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Technologies for diabetes

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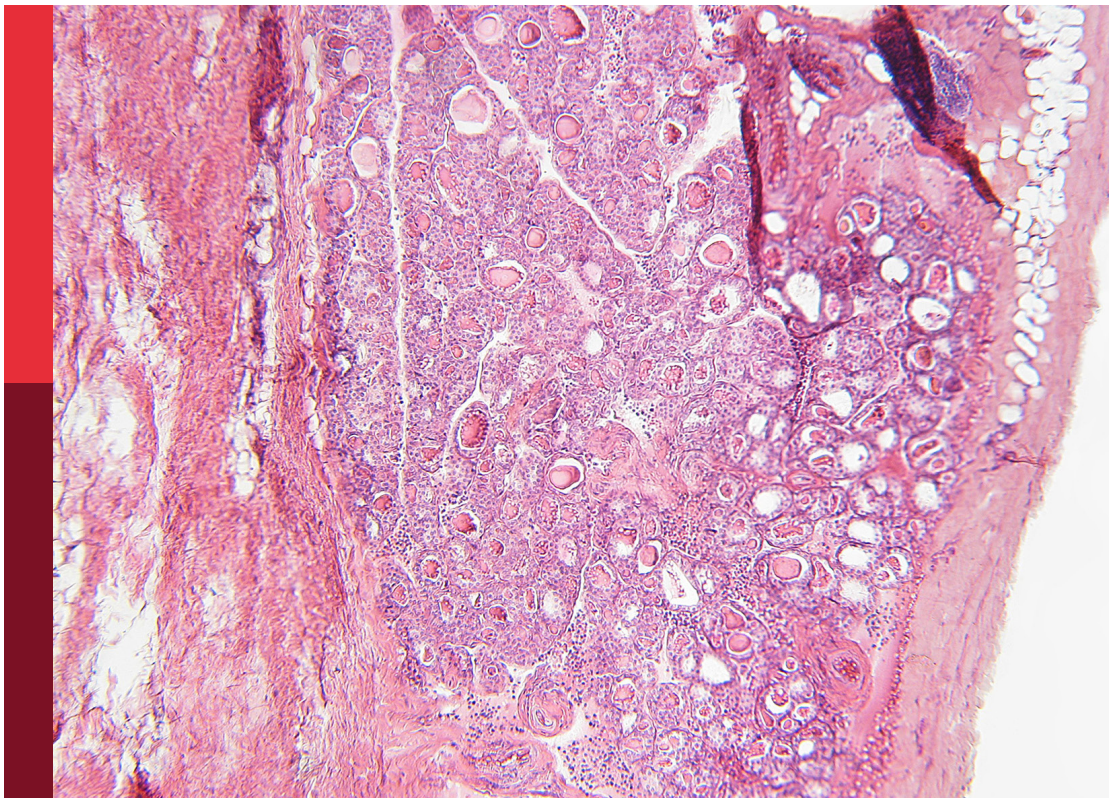

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Technologies for diabetes

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Editorial: Technologies for diabetes

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Editorial on the Research Topic
Technologies for diabetes

Much progress has been made in technologies for diabetes mellitus over the last decade. Continuous glucose monitoring (CGM) and flash glucose monitoring (FGM) systems have achieved high accuracy and reliability, yielding a large use worldwide. The development of progressively smarter closed-loop systems, which combine insulin pumps and glucose monitoring systems allows for the minimization of hypo- and hyperglycemia through automatic insulin delivery. This Research Topic encloses high-quality manuscripts on the topic.

In her review, Templer offers an interesting update about the closed-loop systems used in the treatment of type 1 diabetes. She traces the rapid progress from the past and their use in the present, focusing attention on what future therapeutic strategies will be, including fully closed-loop systems. Questions regarding faster-acting insulin or the addition of other hormones (such as glucagon) to mitigate the risk of hypoglycemia or more advanced algorithms are debated. She concludes that the answers lay in the next generation of closed-loop therapy, which will probably use a combination of different therapeutic options. The step from hybrid closed loop (HCL) to advanced HCL (AHCL) allows an improvement in blood glucose control which is shown by real-world studies.

Flash glucose monitoring (FGM) is a novel device type capable of showing interstitial glucose and trends on a reader in an on-demand fashion, with good reproducibility and similar value to blood glucose measurements (1). The use of FGM is associated with better glucose outcomes in adults with type 1 diabetes (2) but is effective in reducing HbA1c and glucose variability in children and adolescents as well (3). The key role of education in properly using these technologies is highlighted by Lee et al. They demonstrated that personalized and continuous education may significantly improve blood glucose control in adult patients.

FGM and its interpretation have been shown to be effective also in the management of physical activities, using glucose values and trends to adapt therapy before, during, or after exercise (4). In the study by Guo et al., benefits around the system, as well as proper usage, have been shown to be related to actually watching the glucose values, while a blinded use resulted in similar values to usual care. Furthermore, Hohendorff et al. showed through the Hypoglycemia Fear Survey II questionnaire that the use of FGM is associated also with less fear of hypoglycemia, reducing diabetes distress. On the other hand, Franceschi et al. showed that the early use of FGM (within the first month after type 1 diabetes onset) plays an important role in metabolic control and quality of life in children and adolescents. In this real-world study, the authors showed a reduction of HbA1c during the first year and interestingly a longer partial remission phase in the group of patients with early use of FGM compared to the control group. This Research Topic also includes a paper on the effectiveness of FGM in adults with type 2 diabetes on premixed insulin therapy by Yan et al. They showed that real-time FGM improves blood glucose control and diabetes self-care better than retrospective FGM.

Diabetes is the main cause of chronic kidney disease (CKD), and it is mandatory to achieve optimal glycemic control with the aim to reduce the risk of progression of CKD and related death. It has been recently described that the use of CGM is recommended in patients with advanced CKD (5), but unfortunately, data are lacking in this population. Ling et al. review literature data and show that HbA1c and alternative glycemic markers have limitations in patients with advanced CKD, and thanks to CGM-derived glucose management indicator (GMI), it is now possible to monitor the glycemic status with better precision in these patients.

Using last-generation systems to time AHCL, an improvement in main glucose outcomes (namely time below –TBR-, in –TIR-, and above range - TAR) compared to Sensor Augmented Pump (SAP) therapy in a population of patients with type 1 diabetes has been demonstrated. Control-IQ (CIQ) system is one of the algorithms recently approved for children and adults with diabetes (6). The group by Bassi et al. published three papers about the effectiveness of new algorithms in blood glucose management. In the first paper, they investigated the effectiveness of a new function of CIQ in the improvements of glucose values during nighttime (Sleep Activity). They showed that it seems to be less effective than the standard CIQ algorithm in terms of TIR. In a head-to-head study, they compare two AHCL systems, Tandem t:slim X2 Control IQ™ system (Tandem Inc., San Diego, California) and the Minimed™ 780G system (Minimed Medtronic, Northridge, California), in 90 patients (aged 5 to 65 years) with type 1 diabetes enrolled in a retrospective dual-center study. On the basis of their results, the authors report that the Minimed 780G system seems more effective in managing hyperglycemia, while Tandem Control-IQ reduces the number of hypoglycemic episodes and glucose variability and that both systems achieve the recommended glycemic targets (Bassi et al.). On the other hand, the same authors show in their single-center study that after 1 year of use, the CIQ system allowed a TIR of 68%, which is significantly lower than the MiniMed 780G (71%) (Bassi et al.).

In type 1 diabetes pediatric real-world settings, a superiority of HCL systems versus other technologies as demonstrated by higher levels of time spent in the target glucose range and the reduction of both hypoglycemic and hyperglycemic events over a 1-year period (7) is reported.

Recently, Lombardo et al. (8) conducted a multicenter observational real-world 6-month study with the aim to investigate glycemic outcomes in a large cohort of children and adolescents with type 1 diabetes over the first 6-month use of MiniMed™ 780G, and the study shows that the most relevant targets are achieved according to International Consensus. Both at 3 and 6 months, 39.6% of participants reached all the glycemic targets (TIR, CV, GMI, and TBR). Authors also reported that older age, shorter disease duration, and shorter active insulin time are significant predictors of optimal glucose control (8).

The effectiveness of a SAP with predictive low glucose suspend (SmartGuard™) versus a pump with independent FGM (Freestyle libre®) has been investigated in 6 to 14 years old children with type 1 diabetes. No significant difference in blood glucose control is reported among the two groups, but the decision of all families to continue with CGM after the study suggests that this system has a positive impact on diabetes burden, preferring the SmartGuard® system (Schierloh et al.).

Technologies may also reveal how patients manage special events in their daily life. Molveau et al. investigated the impact of daily physical activity on nocturnal hypoglycemia through a blinded CGM. They concluded that patients do not properly report insulin boluses and compensation strategies, suggesting that appropriate education is still needed in such situations. CGM may be used also to investigate blood glucose control in the diagnostic work-up. In their paper, Zhang et al. compared CGM metrics between patients with type 2 diabetes and latent autoimmune diabetes (LADA). Interestingly, they showed that patients with LADA presented wider glucose variation and thus they suggested that data from CGM could be helpful for the diagnostic work-up in a patient with glucose control impairment.

Technologies have backlashes as well and dermatological complication is one of the most frequent. Skin exposure to chemical and mechanical agents may lead to skin disorders and, overall, to contact dermatitis. In their observational study, Passanisi et al. described the clinical impact of this specific complication, providing helpful information for clinicians about the current management and the possible effect of such problems.

Technologies for diabetes are a growing field of research and represent a great promise for patients with diabetes. We would like to end this Editorial by focusing the readers' attention on relevant data for clinical practice. Over the last 5 years, we passed from the HCL system (MiniMed 670G®), which allowed a TIR of approximately 65 to 70% and a TBR below 4% (9), to the new AHCL systems which allow a TIR of approximately 75% and a

further reduction in TBR (10, 11). Blood glucose control improves as fast as technologies for diabetes go on.

Author contributions

All authors listed, have made substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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A Comparison of Two Hybrid Closed-Loop Systems in Italian Children and Adults With Type 1 Diabetes

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Tandem Control-IQ and Minimed 780G represent the most Advanced Hybrid Closed Loop (AHCL) systems currently available in pediatric and adult subjects with Type 1 Diabetes (T1D). We retrospectively compared clinical and continuous glucose monitoring data from 51 patients who upgraded to Minimed 780G system and have completed 1-month observation period with data from 39 patients who upgraded to Tandem Control-IQ. Inverse probability weighting was used to minimize the basal characteristics imbalances. Both AHCL systems showed a significant improvement in glycemic parameters. Minimed 780G group achieved higher TIR increase (p= 0.004) and greater reduction of blood glucose average (p= 0.001). Tandem Control-IQ system significantly reduced the occurrence of TBR (p= 0.010) and the Coefficient of Variation of glucose levels (p= 0.005). The use of ACHL systems led to a significant improvement of glycemic control substantially reaching the International recommended glycemic targets. Minimed 780G appears to be more effective in managing hyperglycemia, while Tandem Control-IQ seems to be more effective in reducing time in hypoglycemia.

Keywords: AHCL (advanced hybrid closed loop), type 1 diabetes, CGM (continuous glucose monitoring), CSII (continuous subcutaneous insulin infusion), TIR (time in range)

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INTRODUCTION

The management of type 1 diabetes (T1D) has changed substantially over the past five years. Evolving technologies offer the potential to improve glycemic control by reducing burden and risk of hypoglycemia and hyperglycemia and decrease the rate of diabetes complications (1–3). Since FDA approved the first Hybrid Closed Loop (HCL) system in September 2016, further advanced devices have been commercialized. These systems integrate insulin infusion with continuous glucose monitoring (CGM) (4, 5).

Advanced Hybrid Closed Loop (AHCL) systems combine automated basal rate and correction boluses to keep glycemic values in a target range (6, 7). Patients are only re-quired to estimate carbohydrate consumption for meal boluses.

In Italy two AHCL systems are provided by the national health system and approved for both pediatric and adult patients: the Tandem t:slim X2 Control IQ™ system (Tandem Inc., San Diego, California); and the Minimed™ 780G system (Minimed Medtronic, Northridge, California).

The Minimed 780G pump is integrated with the Guardian Sensor 3 (Medtronic, Northridge, California), the Tandem Control-IQ is associated with the Dexcom G6 (Dexcom Inc., San Diego, CA) system.

These two systems use different glycemic targets: 100, 110 or 120 mg/dl for Minimed 780G system (personalization based on patients' choice); 112.5-160 mg/dl for Tandem Control-IQ. The Minimed 780G system has an "exercise" target at 150 mg/dl, similar to Tandem (140-160 mg/dl); Control-IQ has a fixed "sleep" target mode of 112.5-120 mg/dl. In the sleep mode the system does not deliver correction boluses.

The systems adopt different algorithms for correction boluses. In particular, the Minimed 780G system can carry out up to 12 correction boluses per hour and decide the basal rate automatically. The Tandem system is able to deliver a maximum of one correction bolus per hour and modifies the basal profile based on a 30-minute prediction horizon of glucose levels.

Furthermore, the Minimed 780G system calculates by itself the daily insulin total in order to define the insulin sensitivity factor. The patient can only change the insu-lin-to-carbohydrate (I/CHO) ratios for meal boluses and the active insulin time.

The Tandem Control IQ system uses the patient's weight and daily insulin total to cal-culate the basal insulin rate. The user can change the basal rate, I:C ratios for meal boluses and insulin sensitivity factor.

Currently, the parameters indicating a good glycemic control are evaluated through the analysis of CGM data (8). A good glycemic control is defined by the International Consensus as: Time in Range (TIR) (70-180 mg/dl) > 70%, Time Below Range (TBR) (<70 mg/dl) < 4%, TBR<54 mg/dl < 1%, Time Above Range (TAR) (>180 mg/dl) < 25%, TAR>250 mg/dl <1% (9).

Data from early studies about Tandem Control-IQ or Minimed 780G in adolescents and adults with type 1 diabetes are encouraging in terms of glycemic outcomes and patient satisfaction (10, 11). The results of a one-year real-world use of Tandem Control-IQ system (12) confirmed the conclusions reached by the two pivotal trials (10, 11). The use of Control-IQ technology increased time in range (TIR 70–180 mg/dl) from 63.2% at baseline to 73.5% at 12 months ($p < 0,001$) in a sample of 7813 patients with T1D (12).

Two multicenter randomized trials in children, adolescents and adults demonstrated the efficacy of Control-IQ compared to sensor-augmented pump (control group) (13, 14).

A recent study in children, that participated in a virtual educational camp, demonstrates an improvement of TIR with Control-IQ technology in comparison with Basal-IQ, a predictive low-glucose suspend (PLGS) algorithm (15). Likewise, the use of Minimed 780G system led to a reduction of time above range (TAR > 180 mg/dl) without increasing time below range (TBR < 70 mg/dl) in 52 patients (aged 15-65 years), that were well-controlled and experienced Minimed 640 users (16). These findings are supported by other evidence that demonstrates safety and effectiveness in controlling day and night glucose levels (17–19). The real-world use of Minimed 780G also provides an increased level of patient satisfaction (20).

Despite the emerging evidence on the efficacy of ACHL systems, there are no clinical studies comparing data on benefits and glycemic outcomes of Minimed 780G and Tandem Control-IQ.

The aim of this study was to compare glycemic control between Minimed 780G and Tandem Control-IQ users one month after starting the therapy.

MATERIALS AND METHODS

A retrospective dual center study was performed from October 2020 to April 2021. A total of 90 T1D patients, followed at the IRCCS G.Gaslini Pediatric Diabetology Center (Genoa, Italy) or San Martino Polyclinic Hospital Diabetes Clinic (Genoa, Italy), were upgraded to Minimed 780G or Tandem Control-IQ. The two diabetes centers involved in the study belong to the same university. and follow the same guidelines in terms of patient management and therapeutic education.

Patients were enrolled according to the following inclusion criteria: T1D diagnosis at least one-year prior to the study, insulin therapy with CSII or MDI, use of CGM with at least one-months' worth of data before and after starting the AHCL. Patients who dropped out of the AHCL system before one month of use were excluded.

The observational period has been divided in Time 0 (T0 – start day of AHCL) and Time 1 (T1 – one month of ACHL therapy). At T0, the following data were collected for each patient: demographical data (sex, date of birth, age), age at clinical onset of T1D, duration of disease and previous type of insulin therapy. At T0 and T1 we compared: glycated hemoglobin (HbA1c) values, and blood glucose control data of the previous 14 days, through the CGM data download (each patient participating in the study wore CGM in the 14 days before T0). The following parameters were evaluated: TIR, TAR, TAR > 250 mg/dl, TBR, TBR < 54 mg/dl, Coefficient of Variation (CV), Standard Deviation (SD) and percentage of sensor use. In this study, the analyses at T1 were performed with both systems in Auto Mode and by excluding the first two-weeks of the run-in phase. CGM data were collected using data download platforms based on the technology used (Carelink™, Tidepool™, Dexcom Clarity™).

All patients (or parents if age < 18 years) provided a written informed consent in accordance with EU regulation 2016/679 to participate in the study.

Mean and SD were used to summarize continuous variables, whereas count and percentages were used for categorical

variables. A separate linear regression model with baseline offset was used to estimate treatment effects on TIR, TAR, TAR>250, TBR, TBR<54, average glucose levels, SD and CV. Inverse probability weighting (IPW) was used to adjust estimates for potential baseline confounders: the subjects are weighted by the inverse of their probability to be assigned to their treatment (21). IPW was estimated by fitting a logistic regression model with the most unbalanced patients' characteristics between the two-treatment groups (TIR, HbA1c and age). For our primary analysis we assumed there was no interaction between current and previous treatment, we then ran an exploratory analysis to test this assumption. The IPW was calculated in the following way: I) a logistic regression model was fitted to determine the propensity of subjects to be treated with their treatment (either Minimed 780G or Tandem Control-IQ); II) based on the estimated model, probabilities were calculated for each participant; and III) the inverse of the probabilities was applied as weights in the linear regression models. IPW adjusted estimates were reported. In head-to-head comparisons, when Minimed 780G or Tandem Control-IQ subgroup-specific p values were reported we applied the Bonferroni adjustment for multiple comparisons.

To test the treatment effect difference among age groups, an interaction term between the treatment group and the age group was included in each regression model.

As sensitivity analysis, patients in treatment groups (Minimed 780G or Tandem Control-IQ) were matched to minimize the imbalance of the baseline characteristics. We used a 1:1 propensity score match performed with nearest neighbour algorithm on the most unbalanced characteristics of the patients between the two-treatment groups (TIR, HbA1c and age). Subsequent analyses were performed with and without adjustments for baseline characteristics that remained unbalanced after the matching (namely HbA1c) to allow further adjustments for residual confounding (**Supplementary Tables 1–3**).

An interaction term between current and previous treatment was considered to investigate the presence of any subgroup-specific effects and the p for interaction was reported for exploratory purposes. Two-sided α less than 0.05 was considered statistically significant. All statistical analyses were performed using R software version 4.0.2 (2020-06-22).

RESULTS

We collected the data of 90 patients (aged 5-65 years) from two Regional Pediatric and Adult Diabetology Centers (IRCCS G.Gaslini and San Martino Polyclinic Hospital, Genoa, Liguria). 51 of these patients (23 children and adolescents < 18 years) carried the Minimed 780G system and 39 (24 children and adolescents < 18 years) the Tandem-Control IQ system. The clinical characteristics of the population at baseline (T0) are summarized in **Table 1**.

At baseline, patients upgraded to Minimed 780G versus patients upgraded to Tandem Control-IQ presented unbalanced characteristics. Tandem users were younger (mean age 16.0 years vs 24.4; p=0.002), with earlier disease onset (mean age 7.8 years vs 11.2; p = 0.041) and shorter disease duration (mean 8.2 years vs 13.2; p = 0.041). Patients in Tandem group compared to patients in Minimed 780G group had lower baseline HbA1c (7.1% vs 7.8%; p=0.002); higher TIR (59.6% vs 52.4%; p=0.031) and lower average glucose (167.2mg/dl vs 181.5mg/dl; p=0.040).

The whole study population has been previously treated with MDI (18.0%), Sensor Augmented Pumps (SAP) (24.7%), PLGS (38.2%) or HCL pumps (19.1%).

TABLE 1 | Patient characteristics at baseline (T0), overall and by treatment group.

	Overall N = 90	Minimed 780G N = 51	Control-IQ N = 39	p
Male, N (%)	47 (52.2)	29 (56.9)	18 (46.2)	0.427
Age, Mean (SD)	20.7 (13.2)	24.4 (15.7)	16.0 (6.5)	0.002
5-11 years, N (%)	26 (28.9)	14 (27.5)	12 (30.8)	0.227
12-18 years, N (%)	21 (23.3)	9 (17.6)	12 (30.8)	
> 18 years, N (%)	43 (47.8)	28 (54.9)	15 (38.4)	
Age at disease onset, Mean (SD)	9.7 (7.8)	11.2 (9.4)	7.8 (4.3)	0.041
Disease duration (yrs), Mean (SD)	11.0 (9.4)	13.2 (10.3)	8.2 (7.1)	0.010
HbA1c (%), Mean (SD)	7.5 (0.9)	7.8 (1.0)	7.1 (0.7)	0.002
TIR (%), Mean (SD)	55.7 (15.5)	52.4 (16.2)	59.6 (13.9)	0.031
TAR (%), Mean (SD)	25.3 (10.4)	25.1 (11.4)	25.5 (9.2)	0.856
TAR250mgdl (%), Mean (SD)	14.7 (12.9)	16.8 (15.0)	12.3 (9.4)	0.107
TBR (%), Mean (SD)	2.1 (1.9)	2.0 (1.7)	2.2 (2.1)	0.587
TBR54mgdl (%), Mean (SD)	0.6 (1.0)	0.6 (1.0)	0.7 (1.0)	0.558
Average glucose (mg/dl) (SD)	174.9 (32.2)	181.5 (36.1)	167.2 (25.1)	0.040
SD (mg/dl), Mean (SD)	63.5 (15.8)	64.7 (17.7)	61.1 (10.8)	0.390
CV (%), Mean (SD)	36.2 (6.1)	35.8 (5.8)	36.8 (6.5)	0.462
Time Active CMG (%), Mean (SD)	88.4 (17.7)	86.5 (17.2)	90.6 (18.3)	0.291
Previous treatment, N (%)				<0.001
MDI	17 (18.9)	10 (19.6)	7 (18.0)	
SAP	22 (24.4)	14 (27.5)	8 (20.5)	
PLGS	34 (37.8)	10 (19.6)	24 (61.5)	
HCL	17 (18.9)	17 (33.3)	0 (0.0)	

Overall, patients reported a significant improvement from T0 to T1 in TIR (+14.6%, p<0.001), TAR (-5.7%, p<0.001), TAR > 250 mg/dl (-7.7%, p<0.001), average glucose value (-19.5 mg/dl, p<0.001) and SD (-12.9 mg/dl, p<0.001); while no significant differences were observed in TBR 54-70 mg/dl and severe hypoglycemia <54 mg/dl (**Table 2**).

Despite both AHCL systems led to an improvement in glycemic control at T1, we observed a significant difference in the treatment effects in Minimed 780G group compared to Tandem Control-IQ system (**Table 3**).

The IPW adjusted estimates showed for the Minimed 780G group a higher TIR increase (respectively +19.1% vs +9.8%; p = 0.004) and a greater reduction of blood glucose average (respectively -31 mg/dl vs -7.1mg/dl; p = 0.001), while Tandem Control-IQ achieved less time spent in TBR (respectively -0.68% vs +0.37%; p = 0.010) and greater CV reduction (respectively -5.68% vs -0.32%; p = 0.005).

No significant differences were observed between the treatment effect of Minimed 780G and the treatment effect of Tandem Control-IQ on TAR, TAR>250mg/dl, TBR<54mg/dl, SD and the proportion of active CGM time.

The analysis on the efficacy of the two AHCL systems in terms of CGM metrics did not show significant evidence of heterogeneity of the results between the age subgroups. The variables significantly associated with a difference in efficacy of the two treatments in the main analysis (TIR, TBR, average glucose and CV) are consistent in the direction of the estimates in all subgroups (**Supplemetary Table 4**).

Exploratory subgroup analysis suggests a limited impact on glycemic parameters determined by the previous therapy (**Supplementary Table 5**).

TABLE 2 | Summary of overall treatment effect.

	T1 – T0 Mean difference (95%CI)	p
TIR (%)	14.6 (11.4, 17.9)	<0.001
TAR (%)	-5.7 (-7.8, -3.5)	<0.001
TAR250mgdl (%)	-7.7 (-10.3, -5.1)	<0.001
TBR (%)	-0.2 (-0.6, 0.2)	0.429
ITBR54mgdl (%)	-0.2 (-0.4, 0.0)	0.076
Average Glucose (mg/dl)	-19.5 (-26.6, -12.4)	<0.001
SD (mg/dl)	-12.9 (-16.9, -9.0)	<0.001
CV (%)	-3.0 (-4.9, -1.0)	0.003
%Time Active CGM	2.0 (-1.7, 5.6)	0.281

DISCUSSION

The aim of this study was to compare real-life glycemic control data between Minimed 780G and Tandem Control-IQ users one month after starting the system. To the best of our knowledge, in clinical setting this is the first study to compare efficacy and safety of the AHCL systems currently available in Italy in children and adults with T1D.

Recent real-world studies have only examined the performance of each ACHL system. As shown by Messer et al. in 191 children and young adults (median age 14 years), Control-IQ system improved TIR from 57% to 66% after 6-months; time spent in hypoglycemia (< 70 mg/dl) decreased from baseline to 6-months; time spent in severe hypoglycemia (<54 mg/dl) did not change (22). Breton et al. in a large data set study confirmed the TIR improvement in 7813 TD1 subjects (62% vs 72%). In parallel, time < 70 mg/dl remained low at – 1% throughout the year (12).

Meanwhile Beato-Vibora et al. reported an immediate improvement in TIR 70-180 mg/dl from 67.3% to 79.6% in the first 30 days after the initiation of the Minimed 780G ACHL system in adults and adolescents with T1D (16). No difference in time in hypoglycemia < 70 or 54 mg/dl were seen at 2 weeks or 1 month. The real-world benefits of the Medtronic 780G system in terms of glycemic control were maintained after 3 months of use of the system (20). These data agree with previous trials of the

TABLE 3 | Treatment effects by group.

Parameter	Group	Treatment effect Mean difference (95%CI)	Control-IQ vs Minimed 780G	p
TIR (%)	Minimed 780G	19.1 (14.3, 23.9)	-9.3 (-15.5, -3.1)	0.004*
	Control-IQ	9.8 (5.9, 13.7)		
TAR (%)	Minimed 780G	-7.3 (-10.6, -4.1)	3.5 (-0.8, 7.8)	0.109
	Control-IQ	-3.8 (-6.7, -1.0)		
TAR 250mgdl (%)	Minimed 780G	-9.9 (-13.9, -5.9)	4.6 (-0.5, 9.8)	0.079
	Control-IQ	-5.3 (-8.5, -2.1)		
TBR (%)	Minimed 780G	0.37 (-0.21, 0.94)	-1.0 (-1.8, -0.3)	0.010*
	Control-IQ	-0.68 (-1.23, -0.12)		
TBR 54mgdl (%)	Minimed 780G	-0.08 (-0.28, 0.12)	-0.2 (-0.6, 0.2)	0.316
	Control-IQ	-0.27 (-0.63, 0.09)		
Average glucose (mg/dl)	Minimed 780G	-31.0 (-41.3, -20.6)	23.9 (10.7, 37.0)	0.001*
	Control-IQ	-7.1 (-14.9, 0.7)		
SD (mg/dl)	Minimed 780G	-11.4 (-16.3, -6.5)	-4.6 (-12.9, 3.8)	0.276
	Control-IQ	-16.0 (-23.2, -8.7)		
CV (%)	Minimed 780G	-0.32 (-1.98, 1.35)	-5.4 (-9.1, -1.7)	0.005*
	Control-IQ	-5.68 (-9.33, -2.03)		
%Time Active CGM	Minimed 780G	2.23 (-1.74, 6.19)	-0.5 (-7.8, 6.8)	0.891
	Control-IQ	1.72 (-5.03, 8.47)		

**Treatment effect, Control-IQ vs Minimed 780Gand p columns are adjusted for baseline confounders with the inverse probability weighting strategy.*

Minimed 780 G system (17, 19). In their multicenter, randomized crossover study Bergenstal et al. found a 4% increase in TIR 70-180 mg/dl compared to Minimed 670G users after 3 months (17). In the pivotal study, Collyns et al. found a 12.5% improvement in TIR 70-180 mg/dl after 1 month of use in children and adults (19). A recently published study by Da Silva et al. showed the real-life report of 4120 Minimed 780G users and showed the achievement of glycemic treatment goals: GMI <7.0% and TIR > 70% in most patients (23).

In our study we compared Minimed 780G and Tandem Control-IQ systems. Both systems showed a significant improvement in glycemic parameters after a month of therapy (T1) and substantially reached the targets recommended by International Consensus on Time in Range (TIR > 70%, TBR<70 mg/dl < 4%, TBR<54 mg/dl<1%, TAR>180 mg/dl <25%, TAR>250 mg/dl <5%) (9).

However, significant differences in the treatment effects were observed. Tandem Control-IQ system significantly reduced time spent in TBR 70-54 mg/dl (-0.68% vs +0.37% p=0.010) and CV (- 5.68% vs – 0.32% p 0.005), whereas Minimed 780G improved TIR (+19.1% vs +9.8% P = 0.004) and blood glucose average (-31% vs -7.1% P= 0.001). No significant differences were observed in the other CGM parameters. In both cases adherence to the sensor use was adequate (> 85%) (9, 24, 25).

As an additional exploratory analysis, we compared the glycemic control of patients in relation to the type of therapy previously used to assess if it impacts the efficacy of these two systems. The subgroups of previous therapy (MDI, SAP, PLGS, HCL) had heterogeneous patient characteristics and a small number of patients, which may have resulted in a statistically underpowered analysis (**Supplementary Table 4**). Aware of the aforementioned limits, we observed no significant impact on glycemic parameters determined by the previous therapy.

Given the absence of other comparative studies in the real-world settings, we can speculate that the Minimed 780G system is more effective in managing hyperglycemia. This result could be obtained by customization of the glycemic target and active insulin time and the possibility to deliver corrective boluses more frequently. This leads to better results in terms of TIR but causes a slight increase of time in hypoglycemia. Glycemic variability is known to be correlated with the risk of hypoglycemia. CV threshold of 36% is used to define stable and unstable glycemia in diabetes because, beyond this limit, the frequency of hypoglycemia is significantly increased (26, 27). Therefore, in the Control-IQ group, the improvement in CV leads to a lower TBR and likely to more stable blood glucose values. The significant reduction of TBR is very important from a clinical point of view. Clinicians place the prevention of hypoglycemia among the primary objectives of therapeutic management, due to the fear of this event itself, due to the inevitable consequences it implies on therapeutic choices, but also for the possible long-term consequences caused by prolonged periods of hypoglycemia.

One possible limitation of our study may be represented by the short period of follow-up, but as shown by Breton et al., regarding Tandem Control-IQ (12) and by Petrovski et al., regarding Minimed 670G (28), we can assume that TIR improvement observed during the first two weeks of analysis will be maintained throughout the following year. It is nevertheless true that, the retrospective observational nature of the study limits interpretation and generalizability of our results.

Strengths and at the same time possible limitations of this study are the broad age-range of the sample, going from school-aged children to adults, and heterogeneity of previous therapeutic schemes. The real-life clinical practice setting is an important strength of our study.

In conclusion this is the first study to compare the Minimed 780G with Tandem Control-IQ systems. In summary, data of this first study showed that the Minimed 780G system seems more effective in managing hyperglycemia, while Tandem Control-IQ reduces the number of hypoglycemic episodes and glucose variability. Aside from these little differences between the two systems, it is clear that they both substantially reach the glycemic target and that further studies with a larger population and a longer follow-up period are needed to draw conclusions about the differences between the two systems. Understanding the strength and limitations of AHCL devices could be useful for "proper candidate selection" and tailoring insulin pump therapy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

MB designed the study and wrote the manuscript. MT designed the study and wrote the manuscript. ML researched data. AI researched data. MS researched data and reviewed the manuscript. LC did statistical analysis. GD'A reviewed the manuscript and contributed to the discussion. NM designed the study and contributed to the discussion. DM designed the study and contributed to the discussion. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.802419/full#supplementary-material

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Real-Time Flash Glucose Monitoring Had Better Effects on Daily Glycemic Control Compared With Retrospective Flash Glucose Monitoring in Patients With Type 2 Diabetes on Premix Insulin Therapy

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Background and Aims: To compare the effects of real-time and retrospective flash glucose monitoring (FGM) on daily glycemic control and lifestyle in patients with type 2 diabetes on premix insulin therapy.

Methods and Results: A total of 172 patients using premix insulin, with HbA1c ≥ 7.0% (56 mmol/mol), or the time below the target (TBR) ≥ 4%, or the coefficient of variation (CV) ≥36% during the screening period, were randomly assigned to retrospective FGM (n = 89) or real-time FGM group (n = 83). Another two retrospective or real-time 14-day FGMs were performed respectively, 1 month apart. Both groups received educations and medication adjustment after each FGM. Time in range (3.9~10.0 mmol/l, TIR) increased significantly after 3 months in the real-time FGM group (6.5%) compared with the retrospective FGM group (-1.1%) (p = 0.014). HbA1c decreased in both groups (both $p < 0.01$). Real-time FGMs increased daily exercise time compared with the retrospective group (p = 0.002).

Conclusions: Real-time FGM with visible blood glucose improves daily glycemic control and diabetes self-care behaviors better than retrospective FGM in patients with type 2 diabetes on premix insulin therapy.

Clinical Trial Registration: https://clinicaltrials.gov/NCT04847219.

Keywords: type 2 diabetes, flash glucose monitoring, premix insulin, time in target range, real-time glucose monitoring

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INTRODUCTION

Effective self-management, such as self-monitoring of blood glucose (SMBG), diet, and physical activity, is foundational to achieving treatment goals for patients with diabetes (1). SMBG is a cornerstone of diabetes self-care, which provides information about current glycemic status, guiding adjustments in diet, exercise, and medication (2). SMBG is especially important for insulin-treated patients to monitor for and prevent hypoglycemia and hyperglycemia (3). However, the frequency of SMBG is commonly low in these patients due to the fear of needles and pain, inconvenience, and unconducive environment for testing (4).

The flash glucose monitoring (FGM) system is a new glucose testing device, which displays an estimate of blood glucose every 15 min and can be scanned for a glucose reading at any time with a long sensor lifetime of 14 days and no need for calibration. There are currently two types of FGM system produced by Abbott Diabetes Care, FreeStyle Libre™ and FreeStyle Libre Pro™. The main difference of these two modes of FGM is that the FreeStyle Libre Pro™ (blinded mode) can mask the glucose levels to patients and reduce the behavior change of patients during glucose monitoring; therefore, clinicians can identify and correct patterns of hyper- and hypoglycemia in patients with diabetes; FreeStyle Libre™ (unblinded mode) provides real-time glucose levels to patients and encourages patients for their diet, exercise, or medication change according to glucose levels immediately. Both of these two modes of FGM are wildly used in patients with diabetes in China.

Previous studies have demonstrated that both blinded and unblinded FGM can improve glycemic control in patients with type 2 diabetes (T2DM) compared with SMBG (5–7), and the main reason was that FGM guided the adjustment of insulin dosage or oral antidiabetic drugs in these patients. Our previous study showed that blood glucose improved during 14 days of unblinded FGM without change of antidiabetic drugs in patients with T2DM (8, 9). We hypothesized that the improvement of blood glucose contributed to the effect of unblinded FGM on self-care behavior, which was also indicated by White et al. (10). However, there was no strong evidence to support our hypothesis yet as we are aware of.

Premix insulins have been widely used worldwide. The MOSAIc study of 18 countries showed that about 30% of people with T2DM taking insulin were using premix insulin globally, and the percentage was 67% in China (11). However, several real-world studies have shown that glycemic control remains unsatisfactory 6–12 months after initiating or switching therapy with premix insulin (12–14). The reasons of poor glycemic control in patients on premix insulin include fear of weight gain and hypoglycemia and the need for frequent self-monitoring of blood glucose (12). FGM may be a good solution to these problems.

Therefore, we performed this randomized controlled study to investigate the effects of real-time FGM (unblinded FGM) on daily glycemic control and the changes of diet and exercise in patients with type 2 diabetes who were on premixed insulin therapy, and we used retrospective FGM (blinded FGM) as control to exclude the effects of drug adjustment from doctors.

RESEARCH DESIGN AND METHODS

Participants

This trial was conducted at 5 diabetes centers in Jiangsu, China, from October 2019 to April 2021.

Patients with type 2 diabetes, who were treated with premix insulin, two or three injections a day, single drug or combination of oral hypoglycemic drugs, and whose treatment regimen was stable for more than 2 months, were considered eligible to be enrolled in the study. Exclusion criteria were the following: (1) patients treated with GLP-1 agonist or any other drugs that may affect appetite in the last 3 months; (2) allergic to insulin; (3) impaired liver and renal function (ALT 2.5 times higher than the upper limit of normal value; serum creatinine was 1.3 times higher than the upper limit of normal); (4) a history of drug abuse and alcohol dependence; (5) used systemic glucocorticoid therapy in the recent 3 months; (6) patients with infection or stress within 4 weeks; (7) patients who cannot tolerate FGM; (8) pregnant or preparing to become pregnant; and (9) considered unsuitable to participate by the investigator.

Study Design

This is a prospective, randomized controlled trial. At baseline, all participants were screened by a blinded FGM for 14 days and a glycosylated hemoglobin (HbA1c). Patients were enrolled when their HbA1c ≥ 7.0% (56 mmol/mol), or the FGM showed that the percentage time spent in hypoglycemia ≤ 3.9 mmol/l (time below the target range, TBR) ≥ 4% or the coefficient of variation (CV) ≥ 36% (15). Then the patients were randomized into blinded FGM and unblinded FGM groups in a 1:1 ratio. All participants were educated by a diabetes specialist nurse. The content of education included the insulin injection technique and self-management of diet and exercise. Diabetes clinicians adjusted the antidiabetic drugs according to the results of FGM and the guideline of care for type 2 diabetes in China (16). Then the participants entered into two successive 45-day follow-up periods (**Figure 1A**) . Both of the groups performed an FGM during the last 14 days of each follow-up period, and educations and drug adjustment were taken immediately after each FGM. The educators and clinicians were not told and should not ask the patients about the type of FGM. Moreover, the results of both FGM modes were reported in the same format.

Ethics Committee approval was granted prior to the study. All procedures were in accordance with the Helsinki Declaration. All patients provided written informed consent forms to participate in the study. This trial is registered with ClinicalTrials.gov (NCT04847219).

Flash Glucose Monitoring

FreeStyle Libre™ and FreeStyle Libre Pro™ (Abbott Diabetes Care, Maidenhead, UK) were used in the unblinded and blinded

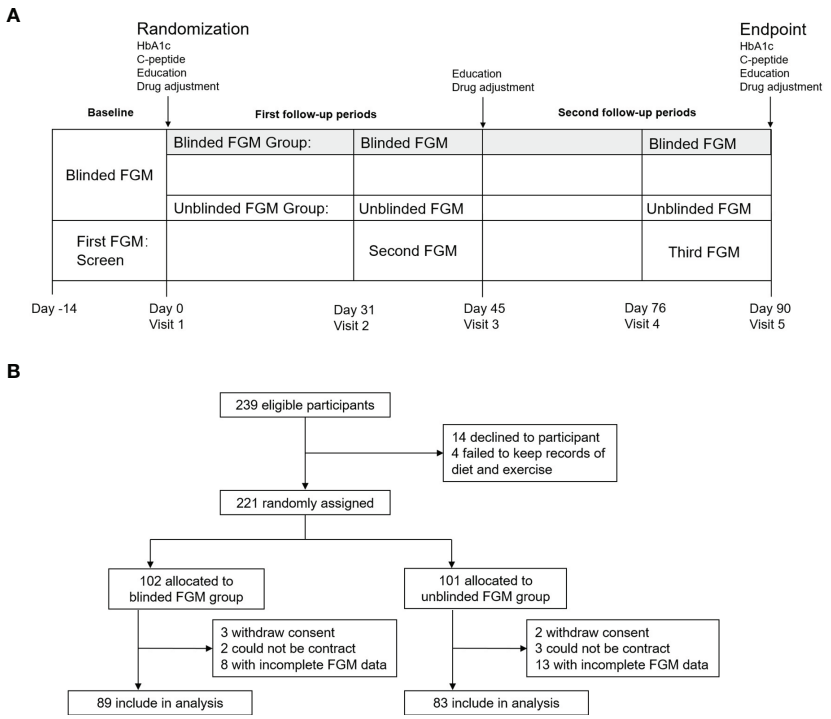

FIGURE 1 | Study design **(A)** and trial profile **(B)**.

groups, respectively. The sensor was worn on the back of the left upper arm for 14 days to record the subcutaneous interstitial glucose concentration at 15-min intervals. For the blinded FGM group, the results of blood glucose in blinded FGM were masked, and patients could take SMBG at any time. For the unblinded FGM group, patients could scan the sensor to read the glucose levels at any time, but they have to scan the sensor every 8 h at least. Patients in both groups were required to keep track of their food intake and exercise while wearing the FGM sensor and could alter their diet and exercise according to the glucose levels. We dispensed a uniform study log for patients to record their diet and exercise for all days during FGMs, including the type (write the names of food) and weight of each food and when it was eaten, and the type of exercise, and the time when the exercise began and ended. However, patients could not change their therapy with glucose-lowering agents during FGM. The dosage of glucose-lowering agents could be adjusted by clinicians according to the results of the FGM when the FGM sensors were removed.

Clinical and Laboratory Assessment

The height, duration of disease, concomitant diseases, and change of weight and medications of all patients were recorded. Blood samples of all patients were collected after overnight fasting (>10 h). Fasting C-peptide and HbA1c were measured immediately after the first and third FGMs. All tests were performed in the Nanjing Clinical Nuclear Medicine Center (ISO/IEC15189/17020).

Outcomes

The primary outcome of this study was the change in percentage time in the target range (glucose 3.9~10.0 mmol/l, TIR) between the first (baseline) and third (endpoint) FGMs. Secondary outcomes included TBR, percentage time spent in hyperglycemia > 10.0 mmol/l (time above target range, TAR), 24 h mean blood glucose (MBG), standard deviation of blood glucose (SDBG), CV, hourly mean blood glucose (the average of 14 days during FGM), HbA1c, C-peptide, and daily exercise time, energy intake, number of meals, and insulin dose per day during FGM.

Statistical Analysis

All statistical analyses were performed using SPSS version 22.0 software (IBM Corp., Foster City, CA, USA). All variables were tested for normal distribution. Data are presented as mean (95% CI) or percentage. Differences between the two groups were examined using Student's unpaired *t*-test (insulin dose) or the Mann–Whitney *U*-test (age, diabetic duration, BMI, exercise time, carbohydrate, calories, and daily meal frequency at baseline). The parameters (TIR, MBG, CV, and SDBG) assessed by three FGMs, and HbA1c, C-peptide, insulin, and metformin dose, and lifestyles at baseline and endpoint were analyzed by a mixed-model ANOVA with time as the within-subject factor and groups as the between-subject factor. The categorical data were examined with the chi-square test. All comparisons were 2-sided at a 5% significance level. A p value < 0.05 was considered statistically significant.

This study is registered with ClinicalTrials.gov, number NCT04847219.

RESULTS

There were 239 eligible patients and 221 patients finished the screening phase. Among these patients, 74 (33.5%) patients had HbA1c<7%, 141 (63.8%) patients had CV<36%, and 131 (59.3%) patients had TBR<4%. Therefore, only 18 (8.1%) patients achieved the composite goal of glycemic control including HbA1c, CV, and TBR, and the other 203 patients were randomized into two groups. There were 8 patients in the blinded FGM group, and 13 patients in the unblinded FGM group failed to complete the two FGMs after randomization because of sensors falling off or data missing. Finally, there were 89 patients in the blinded FGM group and 83 patients in the unblinded FGM group included for analysis (**Figure 1B**). Participant characteristics at baseline were similar between the study groups except insulin dose and the percentage of acarbose use (**Table 1**).

The Changes of Daily Glycemic Control

There were no differences of daily glycemic control (p all >0.05), HbA1c (p = 0.990), and C-peptide (p =0.420) between the blinded and unblinded FGM groups at baseline during the first blinded FGM (**Table 2**). A mixed-model ANOVA showed that TIR increased significantly in the second and third FGMs in the unblinded FGM group (p < 0.001) but did not change in the blinded FGM group (p = 0.709). Therefore, a difference of TIR change appeared between the two groups (estimated treatment difference -7.7 (-13.9,1.4) %, p = 0.014), and the difference remained significant after adjusting for insulin and acarbose dose at baseline (p = 0.031, **Table 2**). Both unblinded FGM showed a higher TIR than baseline (both p < 0.05, **Figure 2A**). TBR, CV, SDBG, and HbA1c were significantly decreased (p all <0.05), and SDBG was lower in the unblinded group than in the blinded group (p = 0.029, **Table 2**).

The hourly mean blood glucose over 14-day FGM periods showed that the blood glucose levels after meals were lower in the unblinded FGM group during the third FGM, especially after lunch (11:00~14:00) and supper (19:00) (p all <0.05, **Figure 2B**), which were similar between the two groups during the first FGM (p all >0.05). There was no difference of nocturnal blood glucose between unblinded and blinded FGMs (p all >0.05, **Figure 2B**). However, the changes of hourly mean blood glucose from the first FGM to the third FGM in each group were not statistically significantly according to the t-test (p all >0.05).

The Changes of Medications and Lifestyle

To explore the factors which may influence the daily glycemic control in different groups, changes (endpoint minus baseline) of medications and lifestyles were compared between blinded and unblinded FGM groups. As a result, the changes of insulin and metformin dose and the proportions of oral antidiabetic agents used at endpoint were all similar in the two groups (p all >0.05, **Table 3** and **Supplementary Table 1**).

As shown in **Table 3**, the daily exercise time increased to 8.0 min every day in the unblinded FGM group [62.4 (51.6, 73.2) vs. 79.0 (63.9, 94.1) min], which decreased to 10.1 min in the blinded group (66.3 (55.2, 77.4) vs. 64.0 (51.4, 76.6) min), p = 0.002. Mean calories per meal increased and daily meal frequency decreased at the endpoint compared with baseline (both p <0.05). However, the changes in calorie intake and daily meal frequency were not significantly different between the two groups (p all >0.05, **Table 3**).

TABLE 1 | Baseline characteristics of participants.

	Blinded FGM Group	Unblinded FGM Group	*p* value[a]
Age (year)	63.8 (61.7,65.9)	61.3 (59.3,63.3)	0.083
Gender (male)	54 (60.7%)	56 (67.5%)	0.427
Diabetic duration (month)	162.9 (144.9,181.0)	164 (145.3,182.7)	0.711
BMI (kg/m^2)	25.2 (24.6,25.9)	24.7 (24,25.4)	0.355
Glucose-lowering drugs			
Insulin dose (IU/day)	39.3 (36.8,41.9)	35.4 (32.8,38.0)	0.034
Metformin (%)	37 (41.6%)	37 (44.6%)	0.759
Acarbose (%)	33 (37.1%)	19 (22.9%)	0.048
Insulin secretagogues (%)	6 (6.7%)	4 (4.8%)	0.748
DPP-4 inhibitors (%)	4 (4.5%)	8 (9.6%)	0.237
TZDs (%)	2 (2.2%)	0 (0%)	0.498
Diabetic complications			
Diabetic kidney disease (%)	16 (18.0%)	9 (10.8%)	0.201
Neuropathy (%)	13 (14.6%)	11 (13.3%)	0.829
Retinopathy (%)	14 (15.7%)	18 (21.7%)	0.334
Coronary heart disease (%)	17 (19.1%)	17 (20.5%)	0.850
Cerebral infarction (%)	19 (21.3%)	16 (19.3%)	0.850
Lifestyle			
Exercise time (min/day)	66.3 (55.2,77.4)	62.4 (51.6,73.2)	0.490
Calories/weight daily (kcal/kg)	25.8 (23.4,28.1)	27.9 (25.5,30.3)	0.174
Mean calories per meal (kcal)	492.1 (444.3,539.8)	535.2 (490.6,579.9)	0.191
Carbohydrate (g)/day)	270.2 (251.6,288.9)	275.5 (259.1,291.2)	0.726
Meal frequency daily (number)	3.6 (3.4,3.7)	3.5 (3.4,3.7)	0.639

Data are mean (95% CI) or number (percentage).

[a]*Difference between two groups with the Mann–Whitney U-test or chi-square test.*

FGM, flash glucose monitoring; BMI, body mass index; DPP-4, dipeptidyl peptidase 4; TZDs, thiazolidinediones.

TABLE 2 | Changes of daily glycemic control in blinded and unblinded FGMs.

		Blinded FGM	Unblinded FGM	Estimated Treatment Difference	p value (Time)	p value (Group)	p value (Time × Group)	Adjusted *p* value[a] (Time × Group)
TIR (%)	First	60.6 (56.1,65.0)	60.6 (56.4,64.8)	-7.7 (-13.9,1.4)	0.010	0.056	0.014	0.031
	Second	61.0 (56.6,65.4)	68.2 (64.2,72.3)					
	Third	59.4 (54.3,64.6)	67.1 (63.1,71.1)					
Endpoint—baseline		-1.1(-5.9, 3.6)	6.5 (2.4, 10.6)					
	p value	0.709	<0.001					
TBR (%)	First	6.5 (4.8,8.2)	5.9 (3.8,7.9)	1.4 (-1.0,3.7)	0.007	0.132	0.222	0.320
	Second	4.7 (3.1,6.3)	3.1 (2.3,3.9)					
	Third	5.5 (3.8,7.1)	3.5 (2.5,4.4)					
Endpoint—baseline		-1.0(-2.7, 0.6)	-2.4 (-4.2, -0.6)					
TAR (%)	First	32.9 (27.7,38.1)	33.6 (28.7,38.5)	6.3 (-0.5,13.1)	0.400	0.215	0.072	0.110
	Second	34.3 (29.5,39.1)	28.7 (24.4,32.9)					
	Third	35.1 (29.3,40.9)	29.5 (25.1,33.8)					
Endpoint—baseline		2.2(-3.0, 7.4)	-4.1 (-8.6,0.3)					
MBG (mmol/L)	First	8.9 (8.3,9.5)	8.8 (8.3,9.3)	0.4 (-0.2,1.1)	0.915	0.215	0.232	0.294
	Second	9.0 (8.5,9.5)	8.6 (8.2,8.9)					
	Third	9.2 (8.5,9.8)	8.6 (8.2,9.0)					
Endpoint—baseline		0.2(-0.3,0.8)	-0.2 (-0.6,0.2)					
CV (%)	First	35.3 (33.9,36.7)	33.9 (32.4,35.4)	0.6 (-1.2,2.4)	0.001	0.057	0.346	0.464
	Second	34.4 (32.8,35.9)	32.3 (30.9,33.7)					
	Third	33.8 (32.3,35.4)	31.8 (30.4,33.2)					
Endpoint—baseline		-1.5(-2.8, -0.2)	-2.1 (-3.4, -0.8)					
SDBG (mmol/L)	First	3.1 (2.9,3.2)	2.9 (2.8,3.1)	0.2 (-0.05,0.4)	0.007	0.029	0.105	0.185
	Second	3.0 (2.9,3.2)	2.8 (2.6,2.9)					
	Third	3.0 (2.8,3.2)	2.7 (2.6,2.9)					
Endpoint—baseline		-0.1(-0.2,0.1)	-0.2 (-0.4,-0.1)					
HbA1c (%)	Baseline	7.5 (7.3,7.8)	7.6 (7.3,7.8)	0.1 (-0.2,0.4)	<0.001	0.851	0.563	0.752
	Endpoint	7.3 (7.0,7.5)	7.2 (7.0,7.4)					
Endpoint—baseline		-0.3(-0.5,-0.1)	-0.4 (-0.5,-0.2)					
C-peptide (ng/mL)	Baseline	1.5 (1.2,1.7)	1.4 (1.2,1.6)	0.01 (-0.3,0.3)	0.444	0.561	0.213	0.817
	Endpoint	1.5 (1.1,1.9)	1.4 (1.2,1.6)					
Endpoint—baseline		0.06(-0.2,0.3)	0.06 (-0.1,0.2)					

Data are mean (95% CI).

[a]*Adjusted for baseline insulin and acarbose dose in mixed-model ANOVA analysis.*

FGM, flash glucose monitoring; TIR, time in target range; TBR, time below target range; TAR, time above target range; MBG, mean blood glucose; CV, coefficient of variation; SDBG, standard deviation of blood glucose.

Different Changes of Daily Glycemic Control, Medications, and Lifestyle in Patients With Different Problems of Glucose Control

Since we included not only patients with hyperglycemia (HbA1c ≥7%) but also patients with hypoglycemia (TBR ≥4%) or high glycemic variability (CV ≥36%), we analyzed the changes of daily glycemic control in patients with each of these problems separately. There were no significant differences of time × group interaction in the mixed-model ANOVA analysis of daily glycemic control (p all >0.05, **Supplementary Figure 1**). In patients with TBR ≥4%, TIR in the blinded group was lower than in the unblinded group (p = 0.048). HbA1c decreased compared with baseline only in patients with HbA1c ≥7% (p < 0.001, **Supplementary Table 2**).

In patients with high TBR or CV, insulin dose decreased significantly at the endpoint compared with baseline (p < 0.001 and p = 0.006, respectively), and the reduction of insulin dose in the unblinded FGM group was more than in the blinded FGM group (p = 0.007 and 0.022, respectively). Moreover, patients had higher elevation of calorie intake/weight and mean calories per meal (p = 0.045 and 0.047, respectively) and higher reduction of exercise time (p = 0.007) than in the unblinded FGM group in patients with TBR ≥ 4% (**Supplementary Table 2**).

DISCUSSION

Although both FGM modes improved HbA1c significantly in patients using premix insulin in the present study, the TIR and parameters that reflect glycemic variability improved better in the unblinded FGM group than in the blinded FGM group. The essence of this result is that on the basis of clinicians' adjustment of diabetic therapy according to retrospective FGM data once a month, patients can improve their blood glucose better, modulating their diet and exercise according to visible FGM

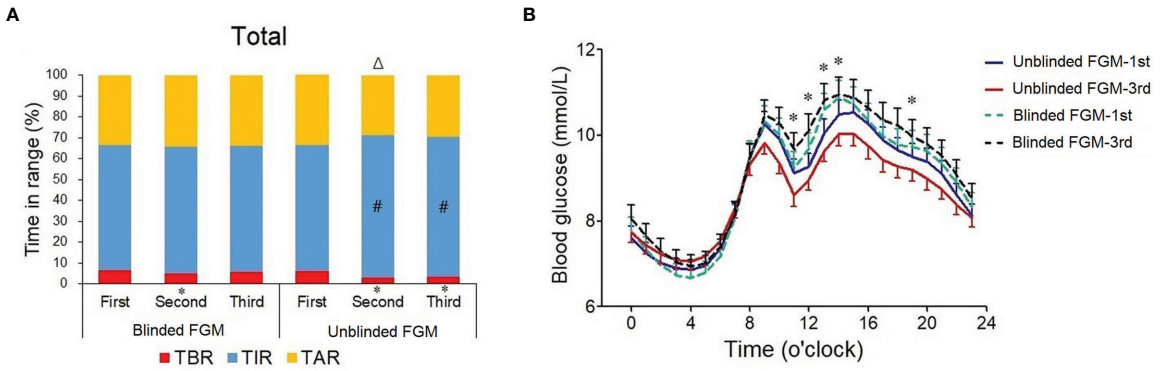

FIGURE 2 | Changes in daily glycemic control during three flash glucose monitorings in professional and unblinded FGM groups. **(A)** Percentage time in the target range of 3.9–10.0 mmol/l (TIR) during the first (baseline, blinded FGM in both groups), second (days 31–45), and third (days 76–90) FGM in the blinded FGM group (n = 89) and unblinded FGM group (n = 83), blue bar; time below the target range (TBR), red bar; time above the target range (TAR), yellow bar. Data are percentage; #, vs. first FGM, *p value* <0.05. **(B)** Hourly mean blood glucose during the first and third FGMs. Blue solid line, first FGM in the unblinded FGM group; red solid line, third FGM in the unblinded FGM group; green dotted line, first FGM in the blinded FGM group; black dotted line, third FGM in the blinded FGM group. **p < 0.05 between two groups*.

TABLE 3 | Changes of medications, and lifestyles from baseline to endpoint.

