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Prevention of hypoglycemia by intermittent-scanning continuous glucose monitoring device combined with structured education in patients with type 1 diabetes mellitus: A randomized, crossover trial

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ABSTRACT

Aims: We conducted a randomized, crossover trial to compare intermittent-scanning continuous glucose monitoring (isCGM) device with structured education (Intervention) to self-monitoring of blood glucose (SMBG) (Control) in the reduction of time below range.

Methods: This crossover trial involved 104 adults with type 1 diabetes mellitus (T1DM) using multiple daily injections. Participants were randomly allocated to either sequence Intervention/Control or sequence Control/Intervention. During the Intervention period which lasted 84 days, participants used the first-generation FreeStyle Libre (Abbott Diabetes Care, Alameda, CA, USA) and received structured education on how to prevent hypoglycemia based on the trend arrow and by frequent sensor scanning (≥10 times a day). Confirmatory SMBG was conducted before dosing insulin. The Control period lasted 84 days. The primary endpoint was the decrease in the time below range (TBR; <70 mg/dL).

Results: The time below range was significantly reduced in the Intervention arm compared to the Control arm (2.42 ± 1.68 h/day [10.1 %±7.0 %] vs 3.10 ± 2.28 h/day [12.9 %±9.5 %], $P = 0.012$). The ratio of high-risk participants with low blood glucose index >5 was significantly reduced (8.6 % vs 23.7 %, $P < 0.001$).

Conclusions: The use of isCGM combined with structured education significantly reduced the time below range in patients with T1DM.

1. Introduction

Hypoglycemia is the burden for type 1 diabetes mellitus (T1DM) patients, because it can lead not only to the deteriorated quality of life, but also trigger traffic accidents, hospitalization due to coma or seizure, and even sudden death [1–4]. To deal with this issue, various diabetes technologies had been introduced to diabetes care to reduce the risk of hypoglycemia, especially that of severe hypoglycemia [5].

Continuous glucose monitoring (CGM) devices display approximate blood glucose levels by measuring the glucose concentration of the interstitial fluid. They provide much more detailed information regarding the glucose trend compared to conventional self-monitoring of blood glucose (SMBG) using finger-prick blood samples. Unlike real-time CGM (rtCGM) devices which show the sensor glucose levels all the time, intermittent-scanning CGM (isCGM) devices show the current glucose level only when the sensor is scanned by a reader or a smartphone on which a special app is installed. Currently in Japan, the first-generation FreeStyle Libre (Abbott Diabetes Care, Alameda, CA, USA), the original isCGM device, is widely used because FreeStyle Libre 2 and FreeStyle Libre 3 are not available yet. Both rtCGM devices and isCGM devices have the capability to display a trend arrow to notify the user whether the glucose level is rising, stable or declining. The utilization of the trend arrow has been considered important for making the most of using rtCGM devices or isCGM devices. However, evidence particularly that regarding education on the use of isCGM is sparse [6].

A downward trend arrow may indicate impending hypoglycemia; however, direct evidence regarding the effects of educating patients on tracking the trend arrow in order to prevent hypoglycemia is lacking. In addition, a previous report from an observational study suggested a relationship between more frequent scanning and a reduced time below

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range (TBR; <70 mg/dL [<3.9 mmol/L]) [7]; however, no interventional study has yet been conducted that educated patients on the recommended frequency of scanning.

A manufacturer-funded randomized controlled trial (RCT) of T1DM patients with glycated hemoglobin (HbA1c) levels of ≤7.5 % (58 mmol/mol) (IMPACT study) revealed that the use of the isCGM device as the replacement of SMBG reduced the TBR by 38.0 % compared to SMBG [8]. However, this study did not include structured education to prevent hypoglycemia, and the mechanism by which the TBR was reduced remained unclear, as the first-generation FreeStyle Libre Reader used in this study did not have the alert functions for hypoglycemia and hyperglycemia. In addition, due to the relatively low HbA1c values of the study participants, there was a limitation to the generalizability of the findings to overall T1DM patients. An RCT of structured educational intervention for patients already using or intending to use isCGM device reported an improvement in HbA1c levels, but no significant difference was observed in the TBR [9]. Therefore, whether educational intervention concerning the use of isCGM device is actually useful for reducing TBR has been unclear.

