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ORIGINAL ARTICLE

Automated Insulin Delivery for Hypoglycemia Avoidance and Glucose Counterregulation in Long-Standing Type 1 Diabetes with Hypoglycemia Unawareness

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Abstract

Objective: Automated insulin delivery (AID) may benefit individuals with long-standing type 1 diabetes where frequent exposure to hypoglycemia impairs counterregulatory responses. This study assessed the effect of 18 months AID on hypoglycemia avoidance and glucose counterregulatory responses to insulin-induced hypoglycemia in long-standing type 1 diabetes complicated by impaired awareness of hypoglycemia.

Methods: Ten participants mean ± standard deviation age 49 ± 16 and diabetes duration 34 ± 16 years were initiated on AID. Continuous glucose monitoring was paired with actigraphy to assess awake- and sleep-associated hypoglycemia exposure every 3 months. Hyperinsulinemic hypoglycemic clamp experiments were performed at baseline, 6, and 18 months postintervention. Hypoglycemia exposure was reduced by 3 months, especially during sleep, with effects sustained through 18 months ($P \leq 0.001$) together with reduced glucose variability ($P < 0.01$).

Results: Hypoglycemia awareness and severity scores improved ($P < 0.01$) with severe hypoglycemia events reduced from median (interquartile range) 3 (3–10) at baseline to 0 (0–1) events/person·year postintervention ($P = 0.005$). During the hypoglycemic clamp experiments, no change was seen in the endogenous glucose production (EGP) response, however, peripheral glucose utilization during hypoglycemia was reduced following intervention [pre: 4.6 ± 0.4, 6 months: 3.8 ± 0.5, 18 months: 3.4 ± 0.3 mg/(kg·min), $P < 0.05$]. There were increases over time in pancreatic polypeptide (Pre:62 ± 29, 6 months:127 ± 44, 18 months:176 ± 58 pmol/L, $P < 0.01$), epinephrine (Pre: 199 ± 53, 6 months: 332 ± 91, 18 months: 386 ± 95 pg/mL, $P = 0.001$), and autonomic symptom (Pre: 6 ± 2, 6 months: 6 ± 2, 18 months: 10 ± 2, $P < 0.05$) responses.

Conclusions: AID led to a sustained reduction of hypoglycemia exposure. EGP in response to insulin-induced hypoglycemia remained defective, however, partial recovery of glucose counterregulation was evidenced by a

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reduction in peripheral glucose utilization likely mediated by increased epinephrine secretion and, together with improved autonomic symptoms, may contribute to the observed clinical reduction in hypoglycemia.

Keywords: Automated insulin delivery, Glucose counterregulation, Impaired awareness of hypoglycemia, Type 1 diabetes, Hypoglycemia-associated autonomic failure.

Introduction

In long-standing type 1 diabetes, increased risk for experiencing severe hypoglycemia (requiring help of a third-party to recover[1]) develops as a consequence of progressive compromise in the physiologic defense mechanisms against the development of low blood glucose in the setting of therapeutic hyperinsulinemia.[2] The near-total destruction of insulin producing β-cells results in a paracrine defect in glucagon secretion from neighboring α-cells in response to hypoglycemia,[3,4] removing the normal islet response to lower the insulin-to-glucagon ratio exposed to the liver and increase hepatic glucose production. The absence of this primary defense against the development of hypoglycemia leaves activation of sympathoadrenal epinephrine that can increase endogenous (primarily hepatic) glucose production (EGP) and decrease peripheral glucose utilization and autonomic symptom generation that can alert the individual to ingest carbohydrate, as critical to defend against the development of low blood glucose.

However, recurrent exposure to hypoglycemia impairs both the sympathoadrenal epinephrine and autonomic symptom responses[5,6] leading to defective glucose counterregulation and impaired awareness of hypoglycemia (IAH),[7,8] collectively recognized as the syndrome of hypoglycemia-associated autonomic failure (HAAF) (reviewed in Cryer;[9] and Rickels[10]). Once established, hypoglycemia unawareness increases the risk of severe hypoglycemia up to 20-fold,[11] and so contributes significantly to disease-related morbidity and mortality.[12–14]

IAH in type 1 diabetes of short duration can improve over several weeks of intervention,[15] however, in long-standing type 1 diabetes complicated by IAH, targeted avoidance of biochemical hypoglycemia over several months is required.[10] Structured educational and psychobehavioral interventions can modestly improve hypoglycemia awareness, reduce the incidence of severe hypoglycemia, and increase the autonomic symptom response to insulin-induced hypoglycemia after 6 months intervention.[16–18] These interventions have utilized flexible basal-bolus insulin delivery with currently available insulin analogs administered by either multiple daily injection (MDI) or pump therapy in conjunction with frequent (at least four times daily) self-monitored blood glucose and/or continuous glucose monitoring (CGM).

High adherence to the use of real-time CGM in this population over at least a 4-month period reduces hypoglycemia frequency and severity without increasing HbA_{1c}, however, does not eliminate severe hypoglycemia and has been shown to only modestly improve hypoglycemia awareness in one[19] but not all[20–22] studies. Continued exposure to hypoglycemia with CGM, especially during the nocturnal period of sleep, likely accounts for on-going impairment in epinephrine secretion and the autonomic symptom response to insulin-induced hypoglycemia defining the persistence of HAAF.[19] Nocturnal hypoglycemia is a significant contributor toward both the induction and maintenance of HAAF as sympathoadrenal responses to hypoglycemia are further diminished during sleep in type 1 diabetes alongside impaired symptom and wakening responses.[7,23,24] Thus, despite the increased availability of and access to CGM, IAH persists in many CGM users[25] and remains a significant risk factor for severe hypoglycemia.[26]

Automated insulin delivery (AID) systems integrate predictive low-glucose suspension (PLGS) of insulin delivery for anticipated hypoglycemia with or without a hybrid closed-loop (HCL) automated increase in basal and/or bolus delivery of insulin for hyperglycemia,[27] providing further opportunity for targeted reduction of hypoglycemia exposure, most notably during the nocturnal period of sleep.[28–30] In individuals with type 1 diabetes and either IAH or a recent severe hypoglycemia event, use of PLGS for 6 months reduced time spent with hypoglycemia by >50% and reduced severe hypoglycemic events sixfold compared to insulin pump therapy without real-time CGM.[31] Moreover, PLGS use was especially effective during the nocturnal period. Two short-term intervention studies (4 and 8 weeks) suggest that AID systems that also automate increased insulin delivery when an elevated glucose concentration is predicted better address excessive glucose variability and further reduce clinically important hypoglycemia in individuals prone to hypoglycemia.[32,33]

The present mechanistic study aimed to assess the effect of 18 months AID intervention on hypoglycemia avoidance and glucose counterregulation in individuals with long-standing type 1 diabetes complicated by IAH. We hypothesized that AID would allow for significant reduction in hypoglycemia exposure, beyond that previously reported as achieved by CGM alone,[19] and lead to improvements in epinephrine, driving increased EGP, and autonomic symptom responses, with improved glucose counterregulation and hypoglycemia symptom recognition indicative of recovery from HAAF, and reduced risk for experiencing severe hypoglycemia.

Participants and Methods

Participants between 25 and 70 years old with C-peptide negative (<0.3 ng/mL on a random sample) type 1 diabetes of more than 10 years duration, disease onset <40 years of age, and active diabetes self-management defined as at least three clinical evaluations with a local diabetology service during the previous 12 months were invited to participate. Inclusion criteria required IAH (Clarke score ≥4)[34] and at least one of: severely problematic hypoglycemia (hypoglycemia severity score [HYPO] ≥1047; 90th percentile); marked glycemic lability index [LI ≥433 mmol/($L^2 \cdot h \cdot$week); (90th percentile)]; or a composite HYPO score ≥423 (75th percentile), and LI ≥329 mmol/($L^2 \cdot h \cdot$week) (75th percentile).[35,36] In addition, inclusion required evidence of ongoing hypoglycemia exposure that would likely be associated with impaired counterregulatory responses,[5,6]

defined as >5% time spent in hypoglycemia (glucose <60 mg/dL)[19] on 7-day real-time or blinded CGM (iPro2; Medtronic Diabetes, Northridge, CA), including at least one episode of nocturnal hypoglycemia.

Study exclusion criteria were the recent use of an AID device with PLGS or other noninsulin hypoglycemic agent within 4 weeks of enrollment; obesity (body mass index ≥30 kg/m^2); insulin resistance (≥1.0 units/kg/day); poor glycemic control (HbA_{1c} ≥ 10%); abnormal liver, kidney, or thyroid function; pregnancy; breast-feeding; anemia; seizure disorder not related to prior severe hypoglycemia; uncontrolled hypertension; untreated proliferative diabetic retinopathy, Addison's disease or Celiac disease; or active cardiovascular disease, including use of β-blocker therapy. Further details are available online (ClinicalTrials.gov identifier: NCT03215914). The study protocol was approved by the Institutional Review Board of the University of Pennsylvania and all participants provided written informed consent to participate.