	Blinded FGM (Endpoint-Baseline)	Unblinded FGM (Endpoint-Baseline)	p value (time)	p value (Group)	p value (Time × Group)
Insulin dose (IU/day)	-1.0 (-2.3,0.3)	-2.3 (-3.7,-0.9)	0.001	0.065	0.152
Metformin dose (g/day)	-0.1 (-0.4,0.1)	0.1 (-0.02,0.2)	0.160	0.370	0.109
Exercise time (min/day)	-10.1 (-19.5,-0.6)	8.0 (1.1,14.8)	0.716	0.312	0.002
Calories/weight daily (kcal/kg)	1.7 (-0.3,3.8)	-0.04 (-1.9,1.8)	0.225	0.393	0.338
Mean calories per meal (kcal)	47.5 (5.7,89.2)	19.7 (-21.6,61.0)	0.024	0.339	0.347
Carbohydrate (g)/day)	-5.3 (-22.9,12.3)	-7.0 (-19.9,5.9)	0.263	0.766	0.880
Daily meal frequency (number)	-0.13 (-0.26,0.003)	-0.08 (-0.21,0.04)	0.022	0.641	0.607

Data are mean (95% CI); data were analyzed by a mixed-model ANOVA.
DPP-4, dipeptidyl peptidase 4; TZDs, thiazolidinediones.

data more effectively compared with regular SMBG. By using the retrospective FGM as a control, the present study was able to compare TIR between the two groups and partially eliminated the interference of physician-led drug adjustment, both of which have not been discussed in previous studies comparing FGM with SMBG (17–19).

The interventions in the blinded FGM group were almost the current pattern of outpatient follow-up for patients with diabetes in China. Patients come to the hospital once a month, and doctors give advices about diet, exercise, and medications according to their SMBG records during the last month. The CCMR-3B study in China showed that 47.7% outpatients with T2DM achieved the target goals for the control of blood glucose (HbA1c <7%) (20), and the proportion in the present study was even lower in patients using premix insulin. Moreover, only 8.1% patients achieved the composite goal of glucose control with additional combination of hypoglycemia and CV in the screening period of this study.

Before the endpoint, patients in both groups received two times of diabetic education and drug adjustment. HbA1c was reduced in both groups; however, TIR in the last blinded FGM did not improve significantly. One reason may be that the effect of education and drug adjustment cannot last for long due to the poor adherence of these patients. The fall after rise of the efficacy of blinded FGM also existed in previous studies (5, 6). On the other hand, nearly half of the patients in this study had hypoglycemic or high glycemic variability. Asymptomatic hypoglycemia was shown to these patients by the first two blinded FGMs. Therefore, the less exercise time compared with the unblinded FGM group during the last FGM may be associated with their prevention of hypoglycemia. As a result, the blinded FGM group had lower TIR than the unblinded group in the TBR ≥4% subgroup. Compared with the blinded FGM group, patients during unblinded FGM had better exercise adherence and flexible mealtimes. A previous study showed that hypoglycemia during aerobic exercise was positively correlated with pre-exercise blood glucose levels (21). ADA/ACSM also recommended that in patients treated with insulin, carbohydrate should be ingested before any exercise when the pre-exercise glucose level <5.5 mmol/l (22). Patients could obtain their blood glucose levels before and after exercise easily by scanning during unblinded FGM. Therefore, we speculate that the fear of hypoglycemia may largely decrease and the effectiveness of exercise on glycemic control was also shown by

unblinded FGM. On the other hand, patients using unblinded FGMs may prevent hypoglycemia by eating when they noticed a rapid drop in blood glucose, while patients in the blinded group tried to prevent hypoglycemia by eating more at each meal in the present study. As a result, the unblinded FGM group showed better TIR compared with the blinded FGM group.

Our previous study showed that the optimal frequency of scanning time required to maintain euglycemia in patients with T2DM was 11.7 times/day during unblinded FGM (8). However, according to the standards of medical care for type 2 diabetes in China 2020, the frequency of SMBG in patients using premix insulin is twice a day (fasting and before dinner), and most of the patients did not perform SMBG every day in the present study in the blinded FGM group because of glucose test strips and the fear of pain.

Ahn et al. also suggested that unblinded continuous glucose monitoring (CGM) should replace blinded CGM in the clinical management of diabetes (23). However, only one randomized controlled crossover study (24) compared the effects of blinded and unblinded CGM directly as we are aware of. In this previous study, HbA1c decreased more, less time was spent in hypoglycemia, and insulin pump was used more frequently when real-time data were available to the subjects compared with those during blinded CGM in patients with type 1 diabetes (T1DM) using insulin pump therapy. Our present study showed similar results in FGMs and extends the applicability to patients with type 2 diabetes using premix insulin with more details on the changes of diet and exercise.

Although unblinded FGM has better effects on daily glycemic control, there are still some shortcomings of unblinded FGM. Patients using an unblinded FGM must scan the sensor at least every 8 h to avoid data interruptions. As a result, the unblinded group had more data missing than the blinded FGM group (not statistically significant, **Figure 1B**). Moreover, unblinded FGM does not have alarms for hypo- and hyperglycemia. It has been demonstrated that real-time CGM with alarm was superior to FGM in reducing hypoglycemia and improving TIR in adults with T1DM with normal hypoglycemia awareness (25). However, no need for calibration remains a superiority of unblinded FGM for patients compared with real-time CGM.

Our study has several potential limitations. Although both blinded and unblinded FGMs had similar accuracy with CGM and SMBG in previous studies (26–28), head-to-head comparison of the accuracy between the two modes of FGM has not been reported yet. Therefore, we cannot exclude the uncertain influence of different accuracies in the two modes of FGMs completely, which needs to be further studied. Moreover, we used self-reported dietary and exercise data, which are normally associated with underreporting and social desirability bias (29, 30).

In conclusion, this randomized controlled trial indicates that real-time FGM with visible blood glucose can improve daily glycemic control and diabetes self-care behaviors better than retrospective FGM. Our study provides strong evidence for the use of real-time FGM/CGM instead of blinded FGM/CGM in clinical practice. In addition to clinicians' guidance of antidiabetic medications and educations for diet and exercise during outpatient sessions, patients' self-care based on their real-time blood glucose monitoring at home may play a more important role in blood glucose control than what we have realized.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Nanjing First Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JHM and YH are responsible for the conception and design of the study. YH carried out statistical analysis. R-nY, T-tC, TJ, LC, L-jJ, X-jX, X-fS, LX, KH, LC, and CC researched data. B-lL approved the final version of the manuscript. J-hM and YH contributed to obtain funding. J-hM is the guarantor of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.832102/full#supplementary-material

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Technologies for Type 1 Diabetes and Contact Dermatitis: Therapeutic Tools and Clinical Outcomes in a Cohort of Pediatric Patients

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The increasing use of technological devices for the management of diabetes is related to the prolonged exposure of patients' skin to chemical and mechanical agents and, consequently, to the increased risk of developing dermatological complications. Among these, contact dermatitis is the most insidious skin disorder. Despite the magnitude of the issue, no universally accepted recommendations on the management of this common complication are currently available. Our observational study aimed to describe all the solutions adopted by patients and their caregivers to treat and prevent the appearance of contact dermatitis and to describe the clinical impact of this cutaneous complication. Twenty-one pediatric patients (mean age 12.1 ± 3.7 years) with type 1 diabetes were recruited in the study. The most common treatment used to treat acute skin lesions was the application of topical corticosteroids, sometimes associated with topical antibiotics (9.5%). In order to prevent the further appearance of dermatitis, the most frequently adopted measure was the use of hydrocolloid and/or silicone-based adhesives, followed by the application of protective barrier films. One patient reported benefit from the off-label use of fluticasone propionate nasal spray. However, only 52.4% of the study participants achieved a definitive resolution of the skin issue, and 38.1% of patients were forced to discontinue insulin pump therapy and/or continuous glucose monitoring. No differences were observed in glycated hemoglobin values between the period before and after the onset of contact dermatitis. Our study confirms the severity of this dermatological complication that may hinder the spread of new technologies for the management of diabetes. Finally, our findings highlight the importance of establishing close collaboration both with pediatric allergy specialists to prescribe the most suitable treatment and with manufacturing companies to ensure that adhesives of technological devices are free of harmful well-known sensitizers.

Keywords: allergic contact dermatitis, continuous glucose monitoring, continuous subcutaneous insulin infusion, fluticasone nasal spray, irritant contact dermatitis, skin barriers, topical corticosteroids

INTRODUCTION

Current advanced technologies for the management of type 1 diabetes (T1D) include the following categories: insulin delivery systems, glucose-sensing technologies, and glucose-responsive insulin delivery systems (1). Continuous glucose monitoring (CGM) systems allow patients and providers to monitor current glucose value in real-time, facilitate the achievement of suboptimal glycemic control (2, 3) as well as increase parenteral comfort and decrease fear of hypoglycemia (4). Two types of CGM systems are currently available: real-time CGM (rtCGM) and intermittently scanned CGM (isCGM), also called flash glucose monitoring (FGM). Continuous subcutaneous insulin infusion (CSII) therapy has been demonstrated to decrease intraday glycemic variability and improve psychological outcomes compared with multiple day injection (MDI) (5–7). Furthermore, the most innovative technological devices (i.e. hybrid closed loop and advanced hybrid closed loop), by using an algorithm that automatically modify the basal insulinization rate based on the expected glucose value, allow the achievement of optimal therapeutic goals (8). All these devices are fixed to the skin with an external adhesive patch. CGM systems are approved to be worn for 7–14 days before replacement (1), while CSII infusion sets should be replaced every 2–3 days (9). The extended amount of time of wearing is related to the increased risk of continued, repeated exposure to chemical and mechanical agents. As a result, acute and chronic skin issues may appear and impede comfortable use of these devices (10).

In the last few years, an increase of dermatological complications related to the use of glycemic sensors and/or insulin pumps has been observed. Some recent studies showed that almost 50% of patients using technological devices for the management of diabetes experience skin reactions including eczema, itch, infections, scars, and lipodystrophies under the adhesives of sensors and pump sets (11–15).

The most insidious among these cutaneous complications is contact dermatitis (**Figure 1**). It is an inflammatory eczematous skin disorder caused by contact irritants that produce irritant effects inducing activation of innate immunity or by contact with sensitizing substances that induce innate and adaptive immune (T-cells) response. Clinical manifestations of contact dermatitis (irritant and allergic) may include erythema, burning, itching, stinging, bleeding and pain (16). In patients with diabetes, contact dermatitis can be caused by the exposure of the skin to potentially harmful chemicals included in the adhesives, plastic catheters and housings of diabetes technological devices (17). This dermatological complication has both a clinical and psychological impact as it affects diabetes-specific emotional distress, leading to a worsening of patients' quality of life (18).

Despite the increasing number of both adults and children with T1D who presented skin complications, there are few data regarding the clinical impact on the management of diabetes caused by the occurrence of contact dermatitis. Furthermore, no universally accepted recommendations on the management of this common complication are available thus far.

The aim of our monocentric retrospective observational study was to describe all the solutions adopted by patients and their caregivers to treat and prevent the appearance of skin manifestations typical of contact dermatitis. Secondary aim was to evaluate dermatological and glycometabolic outcomes.

METHODS

Our study included children and adolescents (aged 0-18 years) with T1D followed at our Pediatric Diabetes Center, which is the only recognized reference center in the Messina district for diagnosis, treatment and follow-up of youth-onset diabetes. Each patient, or alternatively one of the two parents if a minor, provided their informed consent. The study was approved by the local Ethics committee and conducted in accordance with the Helsinki declaration. The only inclusion criteria for the study was the presence of clinical history positive for skin reactions suggestive of contact dermatitis due to insulin pumps and/or glycemic

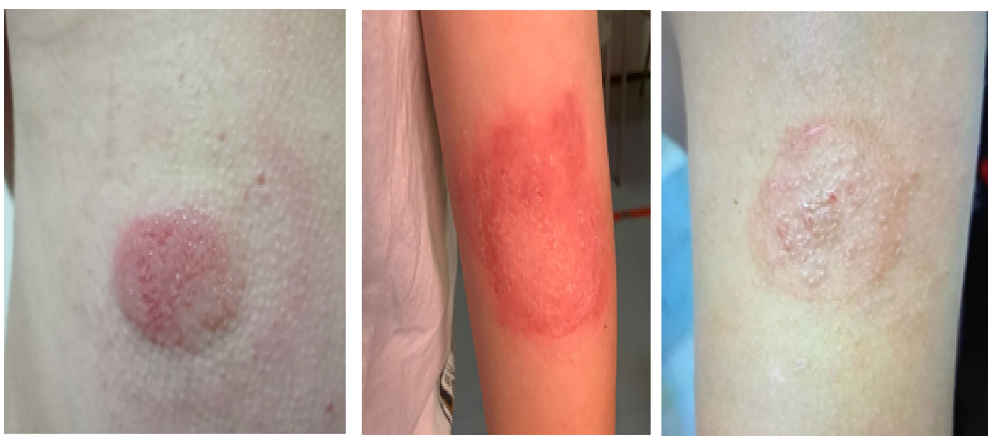

FIGURE 1 | Three cases of contact dermatitis caused by adhesives contained in continuous glucose monitoring devices.

sensors. The exclusion criteria were the presence of partial clinical remission according to the Hvidovre Study Group definition during the entire study period (19), and the use of measures aimed to treat or prevent contact dermatitis <3 months. Anamnestic data included demographic characteristics (age, sex, race), diabetes duration, presence of atopic comorbidities, insulin treatment type, duration of the use of insulin pumps, FGM or CGM, brand and model of insulin insertion sets and/or glycemic sensors, timing of appearance of skin reactions. All the participants undertook a physical examination with particular attention to skin integrity. Patch testing with specific allergens belonging to resin and acrylate classes were carried out. Acute and preventive treatments were prescribed on the basis of each patient's clinical history (e.g. results of patch test, type and severity of contact dermatitis), and according to the clinical experience of pediatric allergy specialists of our Department. To evaluate the impact of contact dermatitis on glycemic control, the one-year mean values of glycated hemoglobin (HbA1c) before and after the appearance of skin lesions were compared using the Wilcoxon-signed rank test. Quantitative variables were described using mean and standard deviation. Categorical variables were described as absolute frequencies and percentages. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22 (Armonk, NY, IBM Corp.). The significance threshold was set up to 0.05.

RESULTS

Out of 252 patients with T1D using technological devices and followed at our Pediatric Diabetes Center, 21 (61.9% males) were recruited for the study. Demographic and clinical characteristics of our study cohort are included in **Table 1**. Mean age of the study population was 12.1 ± 3.7 (range 7-18) years and mean duration of diabetes was 6.4 ± 3.3 (range 3-18) years. Atopic history was present in 47.6% of our patients. Patch test was positive in 12 patients (57.1%). More than half the patients had early onset of contact dermatitis, within 3 months of starting use of the patch pump and/or glycemic sensor.

TABLE 1 | Anamnestic and clinical data of our study cohort.

Age (years)	12.1 ± 3.7
Gender	
Male	13 (61.9%)
Female	8 (38.1%)
Diabetes duration (years)	6.4 ± 3.3
Atopic predisposition	
Yes	10 (47.6%)
No	11 (52.4%)
Age at the onset of contact dermatitis (years)	9.2 ± 3.4
Time of appearance of contact dermatitis	
0-3 months	12 (57.1%)
3-6 months	1 (4.8%)
6-12 months	2 (9.5%)
>12 months	6 (28.8%)
Patch test	
Positive	12 (57.1%)
Negative	9 (42.9%)

TABLE 2 | Relationship between contact dermatitis and the total number of patients using technological devices and followed in our Diabetes Centre.

Device for diabetes management	Total users	Frequency of skin reactions
Medtronic® insulin pump	92	10 (10.9%)
Enlite® glycemic sensor	90	15 (16.7%)
Omnipod® insulin pump	36	3 (8.3%)
Libre® glycemic sensor	54	5 (9.3%)
Dexcom® glycemic sensor	110	4 (3.6%)

Some patients wore more than one device and experienced skin reactions due to different brands of glycemic sensors and/or insulin pumps.

Skin issues were mainly present in subjects wearing Enlite® sensor (16.7% of total users). **Table 2** summarizes the relationship between the appearance of contact dermatitis and the total number of patients using different technological devices followed in our Diabetes Centre.

The most common treatment used to treat acute skin lesions was the application of topical corticosteroids (57.1%), sometimes associated with topical antibiotics (9.5%). Some patients used soothing/emollient creams (23.8%) and more rarely topical antihistamines (9.5%).

To prevent the occurrence of further skin reactions, about 57% of patients used hydrocolloid and/or silicone-based plasters, such as Eurofix® (Eurofarm, Belpasso, Italy) and Suprasorb® H (Lohmann & Rauscher GmbH & Co., Neuwied, Germany) to protect the skin before the application of insulin infusion sets or glycemic sensors. Another recurring solution was the application of protective barrier films, such as Askina® barrier film (B. Braun, Melsungen, Germany), Brava® skin barrier spray (Coloplast, Humlebæk, Denmark), and Cavilon® spray (3M, Saint Paul, Minnesota, United States) to confer a shield against offending agents, associated with the application of supplemental plasters. Finally, one patient used fluticasone propionate nasal spray to preserve skin areas a few minutes before the culprit device insertion. As reported in **Table 3**, clinical responses to these protective tools were heterogeneous. Despite any preventive measures adopted, 47.6% of our study population had a negative dermatological outcome. Consequently, 38.1% of patients were forced to discontinue insulin pump therapy and/or continuous glucose monitoring. Regarding glycemic control, evaluated through analysis of the one-year mean values of HbA1c, no differences were observed between the period before and after the occurrence of contact dermatitis (*p-value* = 0.898) (**Table 3**).

DISCUSSION

Contact dermatitis can be divided into two subtypes: irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD is a nonspecific response of the skin to direct chemical damage that releases mediators of inflammation from epidermal cells, while ACD is a delayed, type 4 hypersensitivity reaction to exogenous contact antigens, that induces immunological responses due to the interaction of cytokines and T cells.

TABLE 3 | Therapeutic and preventive measures for the management of contact dermatitis and clinical outcomes.

Acute treatment for contact dermatitis	
Topical corticosteroids	12 (57.1%)
Topical corticosteroids + antibiotics	2 (9.5%)
Topical antihistamines	2 (9.5%)
Soothing/emollient creams	5 (23.8%)
Preventive measures adopted	
Application of hypoallergenic adhesives	12 (57.1%)
Application of skin barrier spray	6 (28.6%)
Application of hypoallergenic adhesives + skin barrier spray	2 (9.5%)
Use of fluticasone spray	1 (4.8%)
Dermatological outcomes related to the use of different preventive measures	
Resolution with hypoallergenic adhesives	7/12 (58.3%)
Resolution with skin barrier spray	3/6 (50%)
Resolution with hypoallergenic adhesives + skin barrier spray	0/2 (0%)
Resolution with fluticasone spray	1/1 (100%)
Resolution with any preventive measures	11/21 (52.4%)
Discontinuation of CSII and/or CGM systems	
Yes	8 (38.1%)
No	13 (61.9%)
Last year HbA1c mean value (mmol/mol) before the onset of contact dermatitis	49.7 ± 9.1 **p=0.861**
First year HbA1c mean value (mmol/mol) after the onset of contact dermatitis	49.7 ± 8.3

Results are presented as absolute frequencies and percentages for categorical variables, as well as mean and standard deviation for numerical data.
The bold p-value represents a comparison between the "last year HbA1c mean value before the onset of contact dermatitis" and "first year HbA1c mean value before the onset of contact dermatitis".

Although some features (e.g. the timing of onset of the rash, the spread of lesions, patch testing responses) may be helpful to distinguish between ACD and ICD, differential diagnosis is usually hard (20). Nevertheless, these two different subtypes of contact dermatitis are not mutually exclusive as destruction of the skin barrier induced by ICD can increase antigenic exposure and exacerbate the appearance of ACD (21). Patch testing represents the diagnostic gold standard of ACD (22), but sensitivity is approximately 70% (23). The validity of a patch test may be altered by inadequate concentrations of the tested substances (24). Patch testing is useful to define the exact etiologic diagnosis and, thus, to identify the culprit allergens. Several studies have revealed that the allergens most frequently responsible of ACD are isobornyl acrylate and *N*-*N* dimethylacrylamide which were detected within sensors, such as FreeStyle Libre®, Dexcom® and Enlite®, and Omnipod® insulin pumps (25–30). Another common allergen cause of contact dermatitis is colophonium, contained in the Enlite® sensor and Omnipod® (25, 31, 32). Unfortunately, fully, detailed information on the adhesives used in infusion sets and sensors is rarely available: adhesive manufacturers are often reluctant to disclose their exact composition. Furthermore, in producing these devices, different materials can be mixed together, making it difficult to identify which component contained in the adhesive tapes induces contact allergy. Accurate knowledge of potential allergens is fundamental to minimize the risk of false negatives when performing patch testing. The prevalence of ACD caused by technological devices in T1D patients has not yet been well established. Studies available in the literature have shown heterogeneous rates varying from 5.5 to 8.4% (24, 33, 34).

The choice of the most suitable treatment for acute skin lesions is not easy and varies according to the subtype of contact dermatitis. Most of our study population use topical corticosteroids often associated with local application of antibiotics. Topical corticosteroids represent the gold standard for the treatment of ACD, but their prolonged use can cause epidermal atrophy, damage the skin barrier, and increase sensitivity to irritants (35). According to recent evidence, the first-line treatments of ICD consist of physical protection of skin and protective cream/emollient as prescribed to 23.4% of our patients. The use of topical antihistamines should be reserved for the management of mild skin reactions suggestive of irritant contact urticaria, which is clinically characterized by a typical response to the eliciting dose with wheal, flare, and itching on the skin at the site of contact (22, 36). In some cases, the application of topical antibiotics may be helpful to reduce the risk of bacterial infections (37). Moreover, the use of systemic corticosteroids is needed in the presence of concomitant extensive lesions (22, 36). Therefore, the prescription of acute treatment should be personalized to the patient, and close collaboration with a pediatric allergy team with wide experience in both clinical and diagnostic aspects of contact allergy is desirable (38).

Several tools to prevent the appearance of dermatological complications have recently been put forward. Messer et al. proposed a practical guideline to preserve the skin integrity of diabetic patients who chronically use devices for the management of the disease. The authors focused on the importance of correct device placement, good skincare, careful patch removal, and promoting healing of the skin affected by lesions. In addition, they suggested the use of some techniques to minimize the risk of hypersensitivity reactions (21). Among these, the use of potentially hypoallergenic patches was the most frequently reported in our study. It consists of the application of hydrocolloid and/or silicone-based plasters used to block adhesives from sensors and pumps from direct contact with the skin. Unfortunately, hydrocolloid may contain colophonium-like derivatives, thus they are not indicated in colophonium-sensitized individuals. Liquid or spray barrier films were also commonly used in our study. These products are applied before the insertion of insulin pumps or glycemic sensors and can offer sufficient protection from offending agents contained in adhesives. However, other studies showed that the use of barrier sprays is quite limited and some patients often experience incomplete and transient benefits, especially in cases of contact dermatitis due to glycemic sensor that are worn on the skin for up to 14 days (33). Another interesting preventive solution is the off-label use of fluticasone propionate nasal spray, a steroid commonly used to treat acute rhinitis. Recently, Paret et al. reported the benefits of applying fluticasone propionate spray to the skin lesions of 12 patients with skin disease related to the use of CGM systems. The authors demonstrated that the administration of two puffs of this nasal steroid to the skin area before positioning the glycemic sensor was useful to prevent the occurrence of local irritation or dermatitis. Moreover, no significant metabolic or glycemic deterioration was

reported (39). Only one patient of our study cohort used fluticasone propionate nasal spray with satisfactory results. Randomized controlled trials with long-lasting follow-up are awaited to evaluate the effectiveness and safety of this preventive measure.

Regarding glycemic outcomes, no differences in HbA1c values were found between the period before and after the onset of skin lesions. However, this finding does not allow to rule out a potential relationship between contact dermatitis and worse glycemic control. As is known, HbA1c reflects average glucose levels of the previous 2-3 months, but does not identify the magnitude and frequency of glucose variation. Other glucose metrics extracted by analysis of CGM systems (i.e. time within range, time below range, time above range, and coefficient of variation) are currently recognized as appropriate and useful clinical targets that complement HbA1c in the evaluation of glycemic control (40). Unfortunately, these data could not be evaluated as some patients had to discontinue the use of CGM systems due to skin complications. Indeed, the most alarming result of our study is related to the relatively high rate of patients (38%) who were forced to discontinue the use of CSII and/or CGM systems. Despite different preventive measures, the most severe cases of contact dermatitis still remain unresolved and avoiding offending agents contained in the adhesives of technological devices represents the only available therapeutic choice. Therefore, close contact between diabetes specialists and manufacturers should be established to minimize the use of some well-known sensitizers in the adhesives.

In conclusions, contact dermatitis is a fairly common dermatological complication in patients with T1D and it may represent a serious hindrance to the increasing spread of new technologies. Despite the magnitude of the issue, there are no clear, universal recommendations on the most suitable management plan for contact dermatitis caused by the use of diabetes devices. Our study confirms the importance of establishing close collaboration both with pediatric allergy specialists to prescribe the most suitable treatment and with manufacturing companies to ensure that adhesives of technological devices are free of harmful, well-known sensitizers.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was exempt from ethical committee approval since it was confined to anonymized and unidentifiable data routinely collected at our Diabetes Centre. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SP wrote and drafted the paper. GS conceived and designed the study. FG, SA, and LC collected data. GBP and FL contributed to the discussion and reviewed the paper. The paper has been read and approved by all the authors and each author considers that the paper represents their honest work.

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Hybrid Close-Loop Systems Versus Predictive Low-Glucose Suspend and Sensor-Augmented Pump Therapy in Patients With Type 1 Diabetes: A Single-Center Cohort Study

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Introduction: Predictive low-glucose suspend (PLGS) and hybrid closed-loop (HCL) systems may improve glucose control and quality of life in type 1 diabetic individuals. This is a cross-sectional, single-center study to compare the effect on metabolic control and glucose variability of PLGS and HCL systems as compared to standard sensor-augmented pump (SAP) therapy.

Methods: We retrospectively analyzed 136 adults (men/women 69/67, mean age 47.3 ± 13.9 years) with T1D on insulin pump therapy, divided accordingly to type of insulin pump system (*group 1*: SAP, 24 subjects; *group 2*: PLGS, 49 subjects; *group 3*: HCL, 63 subjects). The groups were matched for age, gender, years of disease, years of CSII use, and CGM wear time.

Results: The analysis of CGM metrics, in the three groups, showed a statistically significant different percentage of time within the target range, defined as 70–180 mg/dl, with a higher percentage in group 3 and significantly less time spent in the hypoglycemic range in groups 2 and 3. The three groups were statistically different also for the glucose management indicator and coefficient of variation percentage, which were progressively lower moving from group 1 to group 3. In the HCL group, 52.4% of subjects reached a percentage of time passed in the euglycemic range above 70%, as compared to 32.7% in those with PLGS and 20.2% in those with SAP. A positive correlation between the higher percentage of TIR and the use of auto-mode was evident in the HCL group. Finally, the three groups did not show any statistical differences regarding the quality-of-life questionnaire, but there was a significant negative correlation between CV and perceived CSII-use convenience ($r = -0.207$, $p = 0.043$).

Conclusion: HCL systems were more effective in improving glucose control and in reducing the risk of hypoglycemia in patients with type 1 diabetes, thereby mitigating risk for acute and chronic complications and positively affecting diabetes technologies' acceptance.

Keywords: T1D, HCL, insulin pump, SAP, PLGS, time in range

INTRODUCTION

Insulin therapy in type 1 diabetes (T1D) is a burden in diabetes management. Patients have to face multiple challenges due to the complexities of insulin therapy and the variability in glucose levels from multiple factors, like meals, exercise, illness, and antecedent hypoglycemia. The last three decades showed the emergence of innovative diabetes technologies aimed at improving outcomes and easing the burden of diabetes management (1). Advantages in glucose monitoring and in insulin delivery allow better glycemic control, lower glycemic variability, and fewer hypoglycemic events (2). The development of sensor-augmented pump (SAP) therapy, which is the combination of continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM), has permitted reductions in DKA and severe hypoglycemia (3, 4). More recently, control algorithms were incorporated in SAP. These features allow the discontinuation of insulin delivery when hypoglycemia is predicted by the algorithm (PLGS—*predictive low-glucose insulin suspend*). Pumps using the algorithm were introduced in Europe and Australia in 2015 with the MiniMed 640G pump (Medtronic Diabetes), followed by a Tandem t:slim X2 insulin pump with Basal-IQ PLGS Technology. In RCTs, it has been demonstrated that the utilization of PLGS system technology reduces exposure to hypoglycemia (5, 6). In early 2017, the first hybrid close-loop (HCL) system (MiniMed 670G pump, Medtronic) was introduced in the USA, which utilizes a PID (proportional–integral–derivative) algorithm with insulin feedback (7). In *auto-mode*, this system can provide automated glucose-responsive insulin delivery and improve the maintenance of glucose levels within a healthy range (8). Otherwise, the Control-IQ technology in the t:slim X2 pump uses a model predictive control (MPC) algorithm that predicts future glucose levels based on CGM data and automatically adjusts insulin doses, aiming at keeping blood glucose levels in the target range (9, 10). Finally, the MiniMed 780G (Medtronic) is a new advanced HCL (AHCL) system that incorporates automated correction bolus doses, using the PID algorithm and fuzzy logic control (11). The aim of this study was to evaluate the effectiveness of different categories of insulin pump in maintaining improved metabolic control in T1D subjects. Moreover, we analyzed how new diabetes technology affects quality of life (QOL) and the perceived benefits by the users, in real-life settings.

METHODS

This study was a retrospective and cross-over trial, conducted at Unit of Diabetology and Endocrinology in Fatebenefratelli-Sacco Hospital, Milan, between December 2020 and June 2021. The main inclusion criteria were adult patients with type 1 diabetes aged over 18 years, who used SAP therapy for at least 6 months. Patients were divided into three groups (**Table 1**): group 1 ("SAP group"): CSII and CGM without features; group 2 ("PLGS group"): pumps with features that suspend insulin delivery

TABLE 1 | Different types of insulin pumps used in our study.

	n (%)
GROUP 1 (n=24)	
Omnipod® (*Insulet Corporation*)	6 (25)
Insight (*Accu-Check®*)	7 (29.2)
Combo (*Accu-Check®*)	3 (12.5)
Solo (*Accu-Check®*)	1 (4.2)
DANA RS (*B.C. Trade*)	1 (4.2)
Equil (*B.C. Trade*)	1 (4.2)
YpsoPump (*Ypsomed*)	1 (4.2)
T:slim X2 (*Tandem Diabetes Care*)	1 (4.2)
MiniMed™ 640 g (*Medtronic*) without *Medtronic* CGM	3 (12.5)
GROUP 2 (n=49)	
T:slim X2 (Tandem Diabetes Care) with Basal-IQ	17 (34.7)
MiniMed™ 640 g (Medtronic)	19 (38.8)
MiniMed™ 670 g (Medtronic) without Auto-Mode	10 (20.4)
MiniMed™ 780 g (Medtronic) without SmartGuard	3 (6.1)
GROUP 3 (n=63)	
T:slim X2 (Tandem Diabetes Care) with Control-IQ	6 (9.5)
MiniMed™ 670 g (Medtronic)	42 (66.7)
MiniMed™ 780 g (Medtronic)	15 (23.8)

before low and/or suspend, at low; and group 3 ("HCL group"): HCL and advanced HCL (AHCL) system. Key exclusion criteria were decompensated diabetes, defined as HbA1c >11% or one or more episodes of ketoacidosis requiring admission to hospital in the past 6 months, pregnancy, non-continuous use of CGM, defined as sensor wear time <60%, non-continuous use of the pump, concomitant disease that affects metabolic control or interpretation of HbA1c levels, and use of antidiabetic drugs other than insulin. Moreover, we excluded patients who did not regularly use carbohydrate counting and an insulin bolus calculator. Written informed consent was obtained from each participant, and the study was approved by the Local Ethics Committee. All participants regularly used carbohydrate counting and were individually trained regarding the features of CSII. All patients had at least a visit every 4 months. We collected data available at the last clinic visit, within the study period, including medical history, blood samples, and 14-day AGP (ambulatory glucose profile). We collected data regarding medical history, micro-macrovascular complications, and last blood analysis. Hemoglobin A1c level was measured with a Diabetes Control and Complications Trial standardized analyzer. Data regarding AGP, in particular percentage time spent in hypoglycemic (<54 mg/l and 54–69 mg/dl), euglycemic (70–180 mg/dl), and hyperglycemic (181–250 mg/dl, >250 mg/dl) ranges; CGM-measured mean glucose concentration; estimated HbA1c (eHbA1c); standard deviation (SD) and coefficient of variation (CV) of CGM-measured glucose concentrations; and percentage of sensor use and insulin requirement were collected. To assess quality of life (QOL) regarding treatment with different types of CSII, each patient completed a questionnaire for people with T1D (12), which is divided into three major areas: "Convenience" (CSII-QOL-C), "Social restrictions" (CSII-QOL-SR), and "Psychological problem" (CSII-QOL-PB). The data are expressed as mean ± SD for continuous variables, or n (%) for dichotomic variables. Differences between groups were analyzed using ANOVA or the unpaired t-test. A *post-hoc* analysis, with Bonferroni test, was applied for every ANOVA test. AGP profiles were obtained from the report of *CareLink System* (Medtronic), *Diasend*, *Clarity* (Dexcom), and *DMS Eversense* (Senseonics). All p values were two-sided. $p < 0.05$ was considered significant. Analyses were conducted with IBM SPSS Statistic, version 24.0 (SPSS Inc., Chicago, IL).

RESULTS

The study population consisted of 136 T1D patients, men/women 69/67, the mean age was 47.3 ± 13.9 years, and the duration of diabetes was 25.6 ± 12.6 years. All subjects were divided into three groups, accordingly to characteristics of the insulin pump system used (**Table 1**). Demographic, biochemical, and anthropometric characteristics of groups as well as percentage of microvascular and macrovascular complications were similar among groups. Groups were matched for age, sex, BMI, duration of diabetes, years of CSII use, and frequency in the use of the glucose sensor (**Table 2**). All subjects had undergone SAP therapy for at least 6 months; the percentage of patients that switched from MDI to CSII in the last 12 months was 20.8% (5/24) in group 1, 28.6% (14/49) in group 2, and 38.1% (24/63) in group 3. Plasmatic HbA1c value was not statistically different among groups, even if it was lower in HCL-treated subjects. Also, the daily bolus insulin dose was slightly higher in group 1 (**Table 2**). The analysis of APG among the three groups (**Table 3**) showed a statistically significant reduction in mean glucose concentration and eHbA1c; consensually, also CV and SD progressively decreased from group 1 to group 3. The analysis of time spent in different glycemic ranges is well described in **Figure 1**. The three groups showed a progressive increase in the percentage of TIR, moving from group 1 to group 3 (**Figure 1**). TBR2, which indicates glycemia values <54 mg/dl, significantly reduced from group 1 to group 2 and from group 1 to group 3, without any statically significant difference between group 2 and group 3 (**Figure 1**). Conversely, only group 3 showed a significant reduction in glycemic values above 250 mg/dl (TAR2), compared to group 1 and group 2 (**Figure 1**). A total of 30/63 subjects (52.4%) in group 3 achieved >70% of time spent in the target range, compared to 16/49 (32.7%) in group 2 and 5/24 (20.2%) in group 1 ($p = 0.003$, **Figure 2**). Among patients in group 3, there was a positive correlation between time spent in auto-mode and higher percentage of TIR ($r = 0.356$, $p = 0.009$). There was no difference in the total CSII-QOL score between participants among the three groups of treatment (**Table 3**). However, we found significant and

TABLE 2 | Patients characteristics.

	Group 1 (n=24)	Group 2 (n=49)	Group 3 (n=63)	P
Age (yrs)	47.1±12.1	48.4±15.9	48.6±13.1	0.91
Male (n, %)	12, 50	19, 38.7	36, 42.9	0.15
Duration of DM (yrs)	25.04±9.5	26.3±13.1	25.3±13.1	0.88
CSII use (yrs)	4.1±2.3	5.5±4.5	3.7±3.9	0.06
BMI (Kg/m^2)	25.4±3.7	25.5±4.2	26.7±9.0	0.59
HbA1c (%)	7.6±1.4	7.3±0.8	7.2±0.7	0.24
U-Albuminuria (mg/L)	33.8±88.5	8.1±9.3	9.6±16.4	0.07
Serum Creatinine (mg/dl)	0.9±0.2	0.86±0.2	0.85±0.18	0.41
Basal Insulin dose (U/die)	23.5±10.1	21.5±12.3	19.1±9.0	0.21
Bolus Insulin dose (U/die)	37.1±10.1	18.9±9.7	21.9±11.6	0.05

CSII, continuous subcutaneous insulin infusion; BMI, body mass index; HbA1c, glycated hemoglobin.
Data are expressed as mean ± SD.

TABLE 3 | Overall CGM variables and Quality of Life questionnaire score.

	Group 1 (n=24)	Group 2 (n=49)	Group 3 (n=63)	P
CGM variables				
CGM use (%)	87.0±19.8	82.9±18.2	85.4±15.7	0.624
Mean glucose (mg/dl)	166.6±21.9	163.6±21.9	150±15.6	0.003
eHBA1c (%)	7.3±0.71	7.1±0.73	6.8±0.4	0.004
CV (%)	36.8±6.9	32.8±6.1	31.3±4.1	0.001
SD (mg/dl)	55.4±9.9	54.0±11.8	47.5±9.2	0.002
TBR 2 (<54 mg/dl)	1.35±2.3	0.45±0.6	0.18±0.5	0.000
TBR 1 (<70 mg/dl)	2.5±2.48	1.9±1.8	1.7±1.5	0.220
TIR (70-180 mg/dl)	59.1±13.6	62.3±17.20	70.6±12.9	0.002
TAR 1 (>180 mg/dl)	26.90±9.9	25.6±11.1	23.2±11.3	0.283
TAR 2 (>250 mg/dl)	10.7±8.1	9.3±11.3	4.5±4.7	0.003
Questionnaire QOL score				
Total	97.6±15.6	95.7±12.8	97.6±11.4	0.741
"Convenience" (CSII-QOL-C)	26.8±2.7	26.7±2.5	27.1±2.0	0.675
"Social restrictions" (CSII-QOL-SR)	39.2±6.8	39±6.6	39.5±6.3	0.945
"Psychological problem" (CSII-QOL-PB)	30.6±8.5	29.8±6.8	31.3±5.9	0.545

CGM, continuous glucose monitoring; CV, coefficient of variation; SD, standard deviation; TAR, time above range; TBR, time below range (%); TIR, time-in-range. Data are expressed as mean ± SD.

negative correlations between CV and CSII-QOL-C domain score (r = -0.207, p = 0.043).

DISCUSSION

The purpose of this cross-sectional, retrospective study was to evaluate benefits of different CSII systems, in terms of clinical outcome and quality of life, in real-life settings. A cohort of T1D patients on insulin pump treatment was divided into three groups, according to the type of CSII system used. All groups were comparable regarding sensor wear time, and all participants regularly used the automatic bolus insulin calculator feature, allowing a real comparison between the different categories. To our knowledge, there are no published QOL findings, with current available systems in real-life settings, and the examined population is quite large. The main limitations of this study are the retrospective nature, the lack of control group in MDI treatment, and the fact that

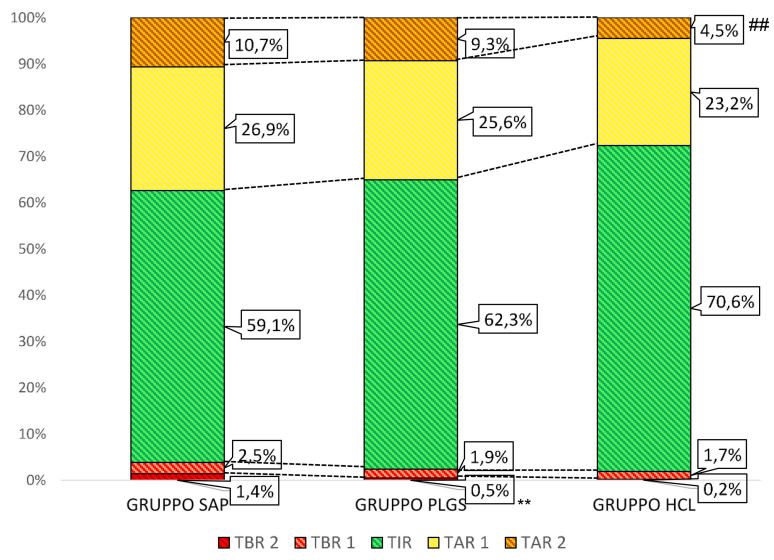

FIGURE 1 | Percentage of time passed in different glycaemia ranges among the three groups of CSII. TAR 1, time above range (181–250 mg/dl); TAR 2, time above (>250 mg/dl), TBR 1, time below range (69–54 mg/dl); TBR 2, time below range (<54 mg/dl); TIR, time in range (70–180 md/dl). ** p values <0.01, HCL group versus PLGS group ## p values <0.01, PLGS group versus SAP group.

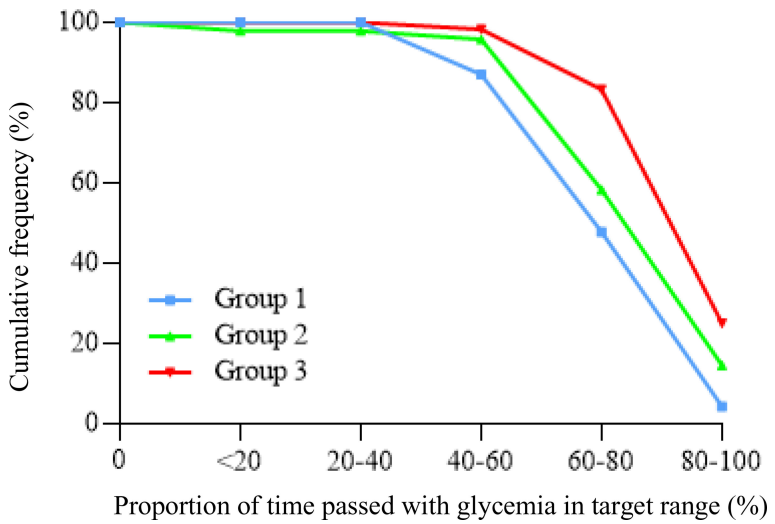

FIGURE 2 | Cumulative frequency of patients reaching target time in range values (>70%) among the three groups of CSII.

participants had different timings of CSII initiation, however comparable between the three groups. Clinically significant differences were found in the subgroup of patients using hybrid close-loop and advanced hybrid close-loop systems. Participants of the HCL group showed a percentage of time spent in the euglycemic range of 11.5% higher than the SAP group, and 8.3% higher than the PLGS group, with 52.4% of subjects achieving the target range proposed by the international consensus on time in range (>70%) (13). These results agree with previous studies that showed similar differences of time in the euglycemic range, demonstrating an increase in TIR values between 5% and 10% with the HCL system (8, 14). The utility of the algorithm was again confirmed by a strong positive correlation, in the HCL group, between TIR values and time spent in auto-mode ($r = 0.356$ and $p = 0.009$). Reaching a higher percentage of time in the euglycemic range resulted in a consensual significant reduction of time spent both in hyperglycemia and hypoglycemia ranges. Exposure to the hyperglycemia range (>250 mg/dl) in the HCL group, was reduced by 6.2%, compared to the SAP group, and 3.1%, compared to the PLGS group, while the reduction was not significant between SAP and PLGS groups, confirming the effectiveness of basal insulin modulation in preventing values above the target range. The prevention of severe hypoglycemia (<54 mg/dl) was not different between HCL and PLGS groups, as expected, but both groups showed a significant reduction compared to the SAP group, -0.9% between SAP and PLGS and -1.17% between SAP and HCL systems. These data are similar to those obtained in the PROLOG and SMILE studies (15, 16) that reported a reduction of glycemia values <54 mg/dl between -0.1% and 3.3% with suspend before low technology, while Garg and colleagues reported a reduction of 0.5% of severe hypoglycemia passing from PLGS to HCL systems (8). The improvement in time spent in the euglycemic range and reduction of glycemia excursions resulted in lower values of glucose variability, expressed as coefficient of variation of CGM-measured glucose values, reduced by 14.9% in the HCL group compared to the SAP group. Thus, together with improvement in estimated HbA1c and mean glucose values, it permitted the HCL group to reach all targets of treatment proposed in the consensus of Advanced Technologies & Treatments for Diabetes (13). Regarding quality-of-life questionnaires, previous studies concluded that technological advancement, used to support people with T1D to manage their diabetes, is also associated with psychosocial benefits (17–20). Previous studies suggest a qualitative difference between using MDI and CSII which centers on experiencing metabolic improvements, feelings of ease, personal control, and confidence in habituating to more complex technology. The REPOSE trial, comparing CSII and MDI, focused on improvements in diabetes self-management due to structured education and ongoing support, also indicating potentially stressful elements in introducing a new and complex technology into everyday life (21). Despite positive evidence regarding the impact of SAP use on QOL, compared to MDI (22, 23), little is known about how recent innovative pumps may influence QOL. Bergenstal et al. examined the impact of the LGS (low-glucose suspend) feature, compared to traditional SAP. LGS did contribute to a decrease in nocturnal hypoglycemia, but without any significant difference in QOL outcomes (24). Published data about QOL findings with HCL and AHCL pumps are still too limited and did not allow any solid conclusion. In our study, no significant differences were found in QOL among different types of insulin pumps; however, this was quite expected, as all subjects used CSII technology and there was a lack of control group in MDI treatment. Starting new pump therapy does take extra effort from both the diabetes team and the patient (21). Based on this, the negative correlation between perceived convenience in CSII use and higher CV values ($r = -0.207$, $p = 0.043$) underlines the relation between a better metabolic control and satisfaction for technology (20). In conclusion, our study demonstrates that HCL and AHCL

systems provide better glycemic control, compared to standard sensor-augmented pumps but also to suspend before low technology, allowing a higher percentage of time in the euglycemic range, lower glucose variability, and lower hypoglycemic risk. These aspects, in particular the reduction of glucose variability, point to a promising trend in improving quality of life and higher acceptance of CSII systems, together with a reduction of acute and chronic complications related to diabetes disease.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Registro Sperimentazioni n 2020/ST/449, Comitato Etico Milano Area 1, ASST Fatebenefratelli Sacco, Milano Italy. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PF, ML, AR, PM, and GZ designed the study. AG, LP, AB, LV, SA, and GZ collected the data. IC and ML performed the statistical analysis. LM, IP, VC, and ML wrote the draft manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Use of Continuous Glucose Monitoring in the Assessment and Management of Patients With Diabetes and Chronic Kidney Disease

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In developed countries, diabetes is the leading cause of chronic kidney disease (CKD) and accounts for 50% of incidence of end stage kidney disease. Despite declining prevalence of micro- and macrovascular complications, there are rising trends in renal replacement therapy in diabetes. Optimal glycemic control may reduce risk of progression of CKD and related death. However, assessing glycemic control in patients with advanced CKD and on dialysis (G4-5) can be challenging. Laboratory biomarkers, such as glycated haemoglobin (HbA_{1c}), may be biased by abnormalities in blood haemoglobin, use of iron therapy and erythropoiesis-stimulating agents and chronic inflammation due to uraemia. Similarly, glycated albumin and fructosamine may be biased by abnormal protein turnover. Patients with advanced CKD exhibited heterogeneity in glycemic control ranging from severe insulin resistance to 'burnt-out' beta-cell function. They also had high risk of hypoglycaemia due to reduced renal gluconeogenesis, frequent use of insulin and dysregulation of counterregulatory hormones. Continuous glucose monitoring (CGM) systems measure glucose in interstitial fluid every few minutes and provide an alternative and more reliable method of glycemic assessment, including asymptomatic hypoglycaemia and hyperglycaemic excursions. Recent international guidelines recommended use of CGM-derived Glucose Management Index (GMI) in patients with advanced CKD although data are scarce in this population. Using CGM, patients with CKD were found to experience marked glycemic fluctuations with hypoglycemia due to loss of glucose and insulin during haemodialysis (HD) followed by hyperglycemia in the post-HD period. On the other hand, during peritoneal dialysis, patients may experience glycemic excursions with influx of glucose from dialysate solutions. These undesirable glucose exposure and variability may accelerate decline of

residual renal function. Although CGM may improve the quality of glycemic monitoring and control in populations with CKD, further studies are needed to confirm the accuracy, optimal mode and frequency of CGM as well as their cost-effectiveness and user-acceptability in patients with advanced CKD and dialysis.

Keywords: continuous glucose monitoring, end stage kidney disease (ESKD), dialysis, diabetes, type 2 (non-insulin-dependent) diabetes mellitus, diabetic kidney disease, diabetic nephropathy

INTRODUCTION

Diabetic kidney disease (DKD) is now the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) in many countries. In 2014, DKD accounted for 50% of patients with ESKD in developed world (1). Data from the United States (US) suggested a slower decline in ESKD incidence compared with other diabetic complications including cardiovascular disease. The US Renal Registry reported a steady increase in incidence of ESKD due to diabetes up to 47% in 2017, compared with 15% in 1985 (2). In the Hong Kong Renal Registry, diabetes was the cause of ESKD in 50% of patients which had replaced glomerulonephritis as the leading cause of renal replacement therapy since 1998 (3).

Patients with diabetes and CKD have increased risk of morbidity and premature mortality than those without renal complications. In the Hong Kong Diabetes Register, patients with CKD had 63% higher risk in all-cause mortality than their non-CKD counterparts, after adjusting for factors such as age, body mass index (BMI), blood pressure and use of oral glucose lowering drugs (OGLDs) (4). Patients with CKD had high risk of cardiovascular events which accounted for 40-50% of mortality in those with estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2. This excess risk could not be explained by comorbid factors such as hypertension and dyslipidaemia (5) and might be attributed to additional factors such as vascular calcification, chronic inflammation and myocardial fibrosis (6). Patients with CKD are at increased risk and more vulnerable to hypoglyceamic episodes (4). In a cohort of over 30,000 US veterans with diabetes transitioning to dialysis, the frequency of hypoglycemia-related hospitalizations was associated with higher post-ESKD mortality in a dose-dependent manner (7).

Optimal glycemic control had been shown to delay progression of CKD and reduce death rate in diabetes. In the Diabetes Control and Complication Trial, 1441 patients with type 1 diabetes (T1D) were randomized to receive intensive or conventional insulin treatment. The risk of microalbuminuria was reduced by 34% in the intensive treatment group after at least four years of follow-up (8). The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial enrolled high risk patients with long duration of type 2 diabetes, (T2D), many of whom had prior history of complications. The in-trial reductions in the risk of ESKD was maintained during a total follow-up period of 9.9 years with a hazard ratio of 0.54 (29 events in the intensive treatment group and 53 events in the usual treatment group) (9). In a randomized controlled study of Japanese patients with 110 T2D lasting for 8 years, intensive insulin therapy reduced the rate of progression in nephropathy compared with conventional treatment (10). In the Dialysis Outcomes and Practice Pattern Study (DOPPS) including 9201 patients on dialysis with either T1D or T2D, there was a U-shaped relationship between HbA_{1c} and all-cause mortality. Using HbA_{1c} 7 – 8% as reference, there was 38% increased risk of mortality in patients with HbA_{1c} ≥9% and 21% for those with HbA1c <7% (11). Based on the available evidence, The Kidney Disease Improving Global Outcome (KDIGO) 2020 guideline recommended an optimal HbA_{1c} target range of 6.5-8.0% for patients with diabetes and CKD, with emphasis on individualization of targets taking age, comorbidities, life expectancy and hypoglycaemia risks into consideration (12).

Optimal glycemic management in patients with diabetes and CKD can be challenging, particularly in those with advanced CKD. Reasons include progressive decline in beta-cell function and increase in insulin resistance along with increased risk of severe hypoglycaemia and limited choices of OGLDs. Indeed, the heterogeneity in glycemic control amongst patients with CKD represents inter- and intra-individual variations amongst multiple interacting factors including insulin secretion, insulin resistance, renal clearance of insulin, renal gluconeogenesis and renal function. Increased insulin resistance in early CKD may be triggered by metabolic acidosis, uremic toxins, and chronic inflammation associated with reduced kidney function (13–16). With progression of CKD, the prolonged glucose-lowering effects of oral glucose lowering-drugs (OGLD) including insulin, together with reduced renal gluconeogenesis, shifts the balance towards increased risk of hypoglycaemia (17, 18). In patients with ESKD, around 30% had "burn-out diabetes" who required reduction or discontinuation of insulin treatment and OGLDs (18). In these patients, initiation of dialysis may remove uremic toxins with restoration of insulin sensitivity. Patients with "burnt-out diabetes' often require only low-dose insulin treatment (19). On the other hand, the dialysis regimen and glucose content of dialysates can significantly influence day-to-day glucose profiles.

One of the greatest challenges in optimizing glycemic management is accurate assessment of glucose control. Conventional markers such as glycated haemoglobin (HbA_{1c}),

Abbreviations: CKD, Chronic Kidney Disease; ESKD, End-Stage Kidney Disease; OGLD, Oral Glucose Lowering Drugs; eGFR, estimated Glomerulus Filtration Rate; KDIGO, Kidney Disease Improving Global Outcome; CGM, Continuous Glucose Monitoring; SMBG, Self-Monitoring Blood Glucose; PD, Peritoneal dialysis; HD, Haemodialysis; TAR, Target Above Range; TIR, Target In Range; TBR, Target Below Range; CV, Coefficient of Variation.

fructosamine or glycated albumin may be less reliable in in advanced CKD and ESKD. With the emergence of continuous glucose monitoring (CGM), this might be a helpful alternative in assessing and managing diabetes patients with advanced CKD and ESKD. The aim of this narrative review is to summarise current clinical evidence on the accuracy and utility of CGM in CKD patients. We have reviewed the literature on clinical reports, observational studies and clinical trials of use of CGM in CKD. Due to potential issues of sensor performance and the impact of dialysis regimens, we have devoted special attention to use of CGM in patients on haemodialysis and peritoneal dialysis, a challenging group who are prone to both hypoglycemic and hyperglycemic excursions.

CHALLENGES IN GLYCEMIC ASSESSMENT IN CKD

The monitoring of glycemic status in patients with diabetes and CKD including ESKD is challenging. HbA_{1c}, the gold standard as a laboratory glycemic marker, can be influenced by multiple factors in CKD. The formation of HbA_{1c} is dependent on the intensity and duration of non-enzymatic interaction between blood glucose and hemoglobin. At any one time, patients may have a mixture of erythrocytes with different ages and varying degrees of exposure to glucose. Therefore, agents that alter erythropoiesis and lifespan of red blood cells will affect HbA_{1c}. For example, HbA_{1c} can be biased towards high values by iron or vitamin B12 deficiency due to reduced synthesis of red blood cells with increased relative amount of HbA_{1c}. On the other hand, HbA_{1c} can be biased towards low values by iron therapy and use of erythropoietin stimulating agents (ESA) with increased turnover of red blood cells (20, 21). The uremic environment in patients with advanced CKD can stimulate carbamylation of haemoglobin which may interfere with HbA_{1c} assays using ion-exchange method, but this can be avoided by using other methods such as high-pressure liquid chromatography (22).

Alternative glycemic indicators such as glycated albumin (GA) and fructosamine have their own limitations in CKD. Extracellular GA is more susceptible to glycation than intracellular hemoglobin (23). Also, GA is unaffected by factors such as iron therapy and ESA frequently used in patients with CKD which can affect HbA_{1c} (21). Due to the shorter half-life of albumin, GA reflects recent glycemic control lasting for 2-3 weeks. However, GA can be affected by albumin metabolism. In patients with low albumin state or increased protein turnover due to chronic inflammation, GA can be falsely low or high (24). In patients treated with peritoneal dialysis (PD) with increased protein loss, GA value may underestimate true glycaemia (25). Although GA can be corrected for serum albumin to reflect the true distribution (26), GA can be affected by oxidative and uremic environments, as well as reduced renal clearance of advanced glycation end products, resulting in positive bias (27).

Fructosamine are ketoamines formed by glycation of albumin and other less abundant serum proteins (28). Although this biomarker involves a wider spectrum of glycated proteins, fructosamine suffers similar bias as GA due to abnormal albumin metabolism and increased protein loss in patients with CKD. In patients with diabetes without CKD and normal serum albumin level, increased albuminuria was associated with low fructosamine value. Besides, fructosamine is sensitive to the fluctuation of serum levels of immunoglobulins and low-molecular-weight molecules (29). In patients with CKD, the uremic environment with altered immunoglobulin levels may affect fructosamine levels (30).

OVERVIEW OF CGM

The introduction of continuous glucose monitoring (CGM) offers an alternative for more reliable and comprehensive glycemic evaluation in patients with CKD. Adherence to self-monitoring of blood glucose (SMBG) is often poor due to inconvenience of finger-pricking. In a survey conducted in China, only 40% of patients adhered to the recommended SMBG frequencies (31). Most commercially-available CGM devices are minimally-invasive by inserting a small filament into subcutaneous tissue for measurement of glucose in interstitial fluid. There is a dynamic equilibrium between interstitial glucose and blood glucose due to diffusion dependent on concentration gradient. The interstitial glucose is absorbed into the filament of the CGM device by capillary action. The concentration of interstitial glucose is determined by electrochemical reaction in the sensor (32). Minute-to-minute interstitial glucose readings are transmitted to and displayed in a mobile device, either a reader or smartphone app.