One of the advantages associated with isCGM device is its lower associated costs than rtCGM devices. In Japan, the Ministry of Health, Labour and Welfare approved the FreeStyle Libre (Abbott Diabetes Care, Alameda, CA, USA) only for adjunct use to self-monitoring of blood glucose [10], unlike the situation in the European Union and United States where non-adjunct use (i.e. isCGM is used to replace SMBG) is approved by the local regulatory authorities. Currently, FreeStyle Libre is not yet labeled for dosing insulin by its sensor glucose levels in Japan, and therefore patients need to conduct confirmatory SMBG before dosing insulin in order to observe its approved condition of use. Noteworthy, in the previous RCT conducted in Europe which demonstrated the effect of isCGM device to reduce TBR [8], isCGM was used to replace SMBG, and it was uncertain whether such observation is reproducible when isCGM is used adjunctly to SMBG in Japan. This given condition highlights the benefit of isCGM devices as the “trend arrow displaying device” compared to SMBG. However, in contrast to rtCGM devices [11–13], evidence concerning the utility of isCGM device is relatively sparse.

As described above, a further investigation is required to clarify the effectiveness of isCGM device after establishing an adequate educational method and adequate frequency of scanning. We hypothesized that structured education mainly focused on the importance of proactive measurements based on the information supplied by the trend arrow and frequent scanning of the isCGM sensor, combined with the use of isCGM device, would help decrease the TBR compared to SMBG. Therefore, we conducted this Effect of Intermittent-Scanning Continuous Glucose Monitoring to Glycemic Control Including Hypoglycemia and Quality of Life of Patients with Type 1 Diabetes Mellitus Study (ISCHIA study) to investigate the effects of isCGM device with structured education regarding the trend arrow and scanning frequency on the prevention of hypoglycemia compared to SMBG.

2. Methods

2.1. Trial design

This randomized, multicenter, open-label, crossover trial was conducted at 17 institutes in Japan.

The study consisted of a Run-in period (28 days), Period 1 of Intervention or Control (84 days), Washout period (28 days) and Period 2 of Control or Intervention (84 days) [14]. We chose a crossover design for this study because T1DM is a relatively rare disease in comparison to type 2 diabetes mellitus in Japan [15–17]. Although there have been no previous crossover trials using isCGM device to our knowledge, a crossover trial using rtCGM device was reported to be feasible [13]. No important changes were made to the methods after trial commencement.

2.2. Participants

Participants were eligible for the study if they met the following inclusion criteria: diagnosed as T1DM [18], 20–74 years old, with disease duration of ≥5 years, being treated by multiple daily insulin injections (MDIs; ≥3 times/day) and who had performed SMBG (≥3 times/day) within the past 30 days, with baseline HbA1c level <8.5 % (69 mmol/mol).

The exclusion criteria were as follows: being pregnant or planning to become pregnant within one year, having end-stage renal disease (under hemodialysis or after kidney transplantation), being blind, using an embedded medical device (cardiac pacemaker device, etc.), using an insulin pump, using premixed insulin, having a history of severe hypoglycemia (SH) episodes within the past one year, using oral hypoglycemic agents to manage T1DM within the past one year and unable to participate due to other factors based on the opinion of the treating clinician at trial entry.

The severity of diabetic retinopathy, diabetic nephropathy and diabetic neuropathy were diagnosed based on the criteria defined by the Japan Diabetes Society [19,20].

This trial was conducted in outpatient setting. The data downloaded from the FreeStyle Libre Pro Sensor (Abbott Diabetes Care) used during the Control period were collected at the data center, and all other data were collected at each study site.

2.3. Interventions

The participants were randomly allocated either to sequence Intervention/Control or to sequence Control/Intervention, and the details of the study schedule have been described elsewhere [14]. All participants were educated on how to conduct SMBG accurately by washing their hands prior to blood sampling (visit 2). They continued to conduct SMBG at least three times a day throughout the study period. They used the FreeStyle Precision Neo (Abbott Diabetes Care) as their SMBG device during the Run-in period, Control period and Washout period and the FreeStyle Libre Reader (Abbott Diabetes Care) during the Intervention period.

During the Intervention period (Period 1 or Period 2), participants used the first-generation FreeStyle Libre Reader and FreeStyle Libre Sensor as the isCGM device. They received structured education on how to prevent hypoglycemia using isCGM device based on the trend arrow and by frequent sensor scanning (≥10 times a day) when they started to use the device at the beginning of the Intervention Period.