AID systems, MiniMed™ 670G (Medtronic Diabetes) or t:slimX2 (Tandem Diabetes, San Diego, CA) were commenced after a 2-week run-in period of standard pump delivery and completion of the baseline clamp procedure. All participants utilized PLGS of insulin delivery for anticipated hypoglycemia and were encouraged to use the HCL predictive increase in basal and/or bolus delivery of insulin for hyperglycemia (Auto-mode/Control-IQ). The hypoglycemia threshold for PLGS was set no lower than 80 mg/dL. The Auto Mode closed-loop algorithm glucose target of 120 mg/dL could be increased to 150 mg/dL for sleep and exercise, and for participants using Control-IQ, the closed loop algorithm could be placed in sleep or activity modes. Sensor compliance was assessed at each visit with >80% required for ongoing study participation.

Device uploads of CGM and insulin delivery data were reviewed at study visits with assessment of compliance and advice to adjust bolus and/or basal insulin dose settings to minimize glycemic excursions while maximizing hypoglycemia avoidance. Study visits, including telephone visits, occurred weekly for the first month and monthly until month 6 to assess the effect of AID alongside intensive provider support. Thereafter, three monthly visits were performed with the frequency of assessment and data collection more closely aligning with standard provider interaction. All visits were conducted by a nurse practitioner (A.J.P.) who provided education and recommendations on AID/CGM use, including adjustment of insulin delivery and glucose monitoring settings under MD supervision (M.R.R.).

Continuous glucose monitoring

AID system CGM data from the 4 weeks before every 3-month visit were used in these analyses. Participants wore a wrist actigraphy monitor (Actigraph wGT3X-BT; ActiGraph, Inc., Pensacola, FL) for a 3-week period before each visit to enable pairing with CGM data for accurate assessment of day- and sleep-associated time in glucose ranges. Actigraphy data were downloaded using ActiLife software (version 6.13.3) and algorithm-detected sleep periods were determined as previously described.[37] Mean glucose; glucose standard deviation (SD); coefficient of variation (CV = SD/mean); low and high blood glucose indices (LBGI and HBGI); total, day- and sleep-associated percentage time-in-range (70–180 mg/dL), time with hypoglycemia (<54, <60, <70 mg/dL), and time with hyperglycemia (>180, >250 mg/dL) were calculated using HypoCount software (version 2.0; PRECISE Center, University of Pennsylvania, Philadelphia, PA).

Assessment of glucose counterregulation

Participants underwent blinded hyperinsulinemic hypoglycemic clamp studies at baseline, 6 and 18 months postintervention following methodology previously described.[19,38,39] Participants were admitted the afternoon/evening before study after avoiding strenuous exercise for 3 days. Near-normoglycemia was maintained during a 12-h period of overnight fasting by an intravenous insulin infusion protocol. At 0700, $t = -120$ min, a primed (5 mg/kg fasting plasma glucose in mg/dL/90 for 5 min) continuous [0.05 mg/(kg·min) for 355 min] infusion of 6,6–$^2H_2$-glucose (99% solution; Cambridge Isotopes Laboratories, Andover, MA) was initiated to assess EGP before and during the clamp procedures with baseline blood samples obtained at $t = -20$, -10, and -1 min. At $t = 0$ min, a continuous infusion of insulin [1 mU/(kg·min) for 240 min] was administered to produce hyperinsulinemia.

Subsequently, a variable rate infusion of 20% dextrose (enriched with 2% 6,6–$^2H_2$-glucose to reduce changes in plasma enrichment during the clamp[40]) was administered according to the glycemic clamp technique to achieve hourly stepped reduction in plasma glucose to targets of 80 mg/dL (Step 1), 65 mg/dL (Step 2), 55 mg/dL (Step 3), and 45 mg/dL (Step 4). Blood samples were taken every 5 min, centrifuged, and measured at the bedside using an automated glucose analyzer (YSI 2300; Yellow Springs Instruments, Yellow Springs, OH) to adjust the glucose infusion rate and achieve the desired plasma glucose concentration. An autonomic symptom questionnaire was completed every 20 min and used to quantitate the autonomic symptom score with the sum of scores ranging between 0 (none) and 5 (severe) for six symptoms: anxiety; palpitations; sweating; tremor; hunger; and tingling.[41]

Additional blood samples were taken at $t = 20$, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, and 240 min for biochemical analysis and verification of the plasma glucose levels. All samples were collected on ice into chilled tubes containing EDTA, with Protease Inhibitor Cocktail (Sigma-Aldrich, St Louis, MO) added to the tubes for peptide hormones, centrifuged at 4°C, separated and frozen at −80°C for subsequent analysis. Enrichment of 6,6–$^2H_2$-glucose in plasma was measured by gas chromatography-mass spectrometry. Plasma insulin, glucagon, and pancreatic polypeptide were measured in duplicate by double-antibody radioimmunoassay (for insulin and glucagon: Millipore, Billerica, MA; for pancreatic polypeptide: ALPCO Diagnostics, Salem, NH). Plasma epinephrine and norepinephrine were measured by high-performance liquid chromatography with electrochemical detection.

Calculations and statistics

The magnitude of counterregulatory responses during the hypoglycemic clamp were assessed by the mean of values over the final hour of hypoglycemia (Step 4).[19,38,39] The rate of appearance (R_a) and disposal (R_d) of glucose during the

hyperinsulinemic hypoglycemic clamp studies was calculated by the Steele nonsteady-state equation modified for the use of stable isotopes and as previously described.[42] EGP was calculated from the difference between the rate of appearance of glucose in the plasma and the infusion rate of exogenous glucose.

The primary outcome for the study was defined as the EGP response to insulin-induced hypoglycemia after 6 months of intervention. Secondary outcomes included EGP in response to hypoglycemia after 18 months of intervention, and glucose counterregulatory hormone, symptom, and R_d responses to hypoglycemia after 6 and 18 months. The sample size was set to 15 participants to have >80% power at $\alpha = 0.05$ (two-tailed) to detect a 0.42 mg/(kg·min) difference in EGP from baseline to 6 months after AID intervention.

Enrollment was closed after 10 participants started intervention and a preliminary analysis using conditional power indicated no effect of AID on EGP after 6 months as the observed effect (Table 3) was in the direction of the null hypothesis and so any further increase in the sample size could not support accepting the alternative hypothesis for the primary outcome with conditional power being <1%.[43] All participants initiated on AID intervention completed the study protocol for assessment of the secondary outcomes.

Data are expressed as mean ± standard error or median (interquartile range) unless otherwise noted. Changes in CGM and hypoglycemia clamp outcomes were compared by Friedman analysis of variance (ANOVA) with comparison of baseline to follow-up measures by Wilcoxon matched pairs testing if ANOVA $P \leq 0.1$ using Statistica software (StatSoft, Inc., Tulsa, OK). Significance was considered at $P < 0.05$ (two-tailed).

Results

Participant characteristics

Twelve participants were recruited and completed study screening. One individual was withdrawn due to poor venous access and did not complete the baseline hypoglycemic clamp. A second participant completed the study run-in and the baseline hypoglycemic clamp procedure but dropped out after the baseline visit due to difficulty managing the new technology, opting to resume MDI of insulin. Ten participants (seven female/three male) completed the 18-month intervention, including all study visits.

Participant demographics and baseline characteristics are shown in Table 1. In general, study participants had >30 years duration of type 1 diabetes and required 0.5 units/(kg·day) of insulin to achieve a mean HbA_{1c} below the ADA consensus target of 7.0% (53 mmol/mol).[1] At recruitment, nine participants had prior insulin pump use and all participants had prior use of real-time CGM. At the time of baseline data collection, eight individuals were using insulin pump therapy and seven were utilizing real-time CGM. The study participants were at high risk of severe hypoglycemia events demonstrated by IAH, marked hypoglycemia severity (median HYPO score ≥90th percentile), and excessive glycemic lability (median ≥75th percentile). All participants had experienced a severe hypoglycemia event in the last year with a median frequency of three events in the previous 12 months.

Nine participants commenced intervention using a study provided Minimed 670G system (Medtronic Diabetes) and one using a commercially acquired t:slim X2 (Tandem Diabetes). All but one participant completed the study on their initial device, with one Minimed 670G user switching to a commercially acquired t:slim X2 during month 11 of the study (Supplementary Table S1). Necessitated as the study intervention, all individuals used PLGS of insulin delivery over the 18-month study period. In addition, the majority of individuals elected to use the AID device in HCL mode (Auto Mode or Control-IQ) with seven participants spending 91% (80%–97%) of time in HCL at 6 months and eight participants using HCL from 12 months onward with 89% (82%–96%) of time spent in HCL.

Two participants utilized PLGS alone for the duration of the study. There were no changes observed in body weight or total daily insulin dose throughout the intervention period; a trend toward an increase in HbA_{1c} was not different at 18 months compared to baseline (Supplementary Table S1).