In general, CGM systems can be classified into three categories based on their principles of operation and clinical usage. For professional CGM devices, readings are principally used for glycemic assessment by health care professionals in clinical trial settings which may be blinded or unblinded to the user. Real-time CGM (rt-CGM) devices display readings to the user continuously and can incorporate hypoglycemic or hyperglycemic alerts and trend prediction. The intermittently-scanned or flash CGM devices display readings to user only when the user scans the transmitter (33). Real-time CGM and flash CGM are gaining popularity to facilitate self-monitoring in diabetes. In some countries, CGM devices are reimbursed or funded by public health systems for patients with T1D, including those on dialysis, and some patients with T2D receiving intensive insulin therapy (34).

PERFORMANCE OF CGM SENSORS IN ADVANCED CKD AND DIALYSIS

The performance of CGM sensor is dependent on the enzymatic electrochemical reactions which may be subject to multiple interferences (**Figure 1**). In early CGM devices, interstitial glucose was detected by glucose oxidase-peroxidase method (36). This method continues to be used by some CGM systems

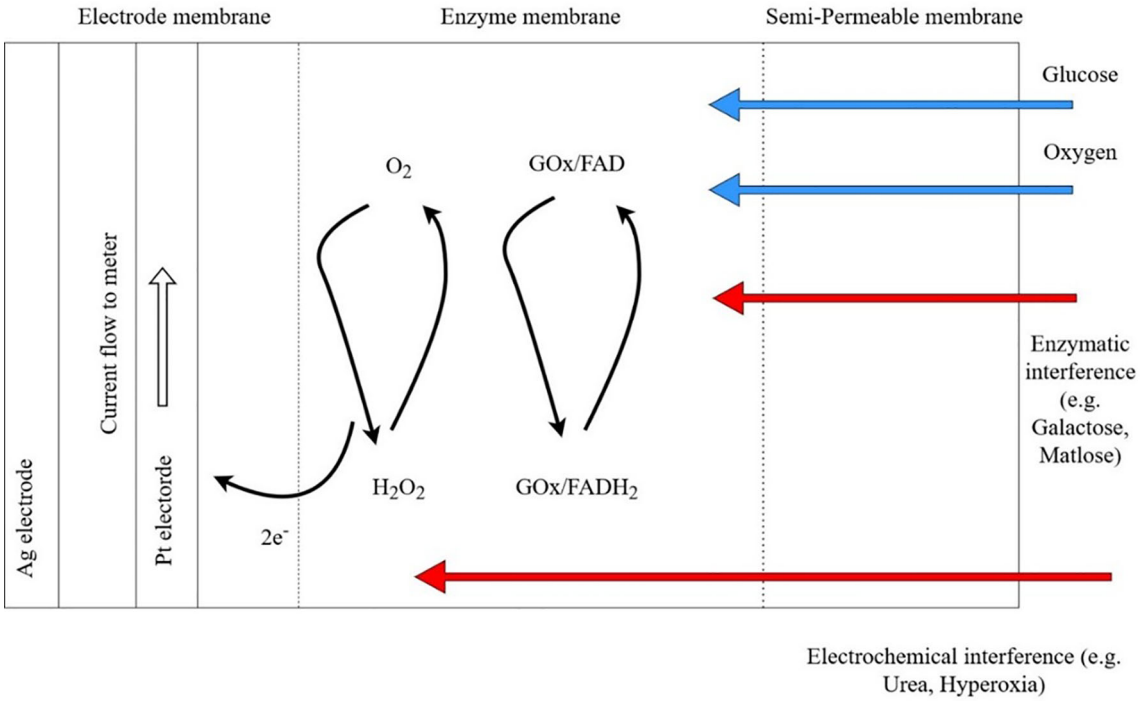

FIGURE 1 | Potential enzymatic and electrochemical interference by substances commonly encountered in patients with chronic kidney disease using continuous glucose monitoring (CGM) systems. In the presence of oxygen (O_2), energy in glucose (G) is gradually released in the form of electrons in a series of electrochemical chains catalyzed by Glucose oxidase (GO), an enzyme with Flavin Adenine Dinucleotide (FAD) as cofactor. Released electron is captured by the electrode membrane to generate electric current between platinum electrode and silver electrode. Platinum and silver are chosen for their excellent biocompatibility, electro-conductivity and non-toxicity. Blue arrows indicate normal substrate for electrochemical chain. Red arrows indicate potential interference of CGM sensors by for example galactose, maltose from peritoneal dialysis fluids. Enzymatic interference includes competitive inhibition on active site of GOx by inhibitors. Electrochemical interference includes interaction between the electrode and interfering chemicals that pass through the semi-permeable membrane. GOx, glucose oxidase; FAD, Flavin Adenine Dinucleotide; H_2O_2, hydrogen peroxide; Pt, platinum; Ag, Silver. Adapted from Boehm et al. (35).

due to the small size and rapid response time of the sensor. However, the electrodes often require pretreatment for attaching to the enzyme surface. Prolonged chemical reactions may pollute the surface of transducer and affect the electrochemical response (37). Both endogenous and exogenous substances may cause interference of the electrochemical sensing of the oxidase-peroxidase reaction.

In patients with advanced CKD, hypoxia or hyperoxia can give rise to false sensor glucose values by changing the oxygen concentration at the initiation of the glucose oxidase chain reaction (38). There had been reports on the effects of hematocrit in altering glucose readings of glucometers that use glucose-dehydrogenase or glucose-oxidase methods (39). Endogenous substances such as uric acid and uremia may affect sensor performance. Ogawa et al. demonstrated significant interference of uric acid, a reducing agent, on glucometers using glucose oxidase method comparing with laboratory glucose hexokinase reference (40) However, uric acid did not significantly interfere with sensor performance of a microdialysis-based CGM system (41). There are no dedicated studies evaluating the effect of pH on CGM sensor performance in ESKD. In critically ill patients, extreme pH <6.95 may affect the performance of point-of-care glucometers but not within pH range 6.97-7.84 (42). One study evaluated the effect of pH on the accuracy of CGM in a group pediatric intensive care patients and did not observe any significant effect (43). It is unknown whether fluid status might affect CGM performance in CKD patients due to lack of dedicated studies, however, a small study comparing hospitalized diabetes patients with and without congestive heart failure shown no differences in sensor accuracy (44).

Amongst exogenous substances, ascorbic acid, paracetamol, xylose, and ethanol have the potential to interfere with glucose oxidase sensors (45, 46) Other metabolites of icodextrin, such as maltose, also interfere with glucose dehydrogenase-based detectors using pyrroloquinoline quinone (GDH-PQQ) due to lack of selectivity on glucose (47). Use of GDH-PQQ glucometers can result in falsely elevated glucose readings in patients with PD using icodextrin dialysate. On the other hand, glucose-oxidase based capillary blood glucometers are mostly unaffected by icodextrin (35). Most commercially available CGM system use glucose-oxidase sensors although interference of CGM sensors by icodextrin had not been explored.

Performance of commercially available enzyme-based CGM systems have been validated in small numbers of patients on dialysis. For example, Yajima et al. evaluated accuracy of two CGM systems, the Freestyle Libre Pro and Medtronic iPro2™

with Enlite™ sensor versus capillary blood glucose in patients undergoing HD. For Freestyle Libre, 49% of readings fell within the Parkes Error Grid zone A and 51% in zone B. The Medtronic Ipro2™ sensor exhibited smaller deviations with 93% of readings within zone A and 6.3% in zone B which are regarded as clinically acceptable. Mean absolute relative difference (MARD) was 19.5% ± 13.2% for Freestyle Libre versus 8.1% ± 7.6% for Medtronic iPro2 (48). In a three-week study comparing the accuracy Freestyle Libre versus capillary blood glucose in 12 patients on haemodialysis, the MARD was found to be higher than people without ESKD (49). Only one study had evaluated the accuracy of Medtronic iPro2™ with Enlite™ sensor in 40 patients on PD. When compared with capillary blood glucose, MARD was 14%-19% (50). The accuracy of Dexcom sensors in haemodialysis is being investigated in ongoing trials (NCT04217161). Larger evaluation studies of sensor glucose against values measured by standard laboratory analyzers are needed in patients on different dialysis regimens.

USE OF CGM METRICS IN GLYCEMIC ASSESSMENT IN CKD

Several studies analyzed the correlation between HbA_{1c}, fructosamine, GA and average sensor glucose across different CKD stages (**Table 2**). In general, correlation between HbA_{1c} and mean sensor glucose values tend to fall in CKD stage G4-5, in part confounded by differences in use of iron and ESA and blood haemoglobin. Lo and colleagues reported good correlation of mean CGM-glucose with HbA_{1c} (r= 0.79) in patients with eGFR 30-59 ml/min/1.73m^2 but fell (r=0.34) in participants (n=43) with eGFR below 30 ml/min/1.73m^2 (51). In another study involving 25 patients with diabetes, the authors reported weak correlation (r=0.38) between mean CGM-glucose and HbA_{1c} in patients with eGFR <30ml/min/1.73m^2 (52).

Nathan et al. first estimated HbA_{1c} by linearly regressing mean sensor glucose with HbA_{1c} in intensively-treated patients with T1D in the Diabetes Control and Complication Trial (DCCT) (53). Bergenstal et al. later proposed the use of glucose management index (GMI) to reflect the relationship between CGM glucose and HbA_{1c} (54). However, these equations were derived predominantly from T1D and T2D patients with normal renal function and the reliability of the current GMI equation is unknown in patients with CKD (55). In one cohort, Zelnick and colleagues reported similar correlations between GMI and HbA_{1c} of 0.78 in patients with eGFR >30 ml/min/1.73m^2 (n=80) and 0.76 in those with <30 ml/min/1.73m^2 (n=24) (56). Nevertheless, the 2020 KDIGO guideline suggested GMI might be an alternative index for guiding treatment in patients with CKD G4-5 or dialysis where HbA_{1c} had been shown to be less reliable (12). (**Table 1**).

Of equal if not greater importance is the use of time-in-ranges which describes the proportion of time the patient spent in hyperglycemia or hypoglycaemia range. In 2019, at the Advanced Technology and Treatment for Diabetes (ATTD) Conference, there was consensus on using a series of CGM-derived metrics as clinical targets for glycemic management. The recommended target in an adult patient with T2D and without complications was >70% Time in range (TIR, % time sensor glucose >3.9 and <10 mmol/L), <25% time in Time above range reflecting significant hyperglycemia (TAR, % time sensor glucose >10 mmol/L), <5% time below target suggesting hypoglycaemia (TBR, % time sensor glucose <3.9 mmol/L) with a Coefficient of Variation < 36% (%CV = SD (standard deviation) of sensor glucose/mean sensor glucose) (57). However, the validity of TIR targets and the prognostic values of CGM-derived metrics on complications and death need to be confirmed in clinical trials involving patients with advanced CKD and dialysis (12).

GLYCEMIC PROFILES OF PATIENTS ON DIALYSIS

CGM systems provide comprehensive 24-hour profiles for assessment of relationships between glycemic variation, timing of dialysis regimens and insulin administration. In addition to the aforementioned CGM metrics, most CGM systems now provide standardized ambulatory glucose profiles (AGPs) which provide a graphical representation of 24-hour sensor glucose trends. **Table 3** summarizes evaluation studies of CGM in patients on HD or PD.

GLYCEMIC PROFILES DURING HEMODIALYSIS (HD)

In patients on HD, the composition of the dialysate and dialysis membrane both contribute to glycemic variability during HD and in the post-HD period. Differences in glucose profiles have

TABLE 1 | KDIGO 2020 recommendations on assessment of glycaemia in patients in chronic kidney disease (CKD) stages 1-4 (12).

Population	HbA_{1c}			Glucose management indicator
	Measure	Frequency	Reliability	
CKD G1-G3b	Yes	• Twice per year • Up to 4 times per year if not achieving target or change in therapy	High	Occasionally useful
CKD G4-G5 Including treatment by dialysis or kidney transplant	Yes	• Twice per year • Up to 4 times per year if not achieving target or change in therapy	Low	Likely useful

TABLE 2 | Summary of studies assessing correlation between continuous glucose monitoring (CGM) metrics and glycemic markers in patients with chronic kidney disease (CKD).

Study	Year	n	Subjects on ESA	Mean blood haemoglobin (g/dL)	CGM metric	Laboratory marker	Reported correlation
Frederick et al. (52)	2012	50	Yes	no CKD: 14.3± 1.1 G4 & G5: 11.5 ± 1.5	Mean sensor glucose	HbA_{1c}	No CKD: n= 25, *r*= 0.66 G4 & G5: n= 25, *r*= 0.38
Lo et al. (58)	2014	147	Yes	no CKD: NA G3b: 12.3 ± 1.1 G4: 11.4 ± 1.6 G5: 11.7 ± 1.0	Arithmetic mean CGM-SMBG glucose	HbA_{1c}	No CKD: n= 104, *r*=0.74 G3b: n= 14, *r*= 0.79 G4 & G5: n= 29, *r*= 0.34
Lubaina et al. (59)	2019	80 (with 49 G4-G5)	Yes	NA	Mean sensor glucose	HbA_{1c}	G3b: n= 31, *r*= 0.85 G4 & G5: n= 49, *r*= 0.81
					Mean sensor glucose	Fructosamine	G3b: n= 31, *r*= 0.69 G4 & G5: n= 49, *r*= 0.51
Zelnick et al. (56)	2020	104 (with 22 G4-G5)	No	no CKD: 13.1 ± 2.0 CKD: 12.2 ± 1.6	GMI	HbA_{1c}	No CKD: n= 24, *r*= 0.76 CKD (G3b-G5): n= 80, *r*= 0.78
					GMI	Fructosamine	No CKD: n= 24, *r*= 0.72 CKD (G3b-G5): n= 80, *r*= 0.78
					GMI	Glycated albumin	No CKD: n= 24, *r*= 0.63 CKD (G3b-G5): n= 80, *r*= 0.71

ESA, Erythropoietin stimulating agent; GMI, glucose management indicator; HbA_{1c}, glycated haemoglobin; SMBG, self-monitoring of blood glucose; NA, not available.

also been reported between HD and non-HD days. The phenomenon of "glycemic disarray" in HD has been described, referring to the fall in glucose during HD followed by rebound hyperglycemia in the post-HD period (**Figure 2**). HD-induced hypoglycaemia is frequently observed. In early studies, Takahashi et al. demonstrated reduction in plasma glucose concentration from pre-dialyser site to post-dialyser site in patients under a dialysate of 5.55 mmol/L glucose. This reduction in serum glucose within the dialyzer might be induced by dialysate-stress triggered diffusion of plasma

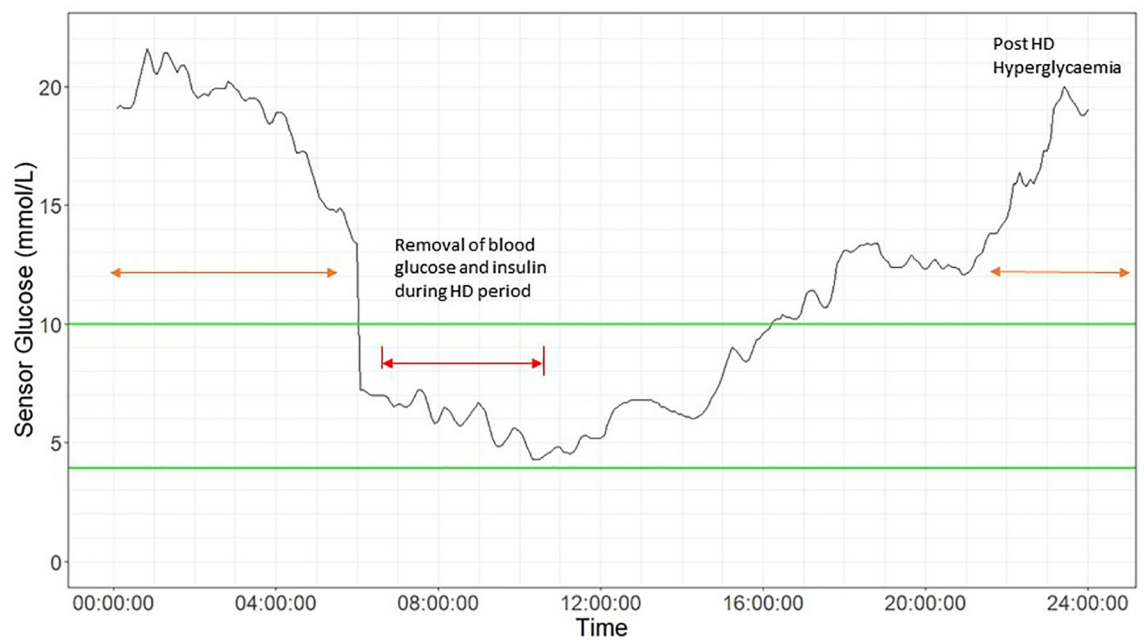

FIGURE 2 | Glycemic disarray showing marked variability in patients during haemodialysis (HD) and post-HD period. 24-hour CGM glucose profile in a 58-year-old man with type 2 diabetes on HD using glucose- free dialysate. He was treated with insulin glargine 24 units in the morning and alogliptin 6.25mg daily with HbA_{1c} of 8.2%. The HD period is indicated by red arrow, showing an acute drop in sensor glucose, followed by post HD-associated hyperglycemia (orange arrow) up to 20 mmol/l at midnight. Green lines indicates target range (3.9 mmol/L to 10 mmol/L).

glucose into erythrocyte, as well as loss into the dialysate (72). In general, patients might lose around 15-30 g of glucose during HD session. In patients with ESKD, defective counter-regulatory effects, reduced renal gluconeogenesis and hypoglycaemia unawareness might result in frequent asymptomatic hypoglycaemic events. In 17 patients with T2D on HD, the mean sensor glucose was lower during the on-dialysis than the off-dialysis days (60). In 12 patients on dialysis, Gai et al. reported that the median CGM glucose level was below the concentration of dialysate of 5.55 mmol/L during most of the HD session (87% of time) (51). In 9 patients with T2D, Jung et al. reported significant reduction in mean sensor glucose during HD session, regardless of the glucose concentration of dialysate solution (5.55 – 11.1 mmol/L) with most of the hypoglycaemic events occurring on the day of HD (61). In 46 patients with ESKD with or without diabetes, Jin et al. reported a significant reduction in mean sensor glucose during HD session irrespective of the status of diabetes although patients with diabetes had greater glucose loss during HD session (62).

In a recent study involving 98 Japanese patients with T2D on HD who had 2-day CGM, sensor glucose showed a sustained decline irrespective of dialysate glucose concentration with 50% of patients with diabetes reaching a glucose nadir lower than the dialysate concentration. In the whole group, 21% experienced HD-related hypoglycaemia <3.9 mmol/L either during the HD session or post-HD and before the next meal. There were no difference in terms of clinical characteristics (e.g. body mass index, duration of diabetes, insulin treatment) and traditional glycemic markers (e.g. HbA_{1c} and GA), between patients with HD-related or post-HD hypoglycaemia and patients without hypoglycaemia. Despite an average HbA_{1c}: 6.4% ± 1.2% for these T2D patients, asymptomatic HD-related hypoglycaemia was frequent and the HD-related hypoglycaemia was only captured by CGM (65).

Rebound hyperglycemia during the post-HD period may be related to choices of dialysate and dialysis membrane, which can influence plasma insulin concentrations during dialysis (73, 74). Insulin is readily removed from plasma by diffusion owing to its small molecular size and low protein-binding capacity. However, during HD, most of the insulin is removed *via* adsorption with dialysis membrane through electrostatic and hydrophobic interactions resulting in hyperglycemia in the post-HD period. The clearance of insulin by absorption depends on the type of dialysis membrane, with greatest absorption in polysulfone membrane and lowest absorption in polyester-polymer alloy (19). The counter-regulatory hormonal responses to HD-induced hypoglycaemia could increase insulin resistance and trigger post-HD hyperglycemia. Kazempour-Ardebili et al. demonstrated that nocturnal sensor glucose was significantly higher on the HD-day than HD-free day (60). This was also confirmed by other studies where time of HD-session was reported in the 24-hour CGM profile (51, 61, 63). Jin et al. confirmed post-HD hyperglycemia especially in patients with diabetes compared with their non-diabetic counterparts (62). Padmanabhan et al. evaluated the effects of different dialysate and dialysis membranes on glycemic control. In a study of 38 patients with and without diabetes, HD-induced hypoglycaemia and post-HD hyperglycemia occurred with the use of glucose-free dialysate but the fluctuation could be attenuated by using glucose-containing dialysate (64). Both HD-induced hypoglycaemia and post-HD hyperglycemia may contribute to heightened glycemic variability, increased oxidative stress and inflammation with worsening of clinical outcomes. By using CGM, these silent events may be detected early to inform treatment.

GLUCOSE PROFILES DURING PERITONEAL DIALYSIS (PD)

One of the determining factors of glycemic profile in patients with PD is the rate of peritoneal absorption of glucose, which is in turn affected by glucose concentration of dialysate, dwell time, and status of membrane transport (75). Ultrafiltration by peritoneal membrane is created by either crystalloid osmosis using a higher glucose concentration in the dialysate, or by colloid osmosis using large colloid agents like icodextrin (76). Icodextrin solution contains a mixture of glucose polymers which are slowly absorbed *via* lymphatics. Together with its osmotic effect, icodextrin leads to sustained ultrafiltration and is widely used as an alternative osmotic agent to dextrose especially in dialysate with long dwelling time (77). Early observational studies using CGM showed that patients with PD spent a large proportion of time in hyperglycemia (66). In a study of 20 patients with well-controlled T1D and T2D and mean HbA_{1c} of 5.9% who were dialysed on glucose-containing dialysates, patients spent on average 33% time above 10 mmol/l and 1% time below 3.9 mmol/l (70). Lee et al. evaluated the impact of glucose influx from dialysate in 25 patients with diabetes on maintenance PD. In patients using glucose-based dialysate, the sensor glucose levels increased by 7-8 mg/dL within 1 hour of exchange using glucose-containing dialysate. The glycemic excursion was similar with 1.25% and 2.25% glucose solutions with larger increments observed with 3.86% glucose solutions (67). **Figure 3** shows an example of CGM profile in a patient on continuous ambulatory peritoneal dialysis (CAPD).

Icodextrin is associated with stable or even decreases in CGM sensor glucose during PD dwells (67). Marshall et al. demonstrated the effect of switching dialysate on CGM profiles in 8 patients with PD. Switching from three 1.36% glucose exchanges and one 3.86% glucose exchange to two bags of 1.36% glucose exchange, one bag of amino acid exchange and one bag of icodextrin was associated with lower sensor glucose and glycemic variability (68). In a retrospective study of 60 patients with 95% of them receiving icodextrin dialysate, the CGM-detected time in hypoglycaemia was 5% which was often asymptomatic (69).

The diffusing capacity of the peritoneal membrane is another crucial factor in determining glycaemia. The exchange rate of serum-dialysate glucose is dependent on the osmotic pressure, as well as the transport status of peritoneal membrane. Osmotic gradient between dialysate and peritoneum is rapidly lost in

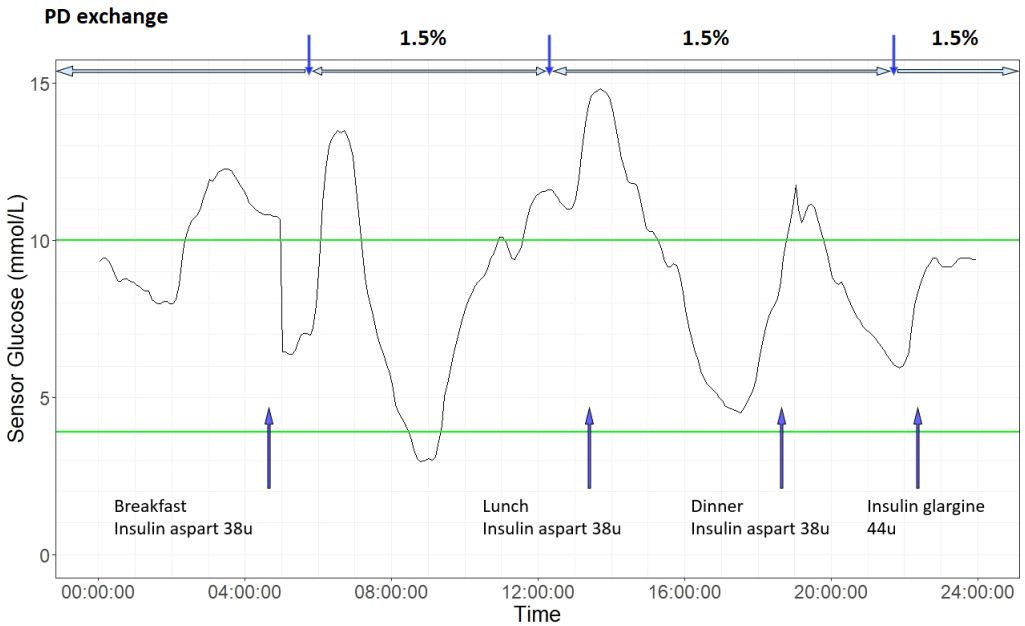

FIGURE 3 | An illustrative 24-hour ambulatory glucose profile in a patient with type 2 diabetes on continuous ambulatory peritoneal dialysis (CAPD). He is on three 1.5% dextrose exchanges daily and basal-bolus insulin regimen. Laboratory measures of glycemic control were HbA_{1c} 7.5% and Fructosamine 224 µmol/L. Based on CGM metrics, glucose management indicator (GMI) was 6.9%, coefficient variation (CV) 36.9%. Blue arrow on bottom indicates times of insulin injection and meal intake. Vertical blue arrow on top indicate PD exchange timing, and horizontal blue arrow on top indicate PD exchange period. Green lines indicates target CGM glucose range (3.9 mmol/L to 10 mmol/L).

patients with high transporter status due to rapid absorption of glucose from dialysate (78). As a result, these patients might have high risk of PD-related hyperglycemia. Skubala et al. demonstrated the effect of peritoneal transport status using CGM in 30 patients with and without diabetes. In their study, patients on 1.36% and 2.27% glucose dialysates had similar HbA_{1c}, mean 24-hour CGM-glucose, mean post-PD glucose, and mean post-PD increment in glucose. However, mean post-PD glucose and mean post-PD increment in glucose was significantly different in patients with high peritoneal transport (HPT) and high average peritoneal transport (HAPT), even in nondiabetic individuals (71).

Another modifiable factor of CGM-glucose is the timing, route and dose of insulin administration in patients on PD. Subcutaneous basal bolus insulin regimen are effective regimens in patients with T1D or T2D on PD but require frequent self-monitoring (50). Intraperitoneal (IP) delivery of insulin can counteract the glucose absorption from dialysate. However, there are no standardised recommendations on initiation or titration of IP insulin for different dialysates (79). Dose adjustments are often based on infrequent fasting and post-meal capillary blood glucose with CGM having the potential to guide adjustment of insulin therapy in patients on PD.

In summary, patients with diabetes on HD or PD display distinct glycemic profiles and patterns which can be comprehensively assessed by CGM. Apart from patient factors (e.g. beta-cell function, PD transporter status), there are a number of modifiable treatment factors, such as choices of dialysate, dialysis regimen and doses/timing of insulin, where data from CGM can help optimize treatment.

USE OF PERSONAL CGM PATIENTS IN ADVANCED CKD OR MAINTENANCE DIALYSIS

Personal use of real-time (rt) or flash CGM devices may reduce hypoglycaemia and improve glycemic control in patients with diabetes without CKD. The benefits of CGM use in patients with T1D on improving glycemic control are now well-established. In the Randomized Controlled Trial Examining the Benefit of CGM Use for Adults with T1D on Insulin Injections (DIAMOND) trial (80), there was a significant HbA_{1c} difference of -0.6% in favour of rt-CGM versus standard SMBG after 24 weeks of intervention in T1D patients on multiple daily injection (MDI). In another randomized study involving 161 patients with T1D treated with MDI, a similar significant difference of -0.43% in HbA_{1c} in favor of rt-CGM versus standard SMBG was reported after 26-weeks of intervention and during 17-weeks of post-intervention washout period (80, 81). In an open-labelled randomized trial in adults with well-controlled T1D on MDI (REPLACE-BG trial), use of flash CGM without confirmatory SMBG was safe and reduced hypoglycaemia (82) with improved treatment satisfaction (83).

TABLE 3 | Key Continuous Glucose Monitoring (CGM) studies in patients on hemodialysis or peritoneal dialysis.

Study	Year	CGM device; study duration	Mode of dialysis	Participants	Key findings
Kazempour-Ardebili et al. (60)	2009	Unknown (48 hours)	HD	19 T2D	• Mean sensor glucose was lower during HD days than HD-free days • Mean sensor glucose and sensor glucose AUC on post-HD days were significantly higher than HD days • Nocturnal sensor mean glucose and sensor glucose AUC showed same pattern
Gai et al. (51)	2014	Medtronic Ipro2 (6 Days, Blinded)	HD	12 DM	• Median CGM reading was lower than dialysate glucose concentration for 87% of time • Post-HD hyperglycemia observed in 75% of subjects
Jung et al. (61)	2010	Medtronic Gold (3 days, Blinded)	HD	9 T2D	• Significantly lower mean sensor glucose during HD sessions regardless of glucose concentration of dialysate solution • Hypoglycaemic events were concentrated on the day of HD session
Jin et al. (62)	2014	Medtronic Minimed (3 days, Blinded)	HD	36 T2D, 10 non-DM	• Significantly lower mean sensor glucose during HD sessions compared with peri-HD sessions in patients with or without diabetes • Diabetes patients suffered greater loss in glucose during HD session, and greater post-HD hyperglycemia than their non-diabetes counterparts
Mirani et al. (63)	2010	GlucoDay (2 days, Blinded)	HD	12T2D	• Hypoglycaemia observed in post-HD period • Rebounded hyperglycemia observed after post-HD hypoglycaemia • Significant higher glycemic variability in SD for HD day when compared with non-HD day
Padmanabhan et al. (64)	2018	Freestyle LibrePro (14 days, Blinded)	HD	16 DM + 16 non-DM	• Significantly fewer hypoglycaemic episodes during days of dialysis with glucose-rich dialysate than glucose-free dialysate • Significantly lower % TBR and lower % TAR during days of dialysis with glucose-rich dialysate than glucose-free dialysate • Significantly less loss in effluent glucose irrespective to diabetic state during days using glucose-rich dialysate than glucose-free dialysate
Hayashi et al. (65)	2021	Medtronic Gold (2 days, blinded) & Medtronic Ipro 2 (2 days, blinded)	HD	98 T2D	• Reduced sensor glucose irrespective of the dialysate glucose concentration (100, 125, 150 mg/dl) 50% of patients reached a nadir lower than dialysate glucose concentration, 21% of patients developed asymptomatic hypoglycaemic events during HD and post-HD session • Glycemic variability and % TBR increase in patients who experienced hypoglycaemic events than their counterparts without events
Schwing et al. (66)	2004	Medtronic Minimed (3 Days, Blinded)	PD	7 DM	• Increase in sensor glucose after dialysate exchange in two representative patients
Lee et al. (67)	2013	Medtronic Minimed (3 days, Blinded)	PD	25 DM	• Increase in sensor glucose within 60 minutes of refilling glucose-rich dialysate • Reduced sensor glucose in icodextrin dialysate after refilling
Marshall et al. (68)	2003	Medtronic Minimed (3 days, Blinded)	PD	8 DM	• Mean sensor glucose and glycemic variability in % CV significantly lower when switching from glucose-rich dialysate to glucose-free dialysate
Qayyum et al. (69)	2016	Dexcom G4 (7 days, real time CGM)	PD	60 T1/T2D	• Sensor-detected hypoglycaemia in subgroup of patients with A1c >9%
Okada et al. (70)	2015	Medtronic Gold (3 days, Blinded)	PD	20 DM	• Frequent sensor-detected hyperglycemia observed despite well controlled A1c
Skubala et al. (71)	2010	Medtronic Minimed (3 days, Blinded)	PD	16 T1/T2D 14 non-DM 13 healthy control	• Significant difference in mean sensor glucose and mean changes in sensor glucose after dialysate exchange in subgroup of patients with HPT versus H-APT • Peritoneal transport status influenced mean 24-hour sensor glucose in non-diabetic patients on PD as well as mean sensor glucose and mean changes in sensor glucose after dialysate exchange in diabetic patients on PD

AUC, area under the curve; HD, hemodialysis; PD, peritoneal dialysis; HPT, high peritoneal transport; HAPT, high average peritoneal transport; T1D, Type 1 diabetes; T2D, Type 2 diabetes; DM, diabetes mellitus; TBR, time below range; TAR, time above range.

Several pilot and small-scale studies supported the potential beneficial effects of professional CGM in patients on HD or PD, whilst data on continuous personal use was limited. Most studies explored the use of blinded CGM for treatment titration. In a pilot-study, Képénékian al. used blinded CGM in 28 T2D patients on HD with suboptimal glycemic control for 54 hours at baseline and during a 3-month follow-up period. After 3 months of intervention, the CGM-adapted insulin regimen was associated with greater reduction in HbA_{1c} without increasing symptomatic hypoglycaemia (84). The DIALYDIAB pilot study involved 15 patients with T1D or T2D and compared the effect of blinded-CGM SMBG using a two-period design. Use of blinded CGM triggered more frequent treatment adjustments compared with SMBG alone. This resulted in better glucose profile with significantly lower HbA_{1c} and time above range without increasing hypoglycaemic episodes (85). There are also few studies in patients with PD where CGM was used to assess effects of structured education (50) or compare different glucose lowering drug regimens (86). These studies demonstrated the potential of CGM in promoting patient self-management and informing providers in treatment adjustment to improve glycemic control.

CGM systems have the potential to be combined with automated insulin delivery in closed-loop systems, also referred

to as an 'artificial pancreas". A recent randomized trial evaluated a fully automated closed-loop system against standard insulin therapy in 26 patients with T2D on HD using a cross-over design (87). In this study, TIR was significantly higher (57.1% *versus* 42.5%) and time above and below range were lower (TAR: 42.6% *versus* 56.6%, TBR: 0.12% *versus* 0.17%) in the closed-loop phase. The mean sensor glucose was also significantly lower in the closed-loop *versus* control phase (10.1 mmol/L *versus* 11.6 mmol/L). Of note, the time spent in extreme hyperglycemia (defined as >20 mmol/L) was significantly lower during the closed-loop phase than the control phase (1.8% *versus* 6.7%). However, the system was given only for short-term use operated by healthcare professionals in a clinic setting rather than home use.

The ease of operation of personal CGM systems in patients with ESKD with multiple comorbidities need to be considered. Many patients with ESKD may have visual impairment due to retinopathy or cataracts, skin problems and cognitive issues that limit their ability to operate these devices. However, personal CGM with real-time alerts might benefit patients with ESKD on complex insulin regimens or vulnerability to hypoglycemia. Future research is required to investigate the utility and cost-effectiveness of personal CGM in patients with advanced CKD and dialysis.

There are some limitations in the use of CGM for patients under dialysis. Apart from potential sensor interference from endogenous and exogenous substances (46), accuracy of CGM is lower in the hypoglycemic range and under rapid changes in blood glucose values (88–90). False hypoglycaemic alerts may occur more frequently under these conditions, which may lead to unnecessary treatment. A confirmatory SMBG value is advisable for treatment decisions at these extreme glucose values. Additionally, repeated false positive alerts could lead to alarm fatigue and increase patient anxiety.

CONCLUSIONS

Optimal glycemic control will delay progression of CKD and improve clinical outcomes. HbA_{1c} and alternative glycemic markers have limitations particularly in patients with advanced CKD. With the advent of CGM, it is now possible to monitor the glycemic status with better precision in patients with CKD. Professional CGM can inform health care professionals on glucose profiles not provided by HbA_{1c} in patients with CKD to optimize treatment regimens. Real-time or flash CGM provide instant or timely feedback to users on impact of meals and treatment on glucose excursion. The inclusion of real-time alerts in CGM, displayed in smart devices, can provide early warnings against hyperglycemia and hypoglycaemia. This information may improve the safety of prescription of GLDs and insulin in these high-risk patients. Finally, the integration of these CGM system with fully automated closed loop insulin delivery systems offer the potential of more precise control.

The use of CGM in patients with ESKD has revealed distinct glycemic patterns during maintenance dialysis. Glycemic pattern in patients under HD are impacted by the glucose concentrations in dialysate and choices of dialysis membrane. Glucose-free dialysate is generally preferred due to lower cost and chance of bacterial infection. However, glucose-containing dialysate may reduce HD-related hypoglycaemia and post-HD hyperglycemia, especially in patients with diabetes. Health care professionals should consider providing glucose-containing dialysate, replenishing post-HD glucose loss by snacks, or adjusting insulin regimen to avoid HD-related glycemic excursion. Similar to HD, glycemic patterns in PD patients are impacted by diasylate glucose concentration and peritoneal membrane transport state. Health care professionals should consider glucose influx from glucose-rich dialysate and adjust insulin treatment to maintain a stable blood glucose. Although switch to glucose-free dialysates may theoretically reduce glucose influx, randomized trials suggested this might be associated with adverse outcomes (91). Pending further evidence, a careful adjustment of insulin and dialysate regimens in patients under PD may strike the balance between optimizing glycemic control and ultrafiltration. Future studies using CGM should be conducted to investigate whether the use of personal CGM with glycemic alerts will reduce hypoglycaemia and complications and improve long-term outcomes in patients with advanced CKD and dialysis.

AUTHOR CONTRIBUTIONS

JL and EC conceived the idea of the paper. JL researched and wrote the manuscript, JL, JN, EC, and JC critically revised the manuscript. All authors contributed to and approved the final manuscript.

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Intermittent Scanning Glucose Monitoring or Predicted Low Suspend Pump Treatment: Does It Impact Time in Glucose Target and Treatment Preference? The QUEST Randomized Crossover Study

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Objective: To compare glycemic control and treatment preference in children with type 1 diabetes (T1D) using sensor augmented pump (SAP) with predictive low glucose suspend (SmartGuard®) or pump with independent intermittent scanning continuous glucose monitoring (iscCGM, Freestyle libre ®).

Methods: In this open label, cross-over study, children 6 to 14 years of age, treated with insulin pump for at least 6 months, were randomized to insulin pump and iscCGM (A) or SAP with SmartGuard® (B) for 5 weeks followed by 5 additional weeks. The difference in percentages of time in glucose target (TIT), (3.9 – 8.0 mmol/l), <3 mmol/l, > 8 and 10 mmol/l, were analyzed using linear mixed models during the final week of each arm and were measured by blinded CGM (IPro2®).

Results: 31 children (15 girls) finished the study. With sensor compliance > 60%, no difference in TIT was found, TIT: A 37.86%; 95% CI [33.21; 42.51]; B 37.20%; 95% CI [32.59; 41.82]; < 3 mmol/l A 2.27% 95% CI [0.71; 3.84] B 1.42% 95% CI [-0.13; 2.97]; > 8 mmol/l A 0.60% 95% CI [0.56, 0.67]; B 0.63% [0.56; 0.70]. One year after the study all participants were on CGM compared to 80.7% prior to the study, with a shift of 13/25 participants from iscCGM to SAP.

Conclusions: In this study, no significant difference in glycemic control was found whether treated with SAP (SmartGuard®) or pump with iscCGM. The decision of all families to continue with CGM after the study suggests a positive impact, with preference for SmartGuard®.

Clinical Trial Registration: [clinicaltrials.gov], identifier NCT03103867.

Keywords: children, type 1 diabetes, insulin pump, iscCGM, predicted low suspend function

INTRODUCTION

To prevent short-and long-term complications, patients with type 1 diabetes (T1D) need an optimal metabolic control (1), which is challenging, especially for children (2).

Augmenting the insulin pump with glucose sensor information has shown to improve outcome (3). While continuous glucose monitoring is associated with decreased HbA1c levels and reduced time spent in hypoglycemia in individuals with T1D using insulin pump therapy in long-term studies, better outcomes depend on longer and continuous sensor use (3).

The use of technologies like sensor augmented insulin pumps and hybrid closed loop systems is increasing in children and adolescents with diabetes. These devices are not globally accessible, whereas continuous glucose measurements (CGM) has become increasingly available.

Minimed 640G® pump with SmartGuard® function combines alerts with an automated basal insulin suspension for prediction of low glucose, in order to prevent a hypoglycemia event. Alerts can be set on or off but the low threshold alert is mandatory (4).

A multicenter study in pediatric diabetes patients showed that SmartGuard® technology showed a significant reduction in risk of hypoglycaemia without increasing HbA1c (5).

Freestyle Libre® is another device measuring continuously the interstitial glucose levels. Results can be obtained when the patient/caregiver actively scans the sensor (iscCGM). No alerts are given when glucose values increase or decrease and no communication exists between the glucose measurement and the insulin pump (4).

The evaluation of iscCGM being as safe as self-monitoring of blood glucose (SMBG) and resulting in a better metabolic outcome than SMBG was demonstrated in children (6, 7).

The impact of these two technologies on metabolic control has been studied previously (8). The sensor augmented pump offers real time glucose values and alerts in case of hypo-and hyperglycemia and a predicted low glucose suspend of insulin infusion. However, concerns of alarm fatigue have been raised (9), though no data on Minimed 640G have been published. An alternative might be the intermittent glucose scanning to obtain glucose values when desired on the persons own initiative. We designed this study in order to get more information about the impact of the technology on metabolic control. Furthermore, we evaluated what device the families choose based on experience with both technologies after finishing the study. We are not aware of any study comparing these two technologies in children.

The objective of this study was to evaluate the impact on time in glucose target (TIT), 3.9 – 8.0 mmol/l, in children with T1D, comparing a sensor augmented insulin pump (Minimed 640G® with SmartGuard® technology) to the use of the same insulin pump with an intermittent scanning continuous glucose monitoring device (iscCGM; Freestyle libre®) that does not interact with the pump.

METHODS

This trial was registered (ClinicalTrials.gov, NCT03103867) and details of the methodology are described elsewhere (4).

Study Design

The study had an open-label, single -center, randomized, two-period crossover design.

Ethical approval from the Luxembourgish National Ethics Commission for the final study was obtained before the start of the study.

In our center we take care of more than 350 patients with diabetes, 90.4% with type 1 diabetes. In this group 85% use a CGM and 62% are pump–users (SWEET report, March 2022). All our patients and their caregivers regularly undergo an age specific diabetes and nutritional educational program at diagnosis and afterwards in our outpatient survey.

Participants

We included participants that fulfilled the following inclusion criteria: between 6 and 14 years of age, T1D for at least 6 months, on insulin pump treatment for at least 6 months, and HbA1c ≤ 11% (≤ 96.72 mmol/mol). These were patients from the pediatric diabetes consultation at the Children's Hospital in Luxemburg.

Exclusion criteria were physical or psychological disease likely to interfere with an appropriate conduct of the study. Prior to enrolment, written informed consent was obtained from the parents and all children gave their informed assent.

Sample Size

A sample size of 36 patients with a minimum of 31 patients was calculated for a power of 80% (4).

Randomization

Randomization (ratio 1:1) was performed by a statistician with 4 blocks of 8 sequences and treatment allocation based on prepared envelopes with the sequence code (A-B or B-A). After consenting, the envelope was opened by the medical team to provide the participant with the allocated treatment sequence (4). Blinding was not possible for the participant nor the medical team.

Procedures

After signing the informed consent/assent, subjects were randomized either to treatment A, insulin pump Minimed ® 640G and independent interstitial glucose measurement (Freestyle libre®) or to treatment B, SAP with the SmartGuard feature (Minimed® 640G), each for 5 weeks. Following a 3 week washout period, subjects crossed over to the other study arm for another 5 weeks. Further details are available and published elsewhere (4).

Freestyle libre®, which was used in our study, has no alarms to alert when high or low glucose values are measured. This has changed in the more recent variant, the Freestyle libre 2®, where an alarm option has been included.

Study visits occurred at randomization (baseline), at treatment start (V1-start first allocation, V3-start second allocation) and at the end (V2-end first allocation, V4-end second allocation) of each treatment period. There were no study visits during the washout period.

Demographic variables were collected at baseline. HbA1c measurements (DCA Vantage®, Siemens) were performed at each visit (V1-V4). A blinded CGM (I-Pro2®) was used to evaluate TIT during the last week of each treatment arm.

The use of the two glucose measurement tools and the features of the Minimed ®640G pump were explained during the training visit V1. All participants had access to a 24/7 diabetes hotline in case of technical or any other issues.

Settings of the Smart Guard were standardized based on the current experience (10). The low limit was set at 3.4 mmol/l, with an insulin suspension at ≤7.3 mmol/l if the predicted value within 30 minutes was 4.5 mmol/l. Parent/patient were informed before insulin was suspended by an alert (4).. At V2, I-Pro2® was placed for 7 days and the patient received instructions to perform two glucose measurements per day for calibration. After that week, the device was collected for analysis.

Thereafter, during the 3 week washout period, the 640G pump was maintained but in combination with a minimum of four blood glucose measurements and no iscCGM nor rtCGM. After the washout period, the second treatment period started with visit V3, on either Freestyle Libre® or SmartGuard®.

At visit V4, after 4 weeks of the second treatment arm, the I-Pro2® was placed again with the same request to perform 2 blood glucose values per day during 7 days. After this week, all devices were collected for analysis and the patient restarted his/her usual pre-study treatment.

During the 7 days-period with blinded CGM, the patients continued their assigned treatment (SAP or iscCGM and insulin pump).

The primary endpoint was defined as the percent of time spent in glucose target, TIT, (3.9 - 8 mmol/l) of treatment A and B during the final 7 days of a five-week device arm. This was measured by a blinded CGM (IPRO2®) at week 5 (V2) and 13 (V4), for participants with glucose sensor compliance > 60% during this week. As published in our protocol (4), we set out intending to use 6 days for analysis. After completion of the study and taking into account that we had enough data, we decided to analyze 7 days instead of 6.

Secondary endpoints included the between arm difference in percentage of time spent below glucose target (< 3.0 mmol/l) and above glucose target (> 8 and >10 mmol/l.

Severe hypoglycemic events (definition according to the current ISPAD guidelines (11) were documented.

Data Management and Data Quality

TIT and between arm differences were evaluated by the blinded CGM (IPro2®). Details on the data extraction have been summarized previously (4). Data from the blinded CGM were extracted by

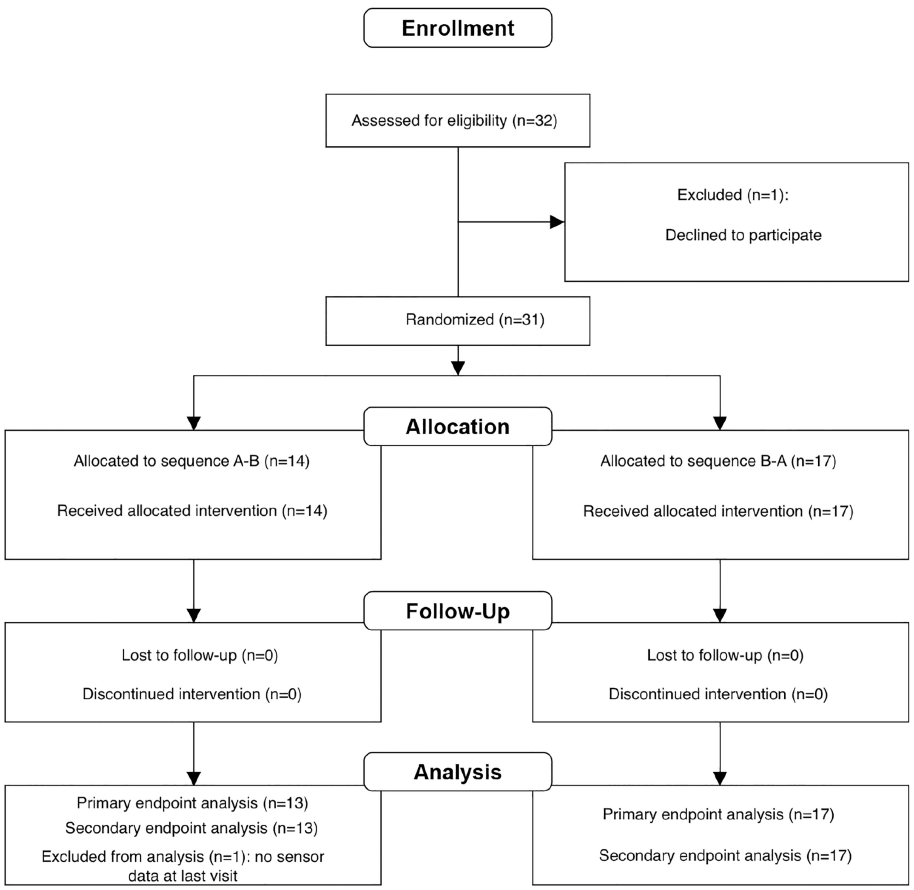

FIGURE 1 | Subject disposition.

Medtronic GlyVaRT software tool, and pump data were transferred through Contour Next Link® glucose meter to Medtronic CareLink therapy Management Software. Data quality was ensured in the data management process by double entry using Ennov Clinical and including online logical controls to detect outliers and missing information. Freestyle Libre® or SmartGuard® data were only used by the patients for daily treatment adjustments.

Statistical Analysis

Baseline characteristics were described using mean [standard deviation (SD)], median [25% quartile (Q1), 75% quartile (Q3)] for normal and not normal distributed continuous variables, respectively, and frequencies (percentages) for binary and categorical variables.

Baseline Characteristics for Children

Age (years), sex, height (cm), weight (kg), BMI (kg/m^2 and z-scores), Hba1c (%, mmol/mol) duration of diabetes, duration of pump use (years), glucose value, percent of time within, below or above defined glucose target.

Primary Outcome

The percentage of time spent in glucose target, TIT, (3.9 - 8 mmol/l) of treatment A and B was analyzed by using a linear mixed model with treatment, sequence of treatments, and period as fixed effects and patient as random intercept effect.

Secondary Outcome

Below glucose target (< 3.0 mmol/l) and above glucose target (> 8.0 mmol/l and > 10.0 mmol/l) during the final 7 days of a 5 week device arm measured by blinded CGM during week 5 and week 13 were compared between device arms using a linear mixed model with device, sequence and period as fixed effects and patients as random effect. Only data with a sensor compliance of > 60% were included in the analysis.

Safety Outcome

The number of severe hypoglycemic events in both treatment arms, defined by ISPAD (11), was analyzed through a table of frequencies.

We performed a sensitivity analysis including all patients in the analysis regardless of their compliance.

RESULTS

A total of 32 children (15 girls), 6 to 14 years of age, mean HbA1c 7.5% (SD 0.6), 58.1 mmol/mol, (SD 6.5) and mean diabetes duration of 5.9 years (SD 3.29), and on insulin pumps consented to participate in this study. Prior to the study, 25 subjects used CGM (iscCGM). As one child dropped out of the study before randomization, based on non-compliance with the use of the sensor, these data were not included. **Figure 1** shows the subject disposition.

For one participant the glucose sensor values of the last visit were missing, therefore 30 participants were analyzed for primary and secondary endpoints. **Table 1** shows the demographic baseline values for study participants (31 children).

Primary Endpoint

Percentage of Time in Glucose Target (3.9 – 8.0 mmol/l)

Only data with a sensor compliance of > 60% were included in the analysis (**Table 2**).

We analyzed the data of sensor compliance > 70%. As there was no statistically significant difference, we show the sensor compliance > 60%, in order to include a maximum of patients.

TABLE 2 | Linear mixed model of time in glucose target.

	Coefficients (95% confidence intervals)
Intercept	36.4 (30.0; 42.9)*
Time to target device B	-0.65 (-6.2; 4.7)
Period (visit V4)	0.09 (-5.3; 5.55)
Sequence of device Arm B-A	2.7 (-4.5, 9.8)

P <0.05.

TABLE 1 | Descriptive baseline characteristics of the participating children.

	All	Sequence A-B	Sequence B-A
N	31	14	17
Age, years	10.5 (2.3)	10.8 (2.0)	10.2 (2.5)
Female, N (%)	15 (48.4)	7 (50.0)	8 (47.1)
Caucasian, N (%)	30 (96.8)	13 (92.9)	17 (100)
Height, cm	143.7 (14.6)	145.6 (15.2)	142.1 (14.4)
Weight, kg	42.8 (13.2)	44.1 (15.7)	41.8 (11.2)
BMI, kg/m^2	20.2 (3.1)	20.1 (3.9)	20.3 (2.5)
Z score BMI[a,b]	1.0 (0.4, 1.3)	1.0 (0.5, 1.2)	1.1 (0.5, 1.3)
HbA1c, %	7.5 (0.6)	7.6 (0.6)	7.3 (0.5)
HbA1c, mmol/mol	58.1 (6.5)	59.9 (6.9)	56.6 (5.9)
Diabetes duration, years[b]	5.6 (3.0, 8.1)	5.7 (3.7, 7.1)	5.6(2.9, 9.8)
Pump use, years[b]	4.0 (2.1, 5.1)	3.9 (2.4, 6.9)	4.5 (1.8, 9.1)

Data are mean (SD), median (Q1, Q3) or n (%).

[a]*Z scores BMI are calculated with the formula z-score = (X-m)/SD; X=BMI; m=mean, SD=standard deviation of BMI of the reference population with same sex and age.*

[b]*Median (Q1, Q3) (variables with non-normal distribution).*

Treatment A had an adjusted mean percentage in glucose target of 37.86% [95% CI (33.21; 42.51)]. The adjusted mean percentage in glucose target in treatment B was 37.20% [95% CI (32.59; 41.82)]. No significant difference between treatment A and B was found (p-value = 0.817). No carry-over effect was observed (2.74; SE =3.66; p-value = 0.461). Interestingly, we observed in both sequences a reduced variability in TIT in the second treatment arms (**Figure 2**).

In a sensitivity analysis including all patients in the analysis (ignoring the compliance of the glucose sensor) no statistically significant difference could be found (data not shown).

Secondary Endpoints

Severe Hypoglycemia

No severe hypoglycemia occurred in both treatment arms.

Percent Time of Glucose < 3.0 mmol/l

No significant differences between treatment A, insulin pump and iscCGM, [2.27% 95% CI (0.71; 3.84)] and B, SAP with SmartGuard® function, [1.42% 95% CI (-0.13; 2.97)] could be found for percent time below 3.0 mmol/l.

One child showed a high percent time of glucose < 3.0 mmol/l with 24.91% in treatment A versus 0% in treatment B compared to other children (median = 0.815%). Linear mixed model excluding one observation with high outcome value lowered the least square means (marginal means extracted from the model fitting the data) of percent time < 3.0 mmol/l, but no significant difference between device A and B was found (**Table 3**).

Most children had no low glucose values < 3.0 mmol/l, therefore the outcome variable shows a high number of zero percentages (19 out of 51 observations, 37.25%).

Percent Time of Glucose > 8 mmol/l and > 10 mmol/l

No significant association between devices A [0.60%; 95% CI (0.53, 0.67)] and B [B 0.63%;95% CI (0.56; 0.70)] and percent time of glucose > 8 mmol/l (p-value: 0.463), **Table 4**, and percent time of glucose > 10 mmol/l was found (p-value: 0.996), **Table 5**.

Treatment Choice 1 Year After Completing the Study

Prior to the study, 6 out of the 31 participants had no regular experience with a continuous glucose measurement, whereas 1 year after the QUEST study, all 6 children used one of the two CGM continuously (2 on iscCGM Freestyle libre® and 4 used the SAP with SmartGuard® function).

One year after the study 14 out of the 25 participants (56%) with prior regular CGM experience had changed their CGM treatment to the sensor augmented pump option with SmartGuard®.

Eight out of 11 patients (73%) who stayed on iscCGM after the study chose this option because of no need to calibrate the sensor.

Reported Harms

No specific harms were reported.

DISCUSSION

In this study, with real-life data using 2 different CGM systems, we did not identify any significant difference in TIT, time below and above target comparing the same insulin pump with two different glucose monitoring systems (iscCGM without alerts compared to the SmartGuard® feature with alerts and predicted low glucose suspend). Based on their experience in the study, even those participants without prior regular CGM use decided to continue the CGM after the end of the study. The use of the CGM itself, iscCGM or rtCGM, seems most relevant for the outcome. This is supported by other studies, exploring participants' experiences (12) or

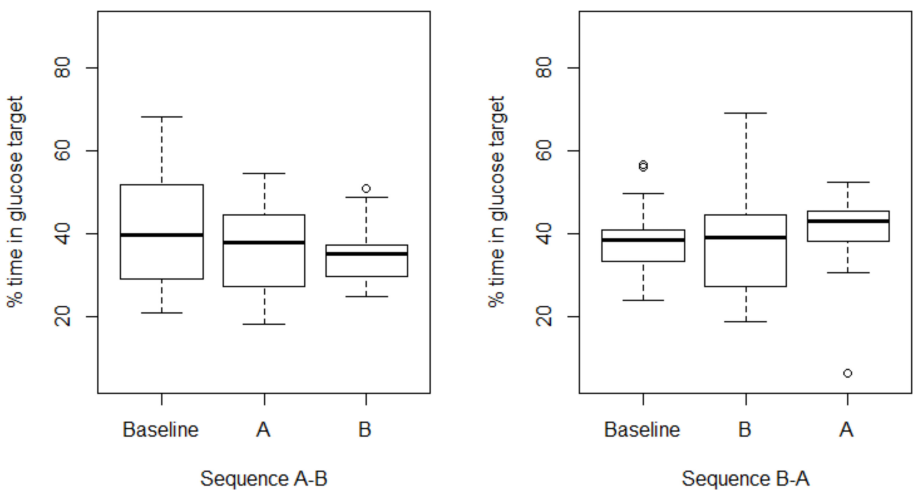

FIGURE 2 | Boxplot of percentage in glucose target, sensor compliance > 60%.

