibly via alterations in the glucose uptake, depletion of energy substrates, 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], reversible[106] or permanent is still unclear[107, 108]. An additional example of the complex interactions between hypoglycemia, CAN and neuropathy is treatment-induced neuropathy (TIN). TIN is a condition described in patients who have experienced a rapid decline in the blood glucose levels following 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 vision[112]. In general it is accepted that subjects who do not develop significant hypoglycemic symptoms around glucose levels of 50-54 mg/dL are considered to have IAH[114]. Additional methods include the assessment of epinephrine levels and other counterregulatory hormones (norepinephrine, glucagon, cortisol, growth hormone, pancreatic polypeptide) during the various stages of hypoglycemia[17]. Techniques in measuring the endogenous glucose production (EGP) for the assessment of hepatic glucose output can also be incorporated into hypoglycemic clamps[115]. Both single-step[116] (from baseline to one single hypoglycemia glucose level target) or step-wise[117] (from baseline to sequentially lower hypoglycemic level targets) clamps are commonly used. Some studies also conduct additional hyperinsulinemic-*eu*glycemic clamps[117], 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. While the hypoglycemic clamp is a well-established method to objectively measure the status of counterregulatory 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 inter-laboratory variabilities in epinephrine assays also prohibit the comparison among studies[118]. (Table 1)

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 questionnaire[43] 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 questionnaire[44] 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 to 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 questionnaire[46] 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 clamps[114]. HypoA-Q[119] 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 may also benefit from the direct reporting of patients' experiences in the real life[120], rather than in highly controlled inpatients settings of hypoglycemic clamps. On the other hand, the subjectivity of the experience (e.g., possibly influenced more by the recent events) or lack of a controlled environment may 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 done in patients with evidence of other chronic complications such as nephropathy, peripheral neuropathy, retinopathy and cardiovascular disease, as well as in patients with IAH[121], with high glucose variability, prior to insulin dose adjustments and/or perioperatively[79]. The symptoms of CAN are less prevalent in contemporary cohorts of patients with diabetes, and most patients with CAN may be 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 bpm) and orthostatic hypotension (a fall in systolic or diastolic blood pressure by >20 mmHg or >10 mmHg, respectively, upon standing without an appropriate increase in heart rate) are both easy to be documented in office[78, 123], but in general present in later stages of CAN[121, 124]. A decrease in heart rate variability (HRV) is the earliest sign of CAN[78, 125, 126] and could be assessed in office by obtaining an electrocardiogram (EKG) during 1-2 minutes of deep breathing and calculating indices of HRV[127, 128]. However, given that both the symptoms and signs described are non-specific, a careful differential diagnosis is needed 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 agents[121].

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 patients[121].

## 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 life[129]. 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 and colleagues[130] conducted a small group randomized clinical trial study to evaluate whether the use of CGMs vs. self-monitoring of blood glucose (SMBG) may improve epinephrine responses during hypoglycemic clamps in adolescents with T1D 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 four 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 of relatively short diabetes duration.

Subsequently, the HypoCOMPaSS group[131] conducted a 2 x 2 factorial (SMBG vs. CGM; multiple daily injections, MDI, vs. continuous subcutaneous insulin infusion, CSII) randomized trial to assess whether hypoglycemia avoidance with intensive education could improve hypoglycemia awareness regardless 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 sub-cohort study[132]. However, the low CGM usage time (<50%) in about 40% of the participants could have significantly confounded the results.

The IN CONTROL study group[133] evaluated glucose control (CGM vs. SMBG) in IAH patients with a crossover 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 to the end of the SMBG phase and to the baseline, respectively. Similar findings, however, were not observed in the Clarke scores. While the crossover 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 and colleagues[134] conducted a small cohort, 18-month pre-post trial evaluating the changes in the EGP 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 revealed a doubled EGP at 18 months, with no statistically significant improvements in epinephrine responses. Improvements in autonomic symptom scores and self-reported hypoglycemia awareness were also observed.