Table 1. Participant Demographics and Baseline Characteristics Including Insulin Delivery and Glucose Monitoring Modality at Screening

Characteristic	*Participants*
Female/male (*n*/*n*)	7/3
Age (years)	49 ± 16
Diabetes duration (years)	34 ± 16
Weight (kg)	66 ± 8
BMI (kg/m^2)	24 ± 1
Insulin requirement [unit/(kg·day)]	0.49 ± 0.09
HbA_{1c} (%)	6.8 ± 1.1
HbA_{1c} (mmol/mol)	51 ± 7
CSII/MDI	8/2
Real-time CGM/SMBG	7/3
Severe hypoglycemia (events/12 months)	3 (2–24)
Clarke score	5 (4–7)
HYPO	1301 (243–2895)
LI	396 (82–702)

Data presented as mean ± SD or median (range).

BMI, body mass index; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; HYPO, hypoglycemia severity score; LI, lability index; MDI, multiple daily injections; SD, standard deviation; SMBG, self-monitoring of blood glucose.

CGM measures of glycemic control

AID system CGM sensor compliance was high and sustained throughout the study at 90% (84%–95%) (Table 2). Mean glucose was unchanged. However, measures of glucose variability, including glucose SD and CV, were reduced ($P < 0.01$ and $P < 0.001$, respectively) with the median CV at 18 months falling below 34%, a proposed target for minimizing the risk of hypoglycemia in individuals with type 1 diabetes.[44]

All measures of hypoglycemia exposure, including total percentage of time spent <54, <60, and <70 mg/dL improved following the study intervention ($P \leq 0.001$) (Table 2). Hypoglycemia exposure while awake was significantly reduced ($P < 0.05$) (Fig. 1A) with an even greater reduction in percentage of time spent <70 mg/dL while asleep (Baseline: 11% [4%–17%] to 18 months: 0% [0%–1%], $P < 0.01$) (Fig. 1B). There was a trend toward a reduction in total time spent in marked levels of hyperglycemia >250 mg/dL

TABLE 2. CONTINUOUS GLUCOSE MONITORING OUTCOMES

Variable	*Baseline*, n = *10*	*3 Months*, n = *10*	*6 Months*, n = *10*	*9 Months*, n = *10*	*12 Months*, n = *10*	*15 Months*, n = *10*	*18 Months*, n = *10*	P
Sensor wear (%)	N/A	89 (77–90)	93 (88–95)	93 (85–95)	91 (83–98)	89 (84–95)	92 (88–99)	0.64
Mean glucose (mg/dL)	138 (133–159)	144 (138–168)	143 (130–157)	141 (130–151)	144 (138–159)	144 (137–157)	146 (137–160)	0.60
Glucose SD (mg/dL)	59 (56–62)	53 (44–54)	46 (43–55)	46 (43–50)	50 (44–52)	50 (41–52)	47 (40–56)	<0.01
Coefficient of variation (%)	43 (40–45)	35 (31–36)	32 (31–33)	33 (30–34)	34 (31–34)	33 (30–36)	31 (28–34)	<0.001
Time <54 mg/dL (%)	4.2 (2.7–7.0)	0.8 (0.2–1.1)	0.4 (0.2–0.7)	0.4 (0.2–1.8)	0.8 (0.5–1.1)	0.7 (0.2–1.4)	0.3 (0.2–1.2)	0.001
Time <60 mg/dL (%)	5.5 (4.4–8.0)	1.4 (0.6–1.9)	0.9 (0.4–1.1)	0.9 (0.4–2.5)	1.1 (0.9–2.1)	1.2 (0.6–1.9)	0.6 (0.4–2.3)	<0.001
Time <70 mg/dL (%)	9.9 (7.9–10.9)	3.3 (1.4–5.1)	2.3 (1.3–2.9)	2.7 (1.4–4.2)	2.8 (1.9–4.5)	2.4 (1.8–3.9)	1.5 (1.0–4.9)	<0.001
Time >180 mg/dL (%)	21.4 (17.0–34.4)	20.9 (15.1–32.2)	19.4 (14.6–28.4)	17.7 (14.6–22.5)	20.7 (16.7–29.5)	19.9 (15.8–25.2)	21.0 (14.5–30.8)	0.96
Time >250 mg/dL (%)	5.6 (3.1–7.7)	3.8 (2.4–8.1)	2.6 (1.5–6.8)	2.2 (1.5–5.2)	3.2 (1.1–7.1)	3.2 (1.3–5.6)	3.3 (0.9–6.5)	0.06
Time in range 70–180 mg/dL (%)	68.1 (58.7–72.4)	74.7 (67.4–83.4)	77.5 (69.4–80.4)	78.4 (76.1–79.8)	75.9 (68.6–78.8)	77.5 (72.1–81.1)	76.5 (64.6–83.3)	0.11
LBGI	1.53 (0.76–2.62)	0.93 (0.49–1.27)	0.72 (0.37–0.93)	0.76 (0.42–1.17)	0.85 (0.54–1.09)	0.80 (0.48–1.02)	0.57 (0.29–1.04)	0.04
HBGI	4.29 (3.30–7.76)	4.75 (3.77–7.57)	4.01 (3.42–6.30)	3.85 (3.42–5.13)	4.52 (3.41–6.50)	4.61 (3.40–5.76)	4.46 (3.13–6.43)	0.77

Data presented as median (IQR). Comparison of baseline and follow-up visits during intervention with automated insulin delivery by Friedman ANOVA. ANOVA, analysis of variance; HBGI, high blood glucose index; IQR, interquartile range; LBGI, low blood glucose index; NA, not applicable.

($P = 0.06$), which was reduced at 18 months from baseline ($P = 0.02$) (Table 2), and was significantly reduced over the study during periods of sleep (Baseline: 8% [5%–11%] to 18 months: 3% [0%–6%], $P = 0.01$) (Fig. 1B).

A weak trend toward improved total time-in-range was observed over the study ($P = 0.11$) with a significant improvement at 18 months compared to baseline ($P = 0.04$) (Table 2). Percentage time in range increased over periods of sleep from 68% (56%–77%) at baseline to 85% (70%–93%) at 18 months ($P < 0.01$) (Fig. 1B). An improvement in the LBGI, a marker of severe hypoglycemia risk,[45] was also observed ($P < 0.05$). However, the HBGI and percentage of time spent >180 mg/dL were unchanged.

Hypoglycemia awareness, assessed by the Clarke score, improved with the median score falling to below <4, the threshold used to define IAH, at 12 and 18 months (Fig. 2A). However, five individuals had persisting IAH as defined by a Clarke score ≥4 over the course of the study. Three of the five individuals who recorded a persistent Clarke score ≥4 experienced a severe hypoglycemia event during the study intervention. When assessing a shortened version of the Clarke survey that removes questions about experience of severe hypoglycemia, the Hypoglycemia Awareness Factor score,[46] a weak trend toward improvement was observed over the study (Baseline: 4 [3–4]; 6 months: 4 [2–4]; 12 months: 3 [1–4]; 18 months: 3 [1–5]; $P = 0.12$; Baseline vs. 18 months, $P = 0.07$). There was a weak trend toward reduction in glycemic LI ($P = 0.12$), and of six individuals starting the study with a LI ≥75th%, only one individual met this threshold at 18 months, with the LI at 18 months significantly less than baseline [Baseline: 396 (283–479) vs. 18 months: 193 (145–234) mmol/($L^2 \cdot h \cdot$week), $P < 0.05$) (Fig. 2B). Hypoglycemia severity, assessed by the HYPO score was markedly improved ($P = 0.001$) with all individuals recording a score <75th% from 6 months onward, compared to nine individuals with a HYPO score ≥75th% at baseline (Fig. 2C). A concomitant reduction in the number severe hypoglycemia events was observed, with 3 (3–10) events/person·year at baseline declining to an annualized rate of 0 (0–1) events/person·year over the 18-month follow-up period ($P = 0.005$) although four individuals experienced 5 severe hypoglycemia events between the 6- and 12-month assessment visits (Fig. 2D).

Glucose counterregulation response to hypoglycemia

The hypoglycemic clamp procedure resulted in comparable levels of hyperinsulinemia (Fig. 3A) and a per protocol reduction in plasma glucose (Fig. 3B) with overlap of baseline and stepped clamp conditions across baseline, 6- and 18-month visits. Prestudy overnight hypoglycemia was avoided in all participants through use of a standardized variable rate insulin infusion protocol. EGP remained suppressed by hyperinsulinemia with no change in response to hypoglycemia despite study intervention (Fig. 4A). In contrast, there was a weak trend toward a reduction ($P = 0.12$) in the exogenous glucose infusion rate required to maintain the final hour of hypoglycemia over the course of the study, with the glucose infusion rate at 18 months significantly less than at baseline ($P = 0.02$) (Table 3 and Fig. 4B).