TABLE 3 | Glucose time percentage < 3.0 mmol/l: p-value=0.4460.

Least Square Means									
Effect	**treatment**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > ltl**	**Alpha**	**Lower**	**Upper**
Treatment	A	2.2729	0.7772	47	2.92	0.0053	0.05	0.7093	3.8364
Treatment	B	1.4210	0.7707	47	1.84	0.0072	0.05	-0.1294	2.9713

TABLE 4 | Glucose time percentage > 8.0 mmol/l; p-value 0.463.

Least Square Means									
Effect	**treatment**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > ltl**	**Alpha**	**Lower**	**Upper**
treatment	A	0.5971	0.0352	44.0	16.98	<2.2	0.05	0.5262	0.6680
treatment	B	0.6264	0.0349	43.8	17.94	<.2.2	0.05	0.5560	0.6968

TABLE 5 | Glucose time percentage > 10.0 mmol/l; p-value 0.9955.

Least Square Means									
Effect	**treatment**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > ltl**	**Alpha**	**Lower**	**Upper**
Treatment	A	38.8971	2.7722	43.4	14.03	<2.2	0.05	33.3077	44.4865
Treatment	B	38.9141	2.7531	43.1	14.13	<2.2	0.05	33.3622	44.4661

treatment adjustments based on sensor information, iscCGM or rtCGM (13).

Although no carry over effect was observed, the reduced variability in TIT suggests that CGM use over time influences diabetes control. The continuous information on glucose levels allows a faster insulin adjustment. These targets may differ between the different participants and different treatments modalities. Hypoglycemia fear, alarm fatigue, family interactions, and more or less confidence in devices or diabetes distress may influence individual target setting and the choice and use of CGM. A recently published review on psychological outcomes in children using iscCGM or rtCGM clearly suggests to consider these human factors while counseling families in their choice of CGM (14).

A limitation of our study is the relatively short study and analysis duration and the limited number of participants. As the blinded sensor had to be changed after 7 days, the evaluation was limited to 7 days to prevent potential drop outs. We controlled for the small number by the study design. As the data are all obtained in the free living at home, they do reflect the real world situation, which in our observation represents the strength of this study.

Even if recent technological development towards closed loop systems shows further near normalization of metabolic control, many countries do not have access to these technologies. The access to CGM, with or without connection to an insulin pump, increases and remains very important to optimise the outcome (15).

Despite the use of the pumps/sensors, glucose time in target in our and other populations remained insufficient (16). Although fast progress in technology is observed, human factors are important to ensure optimal use and outcome. Reduced burden for the patients and families should be considered (17).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité National d'Ethique de Recherche, Luxembourg. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

US and CB: concept of the study and design, protocol, recruitment, data analysis and writing of the paper; MF and CM: recruitment and conduct of the study; GA: study design, data management and data analysis; AS: data management and data analysis; IG: concept of the study; MV: concept and design of the study; OC: protocol; All authors read and approved the final manuscript.

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Conflict of Interest: The sponsor of this project had the right of commenting but the authors retained the right to accept or reject comments or suggestions.

OC is an employee of Medtronic. CB has received a honorary for giving talks on devices, developed by Medtronic, and has been member of Medtronic EU Psychology Advisory board (the development of an e learning tool on diabetes and adolescence).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Closed-Loop Insulin Delivery Systems: Past, Present, and Future Directions

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Closed-loop (artificial pancreas) systems for automated insulin delivery have been likened to the holy grail of diabetes management. The first iterations of glucose-responsive insulin delivery were pioneered in the 1960s and 1970s, with the development of systems that used venous glucose measurements to dictate intravenous infusions of insulin and dextrose in order to maintain normoglycemia. Only recently have these bulky, bedside technologies progressed to miniaturized, wearable devices. These modern closed-loop systems use interstitial glucose sensing, subcutaneous insulin pumps, and increasingly sophisticated algorithms. As the number of commercially available hybrid closed-loop systems has grown, so too has the evidence supporting their efficacy. Future challenges in closed-loop technology include the development of fully closed-loop systems that do not require user input for meal announcements or carbohydrate counting. Another evolving avenue in research is the addition of glucagon to mitigate the risk of hypoglycemia and allow more aggressive insulin dosing.

Keywords: artificial pancreas, closed-loop systems, glycemic control, type 1 diabetes, medical devices

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INTRODUCTION

The mainstay of treatment for type 1 diabetes is intensive insulin therapy, either as multiple daily injections or continuous subcutaneous insulin infusion *via* pump. The goal of intensive insulin therapy is to mimic physiological insulin release by pancreatic beta cells in a basal-bolus fashion to achieve tight glycemic control and thereby reduce the risk of micro- and macrovascular complications of hyperglycemia (1). However, optimal glycemic control in many individuals with type 1 diabetes is limited by hypoglycemia and the high burden of self-management required with frequent monitoring of blood glucose and adjustment of insulin dosing (2). As a result, a majority of people with type 1 diabetes are unable to achieve the recommended therapeutic targets (3).

In the 100 years since the discovery of insulin, there have been significant technological advances in diabetes management. Insulin pumps first became clinically feasible in the 1970s, and have since become miniaturized and more reliable. Continuous glucose monitoring systems (CGMS) are now minimally invasive and more accurate. There is a growing demand for connection of these two types of devices with algorithms that can facilitate automated insulin delivery. These closed-loop systems – also referred to as the "artificial pancreas" – have been likened to the holy grail of diabetes management as they have the potential to improve glycemic outcomes and reduce disease burden (4).

EARLY CLOSED-LOOP SYSTEMS

The first closed-loop insulin delivery system was developed by Arnold Kadish in the early 1960s. Kadish's invention, which he termed a "servomechanism for blood glucose control", comprised an autoanalyzer for continuous blood glucose monitoring *via* an intravenous catheter and two intravenous syringe pumps containing insulin and either glucose or glucagon. Both pumps were shut off when the blood glucose level was within a defined target range; the insulin pump was activated when the glucose level rose above the upper threshold, and the glucose or glucagon pump was activated when it dropped below the lower threshold (5, 6). Kadish published the results of a successful trial of his system in a single diabetic volunteer in 1963 (5).

The first systems to be described as an artificial pancreas were developed in the early 1970s. Albisser and colleagues (a Canadian group) and Pfeiffer and colleagues (a German group) separately designed essentially the same configuration of apparatuses and both published their findings in 1974 (7–9). Both systems utilized a computer programmed to respond to continuous venous glucose monitoring and control the intravenous delivery of insulin and/or dextrose. The apparatus originally developed by Pfeiffer et al. (**Figure 1**) was commercialized in 1977 as the Biostator (Miles Laboratories, Elkhart, Indiana, USA), which consisted of: a pump which controlled continual blood withdrawal; a glucose analyzer for continuous measurement of blood glucose concentration; a computer programmed to calculate the amount of insulin or dextrose to be infused based on blood glucose levels; an infusion pump for insulin and dextrose delivery; and a printer for minute-by-minute blood glucose recording (10, 12).

Because the Biostator was bulky, intricate, and required the patient to be connected to a blood withdrawal catheter in one arm and an infusion line in the other arm, its use was largely limited to research. It was also employed as an investigative tool to study an individual's glycemic patterns over a 24–36 hour hospital admission, in order to help determine their ideal insulin dosage (13). The Biostator was used extensively in research throughout the 1980s and 1990s, with over 200 publications based upon its use (14).

The first wearable artificial pancreas system was developed by a Japanese group led by Motoaki Shichiri in the early 1980s (15, 16). The whole system, consisting of a sensor, a microcomputer and two roller pumps, weighed 400 grams and measured 15 x 12 x 6 cm, and was able to be stored in the pocket of the user's jacket. While the Biostator was an intravenous-intravenous system, using venous glucose sensing and intravenous insulin delivery, Shichiri's technology used a subcutaneous glucose sensor paired with intravenous pumps for insulin and glucagon infusions (16).

CURRENT CLOSED-LOOP TECHNOLOGIES

Progress towards a fully closed-loop system have been accelerating since the mid-2000s, with the development and commercialization of numerous glucose-sensing and insulin delivery systems of increasing sophistication. With the technological progress made regarding insulin pumps and interstitial glucose-sensing devices, attention turned to the development of a subcutaneous-subcutaneous closed-loop system (17). The Juvenile Diabetes Research Foundation (JDRF) established the Artificial Pancreas Project in 2005 with the aim of promoting the research, regulatory approval, and eventual adoption of closed-loop technologies (4). The JDRF defined six categories of artificial pancreas systems based on the level of automation involved (**Figure 2**); at the time, all were in varying stages of development but none were commercially available.

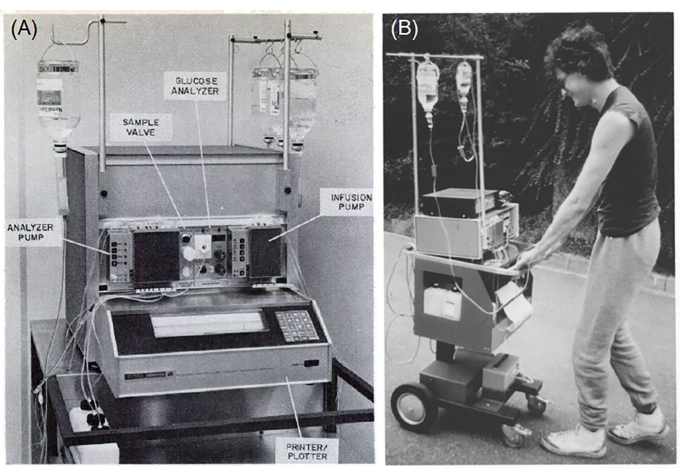

FIGURE 1 | Early closed-loop technologies: **(A)** Components of the Biostator (reproduced from Fogt et al., 1978); **(B)** A mobile version of the Biostator (reproduced from Pfeiffer 1987) (10, 11).

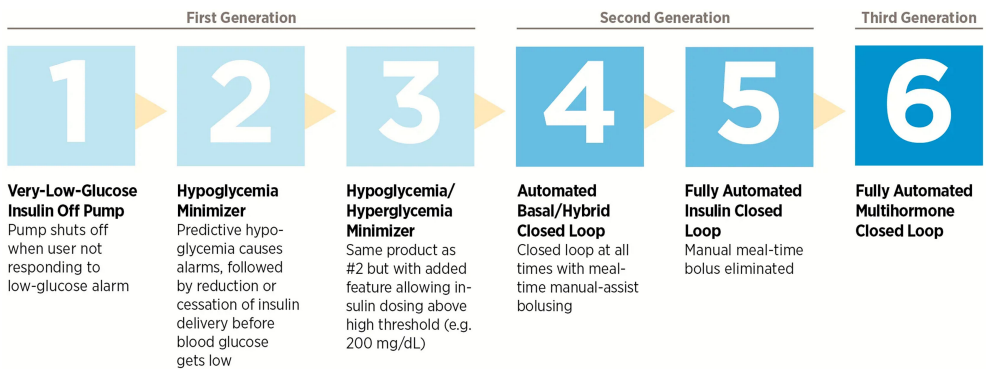

FIGURE 2 | The six categories of closed-loop systems as defined by the JDRF.

Low-Glucose Suspend Systems

Low-glucose suspend (LGS) systems are the simplest form of a closed-loop system. They consist of an integrated glucose sensor and insulin pump with the ability to automatically suspend insulin infusion when glucose levels fall below a certain threshold without requiring any confirmation from the user. In 2009, Medtronic commercialized the first LGS system with the MiniMed Paradigm Veo (Medtronic, Northridge, California, USA), which suspends insulin delivery and alerts the user when a pre-programmed glucose threshold is reached (18). The primary benefit of LGS over sensor-augmented pump therapy is reduced nocturnal hypoglycemia, without an increase in HbA1c (19, 20).

LGS technology was further refined in the form of predictive low-glucose suspend (PLGS) systems, which contain algorithms that predict future hypoglycemia (for example, within the next 30 minutes) and pre-emptively suspend insulin delivery before hypoglycemia occurs. This technology became commercially available in 2015 with the MiniMed 640G (Medtronic), and can also be found in the t:slim X2 with Basal-IQ (Tandem, San Diego, California, USA). Like LGS, use of PLGS is associated with a significantly reduced risk of nocturnal hypoglycemia as well as overall time spent in hypoglycemia, without an increase in hyperglycemia (21, 22).

Hybrid Closed-Loop Systems

Hybrid closed-loop systems aim to minimize hypoglycemia and hyperglycemia and maintain glucose levels within a target range through the use of a computerized algorithm to adjust the basal rate of insulin and administer corrective bolus doses. They are called "hybrid" systems as, unlike fully closed-loop systems, the user is still required to manually program insulin boluses with meals. Development of the first hybrid closed-loop systems began in parallel with LGS technology. The Advanced Insulin Infusion Using a Control Loop (ADICOL) project was launched in 2000, with the collaboration of several European centers to develop one of the first hybrid closed-loop systems (23). A pivotal trial by Weinzimer et al. in 2008 was the first to show that a hybrid closed-loop system significantly improved overnight time spent in the normoglycemic range compared to conventional open-loop insulin delivery (24). Further trials in adult and pediatric populations have demonstrated increased time in target and reduced hypoglycemia, mean glucose levels, and HbA1c in hybrid closed-loop systems (25–28).

The MiniMed 670G (Medtronic), the first commercially available hybrid closed-loop system, was released in 2016. Other systems that have received regulatory approval (**Figure 3**) include the MiniMed 780G (Medtronic), t:slim X2 with Control-IQ (Tandem), and CamAPS FX (CamDiab, Cambridge, UK) (29). These systems use three main types of algorithms: model predictive control (MPC), proportional-integral-derivative (PID), and fuzzy logic. MPC algorithms use a mathematical model of the user's glucoregulatory system to predict glucose excursions and adjust insulin delivery to treat-to-target, taking into account estimated insulin sensitivity. PID algorithms adjust insulin delivery according to three elements: the difference between measured and target glucose levels (the proportional component), the area under the curve between measured and target glucose (the integral component), and the rate of change in measured glucose levels over time (the derivative component). Algorithms based on fuzzy logic are less common, and modulate insulin delivery according to a set of rules designed to imitate the knowledge and reasoning of experienced diabetes clinicians (30).

The pivotal trial establishing the efficacy of the MiniMed 670G system was published by Garg et al. in 2017. The prospective analysis of 124 adults and adolescents using the system at home over three months demonstrated a significantly increased time in range compared to baseline (28). A later trial by Forlenza et al. in children aged 7–13 similarly found that in-home use of the MiniMed 670G resulted in increased time in range and reduced HbA1c compared to baseline (31). A prospective study by Lal et al. of real-world use of the MiniMed 670G over 12 months found significant correlation between time spent in Auto Mode (in which the hybrid closed-loop algorithm is activated) and HbA1c, but this was countered by a high discontinuation rate, with 33% of users having discontinued Auto Mode use by 12 months. The most frequent

FIGURE 3 | Commercially available and in-development hybrid closed-loop systems. **(A)** MiniMed 670G with Guardian Link 3 sensor/transmitter. **(B)** Omnipod Horizon with patch-pump. **(C)** CamAPS FX algorithm hosted on Android. **(D)** Tandem t:slim X2 pump paired with Dexcom G6 sensor. **(E)** Diabeloop DLBG1 algorithm with Kaleido patch-pump and Dexcom G6 sensor.

reasons reported for discontinuation included sensor issues, problems obtaining supplies, and fear of hypoglycemia (32). A recent retrospective analysis of data uploaded over a 15-month period by 14,899 European users of the MiniMed 670G found that users spent a mean 81.4% of the time in Auto Mode and could expect to spend 72% of the time in range with Auto Mode enabled, an increase of 10% compared with pre-Auto Mode initiation (33).

Do-It-Yourself Closed-Loop Systems

The "do-it-yourself" (DIY) closed-loop movement began to gain momentum in 2013 when a group of people with type 1 diabetes and their families began collaborating online to create open-source closed-loop software. Many shared their knowledge and experiences under the hashtag #WeAreNotWaiting in reference to their frustration with the slow progress of medical device development and delays in regulatory approval of closed-loop systems (34, 35). These DIY systems connect commercially available insulin pumps and CGMS to an open-source algorithm, held either in a smartphone application or custom hardware, that analyses glucose data from the sensor and remotely adjusts insulin delivery by the pump. The first DIY closed-loop system contained a radio stick to communicate between the insulin pump and a minicomputer holding the algorithm, but the emergence of Bluetooth-enabled pumps means that an increasing number of these systems use smartphones or other mobile devices to host the algorithm and communicate directly with the pump. While most DIY systems operate similarly to conventional hybrid closed-loop systems, where users manually administer boluses with meals, some users choose to enable features that allow them to skip meal announcements and boluses (34).

Reliable figures of usage are difficult to track but recent estimates suggest that there are over 2000 worldwide users of DIY closed-loop systems including OpenAPS, AndroidAPS and Loop (36). The most attractive features of these systems for users include their low-cost availability and increased customizability compared to commercial hybrid closed-loop systems. Although few clinical trials have been conducted on DIY closed-loop systems, analyses of self-reported data from users have shown benefits in HbA1c, time in range, glucose variability, and fewer episodes of hypoglycemia. Reported quantitative outcomes include reduced mental burden of diabetes management and reduced reliance on carbohydrate counting (37). Objective comparison of data between patients is limited by the highly individualized use of DIY systems between users and the fact that they use open-source software, meaning each user can customize the algorithms. *In silico* studies may overcome this challenge, and have been used by some groups to establish the safety and efficacy of these systems, as well as providing comparison to commercialized technologies (38, 39); indeed, research on many commercially available closed-loop systems began with *in silico* trials (40).

Currently, practitioners are placed in a challenging position when caring for patients who are actively using or interested in using DIY systems. On the one hand, many patients report improvements in glycemic control and quality of life; on the other, these technologies lack formal safety studies and approval from regulatory bodies, and often involve off-label use of approved CGMS and insulin pumps (41).

FUTURE DIRECTIONS IN CLOSED-LOOP TECHNOLOGY

The past five to ten years have seen an explosion in research and published literature about closed-loop systems (selected notable publications are highlighted in **Figure 4**). Multiple further hybrid systems are expected to be commercialized in the near future, in addition to those already available. The DBLG1 (Diabeloop, Grenoble, France) has received the CE mark in Europe for use in adults with type 1 diabetes, while the Omnipod Horizon (Insulet, Billerica, Massachusetts, USA) and insulin-only iLet (Beta Bionics, Boston, Massachusetts, USA) are currently undergoing clinical trials (49). On the DIY front, Tidepool, the non-profit software organization responsible for Loop, has submitted an application to the United States Food and Drug Administration (FDA) with the aim of releasing Loop as an FDA-regulated mobile application, supported by funding from the JDRF (50). Future directions in closed-loop research are principally aimed at the advanced generations of closed-loop systems as outlined by the JDRF: fully automated and multi-hormone systems.

Fully Closed-Loop Systems

Fully closed-loop systems, unlike hybrid systems, are designed to automate all insulin delivery without requiring user input for mealtime boluses. The main challenge in fully closed-loop systems therefore is postprandial hyperglycemia, as there is no manually provided information about the timing and carbohydrate content of meals. These postprandial glucose excursions are often followed by hypoglycemia secondary to the delayed action of current rapid-acting insulins. Fully closed-loop systems can use the same types of algorithms as hybrid systems – MPC, PID, or fuzzy logic – although all fully closed-loop systems included in a 2017 meta-analysis used MPC-based algorithms (51). Investigators have made use of different algorithms to recognize unannounced meals and estimate carbohydrate intake based on either the rate of change in glucose levels or the required insulin boluses (52). Another proposed solution to mitigate postprandial glucose excursions is the integration of GoCARB, a smartphone application that estimates carbohydrate content based on user-submitted images of meals in real time, into an MPC algorithm (53).

An early trial by Kovatchev et al. in 2010 found that use of a fully closed-loop system in adults with type 1 diabetes improved hypoglycemia and time in target range compared to sensor-augmented pump therapy (54). Phillip et al. similarly showed a reduced incidence of hypoglycemia in a pediatric population using a fully closed-loop system (42). However, postprandial glucose excursions remain the largest limitation of fully closed-loop systems in direct comparisons with hybrid systems. In the pioneering study by Weinzimer et al., manual pre-meal insulin boluses reduced peak postprandial glucose excursions and mean daytime glucose compared to a fully closed-loop system (23). Forlenza et al. similarly found an improvement in postprandial hyperglycemia and mean glucose levels with manual mealtime boluses in a closed-loop system (55). Still, fully closed-loop systems may be suited for users who frequently miss or miscalculate mealtime boluses (56, 57).

Another challenge for fully closed-loop systems is glycemic control during and after exercise. An ideal algorithm would account not only for changes in glucose levels associated with exercise, but also the duration, intensity, and type of physical activity. Biometric data such as heart rate, skin temperature, accelerometry, and energy expenditure have been used in trials of

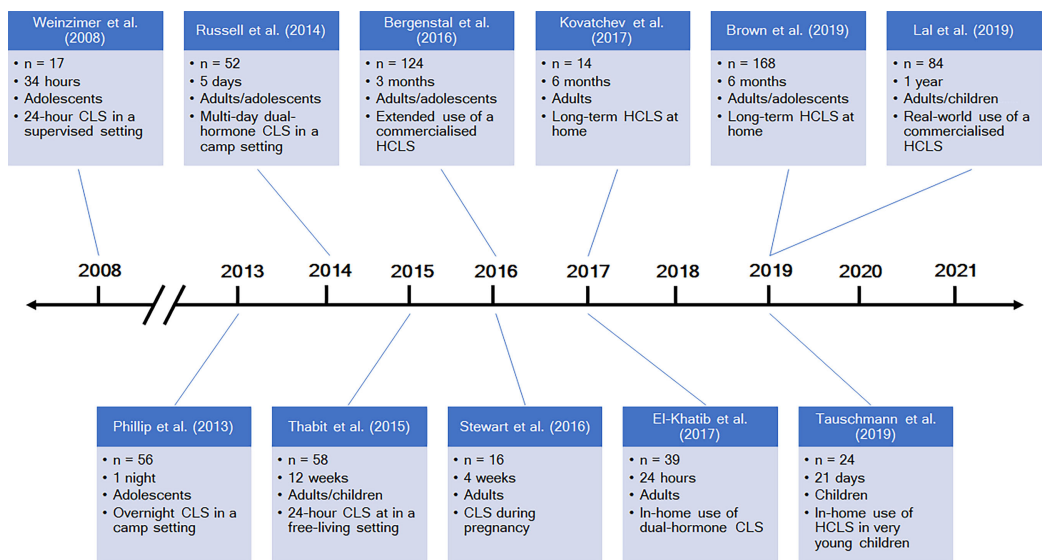

FIGURE 4 | A timeline of selected studies of closed-loop systems. CLS = closed-loop system; HCLS = hybrid closed-loop system. References: Weinzimer et al., (24), Phillip et al., (42), Russell et al., (43), Thabit et al., (26), Bergenstal et al., (27), Stewart et al., (44), Kovatchev et al., (45), El-Khatib et al., (46), Brown et al., (47), Tauschmann et al., (48), Lal et al., (32).

a fully closed-loop system to recognize different types and intensities of exercise without any manual inputs (58). A feasibility study by Breton et al. showed that a heart rate monitor can be integrated into a wireless closed-loop system, although their exercise algorithm did not result in a significant reduction in hypoglycemic events (59).

Currently, the only commercially available fully closed-loop system is the STG-55 (Nikkiso, Tokyo, Japan) and its predecessor, the STG-22. As opposed to the more widely available wearable hybrid technologies, these are bedside devices that use intravenous-intravenous access for glucose sensing and insulin delivery. The STG-55 is only available in Japan, where its approval is limited to the perioperative setting for a maximum of a three-day period (60).

Dual-Hormone Closed-Loop Systems

Two of the earliest closed-loop systems – those developed by Kadish and Shichiri – utilized a dual-hormone approach with a combination of insulin to counter hyperglycemia and glucagon to counter hypoglycemia. However, the use of glucagon in closed-loop systems fell out of practice in the Biostator era and first appeared in subcutaneous closed-loop systems in research in the mid-2000s (61). The primary rationale for dual-hormone systems, which are capable of administering boluses of glucagon in addition to continuous insulin infusion, is that prevention of hypoglycemia is more effective with administration of glucagon than with suspension of insulin delivery. This is due to the pharmacokinetics of subcutaneous insulin and glucagon: currently available rapid-acting insulins have a relatively slow onset (10–15 minutes), delayed time to maximum effect (40–60 minutes) and prolonged duration of action (up to 4–6 hours), while glucagon has an onset of 5 minutes (62).

There are two main approaches to insulin-glucagon systems: the first utilizes small boluses to prevent hypoglycemia without a concomitant increase in insulin delivery, while the second uses intermittent glucagon doses to allow more aggressive insulin delivery to target lower glucose levels (62). Compared with conventional insulin pump therapy, dual-hormone closed-loop systems have been shown to reduce hypoglycemia, improve mean glucose levels, and increase time spent in the target glycemic range (43, 63). A 2017 meta-analysis comparing single-hormone and dual-hormone closed-loop systems showed that the dual-hormone approach resulted in increased time in target (51). The main barrier to the development and uptake of glucagon-containing closed-loop systems is the lack of stable liquid formulations of glucagon; some studies have used glucagon cartridges that require replacement as frequently as every 8 hours (64). Recently, Castellanos et al. have published preliminary results from a trial of the dual-chamber iLet (Beta Bionics), which contains insulin and dasiglucagon, a chemically stable synthetic glucagon analogue (65).

Another dual-hormone approach combines insulin with pramlintide, a synthetic analogue of amylin, which is co-secreted with insulin by healthy pancreatic beta cells and slows gastric emptying, suppresses glucagon production, and prolongs satiety. One study showed in 2016 that the addition of fixed-dose premeal injections of pramlintide to a closed-loop system reduced postprandial hyperglycemia (66). Another trial demonstrated improved daytime glycemic control in a dual-hormone closed-loop system with basal-bolus delivery of pramlintide compared to an insulin-only closed-loop system (67). The practicality of insulin-pramlintide closed-loop systems is limited by the requirement for two separate infusion reservoirs, but this remains an area of ongoing research (68).

Specific Populations

The safety and efficacy of several closed-loop systems have been established in large trials of adults and adolescents with type 1 diabetes in both controlled environments and real-life settings. However, there are many subpopulations who stand to benefit from closed-loop therapy. In the framework of personalized precision medicine, closed-loop control has the potential for success in individuals with unique physiological, pathological, and behavioral characteristics that influence glycemic control, such as pregnant women, very young children, critical care patients, dialysis patients, shift workers, and travelers. Most commercially available hybrid closed-loop systems are licensed for use in children, albeit with varying minimum ages for use (69). CamAPS FX is the only system currently licensed for use in pregnancy, although there are case reports of off-label use of the MiniMed 670G by pregnant women (70, 71). A significant barrier to closed-loop use during pregnancy is the need for a customizable algorithm that allows for adjustment of glycemic targets to the tighter range recommended in pregnancy.

A study of day-and-night hybrid closed-loop control during pregnancy by Stewart et al. found reduced hypoglycemia compared to sensor-augmented pump therapy, but no difference in the primary outcome of overall time spent in range (72). Bally et al. compared a similar hybrid system to conventional subcutaneous insulin therapy in hospitalized patients with type 2 diabetes, finding reduced hypoglycemia, reduced mean glucose, and increased time in range (73). A *post-hoc* analysis of this data focusing on patients undergoing hemodialysis similarly found an increased proportion of time in target and reduced hypoglycemia (74). A recent randomized trial of hybrid closed-loop therapy in children aged 1 to 7 demonstrated significant improvements in time in range, HbA1c, and mean glucose level compared to sensor-augmented pump therapy, without a significant difference in total daily insulin dose (75).

CONCLUSION

Since the era of the first closed-loop systems in the 1960s and '70s, progress in diabetes management has been closely tied to advances in diabetes technology with the proliferation of devices for continuous insulin delivery and glucose monitoring. The past decade has seen rapid advances in the development and uptake of closed-loop systems, with the hybrid closed-loop system transitioning from research to commercial availability. Although the ultimate artificial pancreas – a fully closed-loop

system – has not yet been realized in clinical practice, the success of closed-loop system development thus far, and the timeline in which it has been achieved, is promising.

The key open questions in closed-loop system development surround the capability of sensors, pumps, and algorithms to adapt to complex scenarios. Current technologies often struggle to handle glycemic dysregulation resulting from features of everyday life such as exercise, sleep disruption, and variable meal times and sizes. Will this require better sensors, without the built-in delay of interstitial glucose readings? Faster-acting insulins or alternative routes for insulin delivery, allowing for more rapid onset and offset? The addition of glucagon or other adjuncts to mitigate the risk of hypoglycemia? Or more advanced algorithms that can address not only person-to-person variability but also day-to-day variability in glucose regulation? The answers lie in the next generation of closed-loop therapy, which may well use a combination of these.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor to this work and has approved it for publication.

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Early Initiation of Intermittently Scanned Continuous Glucose Monitoring in a Pediatric Population With Type 1 Diabetes: A Real World Study

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Background: Use of Continuous Glucose Monitoring (CGM) systems early in the course of diabetes has the potential to help glycemic management and to improve quality of life (QoL). No previous research has examined these outcomes in children-adolescents with type 1 diabetes (T1D) who use intermittently scanned CGM (isCGM) starting within the first month after diagnosis.

Aim: To evaluate the impact of isCGM early after T1D diagnosis, on metabolic control and QoL, comparing a group who started the use of the device within one month from the onset with another one who started at least one year later.

Subjects and Methods: Patients who used isCGM within 1 month from T1D diagnosis were enrolled in group A; those who didn't have the device during the first year were considered as control group (group B). HbA1c and total daily insulin were evaluated at 3 (T1), 6 (T2) and 12 (T3) months post-baseline (T0, diabetes onset), QoL after 1 year. In group A, isCGM glucose metrics were also recorded.

Results: 85 patients were enrolled in group A and 67 patients in group B. In group A isCGM was well accepted during follow up: no patient dropped out; percentage of time with active sensor was in mean > 87%; number of scans/day remained stable. QoL was higher in group A than in group B both in children-adolescents ($p<0.0001$) and in parents (p 0.003). Group A presented lower HbA1c during the first year after diagnosis ($p<0.001$), and this data correlated with glucose management indicator (GMI), time in range (TIR) and mean glucose. The honeymoon period lasted more in group A than in B (p 0.028). Furthermore, the mean hypoglycemia duration decreased during follow-up (p 0.001) in group A.

Conclusions: Early use of isCGM, starting within the first month after diagnosis, improves metabolic control and QoL in pediatric patients with T1D.

Keywords: type 1 diabetes onset, instant scanning continuous glucose monitoring, children and adolescents, outcomes, metabolic control

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INTRODUCTION

Children newly diagnosed with type 1 diabetes (T1D) have to adhere to a rigorous and complicated daily medical regimen (1). Improving glycemic control during early months after T1D diagnosis is challenging, because in the honeymoon phase children can experience rapid variations in glucose levels due to unpredictable effects of their own endogenous insulin levels in addition to exogenous insulin administered (2). However, this period is very important to determine future glycemic control and to set habits, beliefs as long as fears (2). Current data suggest that chronically high glucose levels may impair insulin synthesis/secretion, beta cells survival and insulin sensitivity, therefore improving blood glucose (BG) control is the most important step for preserving pancreatic beta cells (3, 4).

Use of Continuous Glucose Monitoring (CGM) systems early in the course of diabetes, has the potential to help glycemic management and to improve quality of life (QoL) (5, 6). However, currently there is a lack of studies about possible outcomes of early initiation of intermittently scanned CGM (isCGM) in pediatric subjects with T1D.

In view of the above, the aim of the study was to measure the impact of early use of isCGM on HbA1c (primary outcome) and QoL (secondary outcome).

SUBJECTS AND METHODS

Ethic Committee

The current study was approved by the Institutional Review Board of "Azienda Provinciale per i Servizi Sanitari della Provincia Autonoma di Trento" (reference number A424). The study was conducted from January 2017 to January 2022. Written informed consent was obtained from each participant and parent/legal guardian, as applicable, prior to enrollment.

Participants

225 patients with diabetes, aged 1-18 years are followed up at the Pediatric Diabetology Outpatient Clinic of Trento, one of the 68 Italian pediatric diabetes centres belonging to the Italian Society for Pediatric Endocrinology and Diabetes (ISPED) (7).

Inclusion criteria for this study were:

- age between 4-18 years (both inclusive);
- diagnosis of T1D confirmed by the positivity of at least one of the antibodies against islet cells (ICA), insulin (IAA), glutamate dehydroxilase (GADA), islet antigen 2 (IA2A) and zinc-transporter protein 8 (ZnT8A);
- acceptance to wear the isCGM system;
- to stay on the current insulin regimen: multiple daily injection (MDI) or continuous subcutaneous insulin infusion (CSII) for the first year after diagnosis.

Exclusion criteria were:

- age < 4 or > 18 years;
- other forms of diabetes out of T1D;
- use of real-time CGM (rtCGM);
- refusal to wear isCGM;
- change of insulin regimen during the first year after diagnosis (from MDI to CSII or vice-versa);
- diagnosis of developmental delay or severe psychiatric disorder;
- comorbid chronic condition.

Study Design

IsCGM first-generation (Abbott FreeStyle Libre 1® Glucose Monitoring System) has been available in Italy since 2016, and in our District (Province of Trento), the device was provided for free from January 2017. In the study, patients with new-onset T1D were consecutively enrolled offering to all of them the opportunity to start isCGM first generation soon after diabetes diagnosis (within 1 month). Structured education to the device, to glucose targets and trends was provided by the diabetology staff. Patient who accepted the device were included in group A, while those who didn't accept the device were excluded from the study.

Patients who presented diabetes onset in the years 2011-2016 that accepted to wear isCGM in 2017, at least 1 year after T1D diagnosis, were considered as control group (group B). For this group data on metabolic control have been retrospectively collected during the first year after diagnosis while QoL at 1 year, as in our centre this parameter is routinely tested.

In group A and B demographic parameters were recorded at diabetes onset (T0), 3 (T1), 6 (T2) and 12 (T3) months post-baseline. Data included: age, anthropometric measurements (height and weight), pubertal status (Tanner stages I-V), total daily insulin dosages, HbA1c. We used HbA1c level as the main indicator of average glycemic control. At diabetes onset we also collected: gender, venous blood pH and serum bicarbonates (HCO3), ethnicity and socioeconomic status (SES).

In group A, from T1 to T3, we recorded isCGM glucose metrics: % of time with active sensor, time in range (TIR), time below range (TBR), coefficient of variation (CV), mean glucose, average number of scans per day, number of hypoglycemia events, mean hypoglycemia duration.

QoL was assessed in children (> 8 years)-adolescents and their parents at 1 year in both groups.

Methods

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres. BMI-SDS was calculated using the WHO BMI charts (8). Pubertal development was assessed according to Tanner staging (9). Children-adolescents were classified according to three

Abbreviations: CGM, Continuous glucose monitoring; isCGM, Intermittently scanned continuous glucose monitoring; rtCGM, Real time continuous glucose monitoring; T1D, Type 1 diabetes; DKA, Diabetic ketoacidosis; HbA1c, Glycated hemoglobin (glycohemoglobin, hemoglobin A1c); TIR, Percentage of time in range 70-180 mg/dL (3.9 – 10 mmol/L); TBR, Percentage of the time below the range <70 mg/dL (3.9 mmol/L); CV, Coefficient of variation; GMI, Glucose management indicator; BG, blood glucose; QoL, quality of life; SES, socio-economic status.

pubertal stages: pre-pubertal (equivalent to the Tanner stage 1), pubertal (Tanner stages 2 to 4), and post-pubertal (Tanner stage 5). Capillary HbA1c level was measured using DCA Vantage® Analyzer (Siemens Healthcare GmbH).

IsCGM data available in the 2-week period preceding every visit were collected, since studies have shown that glucose readings from the last 14 days correlate well with 3 months data and the association between the CGM-measured mean glucose and HbA1c is strong (10–12). QoL was assessed with the Italian version of the PedsQL 3.0 Diabetes Module questionnaire, with the 8-12 years child and parents version, 13-18 years adolescent and parents version (13); range is between 0 to 100, and higher scores indicate higher QoL.

DKA at the diagnosis was defined as venous pH <7.3 or serum bicarbonate <15 mmol/L according to ISPAD guidelines (14). We consider a partial remission or "honeymoon period" according to this definition: HbA1C (%) + [4 * insulin per Kg body weight per day] ≤ 9 (15, 16). The family's socio-economic status (SES) was evaluated by ascertaining the mother's educational level. Educational level has been previously identified as an important indicator for SES (17) and was dichotomized into low- (≤14 years of education) and high- (>14 years of education) SES, which differentiates between families with a mother who has completed medium or higher education, college or university training, from other families (18, 19).

Statistics

In order to determine the optimal number of patients to be consecutively enrolled in the study, when planning the present clinical trial, the calculation of the sample size was performed together with the statisticians. The primary outcome of the study was to identify changes in HbA1c over the first year after diagnosis, between the two groups. We considered a minimum difference of 0,5% and a standard deviation of 0.97 as clinically relevant (5). By accepting a two-tailed 5% α error and a study power of 90% (1-β), a numerosity (n) equal to 86 patients is obtained.

Statistics were analysed using GraphPad Prism version 8.0.2 (GraphPad, San Diego, CA, USA). Every dataset was tested for statistical normality and this information was used to apply the appropriate (parametric or nonparametric) statistical test.

Data are expressed as mean ± SD for variables with normal distribution and with medians (interquartile range) for non-normally distributed variables. Differences between groups of continuous variables were analysed with t-student for paired samples for variables with normal distribution, or with Wilcoxon signed rank sum test for variables with non-normal distribution. The chi-square test with Fisher's test has been used to evaluate differences in categorical data.

Pearson correlations have been used to analyse statistical relationship between the different variables. P values < 0.05 were considered significant.

RESULTS

From January 2017 to January 2021, 110 children-adolescents aged 1-18 years were newly diagnosed with T1D at our pediatric clinic. Among them, 16 patients were started on rtCGM (among these, 12 aged less than 4 years were started on CSII + rtCGM) and 4 refused isCGM, therefore they were excluded. 90 subjects accepted to initiate isCGM within 1 month (group A) and 5 more were excluded because they started a pump during the first year after diagnosis.

Among the 108 patients who presented with T1D onset in the years 2011-2016, 78 subjects accepted to wear isCGM in 2017. Eleven were excluded because they had started CSII within the first year after diagnosis, therefore 67 patients were included in group B and their first year after diagnosis was evaluated retrospectively. Population characteristics are reported in **Table 1**; all the subjects were in MDI and nobody started CSII stand-alone or CSII plus isCGM since diagnosis.

Data at T1D Onset

Age and diabetes onset severity in terms of pH, % of DKA and HbA1c were similar in the 2 groups, as well as gender distribution, ethnicity, SES, BMI z-score and pubertal status (**Table 1**). Patients in group A started isCGM at a mean of 3.82 days after diabetes diagnosis, while in group B after a mean of 832 days from T1D diagnosis.

Follow up Data

No events of severe hypoglycemia or recurrence of DKA occurred during the study, and no patients dropped out from isCGM. No skin reactions occurred due to the use of isCGM systems during the study period. Patients with isCGM (group A) showed lower HbA1c levels than group B at any time (p<0.01) (**Table 2**). HbA1c increased both in group A and B from 3 to 6 and 12 months (group A: p < 0.0001, group B p<0.05) as well as the number of patients in the honeymoon period decreased during the first year after diagnosis at any time, with longer honeymoon duration in patients with isCGM (group A) than in group B (36,5% in honeymoon period at 12 months compared to 14.92% in group B, p 0.0028). Considering only patients who entered remission within the first 3 months, the number of patients in the honeymoon period progressively decreased during the first year after diagnosis in both groups, with group A maintaining longer honeymoon duration than group B (61% in honeymoon period at 12 months compared to 43% in group B, p 0.028).

No significant differences in total daily insulin dose and in BMI z-score were showed during follow up at any time (T1, T2, T3) in group A and in group B and between groups. QoL at 1 year was statistically significant higher in children in group A than in group B (83.14 ± 7.87 vs 74.58 ± 9.29, p < 0.0001), as well as in parents (79.78 ± 10.21 vs 73.68 ± 14.68, p 0.003).

IsCGM Metrics in Group A

During follow up the percentage of time with active sensor slightly decreased (p 0.03), and CV increased at any time (p 0.0036, **Table 3**). Number of hypoglycemia events per week remained stable, while the mean hypoglycemia duration decreased from 3 months to 6 and 12 months (p 0.01).

No significant differences in TIR, TBR, mean glucose and GMI were registered. Average number of scans per day did not change along the follow up period.

TABLE 1 | Population characteristic at the T1D onset (T0).

T0	Group A	Group B	p value
Number	85	67	–
Male (%)	44 (52%)	33 (49%)	n.s (p 0.61)
Age at onset (years)	10.95 ± 3.26	10.09 ± 1.68	n.s. (p 0.06)
DKA at onset (%)	36 (42%)	25 (37%)	n.s. (p 0.97)
Age class (years)	4	0	
0-4	13	16/	
5-9	19	9	
10-14	0	0	
15-19			
Gender	17 M/19 F	13 M/12 F	
Ethnicity	27	21	
Caucasian	7	4	
Morocco	2	0	
Pakistan-India	19	13	
SES	17	12	
High			
Low			
pH	7.32 (7.21-7.37)	7.34 (7.18-7.38)	n.s. (p 0.90)
HbA1c at onset (mmol/mol)	12.25 ± 2.28	11.8 ± 1.98	n.s (p 0.21)
Days to isCGM start	3.82 (2.00-4.00)	809 (422–1177)	**p < 0.0001**
Ethnicity	64 Caucasian (75%)	55 Caucasian (82%)	n.s. (p 0.82)
	19 Morocco (22%)	19 Morocco (28%)	
	2 Indian/Pakistan (2%)		
SES	57 High (67%)	48 High (71%)	n.s. (p 0.55)
	28 Low (33%)	19 Low (29%)	
BMI (Kg/m2)	18.29 ± 2.89	16.89 ± 2.35	n.s. (p 0.07)
BMI z-score	-0.51 ± 1.23	-0.29 ± 0.88	n.s. (p 0.23)
Prepubertal	46 (54%)	41 (61%)	n.s. (p 0.74)
Pubertal	34 (40%)	25 (37%)	
Postpubertal	5 (6%)	1 (1%)	

Group A included patients that accepted to initiate isCGM within 1 month from T1D diagnosis. Group B included patients that started the device at least 1 year after diagnosis.
Age at onset, HbA1c at onset, weight, BMI, and BMI z-score are expressed as mean ± SD.
pH and days to isCGM start are expressed as median ± interquartile range.
IsCGM, Intermittently Scanned Continuous Glucose Monitoring; DKA, diabetic ketoacidosis. SES, socio-economic status; n.s., not significant.
In bold: statistically significant p values.

Correlations

HbA1c strongly correlated with TIR, mean glucose and GMI at any time (**Table 4**).

TIR strongly correlated with HbA1c, GMI, time of sensor usage, mean glucose and CV (**Supplementary Material S1**).

DISCUSSION

We studied the impact of isCGM, started within 1 month from T1D onset, on HbA1c and QoL, as no reports on isCGM in relation to diabetes onset are available in literature (20). According to us three are the main findings:

1. Early initiation of isCGM within 1 month after T1D diagnosis, is feasible and well accepted, as demonstrated by the absence of dropout among our cohort and by the improved QoL in children as well as in parents. It is safe as no events of severe hypoglycemia or recurrence of DKA occurred during the study. Moreover, isCGM did not increase total daily insulin dosage or BMI z-score. Our data are concordant with previous studies about early initiation of rtCGM (from 0 to 12 months), that demonstrated that it is feasible and well accepted by youth and their families (6). In our study compliance with wearing the instrument was high (mean > 87%) and the percentage of time with active sensor just slightly decreased during the first year of follow up, in agreement with previous studies on rtCGM at T1D diagnosis (21). Such findings are important as we know from literature that frequent sensor usage (at least 70%) is associated with greatest improvement in glycemic control in patients with CGM (22). Our patients were compliant to scan the device: an average number of 10 scans per day were maintained during follow up, as we suggested at the start of the device by structured education (before the three main meals, before snacks, before going to bed, in case of symptoms of hyper or hypoglycemia, and for physical activity management).
2. The main outcome of our study was HbA1c. Patients who started isCGM within 1 month after T1D diagnosis (group A) had lower HbA1c at 3, 6 and 12 month follow-up compared to those who did not start early isCGM (group B). The improvement in HbA1c levels within the first 12 months of diabetes is similar to that reported for rtCGM (5). Furthermore, we confirm a correlation between the 2 weeks sensor metrics (TIR, mean glucose, CV, GMI) with 3 months data and HbA1c, as other studies report (10–12).

HbA1c is strongly correlated with GMI, TIR and mean glucose and this data, linked to the use of isCGM during the first year after

TABLE 2 | follow up data in Group A (n = 85) and B (n = 67).

Parameters	Group	T1 (3mo)	T2 (6mo)	T3 (12mo)	p value
HbA1c (%)	A	6.45 ± 0.47	6.58 ± 0.64	6.88 ± 0.72	A: **p < 0.0001**
	B	6.86 ± 0.71	7.00 ± 0.72	7.19 ± 0.76	B: **p < 0.05**
		p < 0.0001	**p 0.0002**	**p < 0.001**	
Total daily insulin dose (U/Kg)	A	0.43 ± 0.25	0.44 ± 0.24	0.47 ± 0.30	A: n.s. p 0.55
	B	0.45 ± 0.22	0.49 ± 0.23	0.52 ± 0.22	B: n.s. p 0.21
		n.s. p 0.58	n.s. p 0.25	n.s. 0.29	
% of basal insulin	A	61.07 ± 20.84	59.93 ± 21.55	60.96 ± 19.05	A: n.s. p 0.92
	B	58.1 ± 15.42	57.10 ± 15.31	53.63 ± 14.95	B: n.s. p 0.21
		n.s. p 0.33	n.s. p 0.36	**p 0.01**	
Number of patients in "honeymoon period"	A	53/85 (62%)	38/85 (44.7%)	31/85 (36.5%)	A: **p 0.0024**
(all patients)	B	29/67 (43%)	16/67 (23.9%)	10/67 (14.92%)	B: **p 0.0007**
		p 0.019	**p 0.0075**	**p 0.0028**	
Number of patients in "honeymoon period"	A	65/85 (76%)	59/85 (69%)	52/85 (61%)	A: **p 0.098**
(patients entered remission within the first 3 months)	B	43/67 (64%)	36/67 (54%)	29/67 (43%)	B: **p 0.05**
		n.s. p 0.098	**p 0.0047**	**p 0.028**	
BMI z-score	A	-0.27 ± 1.04	-0.29 ± 1.01	-0.21 ± 1.04	A: n.s. p 0.86
	B	-0.07 ± 0.80	-0.20 ± 0.81	-0.16 ± 0.84	B: n.s. 0.61
		n.s. p 0.20	n.s. p 0.57	n.s. p 0.78	
Patients PedsQL score	A			83.14 ± 7.87	
	B			74.58 ± 9.29	
		n.a.	n.a.	**p < 0.0001**	
Parents PedsQL score	A			79.78 ± 10.21	
	B	n.a.	n.a.	73.68 ± 14.68	
				p 0.003	

Data are presented as mean ± SD. N.a., not assessed.
n.s., not significant.
In bold: statistically significant p values.

TABLE 3 | four week time glucose metrics in Group A (n = 85).

Parameters	T1 (3mo)	T2 (6mo)	T3 (12mo)	p value
% of time with active sensor	91.9 ± 9.12	90.65 ± 9.53	87.55 ± 13.10	**p 0.03**
% of time in range (70-180 mg/dL)	72.26 ± 11.59	70.82 ± 12.04	68.52 ± 12.51	n.s. p 0.13
% di time below range (< 70 mg/dL)	4.93 ± 3.51	4.74 ± 3.65	5.18 ± 4.18	n.s. 0.75
Mean glucose (mg/dL)	139.49 ± 13.89	141.21 ± 18.05	144.13 ± 18.16	n.s. 0.19
Coefficient of variation (CV) (%)	32.94 ± 6.65	35.30 ± 8.22	36.74 ± 7.16	**p 0.0036**
Glucose management indicator (GMI) (%)	6.65 ± 0.43	6.68 ± 0.62	6.73 ± 0.58	n.s. 0.64
Number of hypoglycemic events/week	7.36 ± 3.80	6.74 ± 4.12	7.73 ± 4.35	n.s. 0.28
Mean hypoglycemia duration (min)	52.85 ± 26.79	39.42 ± 24.62	41.49 ± 23.85	**p 0.001**
Average number of scans per day	10.53 ± 6.10	9.86 ± 5.52	10.19 ± 5.35	n.s. 0.74

Data are presented as mean ± SD. n.s., not significant.
In bold: statistically significant p values.

TABLE 4 | correlations among HbA1c and study variables at T1, T2 and T3 in group A.

Parameters	HbA1c atT1 (3mo)	HbA1c atT2 (6mo)	HbA1c atT3 (12mo)
% of time with active sensor	n.s. p 0.60	n.s. p 0.07	n.s., p 0.064
% of time in range (70-180 mg/dL)	**p 0.003,** r –0.32	**p < 0.0001**, r -0.61	**p < 0.0001**, r -0.45
% di time below range (< 70 mg/dL)	n.s. p 0.51	**p < 0.0001**, r 0.43	n.s., p 0.28
Coefficient of variation (CV) (%)	n.s. p 0.11	n.s. p 0.22	n.s. p 0.078
Mean glucose (mg/dL)	**p 0.001,** r 0.36	**p < 0.0001**, r 0.43	**p < 0.0001**, r 0.67
Glucose management indicator (GMI) (%)	**p < 0.0001**, r 0.37	**p < 0.0001**, r 0.77	**p < 0.0001**, r 0.72
Number of hypoglycemic events/week	n.s. p 0.98	**p 0.002,** r 0.33	n.s. p 0.62
Mean hypoglycemia duration (min)	n.s. p 0.87	**p 0.013**, r 0.27	n.s. p 0.92
Average number of scans per day	**p 0.004**, r – 0.31	n.s. p 0.96	n.s. 0.41

ns, not significant.
In bold: statistically significant p values.

diagnosis, have never been reported in literature before. We interpreted this data, considering that this device allows subjects to have more information about glucose values, trends and to look at patterns. According to this, they can enhance insulin dosage, food intake and physical activity, improving TIR and HbA1c too. At the same time, having more glucose data gradually increases confidence in the device as they could improve hypoglycemia correction, leading to reduction in mean hypoglycemia duration, as we found from 3 to 6 and 12 months. Vice-versa, as we expected, isCGM cannot prevent a number of hypoglycemia events, unlike rtCGM systems (21).

3) We found that even in group A, HbA1c levels increased between 3 months and the 6-12 months follow-up assessments as well as the coefficient of variation for glucose, a measure of glycemic variability. These data are generally consistent with the findings of other authors regarding rtCGM (5, 23, 24), probably due to the ending of partial remission period (honeymoon) in some patients. Interestingly, the percentage of patients that remained in the honeymoon period was higher in the isCGM group compared to group B, probably related to better HbA1c and values of glucose on target. Recent evidence points to the usefulness of new technologies like rtCGM and insulin pumps to improve metabolic control, as this may preserve C-peptide and other outcomes, both with and without additional immunomodulatory therapy at the onset of T1DM (25).

Strengths of the present study are: i) this is a real world study, all the patients with diabetes onset had the opportunity to wear isCGM because private insurance was not required. Low socio-economic groups had the same opportunity to have access to CGM systems. Therefore, the present study can be generalised to other cohorts of children and adolescents with recent-onset T1D in a universal health care system; ii) all the patients enrolled resulted in MDI, then variables due to other technologies are excluded. The main limitation to the present study is that it was conducted at a single site and other studies are needed to confirm whether introduction the of isCGM devices, early in the course of diabetes along with education around glucose targets, has the potential to improve glycemic outcomes and QoL.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of "Azienda Provinciale per i Servizi Sanitari della Provincia Autonoma di Trento" (reference number A424). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

RF designed the study. LS, FB, and EM researched and analysed data. RF, VC, MS, and EM wrote the manuscript. RF is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity and the accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

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Analysis of detrended fluctuation function derived from continuous glucose monitoring may assist in distinguishing latent autoimmune diabetes in adults from T2DM

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Background: We aimed to explore the performance of detrended fluctuation function (DFF) in distinguishing patients with latent autoimmune diabetes in adults (LADA) from type 2 diabetes mellitus (T2DM) with glucose data derived from continuous glucose monitoring.

Methods: In total, 71 LADA and 152 T2DM patients were enrolled. Correlations between glucose parameters including time in range (TIR), mean glucose, standard deviation (SD), mean amplitude of glucose excursions (MAGE), coefficient of variation (CV), DFF and fasting and 2-hour postprandial C-peptide (FCP, 2hCP) were analyzed and compared. Receiver operating characteristics curve (ROC) analysis and 10-fold cross-validation were employed to explore and validate the performance of DFF in diabetes classification respectively.

Results: Patients with LADA had a higher mean glucose, lower TIR, greater SD, MAGE and CV than those of T2DM (P<0.001). DFF achieved the strongest correlation with FCP (r = -0.705, P<0.001) as compared with TIR (r = 0.485, P<0.001), mean glucose (r = -0.337, P<0.001), SD (r = -0.645, P<0.001), MAGE (r = -0.663, P<0.001) and CV (r = -0.639, P<0.001). ROC analysis showed that DFF yielded the greatest area under the curve (AUC) of 0.862 (sensitivity: 71.2%, specificity: 84.9%) in differentiating LADA from T2DM as compared with TIR, mean glucose, SD, MAGE and CV (AUC: 0.722, 0.650, 0.800, 0.820 and 0.807, sensitivity: 71.8%, 47.9%, 63.6%, 72.7% and 78.8%, specificity: 67.8%, 83.6%, 80.9%, 80.3% and 72.4%, respectively). The kappa test indicated a good consistency between DFF and the actual diagnosis (kappa = 0.551, P<0.001).

Ten-fold cross-validation showed a stable performance of DFF with a mean AUC of 0.863 (sensitivity: 78.8%, specificity: 77.8%) in 10 training sets and a mean AUC of 0.866 (sensitivity: 80.9%, specificity: 84.1%) in 10 test sets.

Conclusions: A more violent glucose fluctuation pattern was marked in patients with LADA than T2DM. We first proposed the possible role of DFF in distinguishing patients with LADA from T2DM in our study population, which may assist in diabetes classification.

KEYWORDS

Latent autoimmune diabetes in adults, type 2 diabetes mellitus, beta-cell function, detrended fluctuation function, continuous glucose monitoring

Introduction

Latent autoimmune diabetes in adults (LADA), defined by the presence of islet autoantibody especially glutamic acid decarboxylase autoantibodies (GADA) and progressive islet function failure (1). LADA manifests a broad clinical phenotype between classic type 1 diabetes mellitus (T1DM) and classic type 2 diabetes mellitus (T2DM) (2). Consequently, a moderate proportion of LADA patients might be misdiagnosed as T2DM in the early stage. More importantly, the islet function in patients with LADA progresses much faster than that of T2DM (3). Once LADA patients develop insulin dependency, they will present much greater glucose fluctuation pattern than before. The standardized GADA testing is the recommended screening test for LADA because high GADA titer is correlated with accelerated decline of β-cell function (4). At present, early diagnosis of LADA patients remains a challenge since accurate and efficient islet antibody detection technology has not been widely carried out in many primary hospitals in China (5). The LADA international Expert Panel recommended that all newly diagnosed T2DM patients should be screened for GADA positivity and follow-up of progressing beta-cell failure annually, which might increase the burden of medical care (6). For this reason, there is increasing interest in exploring alternative approaches which may assist in LADA screening and diagnosis.

With gradual maturation of continuous glucose monitoring (CGM) technology and emerging clinical evidence in favor of CGM adoption (7), CGM ushered in a new era of glucose management. Currently, proposed CGM measures of interest such as standard deviation of glucose, mean amplitude of glucose excursions and time spent in given thresholds are mainly applied to reflect the instability of glucose and overall glycemic control. A previous study had reported higher glycemic variability metrics derived from CGM in patients with LADA than in T2DM (8). C-peptide (C-P), a reliable marker of β-cell function, may help discriminate diabetes types (9, 10). Moreover, C-P secretion is deemed to be associated with glycemic variability (11, 12). However, clinical detection of C-P is limited by the need to discontinue insulin. Although increasingly being used in clinical practice for the management of diabetes, few studies have investigated the role of CGM as a tool for the diagnosis of LADA, and whether the massive time series data provided by CGM can reliably distinguish LADA from T2DM is unknown. However, if use of CGM is found to reliably predict the diagnosis of LADA by GADA testing or C-P, then there would be multiple benefits to the patients (no admission, no time lost from work and no intravenous catheter or multiple blood draws) as well as economic advantages (costs of the admission, blood processing, C-P assays and personnel time), which represents an important step for CGM as an alternative and less burdensome approach for collaborative diagnosis of LADA.