HypoDE[135] is the largest randomized trial (CGM vs. SMBG) to-date testing CGMs’ effects in patients with IAH or severe hypoglycemia history. The CGM group demonstrated 72%

less hypoglycemic episodes with glucose ≤54 mg/dL, along with 64% less severe hypoglycemic episodes. The entire cohort also had a 40% improvement in hypoglycemia awareness scores, although with no difference was found between the CGM and SMBG groups.

Flash glucose monitoring systems (FGMs; e.g., FreeStyle Libre™), alike CGMs, can provide glucose levels and trends, but without the feature of automated low/high glucose alarms[136]. FMGs have been documented to reduce the time in hypoglycemia[137] and severe hypoglycemia[138] for T1D patients, and reduce hypoglycemia[139] and improve HbA1c[140] in the T2D population. Reddy and colleagues compared the efficacy of CGMs vs. FGMs in reducing hypoglycemia in T1D patients with IAH or severe hypoglycemia history[141]. The CGM group demonstrated greater hypoglycemia reduction, particularly at nights, attributed to the low glucose alarm systems. However, the improvements in hypoglycemia awareness in these two groups were statistically indistinguishable. Potential confounders include FGMs' lower glucose accuracy in the low glucose range[136, 142, 143] that might have falsely reported more hypoglycemia.

While CGMs have clearly demonstrated 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 above studies demonstrated an absolute avoidance of hypoglycemia, which could explain this finding. Recent observational data[144-146] indicate that IAH is still common and problematic in T1D patients despite CGM use, and thus IAH may unfortunately remain an important clinical obstacle in diabetes management in 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 important[131]. This includes matching subjects for age, duration of diabetes, HbA1c, hypoglycemia awareness scores and hypoglycemia cognition[145] to reduce some effects from the individual variabilities. It also would 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

CGMs[149] 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 T1D 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.

**Acknowledgement Statement***:* SJF is supported by the NIH R01DK118082. RPB is supported by NIH 1R01DK107956-01 and U01DK119083, and the JDRF Center of Excellence at the University of Michigan.

**Author Disclosure Statement:** The authors of this manuscript have no conflicts of interest relevant to this study to disclose.

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**Figure 1. Hypoglycemia Counterregulatory Mechanisms and the Impacts of T1D and Recurrent Hypoglycemia on these Mechanisms.** [1]Or advance type 2 diabetes. T1D, type 1 diabetes.

**Table 1. Current Measures for Assessing Hypoglycemia Awareness**

| | Measurements | Advantages | Disadvantages |
|---|---|---|---|
| **Outpatient** | Questionnaires:<br>• Gold[43]<br>• Clark[44]<br>• Pedersen-Bjergaard[46]<br>• HypoA-Q[119] | • Non-invasive<br>• No/minimal cost<br>• Reporting of experience from real-life hypoglycemic episodes<br>• Amenable to use in large patient cohorts<br>• Feasible for clinical use | • Subjectivity bias<br>• Recall bias<br>• Uncontrolled environment<br>• Lack of sensitivity to detect/quantify changes in awareness with short-term interventions |
| **Inpatient** | Edinburgh Hypoglycemia Scores[112] determined during the hyperinsulinemic hypoglycemic clamp. | • Controlled environment, including reproducible hypoglycemic levels | • Invasiveness<br>• Expense<br>• Patient time commitment<br>• Small patient cohorts |