This reduction in the exogenous glucose infusion rate was associated with a reduction in peripheral glucose disposal during insulin-induced hypoglycemia from baseline to 18 months

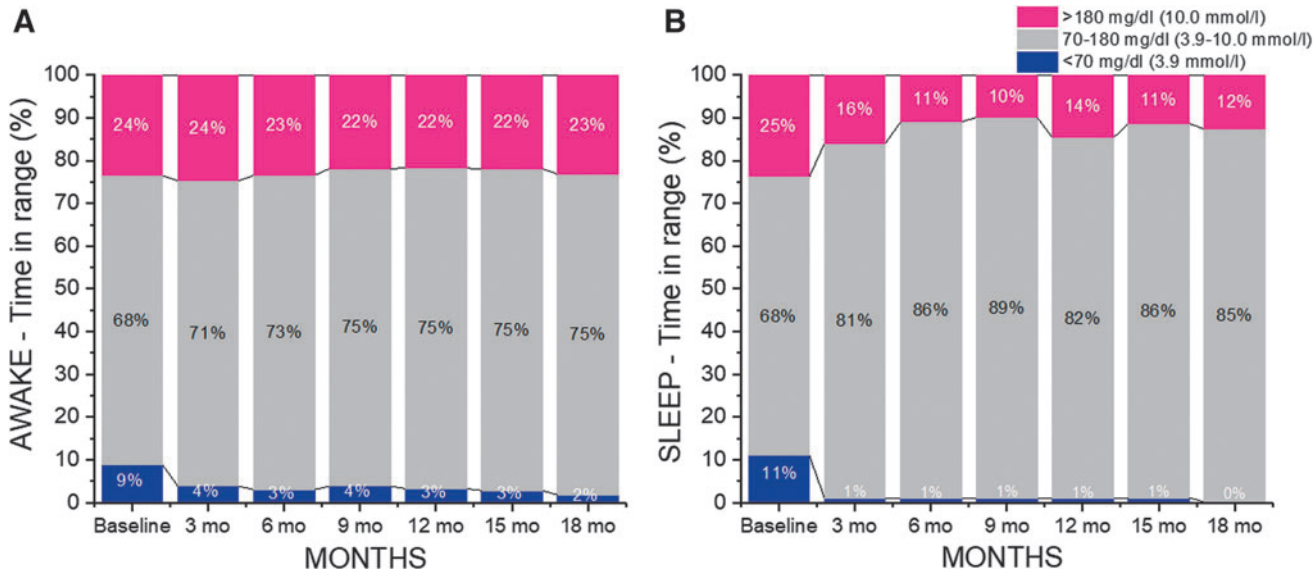

FIG. 1. Continuous glucose monitoring outcomes during time when awake **(A)** and when asleep **(B)**, before, and throughout intervention with AID. Data presented are median % time spent <70, >180 mg/dL, and in-range 70–180 mg/dL derived from HypoCount software with incorporated actigraphy data. AID, automated insulin delivery.

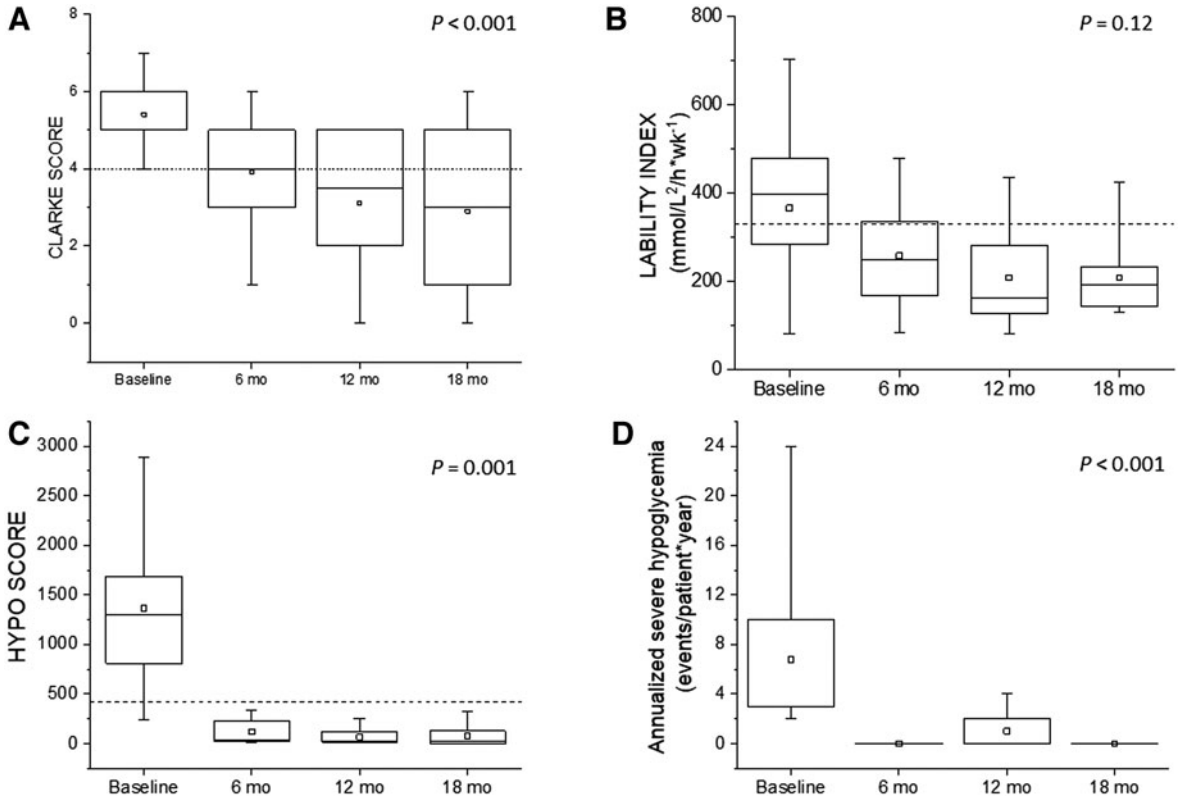

FIG. 2. Impaired awareness of hypoglycemia (Clarke score, **A**); glycemic lability (LI, **B**); HYPO score (**C**); and severe hypoglycemia event rate **(D)** outcomes before and throughout intervention with AID. Data presented as median (IQR) [range] and □ mean. Comparison of baseline and follow-up visits during intervention with AID by Friedman ANOVA. Dotted line represents **(A)** Clarke score ≥4, the threshold to define impaired awareness of hypoglycemia; **(B)** LI ≥329 and **(C)** HYPO score ≥423, the 75th percentiles of a normative group of 100 individuals with type 1 diabetes.[35] ANOVA, analysis of variance; HYPO, hypoglycemia severity; IQR, interquartile range; LI, lability index.

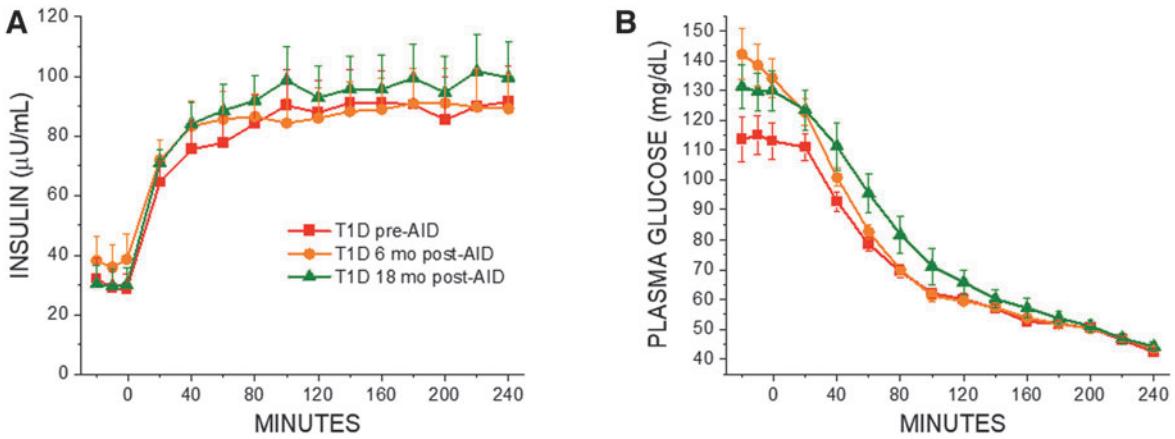

FIG. 3. Hyperinsulinemic hypoglycemic clamp procedure: plasma **(A)** insulin and **(B)** glucose in individuals with type 1 diabetes (T1D) (-■-) before and at (-●-) 6 months and (-▲-) 18 months after intervention with AID. Insulin was infused at a rate of 1 mU/(kg·min) with a variable rate infusion of 20% dextrose adjusted to achieve hourly stepped reductions in plasma glucose targeting 80, 65, 55, and 45 mg/dL. Data presented as mean ± SE. SE, standard error.

($P < 0.05$) (Table 3 and Fig. 4C). Consistent with the absent EGP response, no change was observed in the mobilization of substrates or fuel for gluconeogenesis including lactate (not shown) and free fatty acids (Fig. 4D), which although increased during the final hour of hypoglycemia were no different from baseline to the 6- and 18-month visits.