Therefore, we aimed to:1) find a predictive indicator for serum C-P which can differentiate patients with LADA and T2DM through detrended fluctuation analysis, a modified random-walk analysis method using time series data derived from CGM (13); 2) evaluate its performance in identifying LADA from T2DM. Inspired by the usage of detrended fluctuation function (DFF) proposed by Liu et al. (14) in differentiating patients with T1DM and T2DM, we try to explore the same data-driven analysis in a more indistinguishable group consisting of LADA and T2DM. To our knowledge, studies regarding the glucose fluctuation of LADA are sparse, and this is the first study utilizing CGM metrics to differentiate LADA from T2DM.

Materials and methods

Study population

A total of 223 diabetes patients (71 with LADA and 152 with T2DM) from the outpatient department of the Second Xiangya

Hospital, Central South University were included in this observational study. The inclusion criteria of patients with LADA were as follows: (1) diagnosis of diabetes according to the 1999 WHO criteria (15); (2) age > 18 years old; (3) insulin-independent for at least 6 months post-diagnosis; (4) GADA positivity; (5) no ketosis or ketoacidosis. The inclusion criteria of patients with T2DM were as follows: (1) diagnosis of diabetes according to the 1999 WHO criteria; (2) GADA negative; (3) age > 18 years old. Diabetes classification was made by a specialist and further confirmed by another one. Patients were excluded for one of following reasons: acute infection within 4 weeks prior to the recruitment, history of diabetic ketoacidosis in the past 3 months, abnormal liver/kidney function; with a comorbid autoimmune disease, pregnancy or preparing for pregnancy, receiving steroid therapy, and specific types of diabetes.

The study protocol was approved by the Ethics Review Committee of the Second Xiangya Hospital of Central South University (approval number: 2019-198; granted date: November 12, 2019), and it was carried out in accordance with the Declaration of Helsinki. Signed informed consent was obtained from each participant.

Demographics and clinical measurements

Each patient underwent a physical examination that included measurements of height and weight, blood pressure. Demographics such as age, gender, duration of diabetes were collected. Blood samples for detecting lipid profiles (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and total triglycerides), renal function (blood urea nitrogen, blood creatinine, uric acid), thyroid hormones (FT_3, FT_4, TSH), hemoglobin A1c (HbA1c), fasting blood glucose (FBG), fasting C-peptide (FCP) were drawn after 8-10h of fasting. A mixed-meal tolerance test (MMTT, 44.4% carbohydrates, 47.7% fat and 7.9% protein) was performed before 2-hour postprandial blood glucose (2hBG) and C-peptide (2hCP) measurements. For insulin treated patients, the long-acting insulin the night before the MMTT test was preserved and the morning prandial insulin was omitted. Patients treated with a pump continued their background basal rate but omitted the morning bolus. As for patients who were taking oral antihyperglycemic drugs (OADs) for glycemic control, they were required to discontinue insulin secretagogues (sulfonylureas or glinides) until the blood samples for detecting C-peptide and blood glucose levels were drawn.

Blood glucose levels, lipid profiles and other biochemical indicators were uniformly measured by an automatic biochemical analyzer. The level of HbA1c was determined by automated high-performance liquid chromatography (VARIANT II Hemoglobin Testing System; Bio-Rad Laboratories). Serum C-peptide levels were detected by a chemiluminescence method with an Adiva Centaur XP immunoassay system (Siemens, Germany).

GADA assay

GADA was analyzed by a radioligand assay in our laboratory as previously described (4). As evaluated in the Islet Autoantibody Standardization Program (IASP 2012), the sensitivity and specificity of the assay were 78.0% and 96.7%, respectively.

Continuous glucose monitoring

Dynamic glucose profiles were generated from the blinded CGM system (iPro2 with Enlite sensor, Medtronic MiniMed, Northridge, CA, USA). The glucose sensor of the CGM system (MMT-7008A) was inserted on the lateral upper arm and removed after 5-7 days, yielding a maximum daily record of 288 continuous sensor glucose values. With CGM, the participants were required to perform self-monitoring of blood glucose (SMBG) at least 4 times a day for calibration purposes. The CGM data were exported and analyzed using M-Smart software (CareLink iPro, Medtronic).

The time in range (TIR) was defined as the percentage of time spent in the normoglycemic range (3.9-10.0 mmol/L). Glycemic variability parameters included the standard deviation (SD), mean amplitude of glucose excursions (MAGE) and %CV (%CV= [(SD of glucose)/(mean glucose)]×100).

Detrended fluctuation function

A DFF metric $F_d(l)$ was utilized, in which l was a segment size parameter used to adjust the performance of diabetes classification (14). A methodology of extended random-walk analysis known as detrended fluctuation analysis was adopted (13): first, (1) we integrated the glucose time series $x(t)$, the cumulative deviation was calculated, and $x(t)$ was converted into a new series $y(t)$; Then (2) the new sequence $y(t)$ was divided into m intervals (or windows) with equal length n, where n is the interval length, that is, the time scale; (3) used the least square method to linearly fit the local trend $y_n(t)$ for each sequence; (4) the local trend of each interval in $y(t)$ was eliminated, the root mean square of the new sequence was calculated as $F(n)$; (5) changed the time scale n and repeated step 2,3 and 4. The calculation of $F(n)$ was achieved by the MATLAB software.

Statistical analysis

Normally distributed data were represented by mean ± SD, and skewed data after normality test (Shapiro-Wilk test) were

represented by median and interquartile range (IQR). Independent sample *t* test or Mann-Whitney *U* test were used to compare differences between patients with LADA and T2DM. Spearman correlation analysis was employed to evaluate the correlation between the fluctuation function $F_d(l)$ and beta-cell function parameters including FCP and 2hCP. Moreover, classical CGM-derived glycemic parameters including TIR, mean glucose, SD, MAGE and CV were also evaluated and compared with $F_d(l)$.

The receiver operating characteristics curve (ROC) analysis was performed to compare the classification performance of $F_d(l)$, TIR, mean glucose, SD, MAGE and CV based on all study subjects. Ten-fold cross-validation was employed to test the stability of $F_d(l)$. Moreover, ROC analysis was also performed in 116 insulin-treated patients (66 with LADA and 50 with T2DM). The kappa test was adopted to evaluate the classification consistency between actual classification and our study results.

A two-tailed test was performed, $P<0.05$ was considered statistically significant. SPSS 26.0 software (IBM corporation, Armonk, NY, USA) was used for statistical analysis. The computation of detrended fluctuation functions was performed in MATLAB 2020a (Mathworks, Inc., Natick, Massachusetts) for Windows.

Results

Demographics and clinical measurements

In total, 71 LADA and 152 T2DM patients were enrolled in the analysis, 61.0% of them were male. An average of 7-day CGM wearing was achieved, generating about 1,741 sensor glucose values per patient. The median age was 51.0 (42.0, 58.5) years. The average duration of diabetes was 5.0 (1.8, 9.0) years. Mean BMI level was 23.5 (20.9, 26.8) kg/m^2. HbA1c was 8.2 (7.2, 9.8) % [66 (55, 84) mmol/mol], median FCP level was 1.22 (0.45, 2.13) ng/mL and 2hCP was 3.01 (1.14, 4.94) ng/mL. Glucose profiles derived from CGM were also listed in Table 1.

Optimal *l* selection and the relevant $F_d(l)$ values in LADA and T2DM patients

We calculated all the $F_d(l)$ values from l=2 to l=130 using the glucose data derived from CGM of each patient, and then utilized Spearman correlation analysis to determine the correlation between the corresponding $F_d(l)$ values and beta-cell function parameters (FCP and 2hCP). Supported by the results we got in Figure 1, we decided to explore the value of $F_d(l)$ in diabetes differentiation by adopting the scale with the largest correlation coefficient (r=-0.705), that is, l=100. The average $F_d(l)$ level of all patients was 1.52 (1.25, 1.98), moreover, of LADA patients was 2.17 (1.67, 2.61) and of T2DM patients was 1.36 (1.14, 1.69), respectively, as displayed in Figure 2.

Spearman correlation analysis

As compared with the classical glucose parameters such as TIR, mean glucose, glucose variability indices including SD of glucose, MAGE and CV, $F_d(100)$ exhibiting a higher correlation coefficient with FCP. TIR, an emerging comprehensive indicator of overall glucose control evaluation, was positively correlated with FCP (r = 0.485, $P<0.001$) and 2hCP (r = 0.548, $P<0.001$). Mean glucose, another commonly used index in clinical practice, was inversely associated with FCP (r = -0.337, $P<0.001$) and 2hCP (r = -0.402, $P<0.001$). For glucose variability parameters, MAGE showed a high correlation coefficient with FCP (r = -0.663, $P<0.001$), and SD showed a strong negative association with 2hCP (r = -0.675, $P<0.001$). However, the $F_d(100)$ displayed the strongest correlation with FCP (r = -0.705, $P<0.001$). Details are shown in Table 2.

ROC analysis and the kappa test in all participants

ROC analysis was used to compare the classification performance of $F_d(100)$ and other glycemic parameters, as shown in Figure 3. It could be seen that the $F_d(100)$ showed the best performance in differentiating LADA and T2DM patients, the cut-off value was 1.82, achieving an area under curve (AUC) of 0.862 (95% CI [0.813, 0.912], sensitivity: 71.2%, specificity: 84.9%). When the SD was used, the AUC was 0.800 (95% CI [0.737, 0.863], sensitivity: 63.6%, specificity: 80.9%); the AUC of mean glucose, MAGE, CV and TIR were 0.650, 0.820, 0.807 and 0.722 (95% CI [0.567, 0.733], [0.757, 0.883], [0.749, 0.865] and [0.651, 0.793], sensitivity: 47.9%, 72.7%, 78.8% and 71.8%, specificity: 83.6%, 80.3%, 72.4% and 67.8%), respectively.

Furthermore, the kappa test was performed to evaluate the consistency with the real classification given by endocrinologists. $F_d(100)$ presented a good consistency with the real diagnosis (kappa = 0.551, $P<0.001$).

Ten-fold cross-validation

Ten-fold cross-validation was employed to validate the stability of DFF in the diabetes classification. First, 223 patients were randomly divided into 10 groups. Next, the group 1 to 9 were regarded as the training set, and the group 10 was the test set. Then, the group 1 to 8 and group 10 were the training set, and the group 9 was the test set; repeated 10 times. Results were listed in Table 3. The mean AUC of the 10 training sets was 0.863 (95% CI [0.859, 0.868], sensitivity: 78.8%,

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TABLE 1 Characteristics of all participants.

	LADA (*n* = 71)	T2DM (*n* = 152)	*P*
Sex (M/F)	35/36	101/51	0.015
Age (years)	48.0 (39.0, 57.0)	52.0 (43.5, 59.5)	0.239
Age of onset (years)	43.3 (33.5, 50.5)	45.0 (36.0, 53.0)	0.330
Duration (years)	4.3 (1.7, 10.0)	5.0 (2.0, 8.5)	0.921
BMI (kg/m^2)	20.7 (19.3, 23.3)	25.1 (22.5, 27.3)	<0.001
SBP (mmHg)	113.0 (107.0, 129.0)	130.0 (120.0, 138.0)	<0.001
DBP (mmHg)	73.5 ± 10.5	84.0 ± 9.9	<0.001
FBG (mmol/L)	7.75 (6.00, 10.71)	6.52 (5.43, 8.37)	0.004
2hBG (mmol/L)	14.96 (10.82, 17.70)	10.77 (7.80, 13.28)	<0.001
HbA1c (%)	8.1 (7.3, 9.8)	8.3 (7.1, 9.9)	0.816
HbA1c(mmol/mol)	65 (56, 84)	67 (54, 85)	0.816
FCP (ng/mL)	0.31 (0.07, 0.48)	1.82 (1.20, 2.46)	<0.001
2hCP (ng/mL)	0.54 (0.09, 1.21)	4.18 (2.84, 6.24)	<0.001
Total cholesterol (mmol/L)	4.40 (3.68, 4.81)	4.89 (4.17, 5.38)	<0.001
Triglyceride (mmol/L)	0.77 (0.61, 1.15)	1.48 (1.07, 2.19)	<0.001
HDL-c (mmol/L)	1.38 (1.18, 1.63)	1.22 (1.03, 1.37)	<0.001
LDL-c (mmol/L)	2.60 (2.09, 2.98)	2.66 (2.21, 3.24)	0.142
BUN (mmol/L)	5.50 (4.70, 6.65)	5.00 (4.00, 6.15)	0.011
CR (umol/L)	68.0 (56.0, 75.0)	69.0 (57.0, 77.0)	0.469
UA (umol/L)	267.0 (216.7, 314.9)	327.5 (285.0, 412.5)	<0.001
Diabetes treatment, *n* (%)			
Diet/insulin sensitizers alone	2 (2.8)	54 (35.5)	–
DPP-4i/sulfonylureas	3 (4.2)	42 (27.6)	–
SGLT-2i	0	6 (3.9)	–
Insulin	66 (93.0)	50 (33.0)	–
CGM-derived metrics			
TIR (%)	62.3 (48.6, 79.4)	79.5 (65.7, 90.3)	<0.001
Mean glucose (mmol/L)	9.41 ± 2.13	8.31 ± 1.42	<0.001
SD (mmol/L)	3.31 (2.48, 3.99)	2.14 (1.62, 2.79)	<0.001
MAGE (mmol/L)	6.80 (5.60, 9.25)	4.60 (3.60, 5.60)	<0.001
CV (%)	34.8 (30.3, 39.1)	25.2 (20.9, 30.4)	<0.001
$F_d(100)$	2.17 (1.67, 2.61)	1.36 (1.14, 1.69)	<0.001

Data are shown as mean ± SD, median (first quartile, third quartile) and ratio.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose, 2hBG, 2-hour postprandial blood glucose; HbA1c, hemoglobin A1c; FCP, fasting C-peptide, 2hCP, 2-hour postprandial C-peptide; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; CR, blood creatinine; UA, uric acid; DPP-4I, dipeptidyl peptidase 4 inhibitors; SGLT-2i, sodium-dependent glucose transporter 2; TIR, time in range; SD, standard deviation of glucose; MAGE, mean amplitude of glucose excursions; CV, coefficient of variation.

specificity: 77.8%), and average AUC was 0.866 (95% CI [0.830, 0.903], sensitivity: 80.9%, specificity: 84.1%) in the 10 test sets.

ROC analysis and the kappa test in the insulin-treated population

One-hundred and sixteen participants treated with insulin (66 LADA and 50 T2DM, Table 4) were further included in the ROC analysis to validate the performance of DFF. $F_d(100)$ yielded an AUC of 0.842 (95% CI [0.771, 0.913], sensitivity: 72.1%, specificity: 84.0%), the cut-off value of $F_d(100)$ in this population was 1.84 (data not shown). Moreover, $F_d(100)$ also presented a satisfactory consistency with the real diagnosis (kappa = 0.552, P<0.001).

Discussion

The term LADA is acceptable in clinical practice for its practical impact of highlighting proper treatment and insulin initiation prior to beta-cell function failure (16–18). Jones et al. (19) suggested that LADA may represent a mixed population of autoimmune diabetes (type 1) and non-autoimmune diabetes (type 2). Although the quality of modern islet autoantibody detection has improved (20), abnormally high specificity is

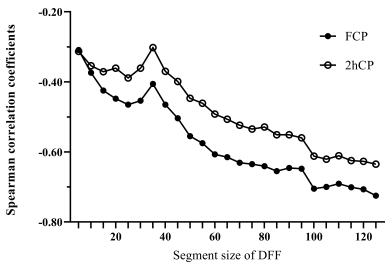

FIGURE 1
Spearman correlation curves between Fd(l) and beta-cell function indices (FCP and 2hCP). Black circles curve, correlation curve between FCP and Fd(l); white circles curve, correlation curve between 2hCP and Fd(l). FCP, fasting C-peptide; 2hCP, 2-hour postprandial C-peptide; DFF, detrended fluctuation function.

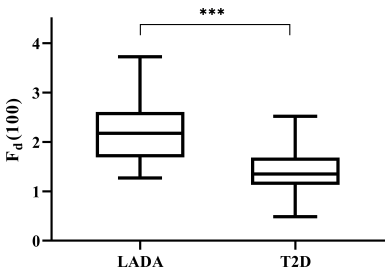

FIGURE 2
Levels of Fd(100) expressed with box plots of LADA and T2D patients. The top and bottom of the boxes denote the 25th and 75th percentiles, and the line represents the median, the upper and lower endpoint represents the maximum and minimum level respectively. LADA, latent autoimmune diabetes in adults; T2D, type 2 diabetes. ***P < 0.001.

required in low-risk groups with rare GADA antibody positivity such as patients with T2DM. The LADA International Expert Panel recommended to measure serum C-peptide levels as a proxy of insulin secretion in patients with positive islet cell-associated autoantibodies (21, 22), since the decline rate of C-peptide in LADA is midway between T1DM and T2DM (5, 23, 24).

The present study was based on the remarkably different beta-cell function in patients with LADA and T2DM, thus resulting in different pattern in glucose variability and other glycemic indices. We investigated the value of calculated DFF based on numerous glucose data retrieved from CGM, and compared the performance of DFF with several classical glucose parameters in distinguishing LADA and T2DM patients. As we know, studies reporting glucose fluctuation patterns in patients with LADA are scarce, and we did notice that glucose variability in LADA was significantly greater than that of T2DM patients who were matched for age and diabetes duration. Consequently, based on this result, we found that the correlation between DFF and beta-cell function assessed by FCP was strongest using $F_d(100)$ values obtained at an appropriate time scale of l = 100 (when the time period of the segmented glucose sequence was 8 hours and 15 minutes). Moreover, we further explored the performance of $F_d(100)$ in diabetes classification with ROC analysis, and we noted that $F_d(100)$ yielded a remarkable value as compared with the current commonly used glucose parameters.

The DFF calculation method we adopted was derived from detrended fluctuation analysis (DFA), a parameter evaluating glucose complexity. In general, it is considered to represent the long-term temporal auto-correlation rather than the glucose variability (13). DFA is supposed to mirror the intrinsic properties of individuals with different glucose metabolism status whether in normal subjects, prediabetic or diabetic patients. A study indicated that higher DFA was associated with worse glucose control in patients with diabetes (25). In addition, DFA was shown to be able to estimate insulin resistance either in healthy individuals or in T1DM (26), predict the probability of developing T2DM in patients at risk (27), and assess mortality in ICU patients (28). In our preliminary analysis, we found a significant difference in DFA levels between patients with LADA and T2DM, but the performance of DFA in diabetes classification was not satisfactory. Inspired by Liu et al. (14), we explored the value of DFF in distinguishing patients with LADA and T2DM. DFF was generated when the optimal time scale was selected on the basis of the calculation of DFA, in order to maximize the ability in reflecting the endogenous insulin secretion in our study population. As l increased, the correlation between $F_d(l)$ and FCP, 2hCP increased gradually and tended to be stable.

TABLE 2 Correlation between glycemic parameters and C-peptide levels.

	All participants (n = 223)					
	TIR	Mean glucose	SD	MAGE	CV	$F_d(100)$
FCP	0.485***	-0.337***	-0.645***	-0.663***	-0.639***	-0.705***
2hCP	0.548***	-0.402***	-0.675***	-0.600***	-0.630***	-0.612***

Values represent Spearman correlation coefficients.
FCP, fasting C-peptide; 2hCP, 2-hour postprandial C-peptide; TIR, time in range; SD, standard deviation of glucose; MAGE, mean amplitude of glucose excursions; CV, coefficient of variation. ***P < 0.001.

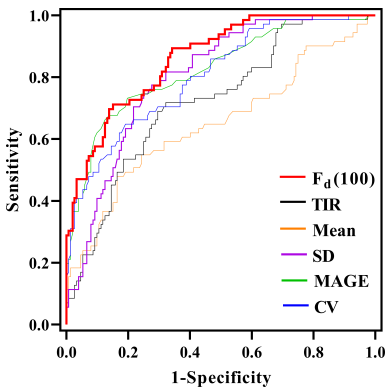

FIGURE 3
Comparison of the area under the curve (AUC) for glycemic parameters in discriminating between LADA and T2D through receiver operating characteristic curves.

Eventually, $F_d(100)$ was selected based on the characteristics of the glucose sequence generated by the CGM system we used. Several previous studies had reported that classical CGM-derived glycemic parameters such as MAGE and CV were closely related to beta-cell function (29–31). In our study, $F_d(100)$ showed a stronger correlation with FCP compared with TIR, mean glucose, SD, MAGE and CV. Similarly, levels of $F_d(100)$ were significantly higher in patients with LADA than that in patients with T2DM. ROC curves were employed to test the performance of $F_d(l)$ and classical glycemic parameters in distinguishing patients with LADA from T2DM. As expected, $F_d(l)$ yielded the largest AUC and achieved a high specificity (84.9%). Furthermore, the performance of $F_d(l)$ was verified to be stable in 10 groups of training and test sets with a 10-fold cross-validation method.

Emerging evidence suggests that CGM provides important information about glycemic variability that have direct implications for the glucose regulation of patients with diabetes. Several studies have indicated the potential role of CGM data in distinguishing people with different glucose metabolism. For example, CGM measures of hyperglycemia and glycemic variability were validated to be superior to HbA1c in distinguishing those with and without cystic fibrosis related diabetes (CFRD), indicating CGM as a diagnostic and screening tool for CFRD (32). Another Two studies developed a polynomial-kernel support vector machine-based approach and demonstrated the ability to distinguish between subjects affected by impaired glucose tolerance (IGT) and T2DM based on a pool of glycemic variability indices complemented by four basic parameters-age, sex, BMI, and waist circumference (33, 34). Hall et al. (35) introduced the concept of "glucotypes" that has attracted enormous attention in precision medicine. They developed an algorithm to identify patterns of glycemic variability based on CGM and argued that glucotypes provide the advantage of taking into account a more detailed picture of glucose dynamics compared with commonly used average-based measures, revealing subphenotypes within traditional diagnostic categories of glucose regulation. We found that CGM data derived measure-DFF significantly correlated with C-P, and that these correlations were stronger than commonly used CGM glycemic variability indices. These findings suggest that the information obtained by DFF is clinically meaningful and perhaps more relevant for clinical care than SD, MAGE or CV in diabetes.

Glucose-lowering medication in our LADA and T2DM patients was different. Approximately ninety percent of our LADA patients were treated with insulin, which is larger than that of T2DM patients. Apparently, insulin treatment is bound to affect both C-P secretion and CGM-related results. Herein, we

TABLE 3 Crossover-validation of performance of $F_d(l)$ in classification.

Groups	l	Training sets			Test sets		
		AUC	Sensitivity (%)	Specificity (%)	AUC	Sensitivity (%)	Specificity (%)
1	101	0.866	71.2	85.3	0.821	71.4	87.5
2	101	0.853	89.5	65.9	0.929	88.9	92.9
3	97	0.865	72.9	85.6	0.901	85.7	92.3
4	101	0.872	90.0	66.7	0.777	72.7	81.8
5	101	0.867	73.0	85.0	0.816	75.0	68.4
6	107	0.871	70.5	87.6	0.844	83.3	80.0
7	102	0.858	88.3	67.2	0.922	83.3	86.7
8	102	0.858	88.3	64.7	0.902	83.3	88.2
9	101	0.867	73.3	84.6	0.857	85.7	68.7
10	98	0.860	70.5	85.2	0.894	80.0	94.1
Mean	101.1	0.863	78.8	77.8	0.866	80.9	84.1
95% CI	99.2, 103.0	0.859, 0.868	72.4, 85.1	70.6, 85.0	0.830, 0.903	76.7, 85.2	77.4, 90.7

AUC, area under curve; CI, confidence interval.

TABLE 4 Insulin use of all participants.

	LADA (n = 71)	T2DM (n = 152)
Type of insulin treatment, n (%)		
MDI	45 (63.4)	4 (2.6)
Basal insulin dose (U/kg·d)	0.1882	0.2915
glargine/degludec/detemir/NPH	33/10/0/2	3/1/0/0
Bolus insulin dose (U/kg·d)	0.2886	0.3272
CSII	4 (5.6)	0
Basal rate (U/kg·d)	0.3732	/
aspart/lispro	2/2	/
Bolus insulin dose (U/kg·d)	0.2316	/
Only basal insulin regimen	10 (14.1)	13 (8.6)
Insulin dose (U/kg·d)	0.1850	0.2257
glargine/degludec/detemir/NPH	8/2/0/0	8/3/1/1
Only premixed insulin regimen	7 (9.8)	33 (21.7)
Insulin dose (U/kg·d)	0.4738	0.4284

MDI, multiple daily injections; NPH, neutral protamine hagedorn; CSII, continuous subcutaneous insulin infusion.

included all insulin-treated LADA and T2DM participants in additional ROC analysis and kappa test to test the stability of DFF. And supported by an AUC of 0.842 (sensitivity: 72.1%, specificity: 84.0%) and a kappa value of 0.552, the added value of DFF in diabetes classification was further validated in identifying both insulin-dependent LADA and T2DM patients in our study population. However, given that LADA patients in our study population were almost insulin treated, we were not able to evaluate the potential value of DFF in identifying insulin-naïve LADA patients, which may be a limitation of our study.

As previously mentioned, the GADA testing is the recommended screening tests for LADA because of its known prediction of β-cell function decline in patients with LADA (4), and screening autoimmune diabetic patients among T2DM patients requires extremely higher specificity (19). Therefore, even if computed specificity in our study was inferior to that of GADA detection in clinical practice, phenotypic T2DM patients could be suspected as LADA by $F_d(l)$ calculation, which might improve the diagnostic rate of LADA patients. Ultimately, large long-term prospective studies will be needed to investigate if DFF will similarly predict β-cell function decline in LADA. In the meantime, identifying CGM measures that correlate with the C-P levels of LADA and T2DM patients establishes an important first step in this process, particularly given the notable benefits of using CGM-derived DFF in this setting. Apparently, obtaining CGM data by simply placing a sensor at a clinic visit is easy and convenient, offering the potential to substantially improve LADA screening rates. In addition, CGM wearing would provide a comprehensive assessment of glucose control, allowing for the identification of glycemic patterns to guide individualized management decisions and insulin therapy in an efficient manner.

Unsurprisingly, our results were not as good as those obtained by adopting $F_d(l)$ to distinguish T1DM from T2DM (14). Since T1DM is known as 'fragile diabetes', absolute insulin deficiency and lifelong insulin-dependent treatment render great glucose fluctuations and frequent hypoglycemia in this population (36). Nevertheless, patients with T2DM who are insulin resistant always present mainly hyperglycemia and rare hypoglycemia, consequently undergo a much smaller glucose variability than that of T1DM. Theoretically, the application of $F_d(l)$ in differentiating T1DM from T2DM would be more effective. Moreover, the insulin secretory capacity of our LADA patients was nearly three times as their T1DM patients, we here broaden the application of DFF in diabetes classification. Last but not least, differentiating LADA from T1DM is surely an important step to validate the clinical significance of DFF since LADA is almost T1DM-phenotypic as the diabetes progresses. LADA shares the autoimmune pathogenesis of T1DM, except that the immune damage to pancreatic β-cells of LADA progresses slower than that of T1DM. Some LADA patients with diabetic ketoacidosis (DKA) onset are likely to be misdiagnosed as T1DM. Moreover, in patients with T1DM at a stage of partial recovery of islet function, such as the honeymoon stage, their insulin secretory capacity may be close to that of LADA patients. With gradual adoption of CGM, it would be of great interest to fully understand the information carried by the numerous glucose data and consequently apply to the precision medicine of diabetes.

To the best of our knowledge, this is the first study to distinguish patients with LADA and T2DM by using CGM data derived parameters. Consistent with the reported studies (8), we marked a more violent glucose fluctuation pattern in patients with LADA. At present, early diagnosis of LADA patients remains a challenge in China. The LADA international Expert

Panel recommended that all newly diagnosed T2DM patients should be screened for GADA positivity and follow-up of progressing beta-cell failure, which might increase the burden of medical care (21). Undoubtedly, GADA positivity, C-P levels and slim body are valuable for differential diagnosis of LADA or T2DM. However, we here provided an additional proof for diabetes classification by calculating $F_d(l)$ as the CGM system is increasingly widely used in glucose management.

We acknowledge that there were a few limitations. First, the sample size of patients with LADA was relatively small compared with that of T2DM, potentially limiting the statistical power in this group of individuals. Second, our findings of cut-off thresholds need to be validated in patients immediately after diagnosis of LADA since insulin treatment is bound to affect both C-P and glucose parameters. There were 2 patients taking pioglitazone in the T2DM group, and we did not evaluate their tiny effect on C-peptide release and blood glucose levels. Third, potential biases caused by uncertain confounding factors in such a cross-sectional and single-center study were difficult to rule out completely. In order to improve the clinical significance of DFF in this study, we will further explore the performance of DFF in other newly-diagnosed, untreated LADA and T2DM patients in the future. Moreover, various patients with specific diabetes diagnosis will also be collected to further validate our data-driven analysis.

To summarize, DFF was able to identify nearly 80 percent of patients with LADA from T2DM in our study population, which may provide additional proof for diabetes classification. At the same time, our study broadened the application of data processing method in the field of diabetes classification. Larger sample size and multi-center research would be focused on the validation and optimization of this data processing method in the future, aiming to make a great effort for precision medicine in diabetes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The Ethics Review Committee of the Second Xiangya Hospital of Central South University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LY and ZZ designed the study and revised the manuscript, LZ and QT conducted the data analysis and wrote the draft of the paper. KG, JW, JY, ZD, QZ helped to prepare and collect the data. GH performed the GADA assay. Thanks to XL who kindly offered administrative support in data collecting. The corresponding author attests that all listed authors meet authorship criteria. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Prevalence of nocturnal hypoglycemia in free-living conditions in adults with type 1 diabetes: What is the impact of daily physical activity?

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Objective: Studies investigating strategies to limit the risk of nocturnal hypoglycemia associated with physical activity (PA) are scarce and have been conducted in standardized, controlled conditions in people with type 1 diabetes (T1D). This study sought to investigate the effect of daily PA level on nocturnal glucose management in free-living conditions while taking into consideration reported mitigation strategies to limit the risk of nocturnal hyoglycemia in people with T1D.

Methods: Data from 25 adults (10 males, 15 females, HbA_{1c}: 7.6 ± 0.8%), 20-60 years old, living with T1D, were collected. One week of continuous glucose monitoring and PA (assessed using an accelerometer) were collected in free-living conditions. Nocturnal glucose values (midnight–6:00 am) following an active day "ACT" and a less active day "L-ACT" were analyzed to assess the time spent within the different glycemic target zones (<3.9 mmol/L; 3.9 – 10.0 mmol/L and >10.0 mmol/L) between conditions. Self-reported data about mitigation strategies applied to reduce the risk of nocturnal hypoglycemia was also analyzed.

Results: Only 44% of participants reported applying a carbohydrate- or insulin-based strategy to limit the risk of nocturnal hypoglycemia on ACT day. Nocturnal hypoglycemia occurrences were comparable on ACT night versus on L-ACT night. Additional post-meal carbohydrate intake was higher on evenings following ACT (27.7 ± 15.6 g, ACT vs. 19.5 ± 11.0 g, L-ACT; P=0.045), but was frequently associated with an insulin bolus (70% of participants). Nocturnal hypoglycemia the night following ACT occurred

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mostly in people who administrated an additional insulin bolus before midnight (3 out of 5 participants with nocturnal hypoglycemia).

Conclusions: Although people with T1D seem to be aware of the increased risk of nocturnal hypoglycemia associated with PA, the risk associated with additional insulin boluses may not be as clear. Most participants did not report using compensation strategies to reduce the risk of PA related late-onset hypoglycemia which may be because they did not consider habitual PA as something requiring treatment adjustments.

KEYWORDS

type 1 diabetes, nocturnal glucose control, hypoglycemia, physical activity level, accelerometer, continous glucose monitoring

Introduction

Type 1 diabetes (T1D) is a chronic condition caused by the autoimmune destruction of pancreatic beta cells, eventually resulting in absolute insulin deficiency, leading to hyperglycemia (1). Thus, people living with T1D require life-long insulin replacement therapy with the goal of maintaining glucose levels close to normal while minimizing the risk of iatrogenic (i.e. complication induced by the treatment) hypoglycemia (blood glucose [BG] < 3.9 mmol/L) (1). Despite therapies (e.g. insulin analogs) and new technologies (e.g. continuous glucose monitoring (CGM)), the risk of hypoglycemia remains high, especially at night (2). Mild to moderate hypoglycemic episodes ([BG] between 3.9 – 3.0 mmol/L) commonly occur during the night (3–5), and can last for over an hour in people living with T1D (6). More than half of severe hypoglycemic episodes (i.e. requiring someone's assistance for recovery) occur during sleep (7). Thus, people with T1D are often still challenged with nocturnal hypoglycemia in their everyday life (8). Several factors in people's daily life, such as bedtime BG level, daytime hypoglycemia and physical activity (PA) have been associated with an increased risk of nocturnal hypoglycemia (9). PA results in significant glucose fluctuations during and after exercise, especially hypoglycemia. Hypoglycemia may occur during, immediately after, and for up to 31-h after PA (10–12). People with T1D are unable to reduce circulating insulin levels without anticipation. In addition to an increased insulin sensitivity in the hours following PA (13), counterregulatory hormone response to glucose lowering is frequently altered in people with T1D (14). Increased insulin sensitivity associated with excessive circulating insulin levels and a frequently altered hormonal counter-regulatory response to hypoglycemia, predispose to nocturnal hypoglycemia, especially when PA is involved late in the afternoon (15–17). Repeated episodes of hypoglycemia may impair hypoglycemia awareness and thus further potentiate the risk of recurrent hypoglycemia (18, 19). Impaired awareness of hypoglycemia in people living with T1D can be fatal (18).

Though regular PA is highly recommended for its numerous health benefits such as improved physical fitness and cardiovascular health (20–22), many people with T1D fail to meet the national PA guidelines (23). The most commonly reported barrier to PA in people living with T1D is the fear of hypoglycemia (24).

Although strategies exist to mitigate the risk of hypoglycemia during and after PA, most studies evaluating these strategies are conducted in standardized, controlled conditions (25–30). Moreover, limited evidence-based data are available on delayed-onset hypoglycemia and very few studies have evaluated mitigation strategies to reduce the risk of PA-associated nocturnal hypoglycemia (31–36). Current guidelines recommend a 20% insulin basal rate reduction around bedtime, for 6 hours for people using continuous subcutaneous insulin infusion (CSII) (37). Evening snacks are an option as well, but evidence supporting this strategy remains mitigated (34). It is unclear whether people with T1D apply some of these strategies or not. Spontaneous PA often results in an accumulation of short bouts of PA throughout the day which can be an easier way for people to meet PA guidelines (38). However, for people living with T1D, identifying whether therapeutic adjustments (such as insulin reduction or carbohydrate (CHO) intake) are needed when PA occurs sporadically throughout the day may be more difficult, especially since the risk of nocturnal hypoglycemia associated with an accumulation of short bouts of PA through the day is not well known. Few studies have shown an increased risk of prolonged nocturnal hypoglycemia with the accumulation of moderate or vigorous intensity PA through the day (12, 39).

PA-associated nocturnal hypoglycemia remains a substantial clinical problem for T1D management, and further research in non-standardized conditions is required to overcome it. The objective of this study is to assess the effect of PA on nocturnal glycemic fluctuations in people living with T1D in free-living conditions, by taking into consideration reported mitigation strategies to limit the risk nocturnal hypoglycemia.

Research design and methods

We carried out a cross-sectional, descriptive study to collect information about PA and glucose management in people with T1D during a usual week. Fifty-eight adults living with T1D were enrolled at the Montreal Clinical Research Institute (IRCM). The present study was approved by the research ethics committee and carried out in accordance with the principles of the declaration of Helsinki.

Inclusion criteria included having a diagnosis of T1D for at least 6 months, age ≥18 years, use of CSII or multiple daily injections (MDI), and the ability to give informed consent. Exclusion criteria included abnormal blood panel and/or anemia, ongoing or planned pregnancy, and impaired decision-making capacity.

Study procedures

Participants were tested at the IRCM during two visits scheduled approximately 1 week apart. During the first visit, an accelerometer (SenseWear Armband Mini® from Bodymedia.) was placed on the participant's right arm and a blinded CGM (iPro™2 professional from Medtronic) was inserted subcutaneously on the opposite arm. Participants were asked to measure capillary blood glucose levels at least four times per day, using their own glucose meter for subsequent CGM sensor calibration. Participants wore the CGM and accelerometer for 6 days following visit 1. Participants were asked to complete a logbook every day during the 6 days they were wearing the CGMs and accelerometer to report their capillary blood glucose values, any hypoglycemic events (with or without symptoms and means of correction) as well as any relevant information regarding their insulin administration (i.e., insulin boluses, insulin reduction etc…). Glycated hemoglobin (HbA_{1c}) levels were obtained *via* veinous sampling during visit 1. Hypoglycemia awareness was measured using the Clarke questionnaire. A score ≥ 4 indicates impaired awareness of hypoglycemia; a score ≤ 2 indicates normal awareness of hypoglycemia; and a score of 3 indicates undetermined awareness status (40, 41).

Identification of active and less active days through objective measurement of PA

The Sensewear Armband includes a two-axis accelerometer and uses sensors to measure heat flux, galvanic skin response, skin temperature and near body ambient temperature to assess energy expenditure. It has been validated to measure daily expenditure in previous studies (42, 43). Data was downloaded on the Sensewear Professional Softwear. PA was divided into four categories: light (1.6 - 3.0 Metabolic equivalent of Task (METs)), moderate (3.0 - 6.0 METs), vigorous (6.0 – 9 METs) and very vigorous (≥ 9 METs) (44). Based on the downloaded data, the software then calculated time spent in different PA intensities each day.

Identification of active and less active days

Our data analysis was based on PA level (defined as energy expenditure divided by basal metabolic rate in 24h). PA score between 1.40 and 1.69 was associated with a sedentary or light activity lifestyle, between 1.70 and 1.99 with an active or moderately active lifestyle, and between 2.0 and 2.40 with a vigorous or vigorously active lifestyle as defined (45, 46). Thus an active day (ACT) was defined as a PA level ≥ 1.7 and a less active day (L-ACT) was defined as PA level ≤ 1.69.

Some data cleaning procedures were required to perform our statistical anlaysis:

- -If the participants' data did not include at least one sedentary day (PA level ≤ 1.69) and one active day (PA level ≥ 1.7), the data was rejected from the analysis.
- -If data from the CGM and/or accelerometer were unreadable or corrupted, they were excluded as well.

Nocturnal hypoglycemia through CGM

The CGMs were blinded to the participant. Data was downloaded by our team on Carelink after the second visit.

CGMs were calibrated retroactively using the participants' daily capillary glucose values reported in their logbook.

Level 1 hypoglycemia was defined as glucose levels between 3.0 and 3.9 mmol/L. Level 2 hypoglycemia was defined as glucose levels below 3.0 mmol/L. Level 1 hyperglycemia was defined as glucose levels above 10.0 mmol/L and level 2 hyperglycemia was defined as glucose levels >13.9mmol/L (47). Coefficient of variation (CV), defined as the standard deviation

divided by the mean was calculated as well. CV < 36% indicated stable glucose levels (47).

Nocturnal glucose levels were analyzed from 00:00 (midnight) to 6:00 am. Nocturnal hypoglycemia was defined as BG < 3.9 mmol/L for at least 15 consecutive minutes. If more than two hours of CGM values were missing between 00:00 am and 6:00 am, the data was rejected from the analysis (Figure 1).

Mitigations strategies reported in the logbook

Information about PA (time of day, duration, and type), hypoglycemia occurring before bedtime, and mitigation strategies (*e.g.* insulin dosage and CHO intake modulations) to reduce the risk of nocturnal hypoglycemia were based on the participants' self-reported data in their logbook. Logbook information about mitigation strategies applied before bedtime was analyzed for ACT and L-ACT days only.

Statistical analysis

We compared nocturnal blood glucose levels after ACT with nocturnal blood glucose levels after L-ACT based on CGM data. Descriptive analysis and condition comparison analysis were performed using IBM SPSS Statistics 27 and survival analysis was performed using GraphPad Prism 9.1.2. Results are reported as mean ± SD. Normality was tested using the Shapiro–Wilk test. PA level as well as the percent of nocturnal time spent in different BG ranges (i.e., hypoglycemia, euglycemia (3.9-10.0 mmol/L), and hyperglycemia (>10.0mmol/L)), as measured by CGM, were compared between "ACT" and "L-ACT" conditions using either paired t-tests or the Wilcoxon matched-pair test. McNemar's chi-squared test was used to compare two proportions and to compare the number of participants experiencing hypoglycemic events as well as the number of participants reporting additional CHO consumption. Effect of condition was assessed using a linear model.

Significant interactions were followed up with Bonferroni adjusted *post-hoc* tests. Spearman's rank correlations were performed to analyze possible associations between PA level/duration of PA and times in, below and above range as well as hypoglycemia duration and mean change in glucose levels from midnight to 6:00 am. Statistical significance was set to $P<0.05$.

Results

A total of 58 participants were recruited. After data cleaning procedures, data from 25 adults (10 males, 15 females) were analyzed (Figure 1). Baseline characteristics of study participants are presented in Table 1. Fourty-four percent of participants were treated with open-loop CSII and 56.0% were treated with MDI. No participant reported a significant macro- or microvascular event prior to the study. Impaired awareness of

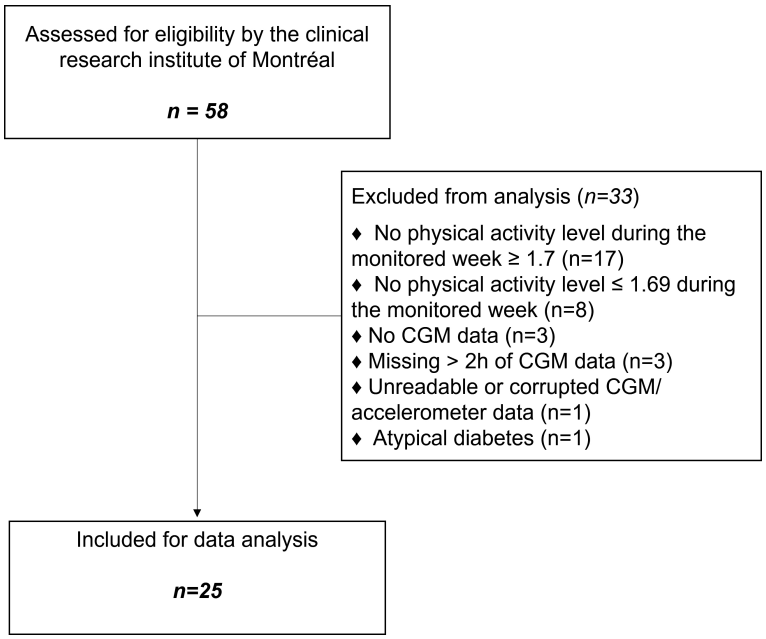

FIGURE 1
Consort flow diagram of the study.

TABLE 1 Baseline characteristics of study participants.

N, total	25
Insulin therapy (CSII/MDI)	11/14
Age, years	34.8 ± 12.3 (20 – 60)
Sex (Male/Female)	10/15
Ethnicity (Caucasian/Arab)	21/4
BMI, kg/m²	25.4 ± 3.9 (20.7 - 34.7)
Glycated hemoglobin (HbA_{1c}), %	7.6 ± 0.7 (5.9 - 8.7)
Glycated hemoglobin ($HbA1_c$), mmol/mol	60 (41 – 72)
Diabetes duration (years)	16.8 ± 9.7
Daily basal or long-acting insulin (u/day)	20.8 ± 7.3 (11 – 36.5)
VO_{2peak} (mL/kg/min)	32.3 ± 9.3
Daily PA level	1.7 ± 0.2 (1.2 – 2.0)

Data are mean ± SD (min – max) or n (%).SD, standard deviation; CSII, Continuous subcutaneous insulin infusion; MDI, multiple daily injections; VO_{2peak}; peak oxygen consumption.

hypoglycemia was identified in three participants (12%) out of 25 by the Clarke questionnaire. Four participants (16%) had undetermined hypoglycemia awareness, 14 (56%) had normal hypoglycemia awareness, and four (16%) did not answer the questionnaire. We made sure that the conditions between ACT and L-ACT were significantly different in terms of PA level, total energy expenditure, and time spent in light, moderate, and vigorous-intensity PA (Table 2).

Nocturnal glucose profiles

Glucose values at bedtime were comparable in both conditions (P=0.250). We found no differences in the nocturnal time spent in level 1 hypoglycemia (3.0 – 3.9 mmol/L) nor level 2 hypogylcemia (<3.0 mmol/L) between conditions. Time spent below range (<3.9 mmol/L) was associated with greater nocturnal glycemic variation the night following ACT (CV) (R=0.648; P<0.001).

We found a significant interaction (Condition '*ACT* vs '*L-ACT*' × Time) reflecting a slight decrease in glucose levels in the first part of the night following L-ACT while glucose levels tended to increase during the second part of the night following ACT. However, there were no pairwise differences between both conditions in *post-hoc* analyses (Figure 2). Accordingly, data showed a greater decrease in glucose levels from midnight to 6:00 am the night following L-ACT (P<0.001) (Table 3).

Based on interstitial glucose concentrations, hypoglycemia occurred in five participants (20%) during ACT night, three participants (12%) during L-ACT night, while 16 participants did not experience hypoglycemia on either night (64%). No participant experienced nocturnal hypoglycemia on both ACT and L-ACT nights. Nocturnal hypoglycemia occurred at similar times during the night in both conditions (P=0.130) (Figure 2B). Four out five nocturnal hypoglycemia events that occurred on ACT night were resolved at 6:00 am. Blood glucose increased to reach levels of 14.9 ± 7.2 mmol/L (min, 4.9 mmol/L; max, 20.5 mmol/L) following nocturnal hypoglycemia resolution. Only one out of three nocturnal hypoglycemia events on L-ACT night was resolved at 6:00 am. Blood glucose increased to reach levels of 4.9 mmol/L while the other two remained in nocturnal hypoglycemia, with one value below 3.0 mmol/L.

Time spent above range (BG > 10 mmol/L) during ACT and L-ACT is reported in Table 3, and was observed in more than half of the participants without any difference between conditions (60% of participants, ACT vs. 64%, L-ACT). Time spent in level 2 hyperglycemia (BG>13.9 mmol/L) was comparable as well (40% of participants, ACT vs. 25%, L-ACT; P=0.217).

The physical activity level on ACT Day was associated with a greater difference in nocturnal glucose levels from midnight to morning (R=0.664; P<0.01) as well as with a greater difference in nocturnal glucose levels from midnight to nadir (R=0.461; P=0.020). No other significant correlations between physical activity level on ACT day and hypoglycemia, euglycemia or hyperglycemia were detected.

Self-reported PA on ACT Day

Sixteen out of twenty-five participants (64%) reported exercising (or leisure PA) on ACT Day. PA included biking, walking, running, swimming, high-intensity interval training, resistance training, skiing, and more. Seven participants (28%) reported exercising in the afternoon, three (12%) in the morning

TABLE 2 The title needs to be updated to: Comparison of accelerometry data between ACT and L-ACT.

	ACT	L-ACT	*P-value*
PA level	2.0 ± 0.3 (1.7 – 3.3)	1.4 ± 0.1 (1.1 – 1.6)	*<0.001*
Light intensity (min)	312.8 ± 109.0 (183 – 668)	247.4 ± 102.3 (71 – 462)	*0.018*
Moderate intensity (min)	172.7 ± 68.8 (66 – 287)	47.0 ± 31.4 (0 – 113)	*<0.001*
Vigorous intensity (min)	43.8 ± 56.5 (0 – 287)	1.4 ± 2.5 (0 – 11)	*<0.001*
Sedentary (min)	864.2 ± 143.4 (556 – 1124)	1096.7 ± 126.3 (835 – 1345)	*<0.001*
Total energy expenditure (kcal)	3195.6 ± 986.4 (2172 – 6498)	2262.2 ± 413.3 (1590 – 3325)	*<0.001*

ACT, Active day; L-ACT, less active day. Data are Mean ± SD (min-max).

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TABLE 3 Nocturnal glucose and nocturnal hypoglycemia outcomes based on intersitial glucose measurements.

	ACT	L-ACT	*P* value
Glucose (mmol/L)			
At midnight	9.1 ± 4.4	10.5 ± 4.04	0.250
At 6:00 am	9.0 ± 4.2	9.1 ± 4.8	0.929
Nadir	6.0 ± 2.9	7.6 ± 3.6	0.150
SD	2.0 ± 1.7	1.3 ± 0.8	0.093
CV (%)	21.2 ± 13.8	15.1 ± 9.4	0.118
Delta glucose (mmol/L)			
Δ Midnight to 6:00 am	0.1 ± 6.2	-1.2 ± 4.1	**>0.001**
Δ Midnight to nadir	-3.2 ± 3.5	-2.8 ± 2.9	0.725
Glucose ranges from 00:00 to 6:00 am (%)			
< 3.0 mmol/L (Level 2)	4.4 ± 11.0	1.8 ± 5.9	0.687
3.0 to 3.9 mmol/L (Level 1)	3.4 ± 8.1	3.1 ± 9.1	0.804
< 3.9 mmol/L	7.5 ± 16.9	4.9 ± 14.2	0.957
3.9 to 10.0 mmol/L	56.1 ± 37.9	60.3 ± 40.2	0.825
> 10.0 mmol/L	36.3 ± 38.9	34.9 ± 42.0	0.856
> 13.3 mmol/L	15.8 ± 27.0	13.4 ± 32.4	0.801
Hypoglycemia			
NH (n)	5	3	0.702
Hypoglycemia duration (min)	139.6 ± 68.7	136.3 ± 70.1	0.950
Level 1 hypoglycemia duration (min)	59.4 ± 39.6	83.3 ± 35.3	0.650
Level 2 hypoglycemia duration (min)	80.2 ± 55.1	53.7 ± 40.2	0.500
Time to first hypoglycemia	115.2 ± 77.5	205.0 ± 52.0	0.130

Data are presented as mean ± standard deviation except for NH, reported as the number of subjects. *Significant difference between conditions. TIR, time in range; SD, standard deviation; CV, coefficient of variation; NH, Nocturnal hypoglycemia.

and six (24%) reported exercising twice: once in the morning and once in the afternoon. Nocturnal hypoglycemia occurred in two participants who reported performing PA twice during the day and in two participants who reported performing PA in the morning. Two nocturnal hypoglycemia events occurred in participants who had not reported PA in their logbook.

Self-reported insulin- or CHO-based strategies the evening following ACT

Almost half of the participants (n=11; 44%) reported applying one, or a combination of insulin- and CHO-based strategies to reduce the risk of nocturnal hypoglycemia the night

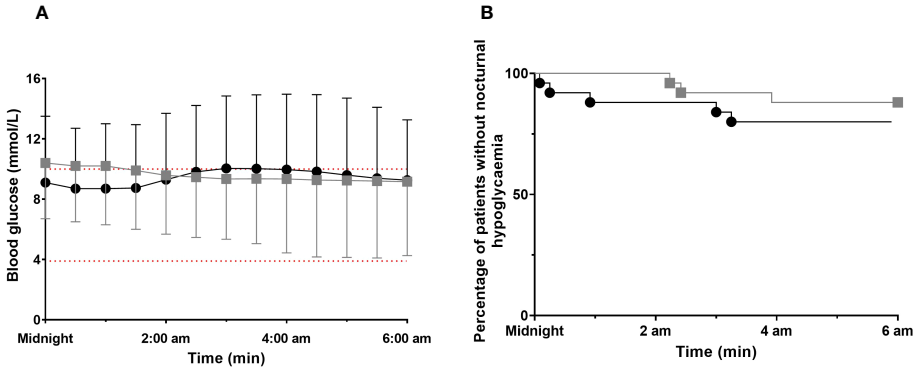

FIGURE 2
Nocturnal glucose profiles for both conditions (ACT vs. L-ACT) ACT, black circle; L-ACT, gray squares. **(A)** Glucose profiles from midnight to 6:00 am for both conditions. Values are means ± SD, Main effects by linear model time (P<0.001); condition ACT vs. L-ACT (P<0.001) and interaction (time x group) (P<0.001). **(B)** Time to first nocturnal hypoglycemic event.

following ACT. Consumption of evening snacks (with or without insulin bolus) was the most frequently reported strategy (40%) (Table 4). CHO intake varied from 12g to 40g (mean 25.6 ± 13.3g) (Table 5).

In participants treated with CSII, only one reported using temporary insulin basal rate reduction (BRR) as a mitigation strategy for nocturnal hypoglycemia which consisted of a 50% BRR for 4-hours. One participant reported increasing the basal rate by 5% until 1 am after consuming a snack without insulin bolus.

Hypoglycemia on the evening and night following ACT

Reported hypoglycemia during the evening following ACT was always treated with CHO. One participant reported a 50% BRR for 3-h during the night in addition to CHO intake. The type or quantity of CHO consumed to treat hypoglycemia was not always clearly reported.

Five participants reported treating hypoglycemia during ACT evening (before midnight), and did not experience subsequent hypoglycemia between midnight and 6:00 am. Two participants reported treating symptomatic hypoglycemia just after midnight and did not experience subsequent nocturnal hypoglycemia either, during midnight and 6:00 am. Based on interstitial glucose values, both participants did not experience what was considered as significant hypoglycemia. One had blood glucose levels > 3.9 mmol/L but reported symptoms, and the other had blood glucose levels <3.9 mmol/L for less than 15 minutes. None of the five participants who experienced significant nocturnal hypoglycemia reported it in their logbook.

Among the participants who experienced nocturnal hypoglycemia the night following ACT, two had administrated additional insulin boluses during the evening (3 and 1.5 u); two had an evening snack (one with, and one without insulin bolus); one had an evening snack with an insulin basal rate increase of 5% and one did not report applying any mitigation strategies or insulin bolus injections.

Self-reported insulin- or CHO-based strategies the evening and night following L-ACT

During the evening following L-ACT, six participants (24%) reported eating an evening snack (≈ 19.5 ± 11.0g CHO). Seven (28%) reported administrating an insulin bolus correction throughout the evening without extra-CHO consumption (mean insulin units: 1.9 ± 0.7).

Hypoglycemia on the evening and night following L-ACT

One participant reported correcting hypoglycemia in the evening without specifying symptoms or means of correction, but did not experience subsequent nocturnal hypoglycemia. Out of the three participants who had nocturnal hypoglycemia the night following L-ACT, only one reported administrating an insulin bolus correction in the evening.

CHO intake the evening following ACT vs. L-ACT

Post-meal CHO was consumed in greater quantities in the evening following ACT (P=0.045). Additional insulin bolus injections tended to be higher in the evening following ACT (P=0.074) (Table 5).

TABLE 4 Participants reporting mitigation strategies to reduce the risk of nocturnal hypoglycemia.

	ACT		L-ACT	
Reported mitigation strategies				
Participants applying a strategy, n (%)	CSII	MDI	CSII	MDI
Evening snack				
-With insulin bolus	3 (27.3)	0 (0)	0 (0)	0 (0)
-Without insulin bolus	2 (18.2)	5 (35.7)	1 (9)	5 (35.7)
Basal insulin reduction	2 (18.2)	0 (0)	0 (0)	0 (0)
Evening snack with basal insulin increase (5%)	1 (9)	0 (0)	0 (0)	0 (0)
Evening meal bolus reduction	0 (0)	0 (0)	0 (0)	0 (0)
Evening insulin bolus correction	3 (27.3)	4 (28.6)	6 (54.5)	2 (14.3)

One participant combined evening snack without insulin bolus and insulin basal rate increase, followed by insulin basal rate reduction during the night.

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TABLE 5 Reported additional CHO and insulin bolus intakes during the evening.

	ACT	L-ACT	P value
Participants consuming additional CHO (post-meal), (n)	10	5	0.217
Participants consuming CHO to treat hypoglycemia	5	1	0.192
- In the evening (before midnight)	2	0	0.470
- After midnight			
Mean CHO consumption, (g)	25.6 ± 13.3 (12 – 47)	19.5 ± 11.0 (9.7 – 33)	0.399
- CHO consumed to avoid hypoglycemia	30.0 ± 20.0 (20 – 60)	(-)**	-
- CHO consumed to treat hypoglycemia	27.7 ± 15.6 (12 – 60)	19.5 ± 11.0 (9.7 – 33)	**0.045***
- Total CHO consumed			
Participants administrating insulin bolus corrections, (n)	7	5	
Mean insulin bolus corrections, (u)	2.3 ± 0.7 (1.5 – 13.7)	1.9 ± 0.7 (1.1 – 2.5)	0.074

Data are Mean ± SD (min – max) or number of participants (n). *Significant difference between conditions "ACT" vs. "L-ACT" (P<0.05). One participant reported treating hypoglycemia during the evening on L-ACT day without specifying means of correction. **One participant reported CHO intake to treat hypoglycemia during the evening (before midnight) but did not specify quantity or quality of CHO consumed.