**Table 2. Clinical Trials Evaluating CGM Use in T1D Patients with IAH**

| Authors (Year) | Main Objective | Trial Design & Targeted Population | Primary Outcome(s) | Baseline Population Characteristics | CGM Models (active usage time) |
|---|---|---|---|---|---|
| Ly, et al. (2011)[130] | Assess if the use of CGMs with preset hypo alarms (at glucose 108 mg/dL) improves counterregulatory response to hypoglycemia. | Randomized, controlled.<br><br>Two arms (CGM vs. SMBG).<br>Duration: 4 weeks. | Epinephrine response to hypoglycemia measured during hypoglycemia clamp study. | CGM n=6; SMBG n=5<br>Female: Not reported<br>Age:<br>CGM:13.7±0.7 yrs<br>Standard: 15±0.8 yrs<br>DoD:<br>CGM: 5.2±1.4 yrs | Medtronic Minimed paradigm real-time system (not reported) |

| | | | | | |
|---|---|---|---|---|---|
| | | Adolescents (aged 12-18 years old) with IAH defined per modified Clarke (N=11). | | Standard: 6.5±1.2 yrs<br>HbA1c:<br>CGM: 7.7±0.2%<br>Standard: 7.9±0.3%<br>MDI: Not reported | |
| Little, et al. (HypoCOMPaSS; 2014)[131]; Leelarathna, et al. (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.<br><br>2 x 2 factorial (CGM vs. SMBG, CSII vs. MDI).<br>Duration: 24 weeks.<br><br>Patients with IAH defined per Gold.<br>(N=96) | Difference in hypoglycemia awareness (assessed with Gold) between the CGM and SMBG groups, and between the MDI and CSII groups.<br><br>Clamp sub-cohort study: the glucose concentration at which participants felt hypoglycemic during progressive hypoglycemia. | 83 patients completed study;<br>CGM n=42 and SMBG n=41<br>Female: 64%<br>Age: 48.6±12.2 yrs<br>DoD: 28.9±12.3 yrs<br>HbA1c: 8.2±1.2%<br>MDI: 97%<br><br>Clamp Sub-cohort<br>N=18 (CGM n=11, SMBG n=7)<br>Female: 66.7%<br>Age: 50±9 yrs<br>DoD: 35±10 yrs<br>HbA1c: 8.1±1%<br>MDI: 50% | Medtronic (median 57%) |
| van Beers, et al. (IN CONTROL; 2016)[133] | Assess whether CGM use improves glycemia control and prevents severe hypoglycemia in patients with IAH. | Randomized, crossover.<br><br>Two arms (CGM vs. SMBG). | Mean difference in the percentages of time in normoglycemia. | CGM n=26, SMBG n=26<br>Female: 46%<br>Age: 48.6±11.6 yrs<br>DoD: 30.5±40.8 yrs<br>HbA1c: 7.5±0.8%<br>MDI: 56% | Medtronic Enlite glucose sensor (median 89.4; IQR 80.8-95.5); |

| | | | | | |
|---|---|---|---|---|---|
| | | Duration: 16-week intervention with 12-week washout.<br><br>Patients with IAH defined per Gold, either on CSII or MDI. (N=52) | | | |
| Rickels, et al. (2018)[134] | Assess if hypoglycemia avoidance with CGMs improves glucose counterregulation in patients with long-standing diabetes and IAH. | Single arm (CGM).<br><br>Duration: 18 months.<br><br>Patients with IAH defined per Clarke and other criteria†. (N=11) | Difference in the endogenous glucose production response during stepped-hypoglycemic and euglycemic clamps. | Female: 55%<br>Age: 44±4 yrs<br>DoD: 31±4 yrs<br>HbA1c: 7.2±0.2%<br>MDI: 27% | Dexcom seven plus/G4 or Medtronic Sof-Sensor (n= 7/4) (median 100%) |
| Heinemann, et al. (HypoDE; 2018)[135] | 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. | Randomized, controlled.<br><br>Two arms (CGM vs. SMBG).<br>Duration: 22-week intervention and 4-week follow-up.<br><br>Patients on MDI with SH within the last | The mean difference in the number of hypoglycemic events (defined as CGM glucose ≤54mg/dL for ≥20 minutes) between baseline and the follow-up phase. | 141 patients in final analysis; CGM n=75, SMBG n=66<br>Female:<br>CGM: 47%<br>Control: 34%<br>Age:<br>CGM: 45.8±12.0 yrs<br>Control: 47.3±11.7 yrs<br>DoD:<br>CGM: 21.6±13.9 yrs<br>Control: 20.9±14.0 yrs<br>HbA1c: | Dexcom G5 (mean 90.7%) |