Counterregulatory hormone response to hypoglycemia

Consistent with long-standing type 1 diabetes no group exhibited a glucagon response to hypoglycemia with levels suppressed by hyperinsulinemia for the duration of the clamp procedure at all assessments (Table 3 and Fig. 5A). An

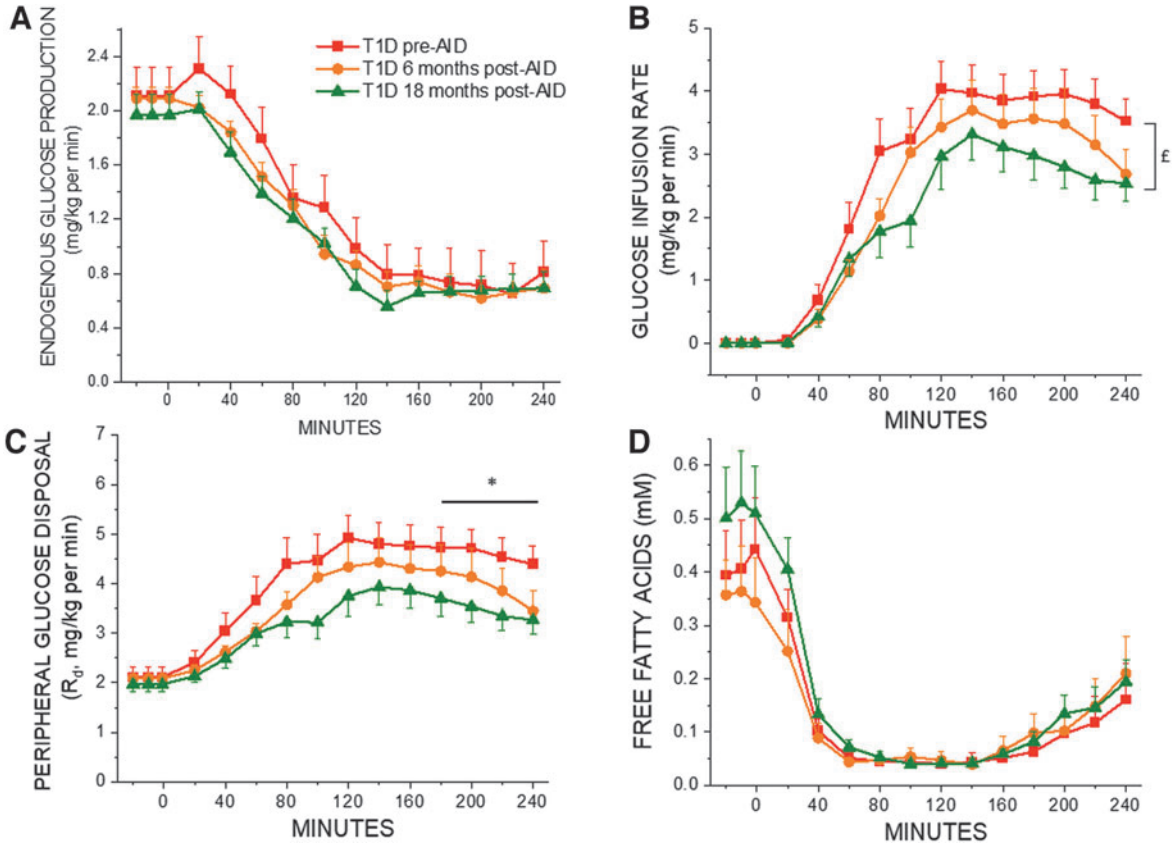

FIG. 4. Glucose counterregulatory fuel utilization and mobilization responses: **(A)** EGP; **(B)** glucose infusion rate; **(C)** peripheral glucose disposal, R_d; and **(D)** free fatty acids in individuals with type 1 diabetes (-■-) before and at (-●-) 6 months and (-▲-) 18 months after intervention with AID. Data are mean ± SE; Friedman ANOVA comparison of baseline, 6-, and 18-month responses, $^*P < 0.05$. Wilcoxon matched pairs comparison between baseline and 18-month timepoints when ANOVA $P \leq 0.10$, $^{£}P < 0.05$; $n = 9$ for baseline EGP and R_d data. EGP, endogenous glucose production.

Table 3. Magnitude of Glucose Counterregulatory, Hormonal, and Symptom Responses to Insulin-Induced Hypoglycemia During the Last 60 Min of the Hypoglycemic Clamp

	Baseline, n = *10*	*6 Months,* n = *10*	*18 Months,* n = *10*	P
Endogenous glucose production [mg/(kg·min)]	0.73 ± 0.23 (*n* = 9)	0.66 ± 0.13	0.69 ± 0.11	0.99
Glucose infusion rate [mg/(kg·min)]	3.8 ± 0.4	3.1 ± 0.5	2.6 ± 0.3[a]	0.12
R_d [mg/(kg·min)]	4.6 ± 0.4 (*n* = 9)	3.8 ± 0.5	3.4 ± 0.3[a]	0.03
Free fatty acids (mM)	0.12 ± 0.05	0.15 ± 0.05	0.16 ± 0.04	0.46
Δ Glucagon (pg/mL)	−14.4 ± 2.9	−11.3 ± 3.2	−11.1 ± 3.7	0.45
Pancreatic polypeptide (pmol/L)	62 ± 29	127 ± 44[b]	176 ± 58[a,c]	0.006
Epinephrine (pg/mL)	199 ± 53	332 ± 91[b]	386 ± 95[a] (*n* = 9)	0.001
Autonomic symptom score (Δ)	5.9 ± 1.8	6.0 ± 1.5	10.1 ± 2.2[a]	0.02

Data presented as mean ± SE. Comparison of baseline and follow-up visits during intervention with automated insulin delivery by Friedman ANOVA, and when $P \le 0.10$, comparison between timepoints was performed using the Wilcoxon matched pairs test.
[a]$P < 0.05$ denoted for baseline to 18 months.
[b]$P < 0.05$ denoted for baseline to 6 months.
[c]$P < 0.05$ denoted for 6–18 months.
R_d, peripheral glucose disposal; SE, standard error.

incremental improvement in the magnitude of the pancreatic polypeptide response to hypoglycemia was observed at 6 months with further recovery of the response at 18 months ($P < 0.01$) (Fig. 5B). The epinephrine response to hypoglycemia improved at 6 months and this effect was sustained at 18 months ($P = 0.001$) (Fig. 5C). Autonomic symptom score in response to hypoglycemia improved over the study by 18 months ($P < 0.05$) (Table 3 and Fig. 5D).

Assessment of autonomic symptom score components demonstrated an increase in sweating, anxiety, and a trend

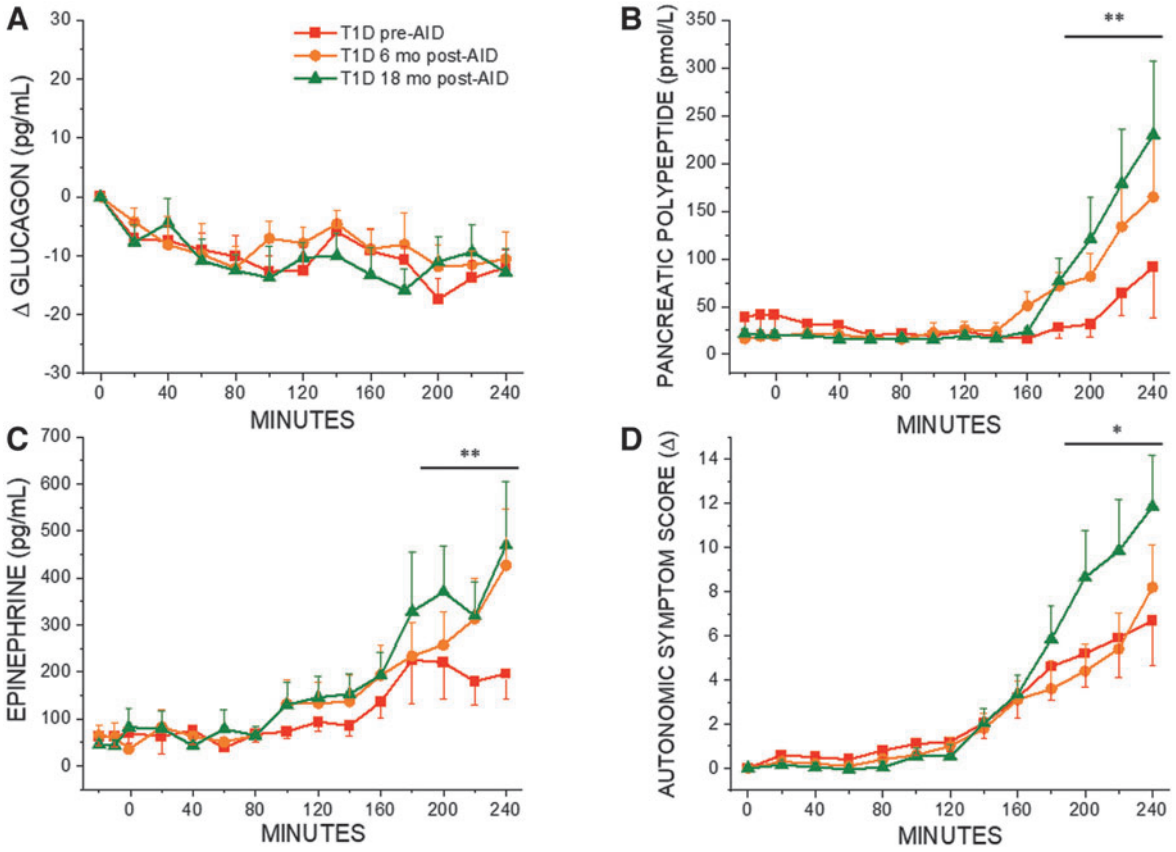

FIG. 5. Counterregulatory hormone and symptom responses to insulin-induced hypoglycemia: **(A)** glucagon; **(B)** pancreatic polypeptide; **(C)** epinephrine; and **(D)** autonomic symptoms in individuals with type 1 diabetes (T1D) (-■-) before and at (-●-) 6 months and (-▲-) 18 months after intervention with AID. Data are mean ± SE; Friedman ANOVA comparison of baseline, 6- and 18-month responses, $*P < 0.05$, $**P < 0.01$; $n = 9$ for 18-month epinephrine data.

toward increase in tremor between the baseline and 18-month visits ($P=0.02$; $P=0.04$; and $P=0.07$, respectively) (Supplementary Fig. S1).