Discussion

Most studies have tested the impact of PA on glycemic excursions under standardized conditions. This work aimed to examine the association between free-living daily physical activity level and nocturnal blood glucose levels in people living with T1D while taking into account possible mitigation strategies reported by participants to avoid nocturnal hypoglycemia. Our results suggest that nocturnal hypoglycemia occurrence and time spent below range are no different the night following an active day versus the night following a less active day, which is likely due to higher carbohydrate intake the evening following ACT day.

Glycemic excursions

It is well known that nocturnal hypoglycemia often occurs in patients with T1D during or up to 31-h following PA (10). Obviously, being active during the day may come at a cost. Previous studies (10–12) have reported that time spent below range tended to increase for several hours following PA. In a recent survey-based study, 49% of people living with T1D reported experiencing nocturnal hypoglycemia following PA (48). In the current study, we found that only 20% of participants experienced nocturnal hypoglycemia the night following ACT day and found no differences in nocturnal hypoglycemia occurrences the night following ACT day versus the night following L-ACT day. Five participants reported correcting hypoglycemia in the evening on ACT day (before midnight) and, two others just after midnight. These were not the same participants who experienced nocturnal hypoglycemia later during the night. This could be an explanation as to why we found no differences in the number of nocturnal hypoglycemia events between ACT day and L-ACT day. Hypoglycemia associated with daily PA may have occurred earlier in the evening.

Times in range (3.9 – 10.0 mmol/L) and below range (<3.9 mmol/L) were comparable the night following an active day versus the night following a less active day. Riddell et al. reported that participants spent more time in range on active days than on less active days, but also more time below range (49). Authors reported increased time below range in the first 12 hours following PA. This disparity might be partly explained by the fact that in the latter study, participants performed structured PA, whereas, in the current study, the chosen distribution is closer to free-living conditions (i.e., uncontrolled PA with variable duration and modality).

In contrast, we found that over 60% of participants actually experienced hyperglycemia the night following ACT day, including participants who had experienced nocturnal hypoglycemia earlier in the night (3 out of 5). This suggests that people may have treated hypoglycemia without reporting it and might also explain why glucose levels increased the night following ACT day while they slightly decreased the night following L-ACT day. More importantly, people living with T1D have frequently reported overeating following hypoglycemia and trying to compensate high-risk situations by maintaining higher BG levels (50). Nighttime constitutes a critical period of the day, leaving people with T1D at higher risk of severe hypoglycemia which could result in seizures or even death (19, 51). This could explain why more than half of the participants spent time above range at night, regardless of their PA the previous day. This suggests that high nocturnal blood glucose levels may be related to participants aiming for higher glucose levels at night to avoid nocturnal hypoglycemia and not to additional CHO intake due to PA.

Our study looks at the percentage of time in glycemic range in people treated with open-loop CSII or MDI. We found that time in range was 56.1 ± 37.9% from 00:00 to 6:00 am the night following ACT. Newer technologies, such as hybrid closed-loop systems are frequently associated with higher time in range (3.9 – 10.0 mmol.L) during and in the hours following exercise. Breton et al. (52) tested closed-loop systems during and after

intense prolonged exercise in adolescents with T1D. Authors found higher time in range with closed-loop systems, compared to standard CSII, especially late at night. Time below range remained similar in both conditions. In line with these results, Tauschmann et al. (53) found that hybrid closed-loop therapy was associated with higher time in range and lower time above range compared to CSII, in free-living conditions in adolescents with T1D. Authors found no difference in time below range between CSII and hybrid closed-loop. Thus, including hybrid closed-loop systems in the current study may have resulted in higher time in range without having an impact on time below range.

Self-reported insulin- or CHO-based strategies

A limited number of studies evaluating strategies used by people with T1D to manage PA-induced glucose variability have been published. Our results showed that only 44% of participants reported applying a strategy in order to reduce the risk of nocturnal hypoglycemia associated with PA. As ACT days were based on mean daily PA level, what was calculated as PA by the accelerometer, was not always reported as PA by the participant. Therefore, habitual PA or a cumulation of activities of daily-living (fast walks, fast walking up the stairs, etc.) throughout the day may have led to a mean physical activity level >1.7. Thus, it may be more difficult for people with T1D to identify their activities as PA and adjust their treatment in consequence. This could be a possible explanation as to why 56% of our participants did not report applying a compensation strategy.

Eating snacks with or without insulin bolus seemed to be the most recurrent strategy used in the evening following ACT day in the current study. This was confirmed by Pinsker et al. (54) in a survey-based study aiming to examine strategies for PA preparation in people living with T1D. Authors reported that most people would consume supplementary CHO to avoid hypoglycemia during and in the hours following PA, regardless of insulin therapy (CSII or MDI) or CGM use (54). In terms of prevention strategies for PA-associated hypoglycemia, carbohydrate feeding often requires less pre-planning compared to basal and bolus adjustments and therefore, may be more common than strategies based on insulin reduction.

We also focused on the impact of treatment (e.g., CSII vs. MDI) on the decisions taken by people with T1D to manage their blood glucose in the hours following PA in free-living conditions. In the current study, two (18.2%) participants reported reducing their basal insulin in the evening following PA. One of them experienced nocturnal hypoglycemia. Paiement et al. (48) showed that among CSII users, those applying insulin BRR during the night following PA reported more nocturnal hypoglycemia (48).

Pinsker et al. (54) found that most people using BRR strategies were those treated with combined CSII and CGM. In our study, participants' CGMs were blinded which could explain why only two participants applied insulin basal rate reduction to prevent hypoglycemia. One participant reported reducing their basal rate to treat hypoglycemia. The authors also found that insulin bolus reduction for the meals around PA was reported by half of the participants (54). No meal insulin bolus reduction was reported in our study. In Groat's (55) survey-based study, no participant reported reducing their insulin meal boluses.

Most of the participants (three out of five) who experienced nocturnal hypoglycemia had reported applying a mitigation strategy. However, some participants either increased their insulin basal rate during the evening or administrated an additional insulin bolus on multiple occasions after CHO intake. This may be the cause of nocturnal hypoglycemia, rather than late-onset effects of PA. Indeed, Desjardins et al. (2) reported that CHO supplementation resulted in higher nocturnal hypoglycemia occurrences when associated with insulin injection. Two others who experienced nocturnal hypoglycemia administrated an additional insulin bolus correction in the evening (9:45 pm – 10:00 pm) nonrelated to CHO supplementation. In the hours following PA, insulin sensitivity is increased, and muscle and hepatic glycogen content need to be restored which results in glucose being diverted from the blood, increasing the risk of hypoglycemia (56). Thus, enhanced insulin sensitivity associated with an additional insulin bolus injection in the evening would increase the risk of hypoglycemia even further.

Strengths and limitations

Overall, the strength of this observational study is to assess life habits with a focus on daily physical activity and glucose control over two days (one considered as active, the other as less-active) in non-standardized conditions. Besides, based on participants' reports, CGMs, and accelerometry data, we were able to assess whether mean daily physical activity level has an impact on nocturnal glucose fluctuations and whether people living with T1D use compensation strategies to reduce the risk of nocturnal hypoglycemia associated with PA. Literature evaluating strategies to reduce the risk of late-onset and post-PA hypoglycemia is scarce and non-standardized studies evaluating these strategies are even less frequent. Our study helps to identify a potential lack of knowledge in terms of post-PA mitigation strategies in people living with T1D.

An important part of our study relied on participants recalling information correctly. Information regarding dietary intakes (quantity and quality) and insulin adjustments as mitigation preventive strategies, as well as nocturnal hypoglycemia or nocturnal hypoglycemia correction, was sometimes incomplete or not reported. There may also have

been discrepancies or inaccuracies in the self-reported data, such as omission of insulin bolus corrections or hypoglycemia correction. Our analysis relied on a small sample-size which may have resulted in a lack of statistical power.

Conclusions

In conclusion, nocturnal hypoglycemia does not seem to appear more frequently on nights following an active day. Post-meal carbohydrate intake was significantly higher on evenings following an active day, indicating compensation strategies to avoid nocturnal hypoglycemia. Nocturnal hypoglycemia occurred more frequently in participants who administrated insulin bolus corrections in the evening with or without extra carbohydrate consumption. These results suggest that, although people with T1D seem to be aware of the increased risk of nocturnal hypoglycemia associated with PA, the risk associated with additional insulin boluses may not be as clear. Most participants did not report using compensation strategies to reduce the risk of late-onset hypoglycemia associated with PA which may be because they did not consider habitual PA as something requiring treatment adjustments.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by IRCM ethics committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JM, RR-L, EM-C and ST contributed to the conception and design of the study. CS and VM coordinated the study and acquired the data. JM and ST analyzed the data. JM, EM-C, RR-L and ST interpreted the data. JM and ST drafted the manuscript. JM, ST, EM-C, CS, VM, KP, EH, RR-L critically revised the manuscript for important intellectual content. All authors approved the final version of this manuscript.

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Conflict of interest

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Publisher's note

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Higher scanning frequency is correlated with less fear of hypoglycemia in type 1 diabetes patients using isCGM

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Background: Frequent scanning of intermittently scanned continuous glucose monitoring (isCGM) devices is associated with improvements in glycemic indices. Limited data is available for its correlation with fear of hypoglycemia (FOH), an established factor affecting quality of life and glycemic control in type 1 diabetes (T1DM).

Aim: The aim of the study was to analyze the association of sensor scanning frequency with FOH and glycemic indices in T1DM patients using isCGM.

Subjects and methods: T1DM patients using isCGM were eligible. Clinical data and Ambulatory Glucose Profile (AGP) reports were obtained from medical records. At outpatient visits, AGP of last 14 days prior to visit were analyzed and FOH was assessed using Hypoglycemia Fear Survey II (HFS II).

Results: We included 77 consecutive T1DM patients (58 females, 19 males). Mean age was 34.1 ± 10.2 years and mean T1DM duration was 14.7 ± 12.0 years. Baseline mean glycemic indices were as follows: mean glucose - 155.8 ± 29.8 mg/dL; GMI - 53.3 ± 7.5 mmol/mol; TIR - 66.4 ± 17.8%; TBR70 - 4.5 ± 4.1%; TBR54 - 0.6 ± 1.2%; TAR180 - 29.2 ± 17.9%; TAR250 - 9.6 ± 10.4%; %CV - 36.7 ± 8.3. Average scanning frequency was 13.8 ± 7.8 scans/day. Mean HFS II scores were 16.1 ± 7.2 and 18.7 ± 12.2 in behavior and worry subscale, respectively. Correlation was confirmed between scanning frequency and mean glucose, GMI, TIR, TBR70, TAR180, TAR250, %CV and HFS II total, and HFS II - B ($p<0.05$ for all statistics).

Conclusions: For the first time, we report that higher scanning frequency is associated not only with better glycemic indices but also with less FOH in T1DM adult patients using isCGM.

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KEYWORDS

continous glucose monitoring, intermittently scanned CGM, ambulatory glucose profile (AGP), fear of hypoglycemia, type 1 diabetes, time in range, time below range

Introduction

Globally, more than 530 million people are living with diabetes, including approximately 9,000,000 (2%) diagnosed with type 1 diabetes (T1DM) (1, 2). In people with T1DM, a strong association is evident between frequent self-monitoring of blood glucose (SMBG) and glycemic control as assessed by glycated hemoglobin A1c (HbA1c) (3, 4). Patients with diabetes on intensive insulin therapy (IIT) with MDI or insulin pumps are advised to perform at least 4 SMBG tests per day or use continuous glucose monitoring (CGM) devices – either intermittently-scanned CGM (isCGM) or real-time CGM (rtCGM) (5, 6). The only isCGM currently available are the FreeStyle Libre® system and FreeStyle Libre 2 system (Abbott Diabetes Care Inc., USA) (7). Many published studies have reported on the frequency of daily scans and glycemic indices in patients using isCGM. Based on de-identified data it was shown within different populations that patients who perform more scans per day have lower mean glucose, lower glucose management index (GMI), spend more time in range (TIR) and less time above range (TAR) and time below range (TBR), as defined by the International Consensus on Time in Range and as visualized in ambulatory glucose profile (AGP) reports (8–12). Moreover, using isCGM is associated with less hospitalizations due to severe hypoglycemia or diabetic ketoacidosis (DKA), less workplace absenteeism, and higher quality of life (13–15). However, only limited data is available that examines the correlation of scanning frequency with fear of hypoglycemia (FOH), an established factor affecting quality of life and glycemic control in people with T1DM. Such an association has been reported in children and adolescents, but not in adults (16–18). As well as affecting glycemic control, FOH has been shown to be associated with high calorie intake and reduced physical activity (19). In this observational cohort study, our aim was to analyze the association between scanning frequency and FOH, as well as glycemic indices in T1DM patients using isCGM.

Materials and methods

Patients

T1DM patients, active isCGM users were recruited between October and December 2021 in a single outpatient academic clinic that provides diabetes care to patients in the University Hospital in Krakow, Poland. Data, such as age, sex, diabetes duration, type of therapy and presence of diabetic complications were obtained from medical records. As in Poland isCGM is reimbursted for T1DM patients aged ≤18 years only, thus all adult patients using isCGM cover all cost of sensors themselves. Women planning pregnancy or being pregnant were not involved in the study. The study was performed in accordance with the Declaration of Helsinki and was approved by local Bioethics Committee. All participants provided informed consent.

Ambulatory glucose profile and scanning details

The FreeStyle Libre sensor measures interstitial glucose levels for up to 14 days (7). Data collected by sensors are uploaded by patients using the LibreLink smartphone app to the LibreView platform (Abbott Diabetes Care Inc., USA), which generates personal AGP reports. Glucose ranges as assessed were defined as: TIR 70-180 mg/dL (3.9-10.0 mmol/L), TBR70 <70 mg/dL (<3.9 mmol/L), and TAR180 >180 mg/dL (>10.0 mmol/L), in accordance with the international consensus ranges (12). Time spent in very high glucose and very low ranges defined as TAR250 >250 mg/dL (13.9 mmol/L) and TBR54 <54 mg/dL (<3.0 mmol/L) were assessed as well (12). Data on scanning frequency was obtained from patients' personal reports generated in LibreView. Last 14 days were analyzed prior to a visit in outpatient clinic. Data was included to analyses only if percentage of time CGM was active was at least 70%.

Fear of hypoglycemia

At the study visit, FOH was assessed using Hypoglycemia Fear Survey II (HFS II), which is a validated measure of FOH in adults with T1DM. HFS II contains both a worry subscale (HFS II – W) and a separate behavior subscale (HFS II – B) (20).

Statistical analysis

Statistical analysis was performed using Statistica, version 13, TIBCO Software Inc., CA, USA. Basic descriptive statistics were calculated for the entire study group, patients treated with

MDI and insulin pump users, and for five scan-rate groups, each containing 20% of subjects from least to most scanners. Parametric t test or nonparametric U test were performed, where applicable, to describe clinical characteristics and differences between patients on MDI and pump users, while for nominal variables the Fisher's exact test was used. Correlations were analyzed between scanning frequency, glycemic control indices and FOH. Moreover, multiple regression model was built to find factors that affect HFS. A $p<0.05$ was considered to be significant.

Results

Characteristics of the study group

77 (58 female, 19 male) adults with T1DM were included in the study. Of these, 39 were treated with MDI, and 38 were insulin pump users. The mean age of subjects was 34.1 ± 10.2 years and mean T1DM duration was 14.7 ± 12.0 years. In the study group, there were 3 patients with a history of episode of severe hypoglycemia and 5 with history of DKA in the previous 12 months. There were no patients with diagnosed advanced chronic complications. Detailed characteristics of the study group are shown in Table 1.

Glycemic indices

The study participants performed on average 13.8 ± 7.8 scans/day, median 13 scans/day. Mean glucose was 155.8 ± 29.8 mg/dL and GMI 7.03 ± 0.68% (53.3 ± 7.5 mmol/mol). Mean TIR was 66.4 ± 17.8%, TBR70 was 4.5 ± 4.1%, TBR54 was 0.6 ± 1.2%, TAR180 was 29.2 ± 17.9%, and TAR250 was 9.6 ± 10.4%. Mean glycemic variability expressed as coefficient of variation (CV) was 36.7 ± 8.3%. Detailed data on glycemic indices across the five scan-rate groups is shown in Table 2 and in Figure 1. As expected, significant correlations were found between scanning frequency and mean glucose (r=-0.54, β=-2.1, 95% CI: -2.8, -1.4), GMI (r=-0.55, β=-0.05, 95% CI: -0.07, -0.03), TIR (r=0.65, β=1.49, 95% CI: 1.09, 1.89), TBR70 (r=-0.25, β=-0.13, 95% CI: -0.25, -0.02), TAR180 (r=-0.58, β=-1.34, 95% CI: -1.77, -0.91), TAR250 (r=-0.56, β=-0.75, 95% CI: -1.00, -0.49), and %CV (r=-0.59, β=-0.62, 95% CI: -0.82, -0.43). No significant correlation was evident between the scanning rate and TBR54 (r=-0.13, β=-0.02, 95% CI: -0.05, 0.01) (Figure 2).

Fear of hypoglycemia

The mean total HFS II score was 34.7 ± 16.6, with 16.1 ± 7.2 and 18.7 ± 12.2 scores for the behavior and worry subscales,

TABLE 1 Clinical characteristics of the study group.

	Entire group	CSII	MDI	p
Number of cases, n	77	38	39	N/A
Sex female/male, n	58/19	34/4	24/15	<0.01
Age, years	34.1 ± 10.2	33.2 ± 8.9	35.1 ± 11.3	0.42
Diabetes duration, years	14.7 ± 12.0	17.2 ± 11.0	12.3 ± 12.5	0.07
BMI, kg/m2	23.7 ± 3.2	23.6 ± 3.5	23.9 ± 2.9	0.69
Mean glucose, mg/dL	155.8 ± 29.8	156.5 ± 26.9	155.2 ± 32.8	0.86
GMI, %	7.03 ± 0.68	7.05 ± 0.63	7.01 ± 0.73	0.81
GMI, mmol/mol	53.3 ± 7.5	53.6 ± 6.9	53.1 ± 8.2	0.78
CV, %	36.7 ± 8.3	38.0 ± 8.2	35.3 ± 8.2	0.15
TAR250, %	9.6 ± 10.4	10.0 ± 10.1	9.2 ± 10.7	0.74
TAR180, %	29.2 ± 9.7	29.4 ± 16.1	28.9 ± 19.7	0.90
TIR, %	66.4 ± 17.8	65.3 ± 16.2	67.5 ± 19.4	0.60
TBR70, %	4.5 ± 4.1	5.3 ± 4.4	3.8 ± 3.6	0.11
TBR54, %	0.6 ± 1.2	0.7 ± 1.1	0.5 ± 1.2	0.59
Scanning frequency, n/d	13.8 ± 7.8	14.0 ± 8.2	13.6 ± 7.5	0.82
HFS II	34.7 ± 16.8	36.3 ± 16.7	33.2 ± 16.9	0.42
HFS II – B	16.1 ± 7.2	15.5 ± 6.2	16.6 ± 8.0	0.49
HFS II – W	18.7 ± 12.2	20.8 ± 13.4	16.6 ± 10.7	0.13

Data shown as n – number of cases or mean ± SD. BMI, Body mass index; CV, Coefficient of variation; GMI, Glucose management indicator; HFS II, Hypoglycemia Fear Survey II; HFS II – B, HFS II Behavior subscale; HFS II – W, HFS II Worry subscale; TIR, Time in range 70-180 mg/dL; TAR250, Time above range >250 mg/dL; TAR180, Time above range >180 mg/dL; TBR70, Time below range <70 mg/dL; TBR54; Time below range <54 mg/dL.

TABLE 2 Glycemic indices and HFS II according to the scan rate group.

Scan rate group	Scanning frequency	Mean glucose	GMI		Glucose CV	TBR54	TBR70	TIR	TAR180	TAR250	HFS II	HFS II - B	HFS II - W
	(scans/day)	(mg/dL)	(mmol/mol)	(%)	(%)	(%)	(%)	(%)	(%)	(%)			
Group 1	4.9 ± 1.5	181.2 ± 30.0	59.6 ± 7.0	7.6 ± 0.6	44.1 ± 8.8	0.8 ± 1.2	6.1 ± 3.8	50.3 ± 16.2	43.6 ± 16.6	20.0 ± 12.2	42.5 ± 19.1	20.0 ± 7.7	22.5 ± 14.4
Group 2	8.6 ± 1.0	160.6 ± 25.3	54.5 ± 6.7	7.2 ± 0.6	37.7 ± 6.9	0.6 ± 1.1	4.9 ± 4.4	61.9 ± 13.7	33.2 ± 15.0	10.3 ± 9.3	34.3 ± 19.3	13.8 ± 7.7	20.5 ± 15.2
Group 3	12.6 ± 1.8	158.3 ± 28.2	54.2 ± 7.2	7.1 ± 0.7	37.6 ± 6.5	0.7 ± 1.4	4.7 ± 4.9	63.3 ± 14.5	31.9 ± 16.9	9.9 ± 8.6	32.8 ± 15.1	16.7 ± 7.3	16.1 ± 9.4
Group 4	17.5 ± 1.8	147.6 ± 24.1	51.2 ± 6.3	6.8 ± 0.6	34.0 ± 5.5	0.3 ± 0.6	3.3 ± 3.5	72.9 ± 14.7	23.9 ± 15.5	5.9 ± 6.4	33.3 ± 14.2	15.3 ± 6.6	18.0 ± 9.3
Group 5	26.5 ± 3.3	129.4 ± 14.8	46.7 ± 4.0	6.4 ± 0.5	29.4 ± 5.7	0.5 ± 1.4	3.5 ± 3.7	84.9 ± 8.6	11.9 ± 8.0	1.3 ± 2.0	30.3 ± 14.4	14.5 ± 5.2	15.9 ± 11.4

Scan groups consists of n=16 (first 2 groups) and n=15 (next 3 groups). All data are shown as mean ± SD. CV, Coefficient of variation; GMI, Glucose management indicator; HFS II, Hypoglycemia Fear Survey II; HFS II – B, HFS II Behavior subscale; HFS II – W, HFS II Worry subscale; TIR, Time in range 70-180 mg/dL; TAR250, Time above range >250 mg/dL; TAR180, Time above range >180 mg/dL; TBR70, Time below range <70 mg/dL; TBR54; Time below range <54 mg/dL.

respectively (Table 1 and Figure 3). Data on FOH across the five scan-rate groups is shown in Table 2. Significant correlations were found between scanning frequency and overall HFS II score (r=-0.25, β=-0.53, 95% CI: -1.01, -0.05), and with the HFS II–B subscale (r=-0.24, β=-0.22, 95% CI: -0.43, -0.02). No significant correlation was found with the HFS II–W subscale (r=-0.19, β=-0.30, 95% CI: -0.66, 0.05) (Figure 4). In multiple regression analyzes, no significant association was observed between HFS II scores with: gender, or type of insulin therapy (MDI or insulin pumps).

Discussion

In this single center observational cohort study, we have examined association between scanning frequency and FOH, and glycemic indices in adults with T1DM treated with insulin pumps or MDI. For the first time, we have found that scanning frequency is negatively correlated with FOH in adults with T1DM. We have shown that increased daily scan rates are associated with reduced fear of hypoglycemia for people with

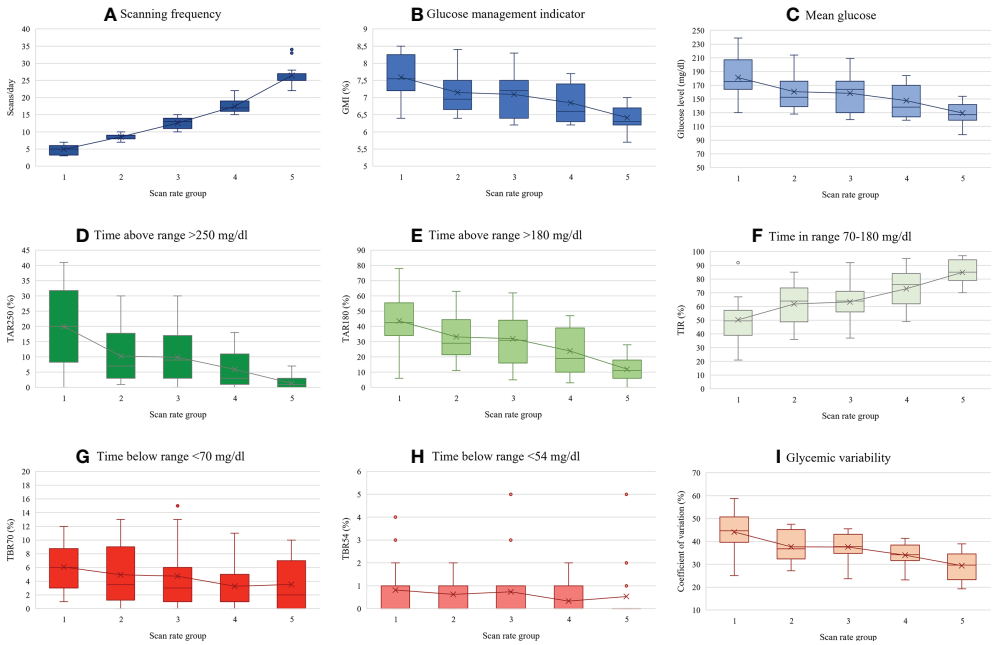

FIGURE 1
Glycemic indices across scan rate groups (each group represents 20% of subjects (first 2 groups – n=16, next 3 groups – n=15). **(A)** Scanning frequency, **(B)** Glucose management indicator, **(C)** Mean glucose, **(D)** Time above range >250 mg/dl, **(E)** Time above range >180 mg/dl, **(F)** Time in range 70-180 mg/dl, **(G)** Time below range <70 mg/dl, **(H)** Time below range <54 mg/dl, **(I)** Glycemic variability expressed as coefficient of variation. Data shown as mean and interquartile range.

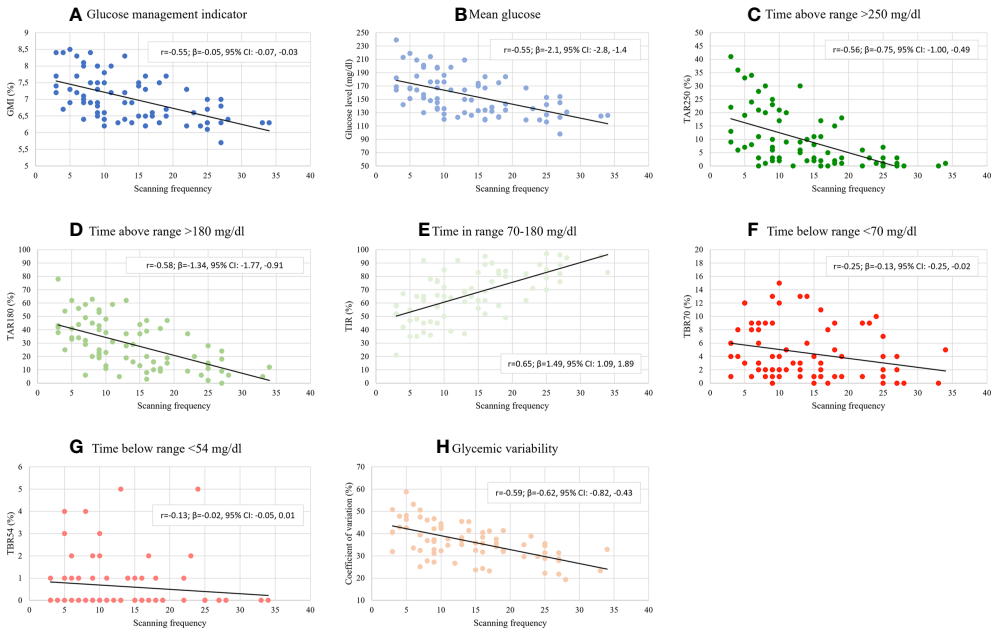

FIGURE 2
Glycemic indices by scanning frequency. **(A)** Glucose management indicator, **(B)** Mean glucose, **(C)** Time above range >250 mg/dl, **(D)** Time above range >180 mg/dl, **(E)** Time in range 70-180 mg/dl, **(F)** Time below range <70 mg/dl, **(G)** Time below range <54 mg/dl, **(H)** Glycemic variability expressed as coefficient of variation. β - beta coefficient, r - Pearson correlation coefficient.

T1DM, as assessed by HFS II scores. Significant negative correlations were found in terms of HFS II total scores and the behavior subscale. No correlation between scanning frequency and worry subscale was demonstrated, although the observed scores were lower at the highest scan rate.

The first randomized clinical study to evaluate clinical effectiveness of isCGM was the IMPACT trial (13). In that study, using isCGM was associated with significant improvement in glycemic outcomes, particularly reduction in time spent in hypoglycemia, and improvement in treatment satisfaction score, but HFS II scores did not differ between intervention and control group (13). Such findings were confirmed in the FUTURE study, in which the impact of isCGM on quality of life (QoL) was assessed in real-world conditions, and showed that, after initiation of isCGM, treatment satisfaction increased, while QoL was maintained (15). Moreover, after initiation of isCGM, hospitalizations due to hypoglycemia and/or DKA were reduced, and less workplace absenteeism was observed (15). Authors of the FUTURE study concluded that FOH and treatment satisfaction were not different subgroups with different scan frequencies (no detailed results were provided) (15).

To the best of our knowledge, there is no published data on the association between scanning frequency and FOH in adults. In children and adolescents (aged 13-19 years) the frequency of isCGM use was negatively correlated with worry and positively with behavior assessed by the Hypoglycemia Fear Survey – Child version tool (16). FOH is an important factor influencing QoL

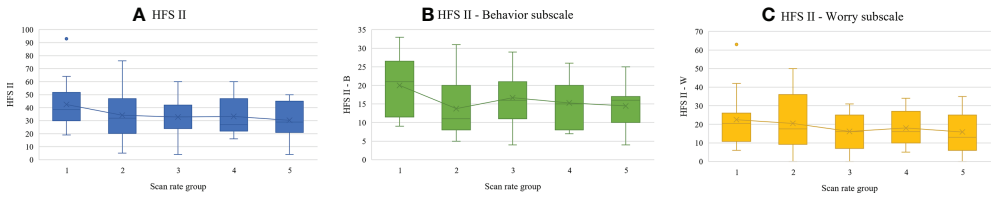

FIGURE 3
Fear of hypoglycemia across scan rate groups (each group represents 20% of subjects (first 2 groups – n=16, next 3 groups – n=15). **(A)** HFS II, **(B)** HFS II - Behavior subscale, **(C)** HFS II - Worry subscale. Data shown as mean and interquartile range.

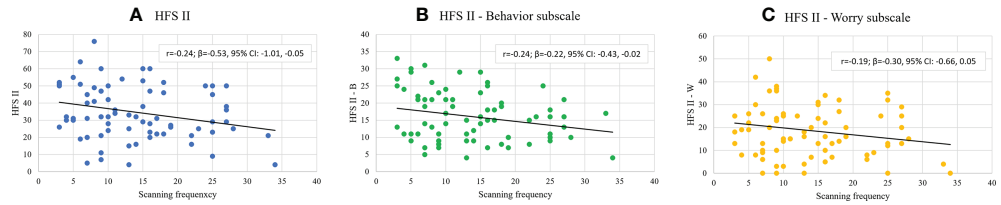

FIGURE 4
Fear of hypoglycemia by scanning frequency. **(A)** HFS II, **(B)** HFS II - Behavior subscale, **(C)** HFS II - Worry subscale. β - beta coefficient, r - Pearson correlation coefficient.

and glycemic control, thus, any strategy that could lower FOH is potentially of clinical value (17, 18). In the STAR 3 randomized trail it was shown that sensor-augmented pump therapy (SAPT) when compared with MDI+SMBG had significant advantages for reducing FOH (21). In another clinical study on SAPT, FOH scores tended to be lower for SAPT users, but results were statistically insignificant (22).

Our study also confirms previous findings on the association between scanning frequency and glycemic indices (8–11). Most previous real-world studies on scanning frequency were based on de-identified data stored in the cloud, thus no clinical characteristics of study subjects could be examined. Our well-characterized study group consisted of adult patients with T1DM, half of them treated with insulin pumps. In that group, a significant imbalance in terms of gender could be seen (Table 1). However, in additional analyses, gender and type of insulin therapy were not found as significant factors affecting FOH. The mean scan rate in our group was above 13 scans per day, which is comparable with the international data (8). However, the number of daily scans performed by the wider international group was lower than observed within the larger Polish cohort, as reported previously by us based on de-identified data (>21 scans per day) (8). Nevertheless, a mean GMI of 7.03% is almost identical to earlier reported eA1c for the same previously reported national cohort (7.04%) and lower than observed in several other countries (7.49%) (8). This data could suggest the influence of country-specific factors on the observed results. First, in Poland, the great majority of subjects using CGM devices are people with T1DM. Second, because in Poland isCGM is partially reimbursed only for people with T1DM under the age of 18 years and not for adults, one could hypothesize that in the adult population it is preferentially used by patients with higher socioeconomic status and with greater awareness of their disease, or people with higher FOH (23). Even in such groups, higher scanning frequency is correlated with better glycemic outcomes.

We must acknowledge that our study has some limitations. First, the research was conducted in one center only and the sample size is small. Second, the study group was preselected as only adult T1DM patients paying for sensors out of pocket were included. Additionally, this group consisted of T1DM patients with good glycemic control who rarely experienced severe hypoglycemia within a year before the study entry. This group was characterized by an over-representation of female T1DM patients. This is related to the fact that they are attracted to our department by a special program dedicated to pregnancy planning and care. These women usually remain under our care after the delivery. However, in the study women currently planning pregnancy or being pregnant were not involved in the study. Moreover, no longitudinal data was analyzed, and no effect of previous sensors use, and patients' experience was investigated. Next, due to the observational nature of our study, we cannot determine whether a cause-and-effect relationship exists between higher frequencies of daily scans and lower HFS II scores in adults with T1DM using isCGM. Such relationship could be established only in a future randomized clinical trial. However, the associations found in the current study are supported by previous reports on higher scanning frequencies and improvements in glycemic indices when using isCGM. Thus, patients who perform fewer daily scans could be advised to scan sensors more frequently to improve their glycemic control and reduce their FOH.

Conclusion

For the first time, we report that higher scanning frequency is associated not only with improved glycemic indices but also with reduced FOH in adults with T1DM using isCGM. This constitutes a new argument for advising T1DM patients to undertake frequent scanning when using isCGM.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The Bioethics Committee, The Medical Chamber in Krakow, Poland. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JH and MM designed the research. All authors were involved in acquisition of the data. JH and MM analysed the data and prepared the manuscript. All authors reviewed and accepted the final version of the manuscript and agreed to submit this version for publication. MM is the guarantor of the study.

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Conflict of interest

KC, MM, PW, and TK have received fees from Abbott, Ascensia, Medtronic, Dexcom, Roche for lecturing and participating in the advisory panels. JH has received fees from Abbott, Ascensia, Dexcom, Roche for lecturing and participating in the advisory panels.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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FGM-based remote intervention for adults with type 1 diabetes: The FRIEND randomized clinical trial

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Background: The use of flash glucose monitoring (FGM) in conjunction with proper education has been reported to improve glycemic control in people with diabetes on insulin therapy. However, there are still few randomized controlled trials on the educational effect, and an ideal educational model has not been established. This study aimed to estimate the efficacy of remote intervention for glycemic control in adults with type 1 diabetes using FGM.

Methods: In this single-center, randomized controlled trial, we enrolled adults with type 1 diabetes (HbA1c ≥7.0%). The participants were randomly assigned (1:1) to either FGM use with remote intervention (intervention group) or FGM use only (control group). Changes in glycemic outcomes such as HbA1c levels and continuous glucose monitoring metrics were evaluated at 12 weeks.

Results: Among 36 randomized participants (mean age, 44.3 years; mean baseline HbA1c, 8.9%), 34 completed the study. The remote intervention did not significantly reduce HbA1c levels. FGM use significantly improved HbA1c levels by −1.4% and −0.8% in both groups with and without remote intervention, respectively (P=0.003 and P=0.004, respectively). However, the intervention group showed significant increases in time with glucose in the range of 70–180 mg/dL (TIR; from 49.8% to 60.9%, P=0.001) and significant decreases in time with hyperglycemia (P=0.002) and mean glucose (P=0.017), but the control group did not. Moreover, the TIR (P=0.019), time with hyperglycemia >250 mg/dL (P=0.019), and coefficient of variation (P=0.018) were significantly improved in the intervention group compared to the control group. In particular, the CGM metrics improved gradually as the remote intervention was repeated. Furthermore, the intervention group reported higher treatment satisfaction (P=0.016).

Conclusions: Ongoing, personalized education during FGM use may lead to amelioration of glycemic control in adults with type 1 diabetes, even remotely.

Clinical trial registration: https://clinicaltrials.gov/ct2/show/NCT04936633, identifier NCT04936633.

KEYWORDS

remote consultation, telemedicine, blood glucose self-monitoring, insulin, diabetes mellitus, randomized controlled trial

Introduction

Multiple randomized controlled trials (RCTs) assessing real-time continuous glucose monitoring (rtCGM) or flash glucose monitoring (FGM) have demonstrated an effect on reducing glycated hemoglobin (HbA1c) levels and/or rates of hypoglycemia in patients with diabetes using intensive insulin regimens (multiple daily injections [MDI] or continuous subcutaneous insulin infusion [CSII]) (1–3). Based on accumulating evidence, the clinical practice guidelines for diabetes (4–6) now recommend using rtCGM or FGM for diabetic management in these patients. Previous studies, however, have shown that the use of rtCGM or FGM without adequate education has led to only modest or partial improvement of outcomes. In a meta-analysis of RCTs comparing rtCGM to usual methods of care in type 1 and type 2 diabetes (7), the use of rtCGM and FGM resulted in a modest (0.23%) or no reduction in HbA1c, respectively, and the use of FGM also resulted in no reduction in time with hyperglycemia.

FGM, also known as intermittently scanned CGM, continuously measures interstitial glucose levels but requires scanning to store the obtained glucose values. Most RCTs evaluating the efficacy of FGM did not indicate an outcome of HbA1c reduction (3, 8–10) except for one RCT involving type 2 diabetes (11). The design of this trial differed from others in that patients were educated about insulin dose adjustment and carbohydrate counting during the study period. Furthermore, a previous RCT on FGM users with type 1 and insulin-treated type 2 diabetes identified the effectiveness of a structured education program, termed FLASH, by comparing educated and uneducated groups (12). Taken together, findings of the previous studies suggested the importance of adequate education for patients using FGM.

Evidence indicating the importance of education is still lacking and an ideal educational model has not been established. The aim of this study was to determine the efficacy of remote intervention for glycemic control in adults with type 1 diabetes using FGM.

Materials and methods

Study design and participants

The FGM data-based Remote IntervEntion for adults with insuliN-dependent Diabetes (FRIEND) trial was a 12-week, investigator-initiated, open-label, parallel, randomized controlled study conducted at the CHA Bundang Medical Center in Korea. The study protocol (Supplementary Figure 1) was approved by the Institutional Review Board of CHA Bundang Medical Center (no. 2021-03-032) and performed in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Council for Harmonization. All the participants provided written informed consent before any trial-related activity. The study was registered at ClinicalTrial.gov (trial number, NCT04936633).

Eligible subjects were adults with type 1 diabetes aged 19–75 years who had been on intensive treatment with MDI or CSII therapy for more than one year, had a HbA1c level of 7.0% or higher, and a desire to use the FGM system. The exclusion criteria were non-insulin-dependent diabetes, diabetes duration <1 year, a history of using a rtCGM or FGM within the previous 12 weeks, pregnancy, end-stage renal disease and on dialysis, current treatment for severe cognitive impairment or psychiatric problems, a history of substance abuse or alcoholism within the previous 12 weeks, a history of corticosteroid therapy for more than seven consecutive days within the previous four weeks, and participation in other clinical trials within the previous four weeks. The flowchart of study participants is shown in Supplementary Figure 2.

Randomization and procedures

The participants were randomly assigned in a 1:1 ratio to either the intervention group or the control group. The intervention group used FGM for 12 weeks with remote intervention by medical staff and the control group used FGM without intervention. The participants were stratified at randomization according to their baseline HbA1c level (<9.0% or ≥9.0%) and age (<47 or ≥47 years).

All participants were provided with a FGM system (FreeStyle Libre; Abbott Diabetes Care, Witney, UK) with basic instructions on how to use it. In the intervention group, the remote intervention was conducted over a phone call at 2-week intervals for a total of five times during the study period if one or more of the following criteria were met in the previous two weeks; i.e., active time of sensor <70%, the number of scans per

day <4, time with glucose in the range of 70–180 mg/dL <70%, time with glucose below 70 mg/dL ≥4%, time with glucose below 54 mg/dL ≥1%, time with glucose above 180 mg/dL ≥25%, time with glucose above 250 mg/dL ≥5%, coefficient of variation ≥33%, and mean glucose level ≥140 mg/dL.

The remote intervention lasted about 10 minutes and was based on CGM data in LibreView. Its contents were as follows: education on the insulin to carbohydrate ratio and the insulin sensitivity factor; carbohydrate counting training; insulin management training including basal dose adjustment, bolus dose titration based on meal content and current glucose level, and use of a sliding scale; identifying the causes of hypoglycemia, hyperglycemia, or glycemic variability; advice on lifestyle modifications such as diet and exercise; and how to use FGM system including using glucose trend arrows. When the sensor activation time was less than 70% during the previous two weeks, both groups received phone calls or text messages encouraging FGM use.

At baseline and week 12, blood samples were taken from all participants to determine HbA1c levels and questionnaires were completed on following characteristics: treatment satisfaction and perception of hyperglycemia or hypoglycemia (Diabetes Treatment Satisfaction Questionnaire [status version and change version, DTSQs and DTSQc], Korean ver. 8.3.06, licence ref CB1202) (13), depression (Patient Health Questionnaire-9, PHQ-9) (14), and anxiety (General Anxiety Disorder-7, GAD-7) (15). The DTSQ questionnaire consists of eight questions with six querying treatment satisfaction, one querying perceived frequency of hyperglycemia, and one querying perceived frequency of hypoglycemia. Higher scores on six items asking about treatment satisfaction indicate greater satisfaction with treatment. Lower scores on two items asking about the perceived frequency of hyperglycemia and hypoglycemia indicate that blood glucose levels were closer to the ideal, while higher scores indicate problems. The PHQ-9 and GAD-7 questionnaires consist of 9 and 7 questions, respectively, with higher scores indicating severe depression or anxiety.

Outcomes

The primary outcome of the study was changes in HbA1c levels from baseline to week 12. Secondary glycemic outcomes included changes in CGM metrics, such as time with glucose in a range of 70–180 mg/dL (TIR), time with hypoglycemia (<54 and <70 mg/dL), time with hyperglycemia (>180 and >250 mg/dL), mean glucose level, and coefficient of variation (CV). CV (%) was calculated using the following formula: dividing the standard deviation (SD) of glucose levels by the mean glucose level and multiplying by 100. The CGM metrics data of the first two weeks and two weeks before week 12 were compared. In addition, changes in the psychosocial, behavioral, and physical variables were assessed as outcomes; i.e., scores of the DTSQs, DTSQc, PHQ-9, and GAD-7 questionnaires, total daily doses of insulin, the number of scans per day, lifestyle factors such as diet and exercise, and anthropometric variables.

Statistical analysis

Among the baseline characteristics of study participants, comparisons of categorical variables were performed with either Pearson's chi-squared test or Fisher's exact test, as appropriate. For continuous variables, either the independent *t*-test or the Wilcoxon-Mann-Whitney test was used, as appropriate. The Shapiro-Wilk test and skewness/kurtosis test were used to test for the normality of data. The outcomes comparing baseline and 12-week follow-up data for each group were analyzed with the paired *t*-test or the Wilcoxon signed-rank test. The analysis of covariance (ANCOVA) was used to compare changes in continuous variables between groups after adjusting for the baseline values, and the rank transform ANCOVA was used when data violated the ANCOVA assumptions. To test the relationship between two variables, either Pearson's or Spearman's correlation analysis was used. For the CGM metrics, *post hoc* analysis was performed separately for daytime (6:00 AM–11:59 PM) and nighttime (12:00 AM–5:59 AM) as well as for 2-week durations at baseline and at weeks 4, 8, and 12. The trend of changes in the CGM metrics with an increasing number of study weeks was evaluated using the one-way analysis of variance and test for linearity. Data are presented as number (%), mean ± SD, or median (interquartile range [IQR]). Statistical significance was defined as 2-sided *P* values <0.05. Statistical analyses were performed using R Statistical Software (v4.1.1; R Core Team 2021).

Results

Baseline characteristics

Participants were recruited between June 2021 and December 2021. A total of 36 participants were randomly assigned to the intervention group (n = 18) or the control group (n = 18; Supplementary Figure 2). A total of 34 participants (94%) with 17 in each group completed the study and were analyzed for the per-protocol population. All participants in the intervention group had five times of remote intervention because they met ≥1 intervention criteria every two weeks.

The baseline characteristics of participants are shown in Table 1. There were no significant differences in baseline demographics and clinical characteristics between the two groups. The mean age of participants was 44.3 (SD, 13.3) years and 52.8% were female. The mean duration of diabetes was 17.1

(SD, 10.4) years and the mean baseline HbA1c level was 8.9% (SD, 1.6).

Changes in HbA1c levels

The changes in HbA1c levels from baseline to week 12 were significant in both groups (from 9.2% ± 2.0% to 7.8% ± 1.0%, P = 0.003 in the intervention group; from 8.6% ± 1.1% to 7.8% ± 0.9%, P = 0.004 in the control group; Table 2 and Figure 1A). The mean reduction in HbA1c levels was greater in the intervention group compared to the control group (−1.4% and −0.8%, respectively), although the difference between groups were not statistically significant (P adjusted for baseline values = 0.506; Figure 1B).

Although changes in HbA1c levels were not significantly different between groups and both groups showed significant changes in HbA1c levels, only the intervention group showed significant correlations between changes in HbA1c levels and changes in CGM metrics, such as TIR (R = 0.640, P = 0.006), time with glucose >180 mg/dL (R = −0.710, P = 0.001), and mean glucose level (R = −0.670, P = 0.005), whereas the control group did not show a correlation (Supplementary Figure 3). This result suggests that HbA1c levels were improved along with the CGM metrics in the intervention group.

Changes in continuous glucose monitoring metrics

The TIR significantly increased from baseline to week 12 in the intervention group (from 49.8% ± 15.7% to 60.9% ± 7.9%; P = 0.001), but not in the control group (from 50.0% ± 15.7% to 54.0% ± 13.9%, P = 0.151; Table 2 and Figure 2A). Participants in the intervention group showed significant decreases in time with hyperglycemia (P = 0.002 and P = 0.026 for >180 and >250 mg/dL, respectively) and mean glucose level (P = 0.017), whereas those in the control group did not show significant changes. The changes in time with hypoglycemia (<54 and <70 mg/dL) and glycemic variability measured by CV from baseline were not significant in either group. When we compared the CGM metrics between two groups, changes in the TIR (adjusted mean difference, 7.0%, P = 0.019), time with glucose >250 mg/

TABLE 1 Baseline characteristics of study participants.

Characteristics	Intervention (n = 18)	Control (n = 18)	P
Age, years	45.4 ± 12.3	43.1 ± 14.6	0.607
Sex			0.504
Female	8 (44.4)	11 (61.1)	
Male	10 (55.6)	7 (38.9)	
Body mass index, kg/m^2	23.9 (20.9–26.4)	22.6 (20.1–25.4)	0.481
Waist circumference, cm	84.2 ± 11.2	82.9 ± 13.0	0.749
Duration of diabetes, years	16.0 ± 10.4	18.2 ± 10.5	0.543
HbA1c, %	9.2 ± 2.0	8.6 ± 1.1	0.251
Fasting blood glucose, mg/dL	124.0 (90.2–145.8)	141.5 (97.5–201.0)	0.343
C-peptide, ng/mL	0.3 ± 0.4	0.2 ± 0.4	0.436
Type of insulin therapy			0.486
Multiple daily insulin injections	18 (100.0)	16 (88.9)	
Continuous subcutaneous insulin infusion	0 (0.0)	2 (11.1)	
Duration of insulin use, years	12.6 (4.8–19.4)	13.7 (7.1–23.0)	0.406
Total daily dose of insulin, units	40.5 (28.0–62.5)	42.5 (38.5–61.8)	0.601
≥1 Diabetes-related complications	8 (44.4)	10 (55.6)	0.739
≥1 Diabetic education history	15 (83.3)	15 (83.3)	1.000
Highest education			0.587
Less than middle school	2 (11.1)	1 (5.6)	
High school	4 (22.2)	7 (38.9)	
More than bachelor's degree	12 (66.7)	10 (55.6)	
Smoking status			0.862
Current	9 (50.0)	7 (38.9)	
Ex-smoker	1 (5.6)	1 (5.6)	
Never	8 (44.4)	9 (50.0)	

Values are presented as the mean ± standard deviation, median (interquartile range), or number (%). HbA1c, glycated hemoglobin.

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TABLE 2 Changes in HbA1c levels and continuous glucose monitoring metrics.

	Baseline	Week 12	Change from baseline (95% CI)	*P*	Adjusted difference between groups (95% CI)	*P*
HbA1c, %						
Intervention	9.2 ± 2.0	7.8 ± 1.0	−1.4 (−2.3 to −0.5)	**0.003**	−0.2 (−0.8 to 0.4)	0.506
Control	8.6 ± 1.1	7.8 ± 0.9	−0.8 (−1.3 to −0.3)	**0.004**		
Continuous glucose monitoring outcomes						
Time with glucose 70–180 mg/dL, %						
Intervention	49.8 ± 15.7	60.9 ± 7.9	11.1 (5.1 to 17.1)	**0.001**	7.0 (1.2 to 12.7)	**0.019**
Control	50.0 ± 15.7	54.0 ± 13.9	4.0 (−1.6 to 9.6)	0.151		
Time with glucose <54 mg/dL, %						
Intervention	0.4 (0.0–0.7)	0.1 (0.0–1.0)	−0.1 (−1.4 to 1.4)	0.708	−0.5 (−6.0 to 5.1)	0.863
Control	0.1 (0.0–2.5)	0.5 (0.0–1.3)	−0.7 (−4.7 to 0.4)	0.726		
Time with glucose <70 mg/dL, %						
Intervention	4.1 (0.6–7.5)	3.1 (1.0–7.6)	0.2 (−1.9 to 2.4)	0.973	−2.1 (−7.2 to 2.9)	0.393
Control	3.4 (1.9–6.5)	4.9 (1.7–10.3)	1.3 (−4.7 to 5.2)	0.491		
Time with glucose >180 mg/dL, %						
Intervention	44.6 ± 19.2	33.3 ± 11.3	−11.4 (−18.1 to −4.7)	**0.002**	−6.3 (−14.2 to 1.5)	0.110
Control	43.2 ± 18.7	38.8 ± 17.8	−4.4 (−12.2 to 3.5)	0.256		
Time with glucose >250 mg/dL, %						
Intervention	18.8 ± 17.3	9.9 ± 5.1	−8.9 (−16.6 to −1.2)	**0.026**	−7.2 (−13.2 to −1.3)	**0.019**
Control	19.0 ± 15.1	17.2 ± 14.2	−1.8 (−6.9 to 3.4)	0.480		
Mean glucose, mg/dL						
Intervention	180.1 ± 43.3	159.4 ± 21.9	−20.7 (−37.1 to −4.2)	**0.017**	−11.9 (−29.2 to 5.4)	0.170
Control	178.6 ± 42.1	170.6 ± 40.1	−8.0 (−24.9 to 8.9)	0.331		
Coefficient of variation, %						
Intervention	40.8 ± 6.5	39.0 ± 7.8	−1.8 (−4.3 to 0.7)	0.151	−6.4 (−11.5 to −1.2)	**0.018**
Control	42.7 ± 9.3	43.1 ± 6.3	0.4 (−2.6 to 3.4)	0.791		

Total of 34 participants (17 in each group) who completed the 12-week study were analyzed. Values of baseline and week 12 are presented as the mean ± standard deviation or median (interquartile range). The change at week 12 from baseline in each group was evaluated using paired *t*-test or Wilcoxon signed-rank test for parametric or non-parametric data, and was presented as the mean or median, respectively. The baseline corrected difference between groups was evaluated using analysis of covariance (ANCOVA) or rank transform ANCOVA, depending on whether the ANCOVA assumptions were met, and was presented as the mean of values or mean residual of rank-transformed values, respectively. Significant *P* values in bold. CI, confidence interval; HbA1c, glycated hemoglobin.

dL (adjusted mean difference, −7.2 mg/dL, $P = 0.019$), and CV (adjusted mean difference, −6.4%, $P = 0.018$) were significantly improved in the intervention group compared to the control group (Table 2). Moreover, the ambulatory glucose profile (AGP) at week 12 compared to baseline showed that the IQR and the interdecile range (5th to 95th percentile) of glucose levels were narrower and the median was stabilized in the intervention group, indicating a reduction in glycemic variability (Figures 2B–E).

Post hoc analyses of continuous glucose monitoring metrics

The CGM metrics at daytime and nighttime and at 4-week intervals were obtained. Overall, the changes in glycemic metrics during both daytime and nighttime were similar to those of all day (Supplementary Table 1). During the daytime, significant decreases in time with glucose >180 mg/dL and mean glucose level were found in the intervention group. During the nighttime, a significant increase in TIR and a significant decrease in time with glucose >250 mg/dL were observed in the intervention group. Although statistical significance was lacking due to a low percentage of time with hypoglycemia, time with nocturnal hypoglycemia (<70 mg/dL at nighttime) was decreased in the intervention group, but it was increased in the control group.

The changes in glycemic variability measured by CV from baseline were decreased in the intervention group, contrary to the increase in the control group, but the changes were not significant in either group. However, the between-group difference of the change in CV was significantly reduced in the intervention group compared to the control group both during the daytime and nighttime (adjusted mean difference, −5.6% and −7.0%, $P = 0.039$ and $P = 0.022$, respectively; Supplementary Table 1).

Furthermore, in the analysis of glycemic metrics at 4-week intervals, unlike the control group, there was an increasing trend of TIR (P for trend = 0.013) and a decreasing trend of time with hyperglycemia >180 mg/dL (P for trend = 0.034) as the length of

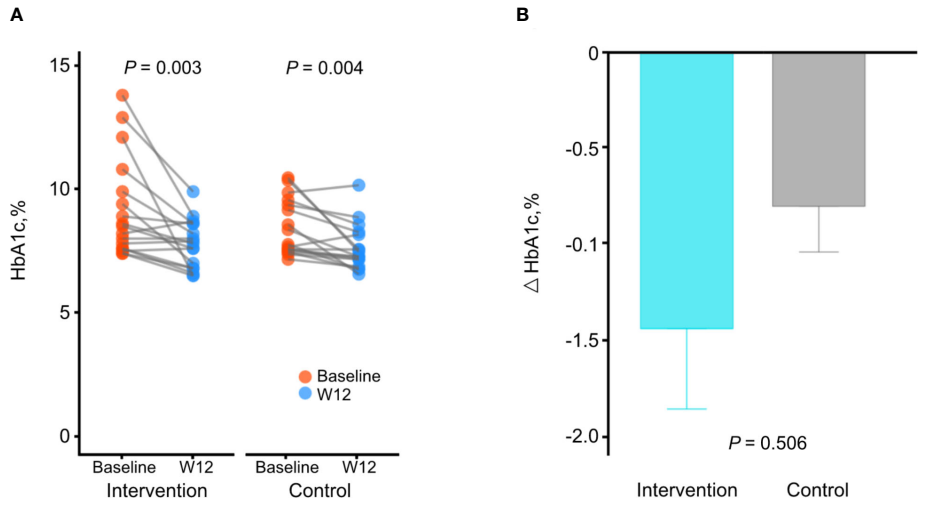

FIGURE 1
Changes in HbA1c levels during the study. **(A)** Comparison of HbA1c levels between baseline and week 12 in each group. *P* by paired *t*-test. **(B)** Comparison of changes of HbA1c levels between the intervention group and the control group. *P* adjusted for baseline values using analysis of covariance. Data are presented as the mean ± SE.

time participants in the intervention group used FGM with remote intervention increasing (Figures 2F, G; Supplementary Table 2). Mean glucose levels and CV decreased gradually in the intervention group, although the linear trend was not statistically significant (Figures 2H, I).

Changes in psychosocial, behavioral, and physical variables

Regarding DTSQs questionnaire items, the satisfaction-related scores increased from baseline at week 12 in both groups, though not significantly (Table 3). The perceived hyperglycemia-related scores decreased significantly in the intervention group (P = 0.015) and the perceived hypoglycemia-related scores increased significantly in the control group (P = 0.041), although the between-group differences were not significant. However, the DTSQc results at week 12 showed that the satisfaction-related scores were significantly higher in the intervention group than the control group (P = 0.016). Although the decrease in PHQ-9 scores was significant in both groups and the decrease in GAD-7 scores was not, the intervention group showed a greater decrease than the control group, indicating that anxiety and depression were further reduced in the intervention group.

The increase in total daily insulin doses was greater in the intervention group, even though there was no statistical significance (Table 4). The number of scans per day was reduced significantly in the control group (P = 0.034), but not in the intervention group. The frequency of meals, snacks, and exercise were not changed in either group, and the hours of exercise decreased significantly more in the control group (P = 0.042). Body mass index and waist circumference increased in both groups, and only the increase in the body mass index in the control group was statistically significant (P = 0.015).