| | | | | | |
|---|---|---|---|---|---|
| | | year or IAH defined per Clarke. (N=149) | | CGM: 7.6±1.0%<br>Control: 7.3±1.0%<br>MDI: 100% | |
| Reddy et al. (I-HART; 2018)[141] | Assess the impacts of CGMs and FGMs on hypoglycemia reduction in patients on MDI with high risk for developing SH. | Randomized.<br><br>Two arms (CGM vs. FGM).<br>Duration: 8 weeks.<br><br>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<br>Female: 40%<br>Age: 49.5 yrs (37.5-63.5)<br>DoD: 30.0 yrs (21.0-36.5)<br>HbA1c: 7.3% (6.5-7.8)<br>MDI: Not reported‡ | Dexcom G5 (not reported) |

Data presented in mean±standard deviation, mean/median [95% confidence interval] or median (IQR).

†Severely problematic hypoglycemia (HYPO score ≥1047), marked glycemic lability (glycemic lability index ≥433 mmol/L$^2$/h/week, or a composite of HYPO score ≥423 and glycemic liability index ≥329 mmol/L$^2$/h/week, and either at least one episode of severe hypoglycemia in the past 12 months or presence of >5% of time spent at <60 mg/dL by 72-hour blinded CGM.

‡The study aimed to assess the CGM effects on MDI-using population; actual percentage not reported.

CGM, continuous glucose monitoring; T1D, type 1 diabetes; IAH, impaired awareness of hypoglycemia; MDI, multiple daily injection; SMBG, self-monitoring of blood glucose; DoD, duration of diabetes; HbA1c, hemoglobin A1C; CSII, continuous subcutaneous insulin infusion; AUC, area under the curve; IQR, interquartile range; SH, severe hypoglycemia.

**Table 3. Reported Time in Hypoglycemia, Hypoglycemia Awareness and Autonomic Response Outcomes in Clinical Trials Evaluating CGM Use in T1D Patients with IAH**

| Author | Time in Hypoglycemia at Study End† (%) | Hypoglycemia Awareness Outcomes | Endogenous Glucoregulatory Response Outcomes |
|---|---|---|---|
| Ly, et al. (2011)[130] | N/A | N/A | Changes in epinephrine levels during hypoglycemic clamps compared to euglycemic clamps (%)<br>*Baseline:*<br>CGM: 214±72%<br>Standard: 288±151% *(P=0.688)*<br>*Study end (4 weeks):*<br>CGM: 604±234%<br>Standard: 114±83% *(P=0.048)*‡<br><br>Changes in epinephrine levels during hypoglycemic clamps at baseline vs. study end:<br>CGM: *P*=0.031<br>Standard: *P*=0.375 |
| Little, et al. (HypoCOMPaSS; 2014)[131]; Leelarathna, et al. (HypoCOMPaSS clamp sub-cohort study; 2013)[132] | Glucose <72 mg/dL<br>CGM: 6.3±9.1%<br>SMBG: 5.2±4.2% (*P*=0.47)<br><br>Glucose ≤54 mg/dL<br>CGM: 2.1±5.1%<br>SMBG: 1.3±2.1% (*P*=0.36) | Gold scores<br>Baseline: 5.1±1.1<br>Study end: 4.1±1.4 (*P*<0.001)‡<br><br>Clarke scores<br>Baseline: 4.1±1.6<br>Study end: 3.2±1.7 (*P*<0.001) | Clamp Study Sub-cohort –<br>AUC of incremental metanephrine levels<br>Baseline: 2,412 (-3,026 to 7,279)<br>Study end: 5,180 (-771 to 11,513) (*P*=0.02)<br><br>Glucose thresholds for metanephrine response<br>Baseline: 43 (41-45) mg/dL |