Safety and adverse events

One adverse event related to the study intervention occurred over the 18-month study period with an emergency room presentation for cauterization of a bleeding sensor insertion site. Five severe hypoglycemia events occurred in four participants over the 18-month study period between the 6- and 12-month visits. These hypoglycemic events were managed by oral carbohydrate in all except in one individual who experienced two events, one requiring paramedic assistance and both necessitating glucagon administration. An additional severe hypoglycemia event requiring hospital admission for intravenous dextrose was experienced in the participant who withdrew from the study due to difficulties adapting to the new technology. Five other unexpected and unrelated adverse events were reported.

Discussion

These results indicate that AID can markedly reduce hypoglycemia exposure and improve glucose variability without compromising glycemic control in adults with long-standing type 1 diabetes complicated by IAH and a recent history of severe hypoglycemia. Severe hypoglycemia risk was reduced as assessed by a reduction in prospectively recorded severe hypoglycemia events, HYPO score, LBGI and improvement in clamp-derived measures of hypoglycemia awareness. Although EGP during hyperinsulinemic hypoglycemic clamp testing remained defective, a reduction in peripheral glucose disposal was observed, likely secondary to the increase in magnitude of the epinephrine response as epinephrine is well known to decrease glucose utilization by skeletal muscle and adipose tissue. In addition to epinephrine, improvements were observed in pancreatic polypeptide and autonomic symptom responses indicating at least partial recovery from HAAF. These physiologic improvements in glucose counterregulatory responses and hypoglycemia symptom recognition are important for defending against the development of low blood glucose in those at greatest risk for experiencing severe hypoglycemia.

Loss of the glucagon response to hypoglycemia early in type 1 diabetes pathogenesis leads to the reliance on epinephrine to increase EGP (predominantly hepatic) and reduce peripheral glucose utilization required for physiologic glucose counterregulation.[47,48] In long-standing type 1 diabetes the magnitude of the epinephrine response is diminished even in those with intact awareness of hypoglycemia with the resultant EGP response reduced in comparison to non-diabetic controls.[39] Our group previously assessed the effect of 18 months real-time CGM on counterregulatory response to hypoglycemia in long-standing type 1 diabetes[19] and demonstrated modest improvement in autonomic symptom and EGP responses to hyperinsulinemic hypoglycemic clamp testing despite no significant recovery in epinephrine response. Importantly, real-time CGM intervention did not eliminate hypoglycemia with significant ongoing exposure (>5% time spent <60 mg/dL) most notable during the nocturnal period.

In the present study, AID facilitated a marked reduction in hypoglycemia exposure with an 85% reduction in total time spent <70 mg/dL and 93% reduction in time <54 mg/dL, corresponding to 121 and 56 min less time spent in hypoglycemia <70 and <54 mg/dL, respectively, per day. Indeed, from 3 months onward the time spent in hypoglycemia was reduced to below thresholds previously shown to predict absent autonomic symptoms to hypoglycemic clamp testing.[39] Moreover, a marked 50-fold reduction in time spent in hypoglycemia (<70 mg/dL) during periods of sleep was achieved. This improvement in sleep-associated hypoglycemia was likely contributory to the effect of the intervention on reversal of HAAF,[23,24] with recovery of autonomic symptom response to insulin-induced hypoglycemia greater than that previously demonstrated with real-time CGM intervention alone.[10,19]

HbA_{1c} trended toward an increase over the study, likely due to the low average HbA_{1c} <7% in the study cohort at baseline. Nevertheless, from 3 months onward, the median percentage of time-in-range (70–180 mg/dL) exceeded the consensus target of 70%, well above the target of >50% recommended in those at high risk of severe hypoglycemia.[49] This change was predominantly driven by the early improvement in hypoglycemia avoidance on AID intervention over periods of sleep as previously reported[29,32] and acting alongside improvement in glucose variability, assessed by glucose SD and CV to reduce overall hypoglycemia risk.[29,30,32,50,51] These findings are supportive of the inclusion of AID[16,19,31] as part of the hierarchical management of problematic hypoglycemia in clinical practice.[52]

As anticipated, glucagon responses to hypoglycemia were absent and unchanged over the course of this study. However, despite a modest improvement in epinephrine, the EGP response, the primary outcome for this study, remained defective and unchanged throughout the intervention. Of note, the EGP response, in our previous study[19] improved with CGM intervention toward the baseline established in the present report (Supplementary Fig. S2B) supporting an effect of CGM intervention alone, used by the majority of participants in this study at baseline, on partial recovery of neural and/or hepatic autoregulatory responses to marked degrees of hypoglycemia which have been shown to occur independently of the neurohumoral response.[53]

Nevertheless, the improvement in epinephrine following AID has not led to a further hormone-dependent improvement in EGP and additional work will be of value to assess whether the EGP response can be improved through a greater degree of epinephrine recovery with further elimination of hypoglycemia or whether glucagon replacement approaches are needed as has been demonstrated by our group with restoration of the EGP response following pancreatic islet transplantation.[42]

Despite the absence of improvement in EGP, we did observe a reduction in peripheral glucose disposal, as demonstrated by a reduction in R_d during the hyperinsulinemic hypoglycemic clamp that contributes to glucose counterregulation by preserving glucose availability to support vital organ functioning. This reduction in peripheral glucose disposal is best attributed to epinephrine-mediated effects to decrease glucose utilization in peripheral tissues such as skeletal muscle and adipose.[7] In addition, the reduced peripheral glucose disposal may also be driven, in part, by an improvement in peripheral beta-adrenergic sensitivity.

Fritsche et al. utilized isoproterenol testing and hypoglycemic clamp procedures in 10 men with type 1 diabetes complicated by IAH to show improved autonomic symptom response and beta-adrenergic sensitivity without improvement in epinephrine response following 4 months of strict hypoglycemia avoidance.[54] Thus, the strict hypoglycemia avoidance demonstrated in the present study may have led to reduced peripheral glucose disposal through both the observed increase in epinephrine response to insulin-induced hypoglycemia and possibly enhanced epinephrine action.

Despite an early reduction in hypoglycemia exposure with AID, improvements in the pancreatic polypeptide, epinephrine, and autonomic symptom responses continued from 6 to 18 months on intervention. This continued improvement in counterregulatory responses supports the sustained use of AID devices to achieve reversal of HAAF. Burckhardt et al., performed a randomized cross-over study assessing the effect of HCL (MiniMed 670G) compared to standard insulin pump therapy on counterregulatory response to hypoglycemia in 17 individuals with type 1 diabetes complicated by IAH (based on Gold score), a third of whom were utilizing real-time CGM at baseline, and noted improvement in autonomic (4 components: sweating, tremor, anxiety, and palpitations) and neuroglycopenic symptoms but not epinephrine following 8 weeks of intervention.[33]

Improvement in autonomic symptom generation but not epinephrine secretion in response to insulin-induced hypoglycemia during short-term hypoglycemia avoidance had previously been reported in individuals with long-duration type 1 diabetes.[55] This disassociation between neurogenic symptom and epinephrine recovery is likely explained by different mechanisms contributing to impaired autonomic symptoms that are predominantly sympathetic neural in origin,[56] and impaired epinephrine secretion that depends on the secretory capacity of the adrenal medulla.[8] The present study supports that at least 6 months of marked hypoglycemia avoidance is likely necessary to improve the epinephrine response to insulin-induced hypoglycemia in long-standing type 1 diabetes.

We previously showed with less complete avoidance of hypoglycemia achieved with real-time CGM that autonomic symptoms in response to insulin-induced hypoglycemia improved modestly after 6 and 18 months intervention without improvement in the epinephrine response.[19] Interestingly in the present study, our participants who had all used CGM at baseline exhibited an autonomic symptom response to insulin-induced hypoglycemia similar to that achieved after 18 months intervention with CGM in our previous study (Supplementary Fig. S2A). Importantly, the greater reduction in hypoglycemia exposure in the present study with AID intervention was associated with even further restoration of autonomic symptoms and was sufficient after 6 months to improve epinephrine secretion that was maintained over 18 months (Fig. 5C).