Discussion

In this 12-week RCT, the remote intervention for adults with type 1 diabetes using FGM did not significantly reduce HbA1c levels. The FGM use significantly improved HbA1c levels by −1.4% and −0.8% in the two groups with and without remote intervention, respectively. However, the TIR, time with hyperglycemia >250 mg/dL, and CV were significantly improved by the remote intervention. In particular, as the remote intervention performed repeatedly, there was a significant trend toward the progressive improvement of CGM metrics such as the TIR and time with hyperglycemia >180 mg/dL. Furthermore, the intervention group reported significantly higher levels of treatment satisfaction compared to the control group.

A previous RCT consisting of 216 patients with diabetes on intensive insulin therapy found that the FLASH education program with FGM use improved glycemic control (12). The FLASH curriculum was a group based, 6-week educational program that consisted of four 90-minute sessions. The FLASH program resulted in a 0.3% reduction in HbA1c levels with a 1.8% (26 min/day) increase in TIR at the 6-month follow-

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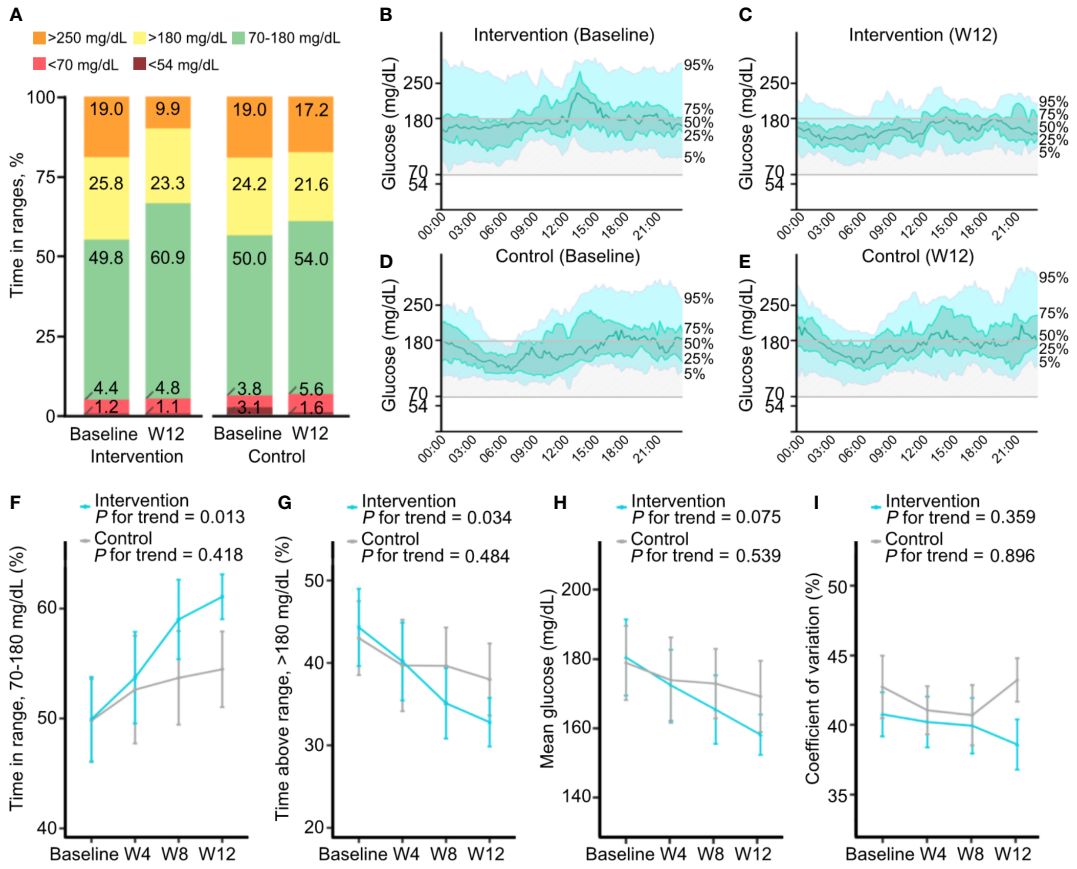

FIGURE 2
Changes in continuous glucose monitoring metrics during the study. **(A)** Mean percentages of time with glucose in ranges of <54, <70, 70–180, >180, and >250 mg/dL at baseline and week 12 in the intervention and control groups. **(B–E)** Ambulatory glucose profiles, which are summaries of glucose values from 14 consecutive days at baseline and at week 12, in the intervention group **(B, C)** and the control group **(D, E)**. The median line (green line) is surrounded by the interquartile range (25th to 75th percentile, shaded in light green) and the interdecile range (10th to 90th percentile, shaded in light blue). **(F–I)** Changes in continuous glucose monitoring metrics at 4-week intervals. Mean percentages of time with glucose in ranges of 70–180 **(F)** and >180 mg/dL **(G)**, mean glucose **(H)**, and coefficient of variation **(I)** at baseline and at weeks 4, 8, and 12 in the intervention and control groups. Data are presented as the mean ± SE.

up. Another recent RCT that included 47 poorly controlled patients with type 1 diabetes using rtCGM showed improvement of glycemic outcomes with the structured education (16). Structured individualized education was delivered during a 12-week study period in three sessions with two in person and one by phone call, each lasting 30 to 120 minutes. The educated group had a 1.2% reduction in HbA1c levels with a 2.3% (33 min/day) increase in TIR at the 12-week follow-up. Our study showed that remote intervention produced a 1.4% reduction in HbA1c levels with a 11.1% (2 h 40 min/day) increase in TIR from baseline at 12 weeks. Therefore, the remote intervention of our study can be considered to be an effective educational model. Taken together, our results further reinforced the importance of education, and one-on-one education could be more effective than group education for insulin-treated patients using CGM. The findings of these studies on educational effects are sources of evidence and should be detailed in future guidelines.

The control group of our study that only using FGM without remote intervention showed significant improvement in HbA1c levels, which was different from the absence or modest effect of FGM in previous RCTs (3, 8, 9, 11, 12, 16). As possible explanations for this considerable efficacy of FGM, we enrolled participants with poorly controlled diabetes (HbA1c ≥7.0%) They may have neglected self-management, including self-monitoring of blood glucose, before the study. However, in contrast to the intervention group, this HbA1c level reduction in the control group was not associated with changes in CGM metrics, and no variables improved among the CGM metrics. Moreover, although there was no difference between groups in HbA1c improvements, the CGM metrics such as TIR and CV were significantly improved in the intervention group compared to the control group. This may be due to remote intervention lowering the rate of hypoglycemia as well as hyperglycemia. Therefore, although FGM may help lower HbA1c levels in

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TABLE 3 Changes in psychosocial outcomes.

	Baseline	Week 12	Change from baseline (95% CI)	*P*	Adjusted difference between groups (95% CI)	*P*
Psychosocial outcomes						
DTSQs score						
Treatment satisfaction						
Intervention	26.6 ± 7.8	28.2 ± 6.7	1.6 (−1.2 to 4.4)	0.243	0.2 (−3.2 to 3.5)	0.917
Control	25.4 ± 5.0	27.3 ± 5.2	1.9 (−0.9 to 4.8)	0.163		
Perceived hyperglycemia						
Intervention	4.2 ± 1.6	3.1 ± 1.8	−1.1 (−1.9 to −0.2)	**0.015**	−1.3 (−2.5 to 0.0)	0.056
Control	2.8 ± 1.0	3.7 ± 1.6	0.9 (0.0 to 1.9)	0.060		
Perceived hypoglycemia						
Intervention	2.5 ± 1.5	2.6 ± 1.5	0.1 (−0.6 to 0.9)	0.743	−0.8 (−1.9 to 0.3)	0.139
Control	2.1 ± 1.5	3.3 ± 1.7	1.2 (0.1 to 2.3)	**0.041**		
DTSQc score[a]						
Treatment satisfaction						
Intervention		16.1 ± 2.3			2.5 (0.5 to 4.5)[b]	**0.016**[b]
Control		13.6 ± 3.3				
Perceived hyperglycemia						
Intervention		0.9 ± 2.2			0.1 (−1.2 to 1.5)[b]	0.789[b]
Control		0.8 ± 1.5				
Perceived hypoglycemia						
Intervention		0.1 ± 1.8			−1.0 (−2.1 to 0.1)[b]	0.063[b]
Control		1.1 ± 1.1				
Depression, PHQ-9 score						
Intervention	6.8 ± 4.5	3.9 ± 3.5	−2.9 (−5.1 to −0.6)	**0.015**	−1.3 (−3.4 to 0.8)	0.214
Control	8.5 ± 6.1	6.3 ± 5.3	−2.2 (−3.4 to −1.0)	**0.002**		
Anxiety, GAD-7 score						
Intervention	3.9 ± 3.8	2.5 ± 3.4	−1.4 (−2.9 to 0.2)	0.081	−1.0 (−3.2 to 1.2)	0.362
Control	4.9 ± 5.1	4.3 ± 5.5	−0.6 (−2.4 to 1.2)	0.496		

Values of baseline and week 12 are presented as the mean ± standard deviation. Values of the change at week 12 from baseline and the adjusted difference between groups are presented as the mean. The change from baseline in each group was evaluated using paired *t*-test. The baseline corrected difference between groups was evaluated using analysis of covariance. Significant *P* values in bold. DTSQs, The Diabetes Treatment Satisfaction Questionnaire status version. DTSQc, The Diabetes Treatment Satisfaction Questionnaire change version; PHQ-9, Patient Health Questionnaire-9; GAD-7, General Anxiety Disorder-7. [a]Data for the DTSQc was collected only at week 12. [b]For the DTSQc score, the unadjusted mean difference between groups were presented. The 95% CI and *P* value were calculated with an independent *t*-test.

poorly controlled patients with type 1 diabetes, patient education and monitoring are essential to achieve the original goal of CGM, such as reducing glycemic variability.

A major factor contributing to glycemic improvement in the intervention group in our study might be the education for insulin dose adjustment. Although statistical significance was lacking, the total daily dose of insulin increased more in the intervention group than in the control group. Moreover, especially the time with hyperglycemia and the AGP interdecile range were reduced considerably, indicating the effect of individualized education on the appropriate dose of prandial insulin, which prevented wide glycemic excursions. On the other hand, no improvements in diet, exercise, body mass index, and waist circumference were found.

Recently, digital health has played an increasingly important role in diabetes care. A meta-analysis of 32 RCTs evaluating the effectiveness of telemedicine interventions for gestational diabetes demonstrated reduction of not only glycemic levels of patients but also maternal and neonatal/fetal complications (17). In this regard, remote intervention based on CGM data is expected to be effective and will be a promising educational method for CGM users.

To the best of our knowledge, this is the first RCT that assessed the effectiveness of one-on-one education, especially remote intervention, in adults with type 1 diabetes using FGM. The previous RCTs comparing FGM and rtCGM revealed that FGM had less favorable glycemic control outcomes (18–21). Nevertheless, we demonstrated the benefits of individualized remote intervention for FGM users. One of the strengths of this study is the fact that the *post hoc* analysis was performed considering both daytime and nighttime, as well as a monthly time series. In particular, the CGM metrics improved gradually as the remote intervention was repeated, showing the importance of continuous patient monitoring and education

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TABLE 4 Changes in behavioral and physical outcomes.

	Baseline	Week 12	Change from baseline (95% CI)	*P*	Adjusted difference between groups (95% CI)	*P*
Behavioral outcomes						
Total daily insulin dose, U						
Intervention	47.6 ± 23.7	50.1 ± 15.0	3.1 (−0.4 to 6.5)	0.079	2.1 (−1.6 to 5.8)	0.256
Control	49.0 ± 14.1	50.1 ± 15.0	1.1 (−0.8 to 2.9)	0.245		
Number of scans per day						
Intervention	11.0 ± 7.3	8.4 ± 4.1	−2.7 (−5.9 to 0.6)	0.103	0.1 (−2.0 to 2.2)	0.712
Control	9.7 ± 3.6	7.4 ± 2.5	−2.3 (−4.4 to −0.2)	**0.034**		
Number of meals per day						
Intervention	2.6 ± 0.5	2.6 ± 0.5	0.0 (0.0 to 0.0)	–	0.0 (0.0 to 0.0)	–
Control	2.5 ± 0.5	2.5 ± 0.5	0.0 (−0.2 to 0.2)	1.000		
Number of snacks per day						
Intervention	0.9 ± 1.0	1.0 ± 1.0	0.1 (−0.1 to 0.2)	0.332	0.1 (−0.1 to 0.3)	0.151
Control	0.6 ± 0.8	0.6 ± 0.8	−0.1 (−0.2 to 0.1)	0.332		
Number of exercise per week						
Intervention	3.9 ± 2.5	2.8 ± 2.4	−1.0 (−3.0 to 0.0)	0.098	1.0 (−0.4 to 2.5)	0.100
Control	2.5 ± 2.7	1.2 ± 2.1	0.0 (−3.0 to 0.0)	0.052		
Hours of exercise per week						
Intervention	3.0 (0.6–5.0)	2.0 (0.0–3.0)	−4.2 (−8.5 to 2.5)	0.139	6.6 (0.3 to 12.9)	**0.042**
Control	1.5 (0.0–3.5)	0.0 (0.0–1.5)	−3.5 (−6.5 to 0.0)	**0.042**		
Physical outcomes						
Body mass index, kg/m^2						
Intervention	23.5 (20.8–26.7)	24.6 (20.9–27.3)	0.5 (0.0 to 1.2)	0.057	0.6 (−1.0 to 2.3)	0.445
Control	23.1 (21.0–25.7)	23.8 (21.2–25.3)	0.6 (0.1 to 1.0)	**0.015**		
Waist circumference, cm						
Intervention	83.9 ± 11.5	84.5 ± 13.0	0.6 (−1.1 to 2.4)	0.445	−0.9 (−3.2 to 1.3)	0.399
Control	83.8 ± 12.9	85.4 ± 13.7	1.6 (0.0 to 3.2)	0.052		

Values of baseline and week 12 are presented as the mean ± standard deviation or median (interquartile range). The change at week 12 from baseline in each group was evaluated using paired *t*-test or Wilcoxon signed-rank test for parametric or non-parametric data, and was presented as the mean or median, respectively. The baseline corrected difference between groups was evaluated using analysis of covariance (ANCOVA) or rank transform ANCOVA, depending on whether the ANCOVA assumptions were met, and was presented as the mean of values or mean residual of rank-transformed values, respectively. Significant *P* values in bold.

based on the patient's retrospective CGM data. Another strength is that, in addition to glycemic outcomes, various variables such as psychosocial, behavioral, and physical outcomes were investigated.

This study has some limitations. First, the number of participants was small; thus, the statistical power of differences between groups may have been undermined. Nevertheless, it was sufficient to test the outcomes of changes at week 12 from baseline in each group, calculating power based on our HbA1c results would require 28 subjects (14 in each group) at the desired 80% power and an alpha level of 0.05 (2-tailed). Thus, we showed the change from baseline at week 12 as well as the baseline-adjusted difference between groups. Second, although we used stratified randomization to assign the same number of participants to each group based on baseline HbA1c levels (<9.0% or ≥9.0%), the intervention group had a slightly higher mean baseline HbA1c level with a larger SD than the control group. The difference in baseline HbA1c levels between the groups, however, was not statistically significant, and both groups showed significant improvement in HbA1c levels at week 12. Third, as a single-center study, it may not be representative of the Korean general population. Moreover, there may be a bias because the structured education was provided by a single endocrinologist, but it can also avoid the influence of differences in education methods and skills. Finally, the study period was relatively short. This could be one of the reasons for the results showing improved TIR and CV but not HbA1c. Therefore, further studies with a larger scale and longer duration are needed.

In conclusion, this RCT demonstrated the importance of ongoing, personalized education for the effective use of FGM in adults with type 1 diabetes. The remote intervention based on CGM data can be an effective educational model.

Data availability statement

The datasets analyzed for this study are not publicly available but de-identified data may be made available upon request, subject to Institutional Review Board approval and a formal data use agreement. Contact the corresponding author for more information and access to these datasets.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of CHA Bundang Medical Center. The patients/participants provided their written informed consent to participate in this study.

Author contributions

S-KK and YSS contributed to the conception and design of the trial. JL, MHL, K-SK, S-KK, Y-WC and YSS acquired patients and analyzed and interpreted the data. JL and YSS wrote the article and edited the manuscript. JL, MHL, JP, K-SK, S-KK, Y-WC, HWH and YSS approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1054697/full#supplementary-material

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To sleep or not to sleep: An Italian Control-IQ-uestion

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Objective: Tandem Control-IQ is an advanced hybrid closed loop (AHCL) system with a Sleep Activity Mode to intensify glycemic control overnight. The aim of the study is to evaluate the effectiveness of using Sleep Mode or not among Tandem Control-IQ users.

Research design and methods: We performed a retrospective Tandem Control-IQ data download for patients followed at IRCCS G. Gaslini Pediatric Diabetes Centre. We divided the patients into group 1 (Sleep Mode users) and group 2 (non-users) and compared their overall glycemic data, particularly during nighttime.

Results: Group 1 (n = 49) does not show better nocturnal glycemic control as expected when compared with group 2 (n = 34). Group 2 shows a nighttime TIR% of 69.50 versus 66.25 (p = 0.20). Only the patients who do not use Sleep Mode and with sensor and automatic mode use ≥90% reached TIR >70% during nighttime, as well as lower nocturnal TAR% (18.80 versus 21.78, p = 0.05).

Conclusions: This is the first study that evaluates the real-life effectiveness of the use of Sleep Mode in young patients with T1D. Control-IQ Sleep Activity Mode may not be as effective in Italian patients as in American patients due to the different habits.

KEYWORDS

TIR (time in range), CGM (continuous glucose monitoring), Type 1 diabetes (T1D), tandem control-IQ, sleep, AHCL (Advanced Hybrid Closed Loop)

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Introduction

The management of type 1 diabetes (T1D) has changed substantially in the last few years. New technologies allow the improvement of glycemic control by reducing the risk of hypoglycemia and hyperglycemia and decrease the rate of diabetes complications (1–3). Since the FDA approved the first hybrid closed loop (HCL) system, further advanced devices which integrate insulin infusion with continuous glucose monitoring (CGM) have been commercialized (4–6).

The goal of advanced hybrid closed loop (AHCL) technology is to reduce the burden of managing diabetes by automatically adjusting insulin delivery based on CGM data. Using CGM data, AHCL systems predict glucose values and adjust insulin delivery in order to keep glycemic values in a target range (7, 8).

The Tandem t:slim X2 insulin pump (Tandem Inc., San Diego, CA, USA) uses a Dexcom G6 sensor (Dexcom Inc., San Diego, CA, USA) and a closed loop algorithm (Control-IQ™) that automates basal insulin delivery and correction boluses, prevents and protects against hypoglycemia, and intensifies control overnight (9).

The Control-IQ system works based on well-defined target and treatment ranges with the aim of implementing the time spent in the recommended target range. When the predicted glucose value in the following 30 min is between 112.5 and 160 mg/dl, the pump delivers the basal insulin rate based on the active personal profile. When the predicted glucose value is <112.5 mg/dl, Control-IQ technology decreases personal insulin delivery rate and completely stops basal insulin delivery when predicted glucose values are below 70 mg/dl. When the predicted glucose value is above 160 mg/dl, the pump increases basal insulin delivery and delivers an automatic correction bolus if the predicted value is greater than 180 mg/dl. The system is able to deliver a maximum of one correction bolus per hour (reduced by 60% compared with the calculated).

Control-IQ technology has two integrated modes to optimize glycemic control during the night and during exercise; these modes can be activated and deactivated manually or scheduled by the patient. The Sleep Activity Mode works on a target range of 112.5–120 mg/dl instead of 112.5–160 mg/dl. When the predicted glucose value is >120 mg/dl, the pump increases the delivery of basal insulin, but it does not deliver correction boluses.

Currently, good glycemic control is defined on the basis of CGM data by the International Consensus as follows: time in range (TIR) (70–180 mg/dl) >70%, time below range (TBR) (<70 mg/dl) <4%, TBR (<54 mg/dl) <1%, time above range (TAR) (>180 mg/dl) <25%, and TAR (>250 mg/dl) <1% (10, 11).

Data from the first studies on the Control-IQ system in children and adults with type 1 diabetes have shown encouraging results in terms of glycemic outcomes and patient satisfaction (12, 13). Several multicenter randomized trials and real-life studies in children, adolescents, and adults demonstrated the efficacy of the Control-IQ technology when compared to the sensor-augmented pump, Basal-IQ technology, and other AHCL systems (14–20). The Control-IQ technology has been shown to be effective in terms of patient satisfaction, improvement of quality of life and quality of sleep for patients and parents, ease of use, and improvement of positive emotions (21–24).

Most studies have shown that the improvement in time in range is better overnight, which is consistent with the Control-IQ algorithm design (12–16, 19). Despite the evidence on the efficacy of the overnight system, there are no clinical studies evaluating the effectiveness of using or not using Sleep Mode among Tandem Control-IQ users.

The aim of this study was to compare glycemic control (globally and overnight) between Sleep Mode users and non-users in a cohort of children and young patients with type 1 diabetes using Control-IQ technology.

Materials and methods

Study design and study population

This was a retrospective study conducted in the Regional Reference Centre for Pediatric Diabetes, Istituto Giannina Gaslini, Genoa, Italy, a tertiary care pediatric hospital of Liguria, northwest Italy.

Patients were enrolled according to the following inclusion criteria: T1D diagnosis at least 1 year prior to the study, Tandem Control-IQ use for at least 1 month, and data download from February to May 2022 during an outpatient visit or a telemedicine visit. The exclusion criteria were as follows: percentage of use of automatic mode and/or sensor less than 80%, infections, or major changes in the usual lifestyle in the 14 days prior to data download (traveling, holidays, sickness).

Data collection

During the first routine follow-up visit in which the inclusion criteria were met, the following data were collected for each patient: demographic data (sex, date of birth, age), age at clinical onset of T1D, duration of disease, time of use of the Control-IQ system, CGM data of the 14 days before the checkup, bolus time, and average consumption of carbohydrates (CHO) at dinner in the previous 14 days.

Study outcomes

We divided the patients into two groups: group 1 (users of Sleep Mode for at least 6 h a night) and group B (non-users of

Sleep Mode). During the Tandem Control-IQ training at our center, the Sleep Mode function is explained to all patients; then, they independently choose whether to set Sleep Mode or not. The following parameters were compared between the two groups: TIR, TAR, TAR >250 mg/dl, TBR, TBR <54 mg/dl, coefficient of variation (CV), standard deviation (SD), mean glucose value, glucose management indicator (GMI), percentage of sensor use, percentage of time in automatic mode, and percentage of time spent in Sleep Mode. We also compared the following data relating only to the night period (from 0 a.m. to 6 a.m.) between the two groups: TIR, TAR, TAR >250 mg/dl, TBR, TBR <54 mg/dl, CV, SD, and mean glucose value.

In addition, we decided to restrict the data analysis to patients who used sensor and automatic mode for a percentage of time greater than 90%, in order to select patients with the best possible use of the Control-IQ algorithm.

Considering the retrospective nature of the study, the informed consent form already signed by parents and/or patients at disease onset and renewed yearly, in which they agree on the use of clinical data for research purposes, was used. In addition, all parents and patients provided a specific informed consent form for the collection of data. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice.

Statistical analysis

Data are described as mean and SD or median and range for continuous variables and as absolute and relative frequencies for categorical variables.

Non-parametric analysis (Mann–Whitney *U* test) for continuous variables and the chi-square or Fisher's exact test for categorical variables were used to measure differences between groups. *p*-values ≤0.05 were considered statistically significant, and all *p*-values were based on two-tailed tests. Statistical analysis was performed using SPSS for Windows (SPSS Inc., Chicago, IL, USA).

Results

Data from a total of 110 T1D patients using Tandem Control-IQ (aged 4 to 35 years) were retrospectively collected at the IRCCS G. Gaslini Pediatric Diabetes Centre. We excluded 27 patients: 13 did not perform a visit or data download in the study period, 6 were diagnosed with diabetes in the previous year, 7 had become Tandem Control-IQ users less than a month prior to the beginning of the study period, and 1 used Sleep Mode for less than 6 h. We collected data of the remaining 83 T1D patients: 49 of these patients (group 1) used Sleep Mode and 34 (group 2) did not use it. Most patients of group 1 ($n = 42$) had scheduled Sleep Mode between 11 p.m. and 7 a.m.; the remaining 7 patients had scheduled it at different times between 10 p.m. and 8 a.m. and always for a duration of at least 6 h.

No significant differences were found in the clinical and demographic characteristics of the patients belonging to the two groups, with the exception of the percentage of nighttime sensor use, which was greater than 95% in both groups, as well as the duration of AHCL use (328.39 ± 111.34 days in group 1 and 181.50 ± 150.83 days in group 2, $p = 0.001$). Particularly, in our study population, the mean time of bolus for dinner was 8:17 p.m., and the mean number of carbohydrates consumed at dinner was 69.31 g; no significant differences were observed between the two groups for these meal parameters. The characteristics of the study population are summarized in Table 1.

The differences in overall and nocturnal glycemic control between the two groups are shown in Table 1. Group 1 had a similar TIR% compared with group 2 both overall (67.80 ± 12.13 versus 70.79 ± 11.07, $p = 0.20$) and during nighttime (66.25 ± 15.45 versus 69.50 ± 13.55, $p = 0.51$).

Limiting the analysis to patients with percentage of time of sensor use and automatic mode use ≥90% (*N* of patients = 71), data confirmed a similar TIR% in group 1 compared with group 2 overall (68.00 ± 12.81 versus 71.97 ± 9.58, $p = 0.20$) and during nighttime (66.52 ± 15.76 versus 70.77 ± 12.46, $p = 0.43$). A statistically significant difference between the two groups in terms of TAR% (21.78 ± 7.10 in group 1 versus 18.80 ± 5.94 in group 2, $p = 0.05$) was observed (Table 2).

No statistically significant differences in terms of TBR, CV, SD, mean glucose, and GMI were found between the two groups in either the original or the restricted analysis (Tables 1, 2). Further stratifying the analysis between age groups (<18 and ≥18 years), no significant differences were found for all the nocturnal parameters analyzed.

Comparing the patients' nighttime TIR (TIR ≥70%, TIR 50%–70%, and TIR <50%), data showed that the percentage of patients that reach the recommended target of TIR ≥70% is 46.9% in group 1 and 58.8% in group 2. Patients who have a nighttime TIR lower than 50% are 20.4% of group 1 and 5.9% of group 2. Restricting the analysis to patients who used automatic mode and sensor for more than 90% of the time, 19.5% of the patients in group 1 and 3.3% in group 2 ($p = 0.09$) had nocturnal TIR <50% (Tables 3, 4; Figure 1).

Discussion

The aim of this study was to compare real-life glycemic control data between Tandem Control-IQ Sleep Mode Users and non-users. To the best of our knowledge, this is the first study to compare the overnight effectiveness of the Tandem Control-IQ Sleep Mode compared with the Standard Control-IQ algorithm.

TABLE 1 Comparison of the overall and nighttime (h 24–6) glycemic control of Sleep Activity Mode users (group 1) and non-users (group 2); analysis included patients using sensor and automatic mode ≥80% (*N* = 83).

	Sleep Activity users (*N* = 49) *X* ± SD	Non-users (*N* = 34) *X* ± SD	*p*-value
Gender, M (%)	23 (46.9)	19 (55.9)	0.50
Age (years)	17.09 ± 6.01	18.51 ± 8.27	0.42
Duration of disease (years)	8.29 ± 5.76	12.13 ± 8.41	0.06
Sensor use (%)	94.61 ± 3.24	94.03 ± 2.91	0.17
Nighttime (h 24–6) sensor use (%)	97.75 ± 3.29	96.19 ± 4.10	**0.05**
Time in automatic mode (%)	94.84 ± 3.89	94.44 ± 3.90	0.47
Time in Sleep Activity Mode (%)	32.71 ± 5.67	–	
Dinner CHO consumption (g)	67.02 ± 23.93	72.62 ± 23.55	0.27
Bolus time for dinner (hh:mm—p.m.)	8:19 ± 37:56	8:13 ± 36:36	0.24
Duration of AHCL use (days)	328.39 ± 111.34	181.50 ± 150.83	**0.001**
TIR (%)	67.80 ± 12.13	70.79 ± 11.07	0.20
TAR (%)	21.59 ± 6.78	19.26 ± 6.19	0.08
TAR >250 mg/dl (%)	8.61 ± 7.63	7.59 ± 6.23	0.70
TBR (%)	1.63 ± 1.72	1.88 ± 1.72	0.26
TBR <54 mg/dl (%)	0.50 ± 0.77	0.56 ± 0.77	0.73
Mean glucose (mg/dl)	159.02 ± 21.09	155.24 ± 19.24	0.30
GMI (%)	7.12 ± 0.62	7.06 ± 0.51	0.59
SD (mg/dl)	56.04 ± 12.31	55.21 ± 10.78	0.89
CV (%)	35.10 ± 5.22	35.41 ± 4.07	0.35
Nighttime TIR (%)	66.25 ± 15.45	69.50 ± 13.55	0.51
Nighttime TAR (%)	23.61 ± 11.01	21.96 ± 8.30	0.88
Nighttime TAR >250 mg/dl (%)	8.35 ± 8.16	7.28 ± 7.10	0.62
Nighttime TBR (%)	1.14 ± 2.01	1.06 ± 1.54	0.96
Nighttime TBR <54 mg/dl (%)	0.56 ± 1.28	0.47 ± 0.83	0.87
Nighttime mean glucose (mg/dl)	161.41 ± 23.61	160.62 ± 21.69	0.91
Nighttime SD (mg/dl)	52.77 ± 13.07	49.41 ± 11.72	0.23
Nighttime CV (%)	32.82 ± 6.60	30.57 ± 4.89	0.09

CV, coefficient of variation; GMI, glucose management indicator; SD, standard deviation; TIR, time in range (70–180 mg/dl); TAR, time above range (>180 mg/dl); TAR >250 mg/dl, time above range (>250 mg/dl); TBR, time below range (<70 mg/dl); TBR <54 mg/dl, time below range (<54 mg/dl) bold = statistically significant.

The Control-IQ system has been shown to be effective in glycemic control and has been appreciated by patients since the first studies on children and adults with type 1 diabetes (12, 13). Several multicenter randomized trials in children, adolescents, and adults demonstrated the efficacy of Control-IQ compared with sensor-augmented pumps, showing an improvement in TIR without increasing hypoglycemia (14–16). A recent study in children demonstrates an improvement of TIR with Control-IQ in comparison with Basal-IQ, a predictive low-glucose suspend (PLGS) algorithm (17). A single multicenter study that compared AHCL systems currently approved for the pediatric population showed the non-inferiority of the efficacy of Tandem Control-IQ in reaching glycemic targets compared with the other systems (18). Recent studies on the real-world use of the Tandem Control-IQ system confirmed the conclusions reached by the pivotal trials and previous studies. The use of Control-IQ technology increased time in range at 12 months in a sample of 7,813 patients (19) and at 6 months in a sample of 191 youth patients with type 1 diabetes (20).

Most studies on the effectiveness of the Control-IQ System included additional analysis focusing on the overnight period; all of these studies have shown that the algorithm is more effective on TIR during nighttime (12–16, 19). Forlenza et al. observed significative improvement of TIR overnight (from 11 p.m. to 7 a.m.) in the Control-IQ group compared with the sensor-augmented pump (SAP) group (Control-IQ: 74.9%–10.1% *vs.* SAP: 49.6%–18.8%; $p = 0.001$), with an overall TIR of 71.0% in Control-IQ users (12). In the first randomized multicenter trial of closed loop control (CLC) in T1D, Brown et al. showed that TIR was 70% in the closed loop group and 59% in the control group during the daytime (6 a.m. to midnight) and was 76% and 59%, respectively, during the nighttime (midnight to 6 a.m.) (13). Comparing CLC with SAP, Breton et al. observed a daytime (6 a.m. to midnight) TIR of 63% in the closed loop group and 56% in the control group, and the corresponding values during

TABLE 2 Comparison of the overall and nighttime (h 24-6–) glycemic control of Sleep Activity Mode users (group 1) and non-users (group 2); analysis included patients using sensor and automatic mode ≥90% (*N* = 71).

	Sleep Activity users (*N* = 41) *X* ± SD	Non-users (*N* = 30) *X* ± SD	*p*-value
Gender, M (%)	17 (41.5)	17 (56.7)	0.24
Age (years)	16.76 ± 6.01	18.60 ± 8.35	0.31
Duration of disease (years)	8.34 ± 6.01	11.71 ± 8.50	0.16
Sensor use (%)	95.49 ± 2.13	94.67 ± 2.06	0.06
Nighttime sensor use (%)	98.39 ± 2.46	97.13 ± 2.58	**0.05**
Time in automatic mode (%)	96.22 ± 2.04	95.47 ± 2.47	0.20
Time in Sleep Activity Mode (%)	32.56 ± 6.05	–	
TIR (%)	68.00 ± 12.81	71.97 ± 9.58	0.20
TAR (%)	21.78 ± 7.10	18.80 ± 5.94	**0.05**
TAR >250 mg/dl (%)	8.59 ± 8.08	6.84 ± 4.82	0.71
TBR (%)	1.39 ± 1.38	1.93 ± 1.78	0.10
TBR <54 mg/dl (%)	0.35 ± 0.53	0.57 ± 0.80	0.92
Mean glucose (mg/dl)	159.78 ± 21.86	153.03 ± 15.91	0.15
GMI (%)	7.14 ± 0.63	7.00 ± 0.47	0.30
SD (mg/dl)	55.07 ± 12.61	54.10 ± 9.35	0.89
CV (%)	34.27 ± 4.80	35.23 ± 4.00	0.13
Nighttime TIR (%)	66.52 ± 15.76	70.77 ± 12.46	0.43
Nighttime TAR (%)	24.10 ± 11.39	21.25 ± 8.26	0.56
Nighttime TAR >250 mg/dl (%)	7.97 ± 8.14	6.35 ± 6.08	0.56
Nighttime TBR (%)	1.00 ± 2.03	1.13 ± 1.62	0.60
Nighttime TBR <54 mg/dl (%0)	0.35 ± 0.90	0.50 ± 0.86	0.43
Nighttime mean glucose (mg/dl)	162.02 ± 23.60	158.63 ± 19.99	0.62
Nighttime SD (mg/dl)	51.51 ± 13.15	48.26 ± 10.65	0.30
Nighttime CV (%)	31.86 ± 6.49	30.28 ± 4.80	0.27

CV, coefficient of variation; GMI, glucose management indicator; SD, standard deviation; TIR, time in range (70–180 mg/dl); TAR, time above range (>180 mg/dl); TAR >250 mg/dl, time above range (>250 mg/dl); TBR, time below range (<70 mg/dl); TBR <54 mg/dl, time below range (<54 mg/dl) bold = statistically significant.

the nighttime (midnight to 6:00 a.m.) were 80% and 54% (14). Kanapka et al. also observed a better improvement in TIR overnight (midnight to 6 a.m.), while Isganaitis et al. showed an improvement in TIR in the Control-IQ group compared with the SAP group especially between 1 a.m. and 8 a.m. (+19% of TIR at night and +11% during the day, $p < 0.0001$) (15, 16). Recently, Breton et al. showed a profound TIR increase at night, reaching a median >90% between 4 and 7 a.m. in T1D Control-IQ users in a 1-year real-world study (19).

Despite the evidence on the efficacy of the system overnight, to date, there are no studies that evaluate the effectiveness of using Sleep Mode or not among Tandem Control-IQ users.

We decided to download the data during the visits that took place between February and May 2022. The choice to download data only in a specific time window derives from the need to avoid as much as possible substantial differences in the life habits of patients related to the pandemic situation and to the seasonal habits and to exclude Italian prolonged periods of holidays (e.g., Christmas or summer holidays); in particular, schools, sports, and extracurricular activities were open in Italy during the study period. Patients followed at the IRCCS G. Gaslini Pediatric Diabetes Centre are both children and young adults (up to 35 years), and this is the reason for the age range of the study population. Despite the wide spectrum of the age of the patients included, stratifying

TABLE 3 Comparison by category of nighttime TIR between Sleep Activity Mode users (group 1) and non-users (group 2); analysis included patients using sensor and automatic mode ≥80% (*N* = 83).

	Sleep Activity users (*N* = 49) *N* (%)	Non-users (*N* = 34) *N* (%)	*p*-value
TIR ≥70%	23 (46.9)	20 (58.8)	0.14
TIR 50%–69%	16 (32.7)	12 (35.3)	
TIR <50%	10 (20.4)	2 (5.9)	

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TABLE 4 Comparison by category of nighttime TIR between Sleep Activity Mode users (group 1) and non-users (group 2); analysis included patients using sensor and automatic mode ≥90% (*N* = 71).

	Sleep Activity users (*N* = 41) *N* (%)	Non-users (*N* = 30) *N* (%)	*p*-value
TIR ≥70%	20 (48.8)	18 (60.0)	0.09
TIR 50%–69%	13 (31.7)	11 (36.7)	
TIR <50%	8 (19.5)	1 (3.3)	

the analysis by age, no significant differences emerged in the parameters analyzed compared with the entire population.

We defined nighttime as the period between midnight and 6 a.m., according to most of the studies that evaluated the effectiveness of Tandem Control-IQ overnight (13–15); all the scheduled Sleep Mode set by the group 1 patients included this time range. The study had predefined inclusion criteria of time in connectivity in closed loop control and CGM of at least 80% overall and during nighttime; a lower percentage of use of the closed loop technology would not allow to evaluate the algorithm and to compare the night mode with the standard mode adequately (8).

Data showed that the use of Sleep Mode does not significantly improve nighttime glycemic control and that the group of non-users surprisingly has a similar overnight TIR (69.50 ± 13.55 versus 66.25 ± 15.45). Further restricting the analysis to patients with an automatic insulin delivery time and sensor use greater than 90%, we also observed that only the group of non-users of Sleep Mode (TIR% 70.77 ± 12.46) reached the recommended TIR (11), and TAR% is surprisingly and significantly reduced in this group (18.80 ± 5.94 versus 21.78 ± 7.10, $p = 0.05$). The overnight TBR% did not significantly increase in group 2 (TBR 1.06 ± 1.54 versus 1.14 ± 2.01). The mean duration of use of AHCL was longer in patients belonging to group 1 (about 6 versus 11 months in group 2); therefore, the experience of using AHCL can be considered a factor in favor of group 1. These data demonstrate the non-inferiority and safety of non-use of the Control-IQ Sleep Mode (Tables 1, 2).

Furthermore, by stratifying the population by TIR groups, we observed that in patients who do not use the Sleep Mode, the percentage of patients who reached the recommended target of TIR ≥70% is higher compared with users (58.8% versus 46.9%), and the percentage of patients with a nighttime TIR lower than 50% is lower compared with those who use the Sleep Mode (5.9% versus 20.4%). Restricting the analysis to patients using automatic mode and sensor for more than 90% of the time, patients with nocturnal TIR <50% were less in the non-user group (3.3% versus 19.5%) (Tables 3, 4 and Figure 1). These data, despite not reaching statistical significance, once again underline the non-efficacy of the Sleep Mode in our sample of young Italian patients.

The Sleep Mode has a narrower target range (112.5–120 mg/dl) to ensure optimal glucose values during the night and has been shown to perform brilliantly in system efficacy studies and in comparison with SAP. Nevertheless, if Sleep Mode is activated, no corrective boluses are delivered; on the one hand, this feature guarantees the safety of the algorithm during the night; on the other hand, the increase in the basal rate alone may sometimes not be sufficient to quickly bring glucose values back to target values. The Sleep Mode may be more effective when bedtime glucose value is in the target range, while in the case of post-dinner hyperglycemia or the consumption of foods with high-fat content, it may have more difficulty in bringing glucose values back to the target. This particular feature assumes great relevance in a country like Italy, where dinner is served late (usually from 8 p.m. to 9 p.m.), often rich in carbohydrates, and children often go to sleep shortly after dinner consumption.

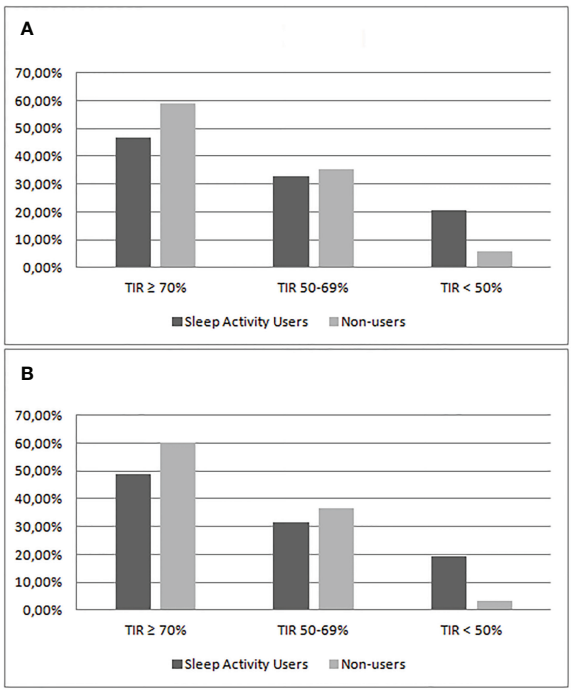

FIGURE 1
Comparison of the percentage of patients divided by categories of nighttime TIR between Sleep Activity Mode users (group 1) and non-users (group 2). The analysis included patients using sensor and automatic mode ≥80% **(A)** or ≥90% **(B)**.

These Italian habits are very different from the American ones, on the basis of which the Control-IQ standard algorithm and activity modes were probably created. All of the system efficacy studies on nocturnal glycemic control were also performed in the USA (12–16, 19).

This is the first study to evaluate the real-life effectiveness of the use of Sleep Mode compared with the Control-IQ standard mode in young patients with T1D, and the results are certainly interesting and challenging. The Control-IQ Sleep Mode may not be effective in Italian patients due to the different habits compared with American patients. The limitations of the study included the low number of patients, the retrospective model of the study, and the real-life nature of the study, which allow us to evaluate the effectiveness of the system in the daily life of patients but can give less uniformity in lifestyle habits. Further studies with a greater number of patients in uniform settings such as school camps or group activities that analyze the effectiveness of Sleep Mode in relation to the consumption of certain foods are certainly needed.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

MB designed the study and wrote the manuscript. MS researched the data and wrote the manuscript. VA researched the data. MC did the statistical analysis. Gd'A reviewed the manuscript and contributed to the discussion. MM reviewed the manuscript and contributed to the discussion. NM designed the study and contributed to the discussion. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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One-year follow-up comparison of two hybrid closed-loop systems in Italian children and adults with type 1 diabetes

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Background and aims: Tandem Control-IQ and MiniMed 780G are the main Advanced Hybrid Closed Loop (AHCL) systems currently available in pediatric and adult patients with Type 1 Diabetes (T1D). The aim of our study was to evaluate glycemic control after 1-year of follow-up extending our previous study of 1-month comparison between the two systems.

Methods: We retrospectively compared clinical and continuous glucose monitoring (CGM) data from the patients included in the previous study which have completed 1-year observation period. The study population consisted of 74 patients, 42 Minimed 780G users and 32 Tandem Control-IQ users. Linear mixed models with random intercept were performed to study the variations over time and the interaction between time and system; Mann-Whitney or T-test were used to compare systems at 1-year.

Results: Both systems have been shown to be effective in maintaining the glycemic improvement achieved one month after starting AHCL. Significant changes over time were observed for TIR, TAR, TAR>250mg/dl, average glucose levels and SD ($p<0.001$). At 1-year follow-up Minimed 780G obtained better improvement in TIR ($p<0.001$), TAR ($p=0.002$), TAR>250mg/dl ($p=0.001$), average glucose levels ($p<0.001$). The comparison of the glycemic parameters at 1-year showed a significant superiority of Minimed 780G in terms of TIR (71% vs 68%; $p=0.001$), TAR ($p=0.001$), TAR>250 ($p=0.009$), average glucose levels($p=0.001$) and SD ($p=0.031$).

Conclusions: The use of AHCL systems led to a significant improvement of glycemic control at 1-month, which is maintained at 1-year follow-up. MiniMed is more effective than Tandem in reaching the International recommended glycemic targets. Continuous training and education in the use of technology is essential to get the best out of the most advanced technological tools.

KEYWORDS

AHCL (Advanced Hybrid Closed Loop), type 1 diabetes, CGM – continous glucose monitoring, TIR (time in range), CSII - continuous subcutaneous insulin infusion

1 Introduction

The management of type 1 diabetes (T1D) has changed substantially over the past ten years. Evolving technologies offer the potential to highly improve glycemic control. Systems which integrate insulin infusion with continuous glucose monitoring (CGM) are now widely used by T1D patients (1–5).

Advanced Hybrid Closed Loop (AHCL) systems combine automated basal rate and correction boluses to keep glycemic values in a target range. Patients are only required to estimate carbohydrate consumption for meal boluses (6, 7). In Italy two AHCL systems are provided for both adult and pediatric populations by the national health system: the Tandem t:slim X2 Control IQ™ system (Tandem Inc., San Diego, California); and the Minimed™ 780G system (Minimed Medtronic, Northridge, California). The Minimed 780G pump is integrated with the Guardian Sensor 4 (Medtronic, Northridge, California), the Tandem Control-IQ is associated with the Dexcom G6 (Dexcom Inc., San Diego, CA) system.

These two systems use different algorithms for basal rate infusion and correction boluses and different glycemic targets. Minimed 780g uses a PID (proportional-integrative-derivative) algorithm. This algorithm adjusts the insulin infusion based on the glycemic trend of the previous few minutes, evaluating: the difference between blood glucose levels measured at in a certain moment and the blood glucose target (proportional component), the difference between the area under the curve of the measured blood glucose level and the blood glucose "target" (integral component) and the speed and direction of change in glucose values (derivative component). Tandem Control-IQ uses a model predictive control (MPC) algorithm. This algorithm predicts glucose levels in the future by minimizing the difference between predicted glucose values and those measured in a given period of time, it "learns" how to autonomously respond to glycemic changes with optimal insulin infusion regimens and it is proactive (anticipates the glucose-lowering effect of insulin).

Minimed 780G can carry out up to 12 correction boluses per hour and decide the basal rate automatically. Control-IQ system is able to deliver a maximum of one correction bolus per hour and modifies the basal profile based on a 30-minute prediction horizon of glucose levels. Both systems have special modes dedicated to sport and physical activity and Control-IQ has a Sleep mode with a narrower target range. Furthermore, Minimed 780G system automatically calculates the total daily insulin need in order to define the insulin sensitivity factor (ISF); the patient can only customize the insulin-to-carbohydrate (I/CHO) ratios for meal boluses, the active insulin time (AIT) and the glycemic target used by the algorithm (SmartGuard). Control-IQ system uses fixed AIT of 5h; the user can change the basal rate, ISF and I/CHO ratios for meal boluses.

Currently, the CGM parameters indicating a good glycemic control are defined by the International Consensus as: Time in Range (TIR) (70-180 mg/dl) > 70%, Time Below Range (TBR) (<70 mg/dl) < 4%, TBR<54 mg/dl < 1%, Time Above Range (TAR) (>180 mg/dl) < 25%, TAR>250 mg/dl <1% (8, 9).

Early studies on the use of Tandem Control-IQ or Minimed 780G in adolescents and adults with type 1 diabetes have shown excellent results in terms of glycemic outcomes and patient satisfaction (10, 11). The results of 6-month and 1-year real-world use of Tandem Control-IQ system confirmed the conclusions reached by the pivotal trial, showing an increase in time in range (TIR 70–180 mg/dl) up to 73.5% at 12 months in a large sample of T1D patients (12, 13). Several multicenter studies conducted in children, adolescents and adults demonstrated the efficacy of Control-IQ compared to sensor-augmented pumps (14–16) and to PLGS algorithm (17). Two recent studies have demonstrated the efficacy of Tandem Control-IQ even in T1D patients with poor baseline glycemic control and in T2D (Type 2 Diabetes) and regardless of users' engagement with the system or type of medical insurance (18–20).

Likewise, the use of Minimed 780G system has shown to be safe and effective and leads to an improvement of glycemic control in both the adult and pediatric populations and regardless of previous insulin strategy and baseline glucose control (21–28). A recent real-world study on 6-month-use of Minimed in more than 12000 adult and pediatric T1D patients showed that more than 75% of users achieved international consensus-recommended glycemic control (29).

Despite the evidence on the efficacy of ACHL systems, there are only two clinical studies comparing data on benefits and glycemic outcomes after 1-month of use of Minimed 780G and Tandem Control-IQ. In both studies, the use of AHCL systems led to a significant improvement of glycemic control (30, 31). The first study involved 90 adult and pediatric patients and results showed Minimed more effective in managing hyperglycemia and Tandem more effective in reducing hypoglycemia (30). Schiaffini et al. compared the two AHCL systems in 31 pediatric patients and their results did not show significant differences in glycemic control between the two systems (31). To our knowledge, there are no clinical studies comparing data on benefits and glycemic outcomes after a longer follow-up.

The aim of our study was to evaluate glycemic control after 1-year of follow-up extending our previous study of 1-month comparison between the two systems (30).

2 Materials and methods

A retrospective dual center study was performed from October 2020 to October 2021. A total of 90 T1D patients, followed at the IRCCS G.Gaslini Pediatric Diabetology Center (Genoa, Italy) or San Martino Polyclinic Hospital Diabetes Clinic (Genoa, Italy), were upgraded to Minimed 780G or Tandem Control-IQ. This is a follow-up study; results from the previous one-month comparison study have already been published (30).

Patients were enrolled according to the following inclusion criteria: T1D diagnosis at least one-year prior to the study, insulin therapy with CSII or MDI, use of CGM with at least one-months' worth of data before and after starting the AHCL. Patients who dropped out of the AHCL system before one year of use and/or of whom we were unable to download glycemic data at T2 were excluded. Patients who were affected by other types of diabetes or had been using AHCL systems since disease onset were also excluded.

The observational period was divided in Time 0 (T0 – first use AHCL) and Time 2 (T2 – one year of ACHL therapy). At T0, the following data were collected for each patient: demographical data (sex, date of birth, age), age at clinical onset of T1D, duration of disease, previous type of insulin therapy, glycated hemoglobin value

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and general glycemic control data. At T0 and T2 we compared: glycated hemoglobin (HbA1c) values, and blood glucose control data of the previous 14 days, through the CGM data download. The following parameters were evaluated: TIR, TAR, TAR > 250 mg/dl, TBR, TBR < 54 mg/dl, Coefficient of Variation (CV), Standard Deviation (SD) and time of sensor use. The analysis at T2 was performed with both systems in Automatic Mode (Control-IQ or SmartGuard). CGM data were collected using data download platforms based on the technology used.

All patients (or parents if age < 18 years) provided a written informed consent in accordance with EU regulation 2016/679 to participate in the study.

2.1 Statistical analysis

Results were reported as median with interquartile range (IQR) for continuous variables and as absolute frequency with percentage for categorical variables, overall and by treatment group.

Comparisons of the baseline characteristics between the two treatment groups were assessed performing Chi-squared or Fisher's exact test (categorical variables) and T-test or Mann-Whitney test (continuous variables) depending on the distribution of the variables.

All the parameters at T0 and T2 were studied performing linear mixed models with random intercept and adjusted for the following baseline variables: age, disease duration, HbA1c and type of previous treatment. To compare the pattern change between the two systems, the interaction between time and system was tested. Transformations were made for some variables due to a skewed distribution (graphically evaluated using histograms and graphs of quantiles against the quantiles of normal distribution). As a sensitivity analysis, the time*system interaction was investigated separately within the subsample of pediatric (age<18 years) and of adult (>=18 years) patients. Additionally, at T2, all the parameters were compared between the two groups using T-test or Mann-Whitney test depending on the distribution of the variables.

Missing data were not imputed, and a complete-case analysis was performed. A two- sided α less than 0.05 was considered statistically significant. All statistical analysis was performed using Stata version 16.0 (Stata Corporation, College Station, TX, USA).

3 Results

We collected the data of 74 patients (38 males, 36 females) from two Regional Pediatric (63 patients) and Adult (11 patients) Diabetology Centers (IRCCS G.Gaslini and San Martino Polyclinic Hospital, Genoa, Liguria). 42 of these patients used the Minimed 780G system and 32 the Tandem-Control IQ system. 16 patients, part of the initial trial, were excluded from this extended one because data download was unavailable at T2. The clinical characteristics of the population at baseline (T0) are summarized in Table 1, overall and divided by type of treatment.

TABLE 1 Patient characteristics at baseline (T0), overall and by treatment group.

	Overall N = 74 (100%)	Minimed 780G N = 42 (57%)	Control-IQ N = 32 (43%)	p-value
Male, N (%)	38 (51%)	22 (52%)	16 (50%)	0.8390
Age, Median (IQR)	17.2 (11.5; 26.1)	22.1 (11.8; 31.0)	15.5 (10.5; 19.9)	0.0141
Disease duration (yrs), Median (IQR)	9.8 (4.5; 17.4)	13.0 (5.0; 19.7)	7.4 (2.4; 11.0)	0.0133
HbA1c (%), Median (IQR)	7.4 (7; 7.8)	7.6 (7.2; 8)	7.3 (6.7; 7.7)	0.0015
TIR (%), Median (IQR)	55 (45; 63)	53.5 (43; 63)	55.5 (49.5; 66)	0.0905
TAR (%), Median (IQR)	27 (21; 34)	28.5 (22; 34)	26 (21; 30)	0.0855
TAR250 (%), Median (IQR)	13 (6; 23)	13.5 (6; 25)	12.5 (6.5; 18)	0.5468
TBR (%), Median (IQR)	1 (1; 4)	1.5 (1; 4)	1 (1; 4)	0.5184
TBR54 (%), Median (IQR)	0.1 (0; 1)	0.1 (0; 1)	0.2 (0; 1)	0.7073
Average glucose (mg/dl), Median (IQR)	174 (161; 190)	177 (162; 195)	174 (151.5; 181.5)	0.1970
SD (mg/dl), Median (IQR)	62.5 (51; 71)	60.5 (51; 74.5)	64 (53; 67)	0.6278
CV (%), Median (IQR)	36 (33; 40)	35 (31.3; 39)	37.6 (34.6; 40.7)	0.2584
Time Active CGM (%), Median (IQR)	95 (88; 98.3)	92.9 (85; 96)	98 (95; 98.9)	0.0005
Previous treatment, N (%)				<0.001
MDI	13 (18%)	7 (17%)	6 (19%)	
SAP	18 (24%)	11 (26%)	7 (22%)	
PLGS	28 (38%)	9 (21%)	19 (59%)	
HCL	15 (20%)	15 (36%)	0 (0%)	

IQR, Interquartile Range; HbA1c - Glycated Hemoglobin; TIR, Time in Range (70-180 mg/dl); TAR, Time Above Range (181-250 mg/dl); TAR250, Time Above Range (>250 mg/dl); TBR, Time Below Range (54-69 mg/dl); TBR54, Time Below Range (<54 mg/dl); SD, Standard Deviation; CV, Coefficient of Variation; CGM, Continuous Glucose Monitoring; MDI, Multiple Daily Injections; SAP, Sensor Augmented Pump; PLGS, Predictive Low Glucose Suspend; HCL, Hybrid Closed Loop. Bold values indicates statistically significant.

The median age of our population was 17.2 years (IQR=11.5; 26.1): Control-IQ users were younger (median age 15.5 years vs 22.1; p=0.0141) and had shorter disease duration (median 7.4 years vs 13.0; p = 0.0133). Patients in Control-IQ group compared to patients in Minimed 780G group had lower baseline HbA1c (7.3% vs 7.6%; p=0.0015).

The whole study population had been previously treated with MDI – Multiple Daily Injections (18.0%), SAP - Sensor Augmented Pumps (24%), PLGS – Predictive Low Glucose Suspend pumps (38%) or HCL – Hybrid Closed Loop pumps (20%).

There were no significant differences between the two groups at baseline when analyzing glycemic parameters; except for time of sensor use that was significantly higher in Control-IQ users (98% vs 92.9%; p=0.0005).

The longitudinal comparison between the two devices is shown in Figure 1 and in Figure 2.

We observed significant variations over time in TIR (p<0.001), TAR (p<0.001), TAR>250mg/dl (p<0.001), average glucose levels (p<0.001) and SD (p<0.001). "Almost significant" differences were observed for TBR and CV (respectively: p=0.086 and p=0.071). No significant variations were found for TBR<54mg/dL (p=0.192) (Figure 1).

The evaluation of ΔT0-T2 brought out the following significant differences between the two devices: MiniMed is more effective than Control-IQ in improving TIR (p<0.001), TAR (p=0.002), TAR>250mg/dl (p=0.001) and average glucose levels (p<0.001), No significant differences were found between the two devices for SD (p=0.082), CV (p=0.821), TBR (p=0.990) and TBR<54mg/dL (p=0.242) (Figure 2). As a sensitivity analysis, the interaction was also assessed within pediatric (age<18: N=38; Minimed 780G: N=18 (47%), Tandem-Control IQ: N=20(53%)) and within adult (age>=18: N=36; Minimed 780G: N=24(67%), Tandem-Control IQ: N=12 (33%)) patients. Results remained consistent between the two groups except for TAR (p=0.245 and p=0.006 respectively) (Supplementary Table 1).