In brief, patients were taught that a downward vertical trend arrow indicates that the glucose level is decreasing at a rate of ≥2 mg/dL (0.1 mmol/L) per minute (=120 mg/dL [6.7 mmol/L] per hour) and were advised to determine whether hypoglycemia was impending by reflecting on their past insulin dosage, timing, physical activity, food intake and glucose trend pattern, even if they had no symptoms of hypoglycemia. If they predicted impending hypoglycemia based on the above information, they were encouraged to check their blood glucose level by a finger-prick glucose test if needed and ingest a sufficient amount of sugar, such as glucose, to stop the rapid decrease in their glucose level. They were encouraged to track the trend arrow by frequent sensor scanning.

The English translation of the educational material used in this study is publicly available [21]. Participants were instructed to conduct confirmatory SMBG before dosing insulin in order to comply with the Clinical Trials Act [22].

During the Control period (Period 2 or Period 1), participants conducted SMBG using the FreeStyle Precision Neo at least three times a day. They wore the FreeStyle Libre Pro Sensor for retrospective CGM. The first-generation FreeStyle Libre Sensor and the FreeStyle Libre Pro Sensor are equivalently accurate according to the manufacturer [23]. After 14 days of use, the participants directly sent all FreeStyle Libre Pro Sensors back to the data center by postal mail. Neither the participants

nor the investigators received any feedback from the FreeStyle Libre Pro data.

2.4. Outcomes

In this crossover trial, the primary endpoint was the decrease in the time below range (TBR; <70 mg/dL [<3.9 mmol/L]) (h/day) during the Intervention period compared to the Control period.

The secondary endpoints included the time in range (TIR; 70–180 mg/dL [3.9–10.0 mmol/L]), time above range (TAR; >180 mg/dL [>10.0 mmol/L]), mean sensor glucose levels assessed by analyzing the log file of the FreeStyle Libre and FreeStyle Libre pro, indices for glucose fluctuation (average daily risk range [ADRR], mean of daily difference in blood glucose [MODD], low blood glucose index [LBGI]), glycated albumin (GA) (visits 3, 6, 7 and 10), the body weight (BW) (visits 1, 3, 6, 7 and 10), emotional burden of diabetes (problem areas in diabetes [PAID]) and fear of hypoglycemia (hypoglycemia fear survey [HFS]) [visits 3, 6, 7 and 10), frequency of SMBG (measured) as assessed by the log file of the FreeStyle Precision Neo or FreeStyle Libre Reader, time wearing CGM (measured) as assessed by the log file of the FreeStyle Libre Reader or FreeStyle Libre Pro sensor, frequency of isCGM scanning (measured) as assessed by the log file of the FreeStyle Libre Reader, total daily dose of prescribed insulin and total daily dose of prescribed basal insulin (visits 1 and 10), frequency of SH (visits 3, 6, 7 and 10), serious adverse events (SAEs), adverse events (AEs), mean absolute relative difference (MARD) and mean absolute difference (MAD).

2.5. Sample size

The sample size of the 104 participants was calculated based on the observation of the IMPACT study [8], using the PASS 15 (NCSS, LLC, Kaysville, Utah, USA) software program. As there was possibility that recruiting isCGM-naïve participants might be difficult, the recruitment of a minimum of 42 and a maximum of 62 participants with history of isCGM use was planned. Further details concerning the sample size calculation are described elsewhere [14].

2.6. Randomization

Participants were randomized by the minimization method in a 1:1 ratio, using a central web randomization system CliSSS Randoman (Medical Edge, Tokyo, Japan). Participants were stratified before allocation according to the history of isCGM use. The minimization factors were the age, sex and HbA1c.

2.7. Blinding

Due to the nature of the intervention, blinding was not possible.