When examining the 6 component symptoms used to calculate autonomic symptom score in our study (Supplementary Fig. S1), incremental changes in sweating and tremor were observed at 6 months and reached significance for change over the course of the study.[41,56] Consistent with previous reports,[56] tingling was a less sensitive measure to hypoglycemia and hunger appeared a poorly specific marker of autonomic symptoms,[56] declining at 6 months before returning to baseline at 18 months. In addition to the autonomic symptom scale used, the older age and high baseline use of real-time CGM in the present study cohort may account for the longer duration of intervention required for a significant improvement in autonomic symptom response compared to that observed by Burckhardt et al.[33]

Nevertheless, the autonomic symptom and pancreatic polypeptide response of the present cohort at 18 months is similar in magnitude to data from nondiabetic controls and individuals with type 1 diabetes and intact hypoglycemia awareness, with recovery of the epinephrine response still less than in nondiabetic controls but similar to that of individuals with type 1 diabetes and intact hypoglycemia awareness.[39]

Both the sympathetic and parasympathetic arms of the autonomic nervous system are affected by HAAF.[7] While the sympathetic nervous system is more important for the glucose counterregulatory response, impaired parasympathetic activation as demonstrated by a defective pancreatic polypeptide response to insulin-induced hypoglycemia has been shown to specifically identify individuals with type 1 diabetes and defective glucose counterregulation.[57] In more recent work, our group has shown that the pancreatic polypeptide response to hypoglycemia is correlated with other physiologic counter-regulatory responses in type 1 diabetes,[39] and most strongly with the autonomic symptom response that is primarily neurally mediated. Thus, the pancreatic polypeptide response can serve as an additional and potentially more objective marker of the presence of HAAF and its recovery.

Despite overall improvement in the epinephrine response to hypoglycemia, we observed evidence of response heterogeneity at least partially explained by a hyperbolic relationship between the change in epinephrine response over the study and percentage of time spent in hypoglycemia as a measure of on-going exposure to hypoglycemia (Supplementary Fig. S3). This suggests more marked avoidance of hypoglycemia on AID intervention is associated with greater recovery of counterregulatory epinephrine secretion. This association may be mediated through incremental recovery of sympathoadrenal synaptic plasticity as recurrent hypoglycemia has been shown to drive negative regulators of tyrosine hydroxylase activity to suppress adrenal chromaffin epinephrine synthesis and release.[8]

Furthermore, we observed a strong negative linear relationship between diabetes duration and improvement in the epinephrine response. This relationship was stronger at 18 months than 6 months, suggesting that diabetes duration may be a limiting factor to epinephrine recovery, especially when marked hypoglycemia avoidance has already been achieved. For individuals with persistent counterregulatory defects, additional psychobehavioral intervention may be of value to support a targeted reduction in hypoglycemia exposure, especially during daytime periods[52] when varying nutrient intake and activity levels challenge current AID systems. Indeed, the trend to an increase in percentage of insulin delivered as a bolus on AID in this study (Supplementary Table S1) may suggest persisting risk-behaviors off-set by HCL algorithm adjustments to suspend basal insulin delivery.

The limitations of this study include the small sample size and the absence of a control group. However, it would have been ethically questionable and unlikely feasible to include a control group of individuals already on CGM with IAH

experiencing severe hypoglycemia events restricted from accessing commercially available AID. Nevertheless, AID systems may not be appropriate for all, as evidenced by the one individual dropped from the study who was unable to adjust to the use of new technology. The 18-month period of observation replicated previous cohort studies from our group,[19,38] allowing for historical comparison of outcomes to intervention (Supplementary Fig. S2).

In addition to the long and complete observation period, this study benefits from robust methodology, including paired CGM and wrist actigraphy data for assessment of hypoglycemia exposure during sleep and gold-standard hyperinsulinemic hypoglycemic clamp testing with assessment of glucose counterregulation by the use of a stable glucose isotope tracer. Measures of neuropathy of interest in predicting response to intervention were not formally assessed. While there is mixed evidence of the importance of autonomic neuropathy in IAH and HAAF,[58,59] it has been shown that measures of peripheral neuropathy may predict persistence of recurrent severe hypoglycemia despite intervention,[60] and of the two participants with a documented clinical history of peripheral neuropathy at baseline, both had persistent IAH by Clarke score over the study.

In conclusion, AID enabled a sustained reduction of hypoglycemia exposure and improved glucose variability especially during sleep. The marked hypoglycemia avoidance was associated with improvement in pancreatic polypeptide, epinephrine, and autonomic symptom responses to insulin-induced hypoglycemia over the 18 months of intervention with a reduction in peripheral glucose utilization. While no improvement was seen in the EGP response indicating continued impairment of physiologic defense against hypoglycemia, the reduction in peripheral glucose disposal, likely consequent to the increased epinephrine secretion during hypoglycemia, evidences partial improvement in glucose counterregulation that may contribute to the clinical reduction in hypoglycemia with AID observed here in those with long-standing type 1 diabetes complicated by IAH.

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Authors' Contributions

A.J.F. was responsible for data analysis and preparing the first draft of the manuscript. S.I. supported data collection and performed the initial exploratory analyses. A.J.P., C.D.-B., and A.J.F. performed study visits and along with H.-L.N. were responsible for data collection. A.M., S.K.M., and N.G. were responsible for analysis and interpretation of actigraphy and sleep data. S.J., J.W., and I.L. supported CGM data collection and analysis. M.R.R was responsible for study design and is the guarantor of this study, has full access to the data and takes responsibility for the integrity and accuracy of the data analysis. All authors reviewed and edited the article.

Author Disclosure Statement

The authors have nothing to disclose.

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Supplementary Material

Supplementary Figure S1
Supplementary Figure S2
Supplementary Figure S3
Supplementary Table S1

References

1. American Diabetes Association Professional Practice Committee, Draznin B, Aroda VR, et al. 6. Glycemic targets: Standards of medical care in diabetes—2022. Diabetes Care 2022;45(Suppl 1):S83–S96.
2. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes 2008;57(12):3169–3176.
3. Raju B, Cryer PE. Loss of the decrement in intraislet insulin plausibly explains loss of the glucagon response to hypoglycemia in insulin-deficient diabetes—Documentation of the intraislet insulin hypothesis in humans. Diabetes 2005; 54(3):757–764.
4. Arbelaez AM, Xing D, Cryer PE, et al. Blunted glucagon but not epinephrine responses to hypoglycemia occurs in youth with less than 1 yr duration of type 1 diabetes mellitus. Pediatr Diabetes 2014;15(2):127–134.
5. Heller SR, Cryer PE. Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. Diabetes 1991;40(2):223–226.
6. Dagogo-Jack SE, Craft S, Cryer PE. Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. J Clin Invest 1993;91(3):819–828.