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|---|---|---|---|
| | Clamp Study Sub-cohort –<br>AUC of the % of time spent with glucose <54 mg/dL (mean±standard error):<br>CGM: 658 ± 223<br>SMBG: 797±193 (*P*=0.64) | HypoA-Q scores<br>Baseline: 13.4±3.4<br>Study end: 9.1±4.2 (*P*<0.001)<br><br>No differences in hypoglycemia awareness scores between the CGM vs. SMBG and CSII vs. MDI models.<br><br>Clamp Study Sub-cohort<br>*Plasma glucose level of first felt hypoglycemia*<br>Baseline: 47±2 mg/dL<br>Study end: 56±4 mg/dL *(P=0.02)*‡<br><br>*Symptom score AUC*<br>Baseline: 500 (364-685)<br>Study end: 650 (365-1,285)<br>*(P=0.02)*<br><br>No differences in the above measures between CGM vs. SMBG and CSII vs. MDI models. | Study end: 49 (41-58) mg/dL (*P*=0.03)<br><br>No differences in the above measures between the CGM vs. SMBG and CSII vs. MDI models. |
| van Beers, et al. (IN CONTROL; 2016)[133] | Glucose ≤70 mg/dL<br>CGM: 6.8% [5.2-8.3] | Gold scores<br>End of CGM phase: 4.6 [4.3-5.0] | N/A |

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|---|---|---|---|
| | SMBG: 11.4% [9.9-13.0] (*P*<0.0001) | End of SMBG phase: 5.0 [4.6-5.4] (*P*=0.035)<br><br>Change in Gold scores from baseline<br>End of CGM phase: -0.5 [-0.8 - -0.1]<br>End of SMBG phase: -0.1 [-0.4-0.2] (*P*=0.076)<br><br>Clarke scores<br>End of CGM phase: 4.4 [3.9-4.8]<br>End of SMBG phase: 4.4 [3.9-4.8] (*P*=0.953)<br><br>Change in Clarke scores from baseline<br>End of CGM phase: -0.1 [-0.5-0.3]<br>End of SMBG phase: -0.4 [-0.8-0.0] (*P*=0.216) | |
| Rickels, et al. (2018)[134] | Glucose <60 mg/dL<br>Run-in: 6.5±1.6%<br>Study end (18-months): 4.0±0.7% (*P*=NS) | Clark scores<br>Baseline: 6 (6-7)<br>6 months: 4 (4-5)<br>12 months: 3 (2-5)<br>18 months: 3 (2-5)<br>(*P*<0.01)<br><br>Clamp Study | Epinephrine levels during hypoglycemia<br>Baseline: 152±37 pg/mL<br>6 months: 204±37 pg/mL (*P*=NS)<br>18 months: 152±36 pg/mL (*P*=NS)<br><br>Norepinephrine levels during hypoglycemia<br>Baseline: 378±44 pg/mL<br>6 months: 317±38 pg/mL (*P*=NS) |