2.8. Statistical methods

The presence of a normal distribution of the data was tested using the Kolmogorov-Smirnov test. Data are presented as the mean ± standard deviation or median (25 %, 75 %). The sensor glucose data obtained during the Intervention or Control period were matched for the 14 days after visits 3, 4 and 5 and visits 7, 8 and 9, respectively. The treatment, period and carry-over effects for continuous variables in this crossover study were estimated using linear mixed-effects models. When a significant carry-over effect was observed, a *t*-test for the comparison of two groups was performed during Period 1. The treatment, period and carry-over effects for categorical variables were estimated using the McNemar, Mainland-Gart and Hills-Armitage tests, respectively. SH, SAEs and AEs were analyzed using the safety set which was determined as the group of patients who received any intervention treatment or control treatment after the randomization, and the Fisher's exact test was used to compare their prevalence during the Intervention period and the Control period. A P-value < 0.05 was considered statistically significant. Analyses were conducted using the software program R version 3.4.3 (R Project for Statistical Computing, Vienna, Austria).

3. Results

Of the 104 participants, 2 withdrew from the study before randomization, and 102 were randomized to each sequence. Participants were enrolled between 15 March 2019 and 2 April 2020, and the observation was completed on 5 January 2021. Ninety-three participants completed the study, and all of them were analyzed; therefore, the retention rate was 91.2 % (Fig. 1).

The baseline data are presented in Table 1. The mean age of the participants was 51.4 ± 15.3 years old, 47.3 % of the participants were male, the median diabetes duration was 16 (10, 25) years, the mean HbA1c was 7.3 ± 0.7 % (56 ± 16 mmol/mol), and the rate of isCGM-naïve participants was 46.2 %. Participants were successfully allocated to sequence Intervention/Control and sequence Control/Intervention; isCGM naïve participants were 44.7 % vs 47.8 % ($P = 0.836$), those younger than 40 years old were 23.4 % vs 26.1 % ($P = 0.831$), male participants were 44.7 % vs 50.0 % ($P = 0.680$) and those with HbA1c levels < 7.5 % (58 mmol/mol) were 48.9 % vs 58.7 % ($P = 0.408$), respectively.

The TBR (<70 mg/dl [<3.9 mmol/L]) as the primary endpoint was significantly reduced in the Intervention arm compared to the Control arm (2.42 ± 1.68 h/day [10.1 ± 7.0 %] vs 3.10 ± 2.28 h/day [12.9 ± 9.5 %], Difference = -0.68 h/day [-2.8 %] [95 % CI: −1.04, −0.31 h/day {-4.3 %, −1.3 %}], Cohen's d = -0.34 [95 % CI: −0.62, −0.05], $P = 0.012$) (Table 2). This corresponded to a 21.9 % reduction in TBR. Detailed data of TBR in each period are displayed in Table 3. Regarding secondary endpoints, the TIR did not differ between the arms (14.54 ± 2.66 h/day [60.6 ± 11.1 %] vs 13.75 ± 2.45 h/day [57.3 ± 10.2 %], $P = 0.451$) (Table 2). As a significant carry-over effect was observed in the overall TAR (7.03 ± 3.12 h/day [29.3 ± 13.0 %] vs 7.15 ± 3.50 h/day [29.8 ± 14.6 %]), measurements limited to Period 1 were analyzed; the TAR in Period 1 did not differ between the arms (7.27 ± 3.05 h/day [30.3 ± 12.7 %] vs 6.02 ± 3.24 h/day [25.1 ± 13.5 %], $P = 0.058$). Detailed data of TIR and TAR in each period are also displayed in Table 3. The mean glucose level was significantly higher in the Intervention arm than in the Control arm (151.2 ± 24.8 mg/dl [8.40 ± 1.38 mmol/L] vs 139.5 ± 27.4 mg/dl [7.75 ± 1.52 mmol/L], $P = 0.034$) (Table 2). The LBGI was significantly reduced in the Intervention arm compared to the Control arm (2.51 ± 1.81 vs 3.26 ± 2.55, $P = 0.013$). The ratio of high-risk participants with an LBGI > 5 was significantly reduced in the Intervention arm compared with the Control arm (8.6 % vs 23.7 %, $P < 0.001$). Post-hoc analyses of time below 54 mg/dl (3.0 mmol/L) in the Intervention arm compared to the Control arm were 1.03 ± 1.03 h/day (4.3 ± 4.3 %) vs 1.54 ± 1.54 h/day (6.3 ± 6.3 %), respectively ($P = 0.022$); post-hoc analyses of coefficient of variation for glucose (%CV) in the Intervention arm and in the Control arm were 41.7 ± 6.0 % and 46.0 ± 7.5 %, respectively ($P = 0.003$).