7. Cryer PE. Mechanisms of sympathoadrenal failure and hypoglycemia in diabetes. J Clin Invest 2006;116(6):1470–1473.
8. Ma Y, Wang Q, Joe D, et al. Recurrent hypoglycemia inhibits the counterregulatory response by suppressing adrenal activity. J Clin Invest 2018;128(9):3866–3871.
9. Cryer PE. Hypoglycemia-associated autonomic failure in diabetes. Handb Clin Neurol 2013;117:295–307.
10. Rickels MR. Hypoglycemia-associated autonomic failure, counterregulatory responses, and therapeutic options in type 1 diabetes. Ann N Y Acad Sci 2019;1454(1):68–79.
11. Pedersen-Bjergaard U, Pramming S, Heller SR, et al. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: Influence of risk markers and selection. Diabetes Metab Res Rev 2004;20(6):479–486.
12. Weinstock RS, Xing DY, Maahs DM, et al. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: Results from the T1D Exchange clinic registry. J Clin Endocrinol Metab 2013;98(8):3411–3419.
13. Gagnum V, Stene LC, Jenssen TG, et al. Causes of death in childhood-onset type 1 diabetes: Long-term follow-up. Diabet Med 2017;34(1):56–63.
14. Lacy ME, Gilsanz P, Eng C, et al. Severe hypoglycemia and cognitive function in older adults with type 1 diabetes: The study of longevity in diabetes (SOLID). Diabetes Care 2020;43(3):541–548.
15. Fanelli CG, Epifano L, Rambotti AM, et al. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. Diabetes 1993;42(11):1683–1689.
16. Leelarathna L, Little SA, Walkinshaw E, et al. Restoration of self-awareness of hypoglycemia in adults with long-standing type 1 diabetes: Hyperinsulinemic-hypoglycemic clamp substudy results from the HypoCOMPaSS trial. Diabetes Care 2013;36(12):4063–4070.
17. de Zoysa N, Rogers H, Stadler M, et al. A psychoeducational program to restore hypoglycemia awareness: The DAFNE-HART pilot study. Diabetes Care 2014;37(3):863–866.
18. Little SA, Leelarathna L, Walkinshaw E, et al. Recovery of hypoglycemia awareness in long-standing type 1 diabetes: A multicenter 2×2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). Diabetes Care 2014;37(8):2114–2122.
19. Rickels MR, Peleckis AJ, Dalton-Bakes C, et al. Continuous glucose monitoring for hypoglycemia avoidance and glucose counterregulation in long-standing type 1 diabetes. J Clin Endocrinol Metab 2018;103(1):105–114.
20. Choudhary P, Ramasamy S, Green L, et al. Real-time continuous glucose monitoring significantly reduces severe hypoglycemia in hypoglycemia-unaware patients with type 1 diabetes. Diabetes Care 2013;36(12):4160–4162.
21. van Beers CA, DeVries JH, Kleijer SJ, et al. Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): A randomised, open-label, crossover trial. Lancet Diabetes Endocrinol 2016;4(11):893–902.
22. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): A multicentre, randomised controlled trial. Lancet 2018;391(10128):1367–1377.
23. Jones TW, Porter P, Sherwin RS, et al. Decreased epinephrine responses to hypoglycemia during sleep. N Engl J Med 1998;338(23):1657–1662.
24. Banarer S, Cryer PE. Sleep-related hypoglycemia-associated autonomic failure in type 1 diabetes: Reduced awakening from sleep during hypoglycemia. Diabetes 2003;52(5):1195–1203.
25. Zekarias K, Kumar A, Moheet A, et al. Real life evidence that impaired awareness of hypoglycemia persists for years in patients with type 1 diabetes. J Diabetes Complications 2018;32(12):1097–1099.
26. Lin YK, Hung M, Sharma A, et al. Impaired awareness of hypoglycemia continues to be a risk factor for severe hypoglycemia despite the use of continuous glucose monitoring system in type 1 diabetes. Endocr Pract 2019;25(6):517–525.
27. Infante M, Baidal DA, Rickels MR, et al. Dual-hormone artificial pancreas for management of type 1 diabetes: Recent progress and future directions. Artif Organs 2021;45(9):968–986.
28. Ruan Y, Bally L, Thabit H, et al. Hypoglycaemia incidence and recovery during home use of hybrid closed-loop insulin delivery in adults with type 1 diabetes. Diabetes Obes Metab 2018;20(8):2004–2008.
29. Akturk HK, Giordano D, Champakanath A, et al. Long-term real-life glycaemic outcomes with a hybrid closed-loop system compared with sensor-augmented pump therapy in patients with type 1 diabetes. Diabetes Obes Metab 2020;22(4):583–589.
30. Brown SA, Kovatchev BP, Raghinaru D, et al. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med 2019;381(18):1707–1717.
31. Bosi E, Choudhary P, de Valk HW, et al. Efficacy and safety of suspend-before-low insulin pump technology in hypoglycaemia-prone adults with type 1 diabetes (SMILE): An open-label randomised controlled trial. Lancet Diabetes Endocrinol 2019;7(6):462–472.
32. Anderson SM, Buckingham BA, Breton MD, et al. Hybrid closed-loop control is safe and effective for people with T1D who are at moderate to high risk for hypoglycemia. Diabetes Technol Ther 2019;21:356–363.
33. Burckhardt MA, Abraham MB, Dart J, et al. Impact of hybrid closed loop therapy on hypoglycemia awareness in individuals with type 1 diabetes and impaired hypoglycemia awareness. Diabetes Technol Ther 2021;23(7):482–490.
34. Clarke WL, Cox DJ, Gonder-Frederick LA, et al. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care 1995;18(4):517–522.
35. Ryan EA, Shandro T, Green K, et al. Assessment of the severity of hypoglycemia and glycemic lability in type 1 diabetic subjects undergoing islet transplantation. Diabetes 2004;53(4):955–962.
36. Senior PA, Bellin MD, Alejandro R, et al. Consistency of quantitative scores of hypoglycemia severity and glycemic lability and comparison with continuous glucose monitoring system measures in long-standing type 1 diabetes. Diabetes Technol Ther 2015;17(4):235–242.
37. Malone SK, Peleckis AJ, Grunin L, et al. Characterizing glycemic control and sleep in adults with long-standing type 1 diabetes and hypoglycemia unawareness initiating hybrid closed loop insulin delivery. J Diabetes Res 2021;2021:6611064.

38. Rickels MR, Peleckis AJ, Markmann E, et al. Long-term improvement in glucose control and counterregulation by islet transplantation for type 1 diabetes. J Clin Endocrinol Metab 2016;101(11):4421–4430.
39. Flatt AJ, Chen E, Peleckis AJ, et al. Evaluation of clinical metrics for identifying defective physiologic responses to hypoglycemia in long-standing type 1 diabetes. Diabetes Technol Ther 2022;24(10):737–748.
40. Bernroider E, Brehm A, Krssak M, et al. The role of intramyocellular lipids during hypoglycemia in patients with intensively treated type 1 diabetes. J Clin Endocrinol Metab 2005;90(10):5559–5565.
41. Towler DA, Havlin CE, Craft S, et al. Mechanism of awareness of hypoglycemia. Perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. Diabetes 1993;42(12):1791–1798.
42. Rickels MR, Fuller C, Dalton-Bakes C, et al. Restoration of glucose counterregulation by islet transplantation in long-standing type 1 diabetes. Diabetes 2015;64(5):1713–1718.
43. Lan KK, Wittes J. The B-value: A tool for monitoring data. Biometrics 1988;44(2):579–585.
44. Monnier L, Wojtusciszyn A, Molinari N, et al. Respective contributions of glycemic variability and mean daily glucose as predictors of hypoglycemia in type 1 diabetes: Are they equivalent? Diabetes Care 2020;43(4):821–827.
45. Kovatchev BP, Cox DJ, Gonder-Frederick LA, et al. Assessment of risk for severe hypoglycemia among adults with IDDM: Validation of the low blood glucose index. Diabetes Care 1998;21(11):1870–1875.
46. Sepulveda E, Poinhos R, Nata G, et al. Differentiating hypoglycemia awareness status from hypoglycemia experience in tools for measuring impaired awareness of hypoglycemia. Diabetes Technol Ther 2020;22(7):541–545.
47. Cryer PE, Gerich JE. Relevance of glucose counterregulatory systems to patients with diabetes: Critical roles of glucagon and epinephrine. Diabetes Care 1983;6(1): 95–99.
48. Rizza RA, Cryer PE, Gerich JE. Role of glucagon, catecholamines, and growth hormone in human glucose counterregulation. Effects of somatostatin and combined alpha- and beta-adrenergic blockade on plasma glucose recovery and glucose flux rates after insulin-induced hypoglycemia. J Clin Invest 1979;64(1):62–71.
49. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the international consensus on time in range. Diabetes Care 2019;42(8):1593–1603.
50. Da Silva J, Bosi E, Jendle J, et al. Real-world performance of the MiniMed 670G system in Europe. Diabetes Obes Metab 2021;23(8):1942–1949.
51. Rodbard D. Hypo- and hyperglycemia in relation to the mean, standard deviation, coefficient of variation, and nature of the glucose distribution. Diabetes Technol Ther 2012;14(10):868–876.
52. Choudhary P, Rickels MR, Senior PA, et al. Evidence-informed clinical practice recommendations for treatment of type 1 diabetes complicated by problematic hypoglycemia. Diabetes Care 2015;38(6):1016–1029.
53. Bolli G, De Feo P, Perriello G, et al. Role of hepatic autoregulation in defense against hypoglycemia in humans. J Clin Invest 1985;75(5):1623–1631.
54. Fritsche A, Stefan N, Haring H, et al. Avoidance of hypoglycemia restores hypoglycemia awareness by increasing beta-adrenergic sensitivity in type 1 diabetes. Ann Intern Med 2001;134(9 Pt 1):729–736.
55. Dagogojack S, Rattarasarn C, Cryer PE. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. Diabetes 1994;43(12):1426–1434.
56. DeRosa MA, Cryer PE. Hypoglycemia and the sympathoadrenal system: Neurogenic symptoms are largely the result of sympathetic neural, rather than adrenomedullary, activation. Am J Physiol Endocrinol Metab 2004;287(1): E32–E41.
57. White NH, Gingerich RL, Levandoski LA, et al. Plasma pancreatic-polypeptide response to insulin-induced hypoglycemia as a marker for defective glucose counterregulation in insulin-dependent diabetes-mellitus. Diabetes 1985;34(9):870–875.
58. Hoeldtke RD, Boden G. Epinephrine secretion, hypoglycemia unawareness, and diabetic autonomic neuropathy. Ann Intern Med 1994;120(6):512–517.
59. Ryder RE, Owens DR, Hayes, TM, et al. Unawareness of hypoglycaemia and inadequate hypoglycaemic counterregulation: No causal relation with diabetic autonomic neuropathy. BMJ 1990;301:783–787.
60. Flatt AJS, Little SA, Speight J, et al. Predictors of recurrent severe hypoglycemia in adults with type 1 diabetes and impaired awareness of hypoglycemia during the HypoCOMPaSS study. Diabetes Care 2020;43(1):44–52.

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