| | | | |
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| | | Autonomic symptoms during hypoglycemic vs. euglycemic clamps:<br>Baseline: 3.7±0.9 vs. 2.5±0.3 (*P*= NS)<br>6 months: 5.1±1.0 vs. 1.5 ±0.7) (*P*<0.05)<br>18 months: 5.6±1.2 vs. 2.2±0.6 (*P*<0.05)<br><br>No statistical significance when comparing the symptom scores at 6 and 18 months to baseline. | 18 months: 362±60 pg/mL (*P*=NS)<br><br>Endogenous glucose production (compared to baseline):‡<br>Baseline: 0.42±0.08 mg/kg/min<br>6 months: 0.54±0.07 mg/kg/min (*P*=NS)<br>18 months: 0.84±0.15 mg/kg/min (*P*<0.05) |
| Heinemann, et al. (HypoDE; 2018)[135] | Glucose ≤70 mg/dL<br>CGM: 1.6% (0.9-3.7)<br>Control: 6.4% (3.7-12.0)<br>Adjusted between-group differences: *P*<0.0001<br><br>Glucose ≤54 mg/dL<br>CGM: 0.3% (0.1-0.9)<br>Control: 2.5% (1.0-6.1)<br>Adjusted between-group differences: *P*<0.0001 | Clark scores<br>*Baseline*<br>CGM: 5.0 (4.0-6.0)<br>Control: 5.0 (4.0-6.0)<br>*Follow-up*<br>CGM: 3.0 (1.0-4.0)<br>Control: 3.0 (1.0-5.0)<br>*Adjusted between group differences: P*=0.7662 | N/A |
| Reddy et al. (I-HART; 2018)[141] | Glucose <70 mg/dL<br>CGM: 6.2% (3.1-10.2)<br>FGM: 11.0% (8.2-17.0) | Gold scores<br>*Baseline:*<br>CGM: 5 (5-6)<br>FGM: 5 (4-5) | N/A |

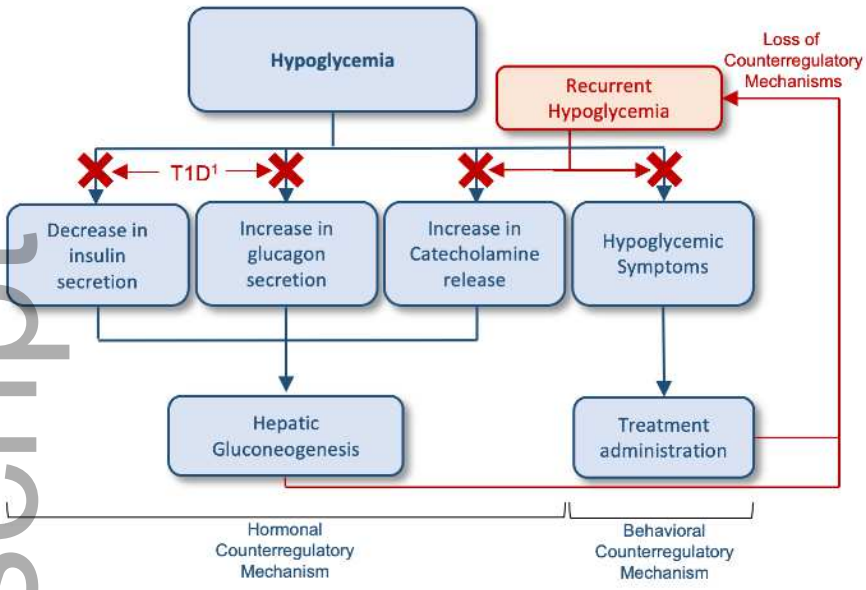
| | | | |
|---|---|---|---|
| | Median change from baseline:<br>*P*<0.01<br><br>Glucose <50 mg/dL<br>CGM: 0.9% (0.2-1.8)<br>FGM: 3.8% (3.0-6.4)<br>Median change from baseline:<br>*P*<0.003 | *Study end (8 weeks):*<br>CGM: 4.5 (3.0-5.0)<br>FGM: 5.0 (3.5-6.0)<br><br>*Median change from baseline:*<br>CGM: 0.0 [-1.0-0.0] (*P*=NS)<br>FGM: 0.0 [-0.8-0.0] (*P*=NS)<br>*Differences in median changes from baseline to study end: P*=0.23 | |

Data presented in mean±standard deviation or median (interquartile range), unless noted otherwise.

† Variable definitions for hypoglycemia were used. These trials were performed prior to the current CGM/hypoglycemia guidelines. For SMBG groups or run-in phase, time in hypoglycemia were assessed with blinded CGMs.

‡Primary outcomes of the trials.

CGM, continuous glucose monitoring; T1D, type 1 diabetes; IAH, impaired awareness of hypoglycemia; SMBG, self-monitoring of blood glucose level; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; AUC, area under the curve.

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