The change in GA did not differ between the two arms (Table 4). No significant difference was observed in the change of the PAID score and HFS score between the two arms. Both of the SMBG frequency and the time wearing the CGM device (isCGM during the Intervention period or retrospective CGM during the Control period) did not differ between the two arms. The mean frequency of isCGM scanning during the Intervention period was 11.9 ± 6.8 times/day (Table 2).

The total daily insulin dose (TDD) per BW (0.60 ± 0.20 unit/kg/day vs 0.60 ± 0.20 unit/kg/day, $P = 0.353$) and the ratio of basal insulin to TDD (34.8 ± 12.6 % vs 34.6 ± 12.0 %, $P = 0.638$) did not differ between the baseline and after the study.

In the safety set (n = 101), the overall prevalence of SH, SAE and AE was 4.0 %, 6.9 % and 28.7 %, respectively. The prevalence of SH did not differ between arms (1.1 % during the Intervention period [n = 94] vs 3.1 % during the Control period [n = 97], $P = 0.621$). The prevalence of

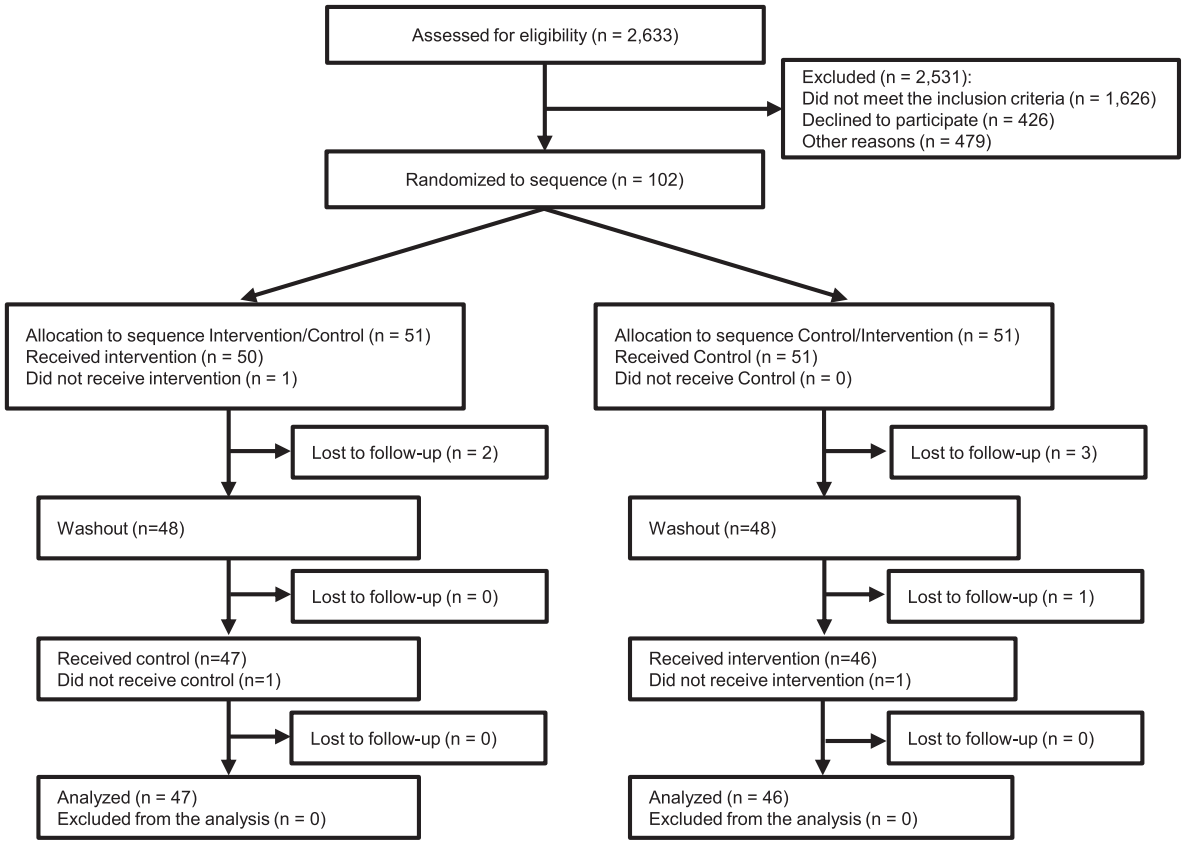

Fig. 1. CONSORT flow diagram.