The comparison of the two devices at T2 is illustrated in Table 2. Both devices improved glycemic control parameters. At T2 TIR is higher in MiniMed patients than in Control-IQ patients (71% vs 68%; p=0.001); TAR>250mg/dL (4.5% vs 9%; p=0.009) and TAR (20% vs 21%; p=0.001) are lower in MiniMed patients. Average blood glucose levels (148.5 mg/dL vs 162 mg/dL; p=0.001) and SD (50 mg/dL vs 58 mg/dL; p=0.031) are lower in MiniMed patients. There are no significant differences between the two groups when considering TBR, TBR<54mg/dL and CV.

4 Discussion

The aim of this study was to compare real-life glycemic control data between Minimed 780G and Tandem Control-IQ users one year after starting the system. To the best of our knowledge, this is the first study to compare efficacy and safety of the AHCL systems currently available in Italy in children and adults with T1D over such a long period of time.

Schiaffini et al. (31) carried out another study only on pediatric patients affected by T1D and compared the efficacy of Minimed 780G and Control-IQ in improving glycemic control 1-month after starting the devices. Their results are similar to ours when considering the rapidity with which AHCL devices improve glycemic control, but they don't highlight significant differences between the two devices evaluated; therefore, according to their study, they appear to be equivalent after 1-month of therapy.

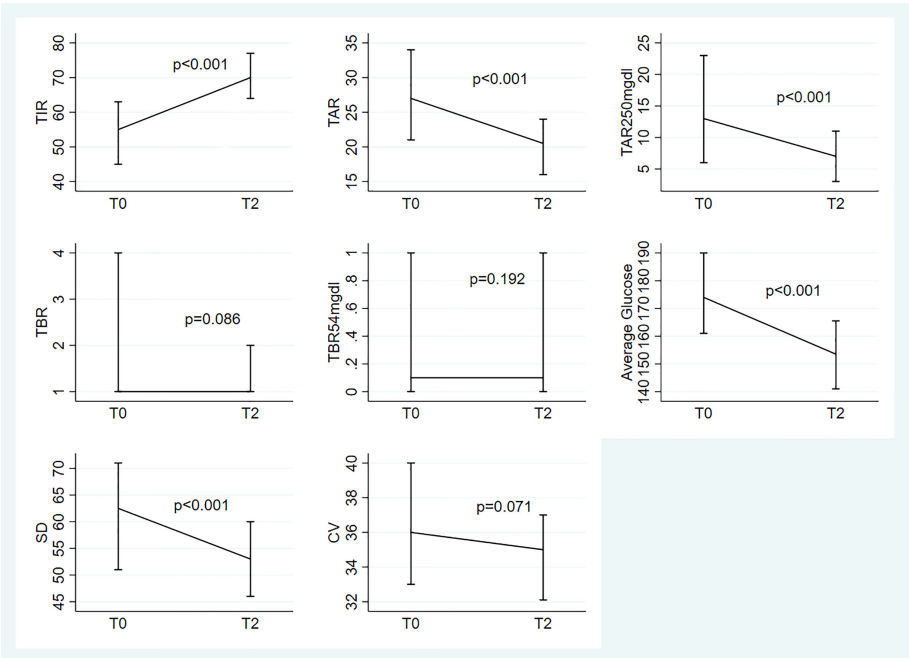

FIGURE 1
Median(IQR) at To and T2 for the 8 parameters under study; evaluation of the change from T0 based on the linear mixed models with random intercept adjusted for the following baseline variables: age, disease duration, HbA1c and type of previous treatment.

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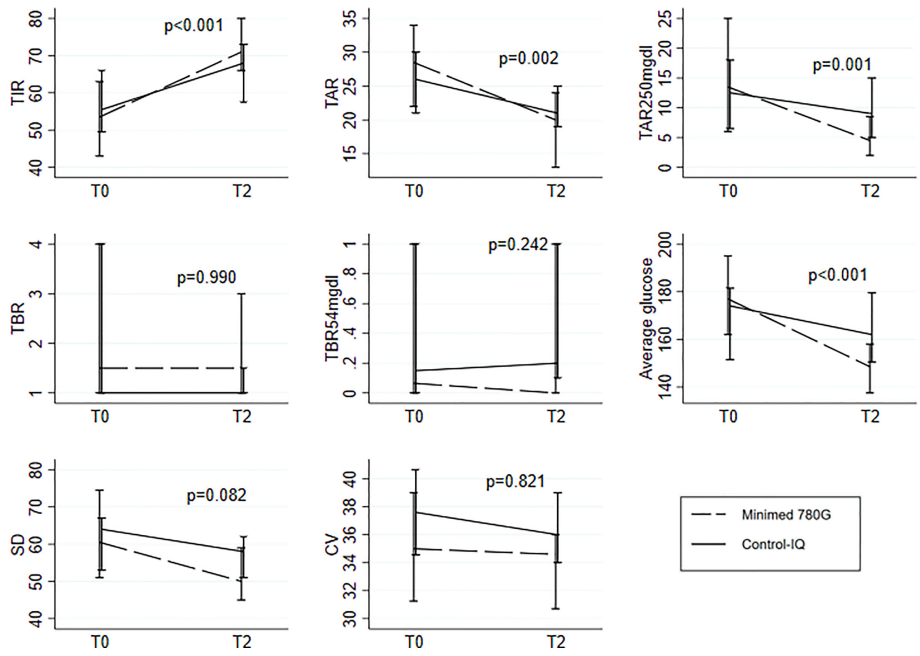

FIGURE 2
Median(IQR) at To and T2 for the 8 parameters under study separately for the two systems; comparison of the pattern change between the two groups testing the Time-Group interaction in the linear mixed models with random intercept. All the models were adjusted for the following baseline variables: age, disease duration, HbA1c and type of previous treatment.

Considering our previous 1-month study, the results are only partially confirmed at one-year follow up (30): Minimed 780G still appears to be superior in managing hyperglycemia, whereas we couldn't confirm Control-IQ's superiority in reducing glycemic variability and hypoglycemic events. Minimed 780G is still more efficient in improving TIR and reducing average blood glucose levels. Both devices improve glycemic control significantly. Minimed 780G achieves all targets recommended by the International Consensus at T2, whereas Control-IQ is slightly below target when considering TAR>250mg/dl (9%) and TIR (68%). Minimed is significantly more efficient than Control-IQ when considering average blood glucose levels, TIR, TAR and TAR>250mg/dl.

Despite the differences between the two devices in terms of effectiveness, there is an important age difference and disease duration between the two groups. Control-IQ users are younger and have a shorter disease duration. This is inevitable considering that all Control-IQ users were followed by Giannina Gaslini Pediatric Institute Diabetology Center. Of course, this data must be considered while we discuss the results of the study, because childhood and adolescence are certainly more critical moments in the management of glycemic control than adulthood due to physiological (eg. hormonal changes) and environmental (eg. lifestyle) factors. Furthermore, a shorter disease duration could correspond to less-skilled patients in the management of T1D. The slight inferiority of Tandem in the improvement of glycemic parameters and in the targets obtained at T2 must also be considered in relation of this data.

TABLE 2 Treatment effects overall and by group at T2.

	Overall	Minimed 780G	Control-IQ	p-value
TIR (%), Median (IQR)	70 (64; 77)	71 (66; 80)	68 (57.5; 73)	0.001
TAR (%), Median (IQR)	20.5 (16; 24)	20 (13; 24)	21 (19; 25)	0.001
TAR>250mgdl (%), Median (IQR)	7 (3; 11)	4.5 (2; 8.5)	9 (5; 15)	0.009
TBR (%), Median (IQR)	1 (1; 2)	1.5 (1; 3)	1 (1; 1.5)	0.381
TBR<54mgdl (%), Median (IQR)	0.1 (0; 1)	0 (0; 1)	0.2 (0.1; 1)	0.447
Average glucose (mg/dl), Median (IQR)	153.5 (141;165.5)	148.5 (137.5;158)	162 (150.5;179.5)	0.001
SD (mg/dl), Median (IQR)	53 (46; 60)	50 (45; 59)	58 (51; 62)	0.031
CV (%), Median (IQR)	35 (32.1; 37)	34.6 (30.7; 36)	36 (34; 39)	0.620
Time Active CGM (%), Median (IQR)	96 (90; 98)	93.5 (85; 97)	98 (94; 99)	0.0001

TIR, Time in Range (70-180 mg/dl); TAR, Time Above Range (181-250 mg/dl); TAR250, Time Above Range (>250 mg/dl); TBR, Time Below Range (54-69 mg/dl); TBR54, Time Below Range (<54 mg/dl); SD, Standard Deviation; CV, Coefficient of Variation; CGM, Continuous Glucose Monitoring. Bold values indicates statistically significant.

Another interesting result to discuss regards the CGM use; MiniMed 780G is in disadvantage when compared to Control-IQ in terms of time of sensor use. Our interpretation of this result is based on the fact that MiniMed 780G users were all using Guardian 3 at the time of the study. Guardian 3 sensor requires capillary glycemia calibrations twice daily and SmartGuard (automatic mode) is deactivated by the system if no calibrations are performed. On the other hand, Control-IQ users use Dexcom G6 sensor that doesn't require calibrations. This could mean that the Tandem users have had less possibility of deactivation of automatic mode (Control-IQ) than the Minimed users (SmartGuard). Minimed 780G could be even more effective in improving glycemic control using the new Guardian 4 sensor which does not require calibration to run the system in automatic SmartGuard mode.

Comparing the results of our previous 1-month study and this 1-year follow-up study, even if Minimed 780G appears to be more effective, especially over a longer period, both devices better improve glycemic control in the first month of treatment and then this tends to stabilize over the following months; glycemic parameters don't improve ulteriorly, on the contrary they may even slightly worsen. This could be due to the fact that the patients were followed more attentively after positioning the new pump since follow-up visits are more frequent. Furthermore, positioning a new pump is a moment of great change for the patients, characterized by motivation, thrive to improve and major attention to treatment regimens and glycemic control. In our opinion, it is very important to reinforce the patient's motivation to take better care of themselves and perform frequent retraining during the follow-up visits on the correct use of the devices and their functionality and potential. This constant reinforcement of patient education and technological support can be fundamental in maintaining the improvement in glycemic control achieved 1-month after starting the device and in creating possibilities for further improvement in glycemic control over time.

A limitation of our study is the number of the study population. Due to the nature of the extended study, no sample size calculation was performed since all the patients with available T2 data were included and the sample was smaller when compared to our first study. The 16 patients who weren't included in this extended study continued using AHCL system but weren't available for follow-up visits and data download at T2. Another limitation of this study is the heterogeneity between the two groups due to the nature of the study (no randomization). There are two main limitations concerning age: wide age-range of patients involved and the difference of age between the two groups. To take into account these design issues, we adjusted the models for baseline confounders and we presented a sensitivity analysis separately for pediatric and adult patients. However, further studies involving a greater number of patients and with a more uniform age and characteristics between the comparison groups are necessary. Furthermore, it would be interesting to evaluate the glycemic parameters obtained by Minimed 780G in association with the Guardian 4 sensor.

In conclusion, both AHCL systems improve glycemic control, even after just one month of treatment. After 1-month of AHCL use, further improvement in glycemic control was not observed. Minimed 780G is slightly superior to Tandem Control-IQ in improving glycemic control at 1-year follow-up.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

BM designed the study and wrote the manuscript, PL designed the study and wrote the manuscript, SI researched data, SF researched data and reviewed the manuscript, PM did statistical analysis, MN designed the study and contributed to the discussion, MD designed the study and contributed to the discussion. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1099024/full#supplementary-material

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Efficacy of unblinded and blinded intermittently scanned continuous glucose monitoring for glycemic control in adults with type 1 diabetes

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Objective: Intermittently scanned continuous glucose monitoring (isCGM) is used for unblinded or blinded monitoring of interstitial glucose. We aimed to compare the efficacy of blinded and unblinded isCGM with the FreeStyle Libre system for glycemic control in adults with type 1 diabetes (T1D).

Research design and methods: This randomized clinical trial conducted between October 2018 and September 2019 across four endocrinology practices in China included 273 adults aged ≥18 years with T1D, who were randomly divided in a 2:1 ratio into the unblinded (n = 199) or blinded isCGM group (n = 78). In the blinded group, the clinician used FreeStyle Libre Pro system for monitoring, but self-monitoring was also performed by the patients.

Results: Two hundred sixteen (78%) participants completed the study (152 [75%] in the unblinded and 64 [82%] in the blinded group). At 12 weeks, a significant increase in TIR (3.9-10.0 mmol/L) was only observed in the unblinded group, along with a significant decrease in hyperglycemia (>13.9 mmol/L), hypoglycemia (<3.0 mmol/L), glycemic variability. Further, the mean HbA1c reduction from baseline to 12 weeks was 0.5% in the unblinded isCGM group and 0.4% in the blinded isCGM group respectively (P < 0.001), but the significance did not remain after adjustment for between-group differences. Finally, 99.5% of the blinded isCGM values and 93.8% the of unblinded isCGM values were obtained at the final visit.

Conclusions: The unblinded isCGM system was associated with benefits for glucose management, but nearly 100% of the attempted profiles were obtained successfully with the blinded isCGM system. Thus, combining real-time and retrospective data with isCGM might be the most impactful way to utilize flash glycemic monitoring devices.

KEYWORDS

clinical trial, continuous glucose monitor, sensors, type 1 diabetes, blinded and unblinded

Introduction

Monitoring of glucose levels is essential for effective management of type 1 diabetes (T1D). Self-monitoring of blood glucose (SMBG) with glucose meters remains the mainstay of glycemic monitoring in T1D. However, this method can only provide point-in-time measurements of current glucose levels and does not indicate the trend in glucose levels. Therefore, silent glucose excursions could be missed with the SMBG method. In contrast, methods for continuous glucose monitoring (CGM) have been shown to have significant benefits in improving glycemic control in patients with type 1 and type 2 diabetes (1–3). In particular, they can help reduce the risk of hypoglycemia and hyperglycemia in patients with T1D (4–7).

CGM is an important adjunctive data collection strategy that provides a comprehensive 24-h glycemic profile compared to the relatively sparse information available with SMBG. Currently, three types of CGM devices are used in clinical practice: retrospective systems, real-time systems, and flash or intermittently viewed systems (8). Retrospective CGM systems are typically used in a blinded manner over a 3- 7 days wear period, and the data are reviewed retrospectively by clinicians. Real-time CGM devices are also used for short-term monitoring, but they are used in an unblinded manner. The data obtained enable patients and clinicians to respond to medication requirements in a timely way in order to prevent acute glycemic events, and the data are also useful in other areas of their daily diabetes self-management (9). Intermittently scanned CGM (isCGM) was developed for continuous monitoring of interstitial glucose and has a longer sensor life of 14 days, and it is often referred to as flash glucose monitoring.

FreeStyle Libre Flash Glucose (Abbott Diabetes Care, Alameda, CA) is the only isCGM system that is currently commercially available. The device is factory calibrated and does not need calibration against SMBG data over the course of the 14-day wear time. The use of isCGM has been associated with an increase in the amount of time in range (TIR), lower glycemic variability in randomized controlled trials with T1D cohorts, and reductions in hypoglycemia. Unlike real-time CGM systems that automatically transmit data to the patient's receiver, isCGM requires the patient to swipe the receiver close to the sensor to obtain current and historical glucose data every 8 h (8). If there is a gap of more than 8 h between scans, only the data over the most recent 8 h will be retained and available for review. Overall, isCGM technology has made the collection, transmission, and monitoring of glucose data convenient.

The FreeStyle Libre Pro system for clinicians (blinded isCGM), which is available only in China, can automatically transmit data to the patient's receiver; this method does not require the patient to scan the reading every 8 h and provides blinded retrospective data for up to 14 days (10). However, blinded CGM has not been convincingly proven to improve glycemic control (11, 12). Flash glycemic monitoring has been shown to improve glycemic control in adults with T1D, but no study so far has demonstrated the efficacy of blinded and unblinded isCGM in glycemic control. Person-reported outcomes (PROs) are usually assessed as secondary outcomes in glycemic technology studies. PROs show that the use of isCGM in adolescents can improve diabetes related distress with validated questionnaires. isCGM which allows greater benefits on psychological outcomes (13). However, several studies showed contradictory findings improvements associated with the use of glycemic technologies (14). In the current randomized study, for the first time, we have explored clinically meaningful data to determine the degree of agreement between the blinded and unblinded isCGM systems for T1D management in the real-world setting. Moreover, we used PRO to explore the benefits of technologies on psychological outcomes.

Methods

Study design and participants

Adults with T1D were consecutively recruited for this 12-week, multi-center, prospective, 2:1 randomized controlled trial (Figure 1). The participants were recruited from four endocrinology practices in China, including Beijing Hospital, Peking Union Medical College Hospital, the First Affiliated Hospital of Nanjing Medicine University, and the First Affiliated Hospital of Harbin Medicine University.

The major eligibility criteria were clinical diagnosis of T1D, age ≥18 years, use of insulin therapy, and no use of CGM in the 3

months prior to enrollment. Willingness to participate in a 2-week screening period and use the blinded isCGM system were other inclusion criteria. In addition, the individual was required to perform SMBG at least four times a day (before every meal and before sleeping) with the blinded isCGM device.

The exclusion criteria were current or previous use of CGM or sensor-enhanced insulin pump therapy; known allergy to medical-grade adhesive; adverse events that endanger life or could cause death and serious systemic diseases; known severe diabetic retinopathy and/or macular edema; lactation, pregnancy, or intention to become pregnant during the study; presence of any condition that is likely to require MRI; use of medication containing acetaminophen or vitamin C; and unwillingness to use the study device.

During the study period, all the patients were free to use unblinded isCGM real-time glucose values or SMBG to adjust their diet, physical activity, and insulin therapy. All participating centers provided ethical approval for the study prior to its commencement, and all the participants provided their written informed consent.

Procedures

This study was scheduled to include a total of six clinic visits—from the screening visit to the final visit (Figure 1). At the screening visit, the investigators obtained information about the medication history of the participants, preformed a physical examination, and completed patient-reported outcome assessments including AST, ALT, eGFR, urinary human chorionic gonadotropin, and electrocardiogram readings. A 2-h mixed meal tolerance test was performed, and blood samples were obtained for laboratory analysis of relevant parameters, including HbA1c, plasma glucose (glucose oxidase method, which was performed at each participating institute) and C-peptide (chemiluminescence analysis, which conducted at the central laboratory), at three time points (0 min, 60 min, and 120 min). Participants filled out the Chinese version of the scale for diabetes self-care activities (SDSCA), diabetes distress scale (DDS), hypoglycemia fear survey (HFS-II), and hypoglycemic confidence scale (HCS). At the second, fourth, and sixth visit, participants again underwent the physical examinations and completed the SDSCA, DDS, HFS-II, and HCS questionnaires. HbA1c was measured at the central laboratory in a randomized way and at 12 weeks, with the high-performance liquid chromatography method.

Over the 2-week measurement period, the eligible participants were randomly divided in a 2:1 ratio *via* a computer-generated sequence into the blinded isCGM group (clinician FreeStyle Libre Pro system), in which patients could use fingerstick blood glucose meter checks as needed, and the unblinded isCGM group (FreeStyle Libre system). The blinded isCGM group used the fingerstick blood glucose test data for management of glucose levels, while the unblinded isCGM group was required to scan the sensor at least three times a day. The participants, investigators, and staff were not blinded to the group allocation.

At each visit, participants in both study groups provided sensor glucose data, and the sensor was replaced. They also provided information about their daily diet, exercise, adverse events, and sensor insertion-site symptoms. Further, they received general diabetes management education and were provided with

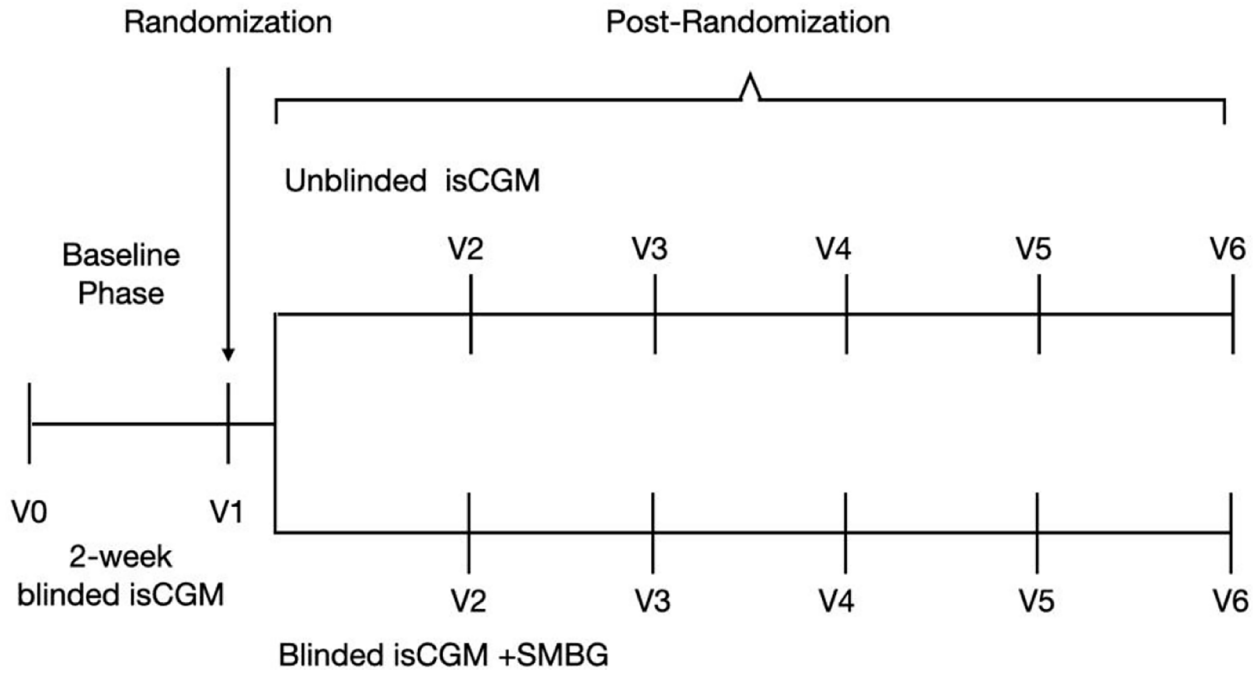

FIGURE 1
Study flow in a study of the efficacy of unblinded and blinded intermittently flash continuous glucose monitoring on glycemic control in adults with type 1 diabetes.

individualized treatment recommendations based on their glucose data (isCGM and SMBG data). Participants completed patient-reported outcome assessments prior to randomization and at 12 weeks.

Outcomes

Outcomes were calculated at the follow-up visit based on data pooled over the 14-day measurement period after the screening visit and the 14 days prior to the final visit. The primary outcome was TIR or the percentage of time during which the glucose level was in the target range of ≥3.9-≤10 mmol/L from baseline to 12 weeks (15).

Secondary outcomes were changes in the percentage of time in which glucose level was in the range of >10.0- ≤13.9 mmol/L, > 13.9 mmol/L, in the range of ≥3.0-<3.9 mmol/L, and <3.0 mmol/L; coefficient of variation (CV); standard deviation (SD) and mean amplitude of glycemic excursions (MAGE); and HbA1c. The other secondary outcomes included patient-reported outcomes, namely, changes in daily dietary calories and proportions of carbohydrates and fat; changes in the number of daily steps; and changes in the SDSCA, DDS, HFS-II, and HCS scores.

The safety objective was to evaluate the safety of wearing the FreeStyle Libre Flash Glucose Monitoring System device in patients with T1D. Reportable adverse events included severe hypoglycemia (defined as an event that required assistance from another person due to altered consciousness), adverse events regardless of causality, and serious adverse events that require hospitalization, prolong hospitalization, cause disability, endanger life or result in death, or result in birth defects.

Statistical analysis

A sample size of 216 participants was determined to detect a between-group difference in the target range (3.9–10 mmol/L), assuming a significant difference of an α-level of 0.05, power of 80% (β = 0.2), and a SD of 14. This number was increased to 270 participants to account for 20% with missing follow-up data.

All participants were analyzed according to their randomization group and included in the primary analysis. For the primary analysis, differences in the primary and secondary CGM outcomes between the final visit and screening visit in the two groups were assessed using paired *t*-tests. Missing data were managed with the direct likelihood method, which maximizes the likelihood function integrated over possible values of the missing data.

Analyses of prespecified secondary outcomes were conducted in parallel with the analysis of the primary outcome (CGM data were pooled across follow-up time points). Analysis of covariance was used to adjust for chance imbalances in baseline measurements between the treatment groups. Modification of the treatment effect by baseline variables was assessed by including an interaction term in the primary model. Secondary outcomes were analyzed by analysis of covariance of the differences between post-baseline and baseline values with study center, diabetes duration, baseline BMI, baseline SD, and baseline HbA1c as covariates in the two groups. Confidence intervals were calculated for the group least-square mean of each measure and the difference between group least-square means. Two-sided statistical tests were performed, and a significance of 0.05 was used in all tests.

The results were reported as the mean ± SD [minimum, maximum] or documented as the constituent ratio. Analyses were conducted with the SPSS 23.0 software.

Results

Clinical characteristics of the study participants

From October 2018 to September 2019, a total of 273 eligible participants were randomly assigned to the unblinded isCGM (n = 199) group or the blinded isCGM group (n = 78). The 12-week visit was completed by 152 participants (75%) in the unblinded isCGM and 64 participants (82%) in the blinded isCGM group (Figure 2).

The included participants had comparable baseline characteristics (Table 1): There was no significant difference in age (mean = 40.8 years [range = 18–77] versus 42.6 years [range = 19–71]), duration of diabetes (mean = 10.0 years [range = 0–52.2] versus 10.2 years [range = 0.3–32.1]), proportion of females (58.8% versus 62.5%), use of multiple daily injections (80.3% versus 79.7%), HbA1c (mean ± SD = 8.0 ± 1.8% versus 7.7 ± 1.7%), and C-peptide levels (mean ± SD = 0.2 ± 0.4 ng/mL versus 0.2 ± 0.4 ng/mL) between the unblinded isCGM group and the blinded isCGM group (P > 0.05 for all the variables). No episodes of severe hypoglycemia or diabetic ketoacidosis were reported.

Comparison of scanning frequency and intra-day patterns

With regard to data reporting, 99.5% of the blinded isCGM values and 93.8% of the unblinded isCGM values were obtained at the final visit (Figure 3). Scanning was performed four times more often during typical awake hours (6 AM to 12 AM) than during typical sleeping periods (12 AM to 6 AM). Scanning was most frequently performed between 8 and 10 PM, while the frequency was the lowest at 2–3 AM. The pattern of daily scanning is shown in Figure 4.

Glycemic metrics

The mean TIR percentage between 3.9 and 10 mmol/L was 55.2% at the baseline and 61.3% at 12 weeks in the unblinded isCGM group, and 57.4% at the baseline and 59.7% at 12 weeks in the blinded isCGM group. The values were significantly higher in the unblinded isCGM group (P < 0.001), but were not significant in the blinded isCGM group (Table 2, Figure 5A).

The percentage of time in which hyperglycemia occurred (>13.9 mmol/L) was 12.8% at the baseline and 8.5% during follow-up in

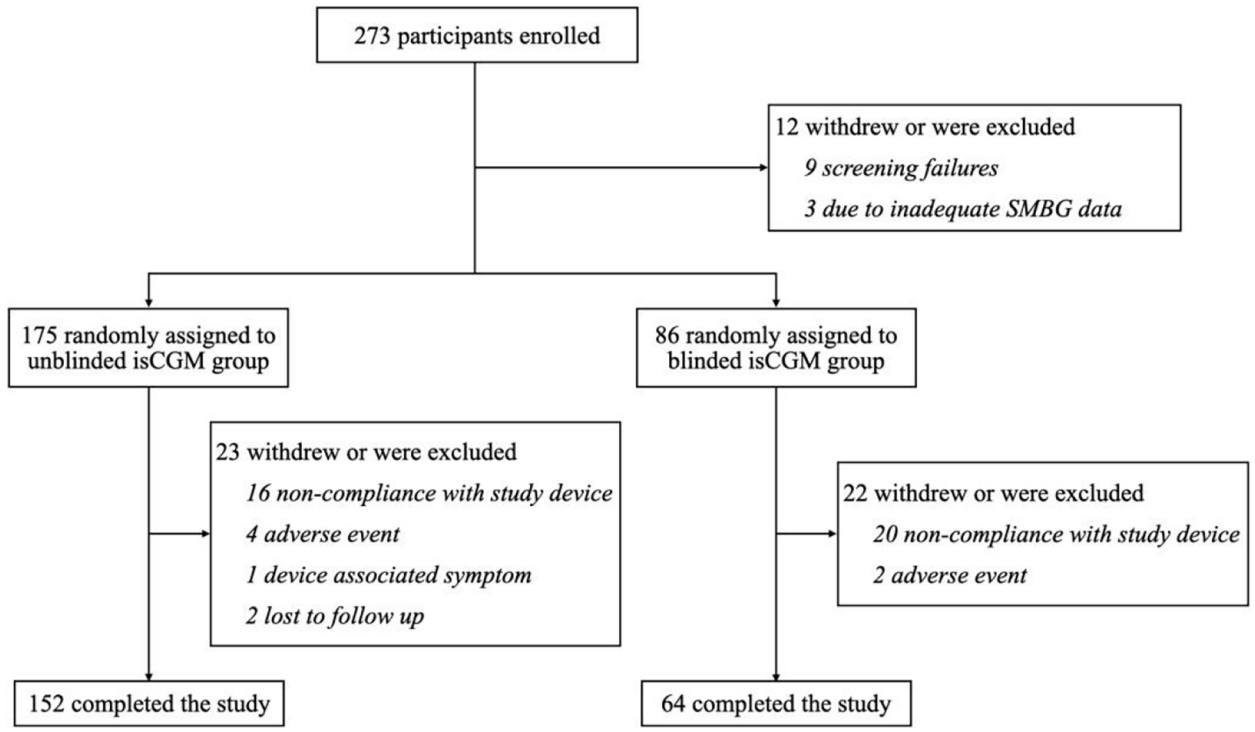

FIGURE 2
flow of participants in a study of the efficacy of unblinded and blinded intermittently flash continuous glucose monitoring on glycemic control in adults with type 1 diabetes.

the blinded isCGM group, and 11.4% at the baseline and 9.1% at 12 weeks in the blinded isCGM group. The mean hyperglycemia time was significantly lower in the unblinded isCGM group ($P < 0.001$), but the difference between the baseline and 12-week values were not significantly different in the blinded isCGM group (Table 2, Figure 5B). The mean percentage of time in which the glucose levels were in the hypoglycemia range (10-13.9mmol/L) was not compare in the two groups (Table 2, Figures 5C, D). The mean percentage of time in the hypoglycemia range (<3.0 mmol/L) was 5.3% at the baseline and 3.4% at 12 weeks ($P = 0.032$) in the

TABLE 1 Baseline characteristics of participants in a study of the efficacy of unblinded and blinded intermittently flash continuous glucose monitoring on glycemic control in adults with type 1 diabetes.

Characteristic	Unblinded isCGM(N=152)	Blinded isCGM (N=64)	P values
Age,year, Mean(SD)[range]	40.8 (14.4) [18-77]	42.6 (14.4) [19-71]	0.406
Diabetes duration, year			
Mean(SD)[range]	10.0 (9.5) [0.0-52.2]	10.2 (9.3) [0.28-32.14]	0.896
Sex			
Female[n(%)]	90 (58.8)	40 (62.5)	0.654
Male[n(%)]	63 (41.2)	24 (37.5)	/
BMI, kg/m^2, Mean(SD)[range]	22.0 (2.5) [16.8-29.2]	21.3 (2.6) [16.7-32.7]	0.068
therapy			
multiple daily injection[n (%)]	122 (80.3)	51 (79.7)	0.923
Insulin pump use[n(%)]	30 (19.6)	13 (20.3)	/
HbA1c, %, Mean(SD)[range]	8.0 (1.8) [5.0-15.2]	7.7 (1.7) [5.3-14.1]	0.256
C-peptide, *Mean(SD)[range]*	0.2 (0.4) [0-2.7]	0.2 (0.4) [0-2.5]	0.980

unblinded isCGM group, but the difference between the baseline and 12-week values were not significantly different in the blinded isCGM group (Table 2, Figure 5E).

The CV (-2.4%), SD (-0.3 mmol/L), and MAGE (-0.7 mmol/L) were significantly lower at 12 weeks in the unblinded isCGM group ($P < 0.001$), but these values did not decrease significantly compared to the baseline in the blinded isCGM group (Figures 5F–H).

Mean HbA1c was 8.0% at the baseline and 7.5% at 12 weeks in the unblinded isCGM group, and it was 7.7% at the baseline and 7.3% at 12 weeks in the blinded isCGM group. HbA1c showed a significant reduction of 0.5% in the unblinded isCGM group and 0.4% in the blinded isCGM group ($P < 0.001$ for both groups) (Table 2, Figure 5I).

After adjusting for between-group differences, no significant difference remained in the effect of the study treatment between the unblinded isCGM and blinded isCGM groups with regard to 12-week TIR, hypoglycemia time, hyperglycemia time, CV, SD, MAGE, and HbA1c ($P > 0.05$) (Table 2).

Psychological questionnaires

The mean diabetes distress percentage was 34.5% at the baseline and 31.5% at 12 weeks in the unblinded isCGM group, and was 33.6% at the baseline and 29.4% at 12 weeks in the blinded isCGM group. Diabetes distress was significantly reduced from the baseline to 12 weeks in both groups ($P < 0.05$). Hypoglycemia fear behavior increased significantly from 8.2% at the baseline to 10.0% at 12 weeks in the blinded isCGM group ($P < 0.05$), but there was no significant change in the unblinded isCGM group. However, hypoglycemic confidence decreased from 18.3% at the baseline to 16.8% at 12 weeks in the unblinded isCGM group ($P < 0.05$). After adjusting for between-group differences, no significant difference remained between the unblinded isCGM and blinded isCGM groups (Table 2).

Self-management questionnaires, steps, and diet

The questionnaire scores for SDSCA did not significantly favor either monitoring system. The number of daily steps was significantly reduced in the unblinded isCGM group (9933.0 ± 4198.4 *vs.* 9143.5 ± 4200.1, $P < 0.05$), while there was no significant difference in the blinded isCGM group (9614.3 ± 4147.9 *vs.* 8920.4 ± 4679.3, $P > 0.05$). There was no significant change in the self-management questionnaire scores for calories, carbohydrates, protein, and fat in either group (Table 2).

Discussion

This prospective, randomized study was conducted to compare the unblinded and blinded isCGM glucose profiles in adults with T1D, and the findings showed that over 12 weeks of isCGM use is beneficial in the management of T1D.

Clinical application of CGM has been generally indicated to result in a significant improvement in diabetes management (8). However, some studies have shown that retrospective CGM systems do not improve glycemic control. A study on 102 patients with T1D

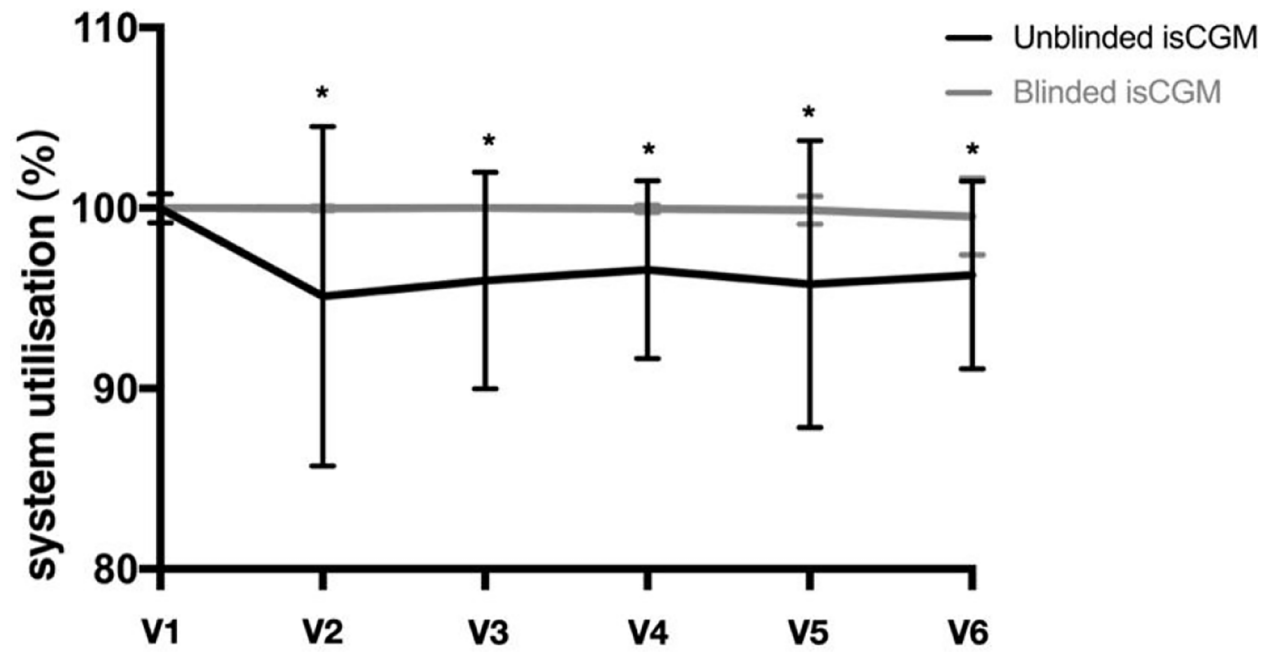

FIGURE 3
Glucose monitoring system utilization in a study of the efficacy of unblinded and blinded intermittently flash continuous glucose monitoring on glycemic control in adults with type 1 diabetes.*P<0.05 between unblinded isCGM and blinded isCGM.

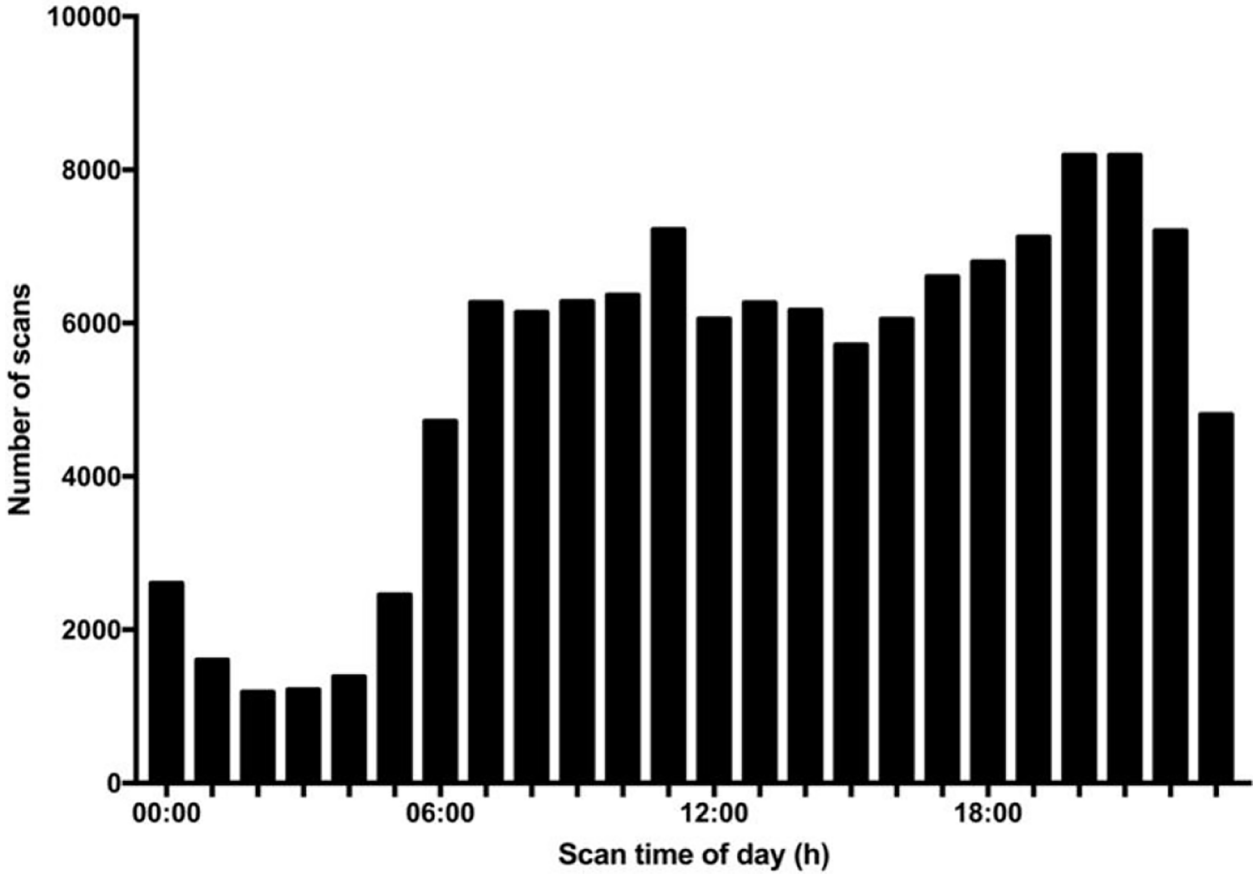

FIGURE 4
Glucose monitoring frequency in a study of the efficacy of unblinded and blinded intermittently flash continuous glucose monitoring on glycemic control in adults with type 1 diabetes. Total number of scans by time of day in the unblinded isCGM.

in a 3-day blinded CGM trial with iPRO (Medtronic, Northridge, CA) did not find any significant improvement in HbA1c for up to 7 months after the CGM device was worn (16). Another study did not find a significant difference in HbA1c levels in patients with T1D when those using SMBG were compared with those using a 72-h blinded CGM device (11). However, retrospective CGM systems have been found to be valuable for collecting detailed glycemic excursion data (17).

Real-time CGM devices enable patients to respond immediately to mitigate or prevent acute glycemic events and allow patients to make better informed decisions about their medication requirements and other areas of their daily diabetes self-management. In the IMPACT study, the use of an intermittently viewed system was associated with a reduction in hypoglycemia as compared with a conventional SMBG device in adults with well-controlled T1D (1, 3). This indicates that increasing the frequency of glucose monitoring is sufficient to reduce hypoglycemic risk, even in the absence of alarms. The isCGM system provides actual and unblinded interstitial glucose concentrations, but the earlier generation of isCGM devices required patients to perform a sensor scan every 8 h. If more than 8 h elapsed between scans, the device would only display a plot profile of the last 8 h. Missing data in the isCGM system cannot be recovered after the fact. Therefore, one of the challenges with this system is to determine whether CGM data collection has been successful in real time versus after the CGM process has been completed.

Unlike unblinded isCGM, blinded isCGM can automatically transmit data to the patient's receiver and provides blinded retrospective data for up to 14 days (10, 18). A key strength of our study was the use of the clinician isCGM systems. So far, no study has reported the efficacy of blinded and unblinded isCGM for glycemic control.

According to recent international consensus, individuals with T1D should strive to achieve 4% of time below the target range (<3.9 mmol/L), >70% of time within the target range (3.9–10.0 mmol/L), and <25% above the range (>10.0 mmol/L), with a glycemic variability (%CV) of <36% (18, 19). In our study, compared with the baseline phase, unblinded isCGM use was associated with a significantly greater TIR percentage, which increased from 55.2% at the baseline to 61.3% at the end of the study. We also found lower values for hyperglycemia time (>13.9 mmol/L), hypoglycemia time (<3.0 mmol/L), CV, SD, and MAGE in the unblinded isCGM users. Further, both isCGM systems resulted in a significant reduction in HbA1c. Taken together, these data indicate that while both blood glucose monitoring methods could improve blood glucose control, unblinded isCGM could increase the TIR while reducing time above

TABLE 2 Glycaemic and glucose variability outcomes in a study of the efficacy of unblinded and blinded intermittently flash continuous glucose monitoring on glycemic control in adults with type 1 diabetes.

	Screening visit		*End visit*		*difference in adjusted means in the unblinded and blinded group*	*P value*
	Unblinded isCGM (N=152)	Blinded isCGM (N=64)	Unblinded isCGM (N=152)	Blinded isCGM (N=64)		
Sensor data						
Percent of isCGM data	99.2 (8.2)	99.9 (0.9)	93.8 (13.8)*	99.5 (2.1) †	-4.7 (-8.8, -0.6)	0.026
Time in range						
Glucose 3.9～10mmol/L (%)	55.2 (20.28)	57.4 (19.56)	61.3 (18.08)*	59.7 (18.94)	3.3 (-2.2,8.82)	0.236
Time in hyperglycemia						
Glucose >13.9mmol/L (%)	12.8 (17.42)	11.4 (16.69)	8.5 (11.01)*	9.1 (13.24)	-0.4 (-4.1,3.4)	0.849
Glucose >10～≤13.9mmol/L (%)	19.8 (11.40)	19.6 (12.23)	20.4 (12.47)	19.3 (12.10)	1.2 (-2.4,4.7)	0.510
Time in hypoglycemia						
Glucose ≥3.0～<3.9mmol/L (%)	6.1 (4.90)	6.1 (5.72)	5.7 (5.02)	5.6 (4.40)	-0.1 (-1.5,1.4)	0.941
Glucose <3.0mmol/L (%)	5.3 (10.79)	5.5 (7.80)	3.4 (4.59)*	4.7 (8.24)	-1.6 (-4.5,1.3)	0.280
Glucose variability						
CV (%)	39.9 (8.4)	38.9 (9.4)	37.5 (7.4)*	37.8 (6.9)	-1.1 (-3.1,0.9)	0.299
SD (mmol/L)	3.4 (1.11)	3.2 (1.11)	3.1 (0.95)*	3.1 (0.91)	-0.05 (-0.3,0.2)	0.692
MAGE (mmol/L)	7.4 (2.30)	6.9 (2.33)	6.7 (2.25)*	6.3 (1.94)	0.1 (-0.5,0.6)	0.799
Number of hypoglycemia events	15.5 (12.2)	11.0 (10.4)	13.2 (11.2)	10.8 (7.5)	-2.4 (-7.1,2.3)	0.318
HbA1c (%)	8.00 (1.78)	7.7 (1.69)	7.5 (1.16)*	7.3 (1.30)*	-0.02 (-0.3,0.2)	0.861
difference in HbA1c compared to baseline<0.5% (n, %)	–	–	126 (82.9)	50 (78.1)	–	0.445
difference in HbA1c compared to baseline<1.0% (n, %)	–	–	144 (94.7)	62 (96.9)	–	0.727
Psychological Quality Questionnaires						
DDS	34.5 (13.4)	33.6 (16.0)	31.5 (15.0)*	29.4 (15.0)*	1.1 (-3.2,5.4)	0.601
HFS-II	10.4 (8.0)	8.2 (6.6)	10.0 (8.2)	10.0 (7.4)*	-2.1 (-4.2,-0.03)	0.046
HCS	18.3 (6.0)	16.0 (7.0) †	16.8 (7.2)*	15.8 (7.4)	0.9 (-3.0,1.3)	0.431
Self Management Questionnaires						
SDSCA	41.1 (12.4)	44.5 (16.4)	42.1 (16.8)	42.6 (17.6)	3.0 (-2.2,8.2)	0.255
Steps	9933.0 (4198.4)	9614.3 (4147.9)	9143.5 (4200.1)*	8920.4 (4679.3)	-338.3 (-1803.4, 1126.8)	0.649
Diet						
Calorie (kcal)	1363.3 (433.1)	1429.2 (418.1)	1396.1 (380.3)	1481.5 (886.5)	113.7 (-16.7,244.1)	0.087
Carbohydrates (%)	51.0 (9.0)	51.8 (8.3)	49.6 (7.5)	49.9 (7.0)	0.6 (-3.1,4.3)	0.749
Protein (%)	18.7 (5.3)	18.4 (3.0)	18.9 (3.5)	19.3 (4.1)	-0.5 (-2.3,1.1)	0.509
Fat (%)	31.2 (8.4)	30.0 (7.1)	31.4 (6.7)	30.9 (6.1)	-0.04 (-3.1,3.1)	0.978

Values are mean ± SD.
*P<0.05 between screening visit and end visit in the unblinded isCGM group or blinded isCGM group.
†P<0.05 between unblinded isCGM group and blinded isCGM group in the screening visit or end visit.

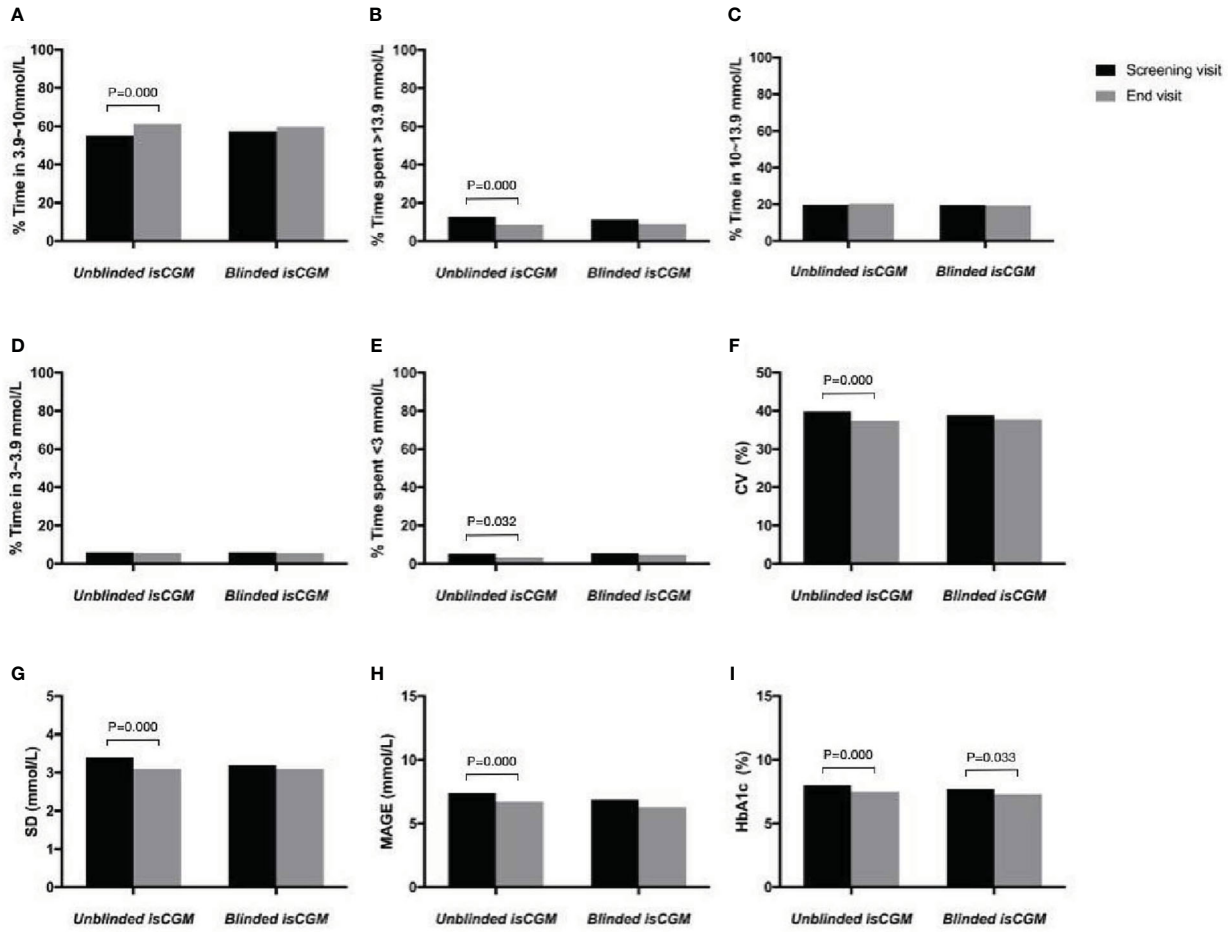

FIGURE 5
The efficacy of unblinded and blinded intermittently flash continuous glucose monitoring on glycemic control in adults with type 1 diabetes. Percentage of time in range **(A)**, hyperglycemia **(B, C)**, hypoglycemia **(D, E)**, Glucose variability **(F–H)** and HbA1c **(I)**.

range, time below range, and glycemic variability. Thus, the use of these variables for generating predictive alerts might result in even greater glycemic improvements. However, after adjustment for between-group differences, no significant difference was found in the effect of study treatment at 12 weeks between the unblinded isCGM and blinded isCGM groups in terms of 12-week HbA1c, TIR, hypoglycemia time, hyperglycemic time, CV, SD, MAGE, and HbA1c ($P > 0.05$). This emphasizes the greater challenges that are present in the management of T1D in the real world.

In the present study, we found that that 99.5% of the blinded isCGM values were obtained, compared with only 93.8% of the unblinded isCGM values at the final visit. The data showed that the majority of scanning was conducted during the awake hours spanning 6–18 h, while only a few scans were performed over the night-time hours spanning 0–6 h. The possible reasons for missing data in the unblinded isCGM group may be scanning frequency and the time of day for measurements according to the patient's age, lifestyle, eating habits, level of physical activity, and understanding and motivation with regard to maintenance of glucose monitoring (20). The use of safety features may contribute to avoiding missing abnormal glycemic data and further improving glycemic control.

Diet, physical exercise, and psychological reactions are important components in the management of T1D across a patient's lifespan (21, 22). Therefore, in this study, we also explored data on these self-managed key aspects. During the study period, both groups of patients were free to use unblinded isCGM real-time glucose values and SMBG to adjust their diet, physical activity, and insulin therapy. The results showed that the number of daily steps was reduced in the unblinded isCGM group, while there was no difference in the blinded isCGM group at the end of the study. However, there was no change in calorie, carbohydrate, protein, and fat consumption in both groups. The challenging management of diabetes could result in diabetes distress and risk for psychological disorders. However, the real-world study showed no significant association of CGM use and the level of diabetes distress (23). Our study showed that the participants of both groups reported improved diabetics distress, especially unblinded isCGM users. Our findings suggest that technology use, at least in the short term, may reduce diabetes distress. However, our findings also indicated that technology couldn't address every aspect of living with diabetes. Not only individuals with T1D but also healthcare professionals should be involved in the interpretation of data in

order to maximize the technological potential of these devices and improve their efficiency.

A major limitation of our study is that the intervention period of 12 weeks is relatively short. An extended monitoring period may provide insight into longer-term use of CGM and reflect the real-world setting. Additionally, these results also need to be confirmed in a large study population.

In conclusion, the use of isCGM systems resulted in a decrease in HbA1c level over 12 weeks among the adults with T1D in this study. The unblinded isCGM system was associated with benefits for glucose management, but with the blinded system, nearly 100% of the profiles were obtained successfully. It appears that the blinded isCGM systems can overcome both expected and unexpected data collection hurdles. Thus, combining both real-time and retrospective data gathered by isCGM might be the most appropriate and impactful way to utilize flash glycemic monitoring devices. However, further research is needed to understand the clinical importance of this finding and the applicability of these systems in the real world.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committees of Beijing Hospital, Peking Union Medical College Hospital, the First Affiliated Hospital of Nanjing Medicine University, and the First Affiliated Hospital of Harbin Medicine University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LG, YL, XX, HK, and TY directed the study and were responsible for study design. LG, YL, MZ, XX, HK, TY, XJ, and XZ contributed to the project recruitment. MZ performed statistical analyses and drafted the initial manuscript. LG, YL, MZ, XX, HK, and TY contributed to the discussion and helped edit the manuscript and suggested revisions. LG, YL, MZ, XX, HK, TY, XJ, and XZ approved the final manuscript. LG is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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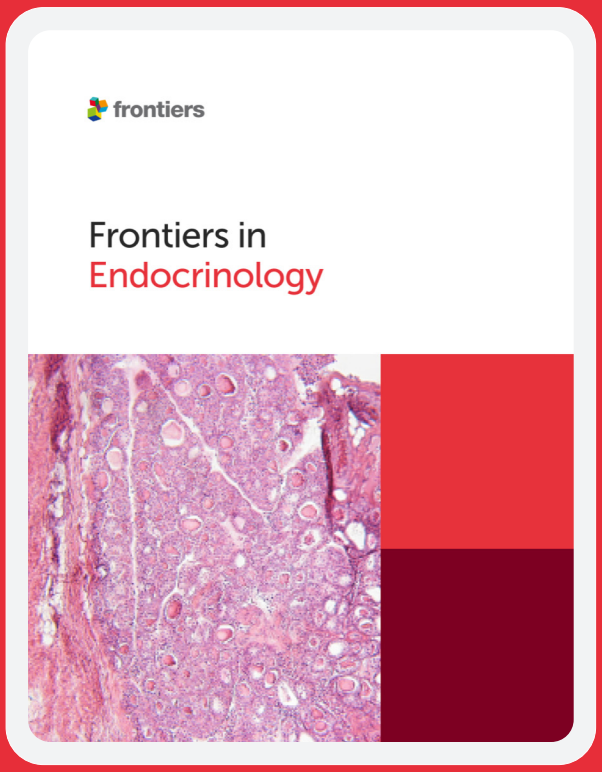

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