Table 1
Clinical characteristics of participants.

Age, years	51.4 (15.3)
Male, %	47.3
BMI, kg/m^2	22.7 (2.9)
Diabetes duration, years	16 (10, 25)
Diabetic retinopathy, %	
None	76.9
Background retinopathy	15.4
Pre-proliferative retinopathy	0
Proliferative retinopathy	0
Post-photocoagulation	7.7
Diabetic nephropathy, %	
None	87.0
Microalbuminuria	12.0
Macroalbuminuria	1.1
eGFR < 30 ml/min/1.73 m^2	0
Diabetic neuropathy, %	19.4
SMBG frequency (health insurance basis) per month, %	
90 times	21.5
≥120 times	78.5
HbA1c, %	7.3 (0.7)
mmol/mol	56 (16)
Prescribed insulin	
TDD per BW, unit/kg/day	0.60 (0.20)
Ratio of basal insulin to TDD, %	34.8 (12.6)
isCGM-naïve, %	46.2

Numbers are mean (standard deviation), median (25%, 75%) or percentage. BMI, body mass index; eGFR, estimated glomerular filtration rate; SMBG, self-monitoring of blood glucose; HbA1c, glycated hemoglobin; TDD, total daily insulin dose; BW, body weight; isCGM, intermittent-scanning continuous glucose monitoring.

SAE (2.1 % vs 3.1 %, $P > 0.999$) and that of AE (13.8 % vs 16.5 %, $P = 0.689$) did not differ between arms, too. Details of SAE and AE are described in Table S1.

MARD and MAD of FreeStyle Libre sensor were 15.6 % and 23.2 mg/dl (1.29 mmol/L), respectively.

4. Discussion

This is the first randomized, crossover trial to compare the use of isCGM device combined with structured education regarding the trend arrow and the frequency of scanning to SMBG in patients with T1DM. The main finding of this crossover trial was that TBR was significantly reduced in the Intervention period compared to the Control period, without deteriorations in the TIR, TAR or GA. The result of the post-hoc analyses of time below 54 mg/dl (3.0 mmol/L) was similar to that of TBR below 70 mg/dl (3.9 mmol/L). The increase in the average blood glucose in the Intervention arm may be attributed to the reduction in the TBR, rather than the worsening of the control of the blood glucose levels; however, considering there was no deterioration in GA, the possibility of worsening long-term risk of microvascular and macrovascular complications would be negligible. The improvement of %CV may also be attributed to the reduction in TBR. The use of isCGM device significantly reduced the LBGI, with much fewer patients included in the high-risk categories. As the classification of the LBGI (high, moderate and low) was reported to predict the occurrence of future SH [24], our findings suggest the use of isCGM device combined with structured education might reduce the risk of SH in patients with T1DM. There is possibility that this study was not enough powered to directly detect the difference of the prevalence of SH between the two arms.

The present study proved the benefit of the use of isCGM device combined with structured education. The frequency of isCGM scanning (≥10 times a day) included in structured education was considered to be feasible, as the mean frequency of scanning observed during the

Table 2
Primary and secondary outcomes.

Variables		Intervention (isCGM with structured education)	Control (SMBG)	*P* value
Primary outcome				
TBR (<70 mg/dL [<3.9 mmol/L])	h	2.42 (1.68)	3.10 (2.28)	0.012*
	%	10.1 (7.0)	12.9 (9.5)	
Secondary outcomes				
TIR (70–180 mg/dL [3.9–10.0 mmol/L])	h	14.54 (2.66)	13.75 (2.45)	0.451
	%	60.6 (11.1)	57.3 (10.2)	
TAR (>180 mg/dL [>10.0 mmol/L])	h	7.27 (3.05)	6.02 (3.24)	0.058
	%	30.3 (12.7)	25.1 (13.5)	
Mean glucose	mg/dL	151.2 (24.8)	139.5 (27.4)	0.034*
	mmol/L	8.40 (1.38)	7.75 (1.52)	
ADRR	mg/dL	43.88 (9.63)	46.19 (8.82)	0.711
	mmol/L	2.44 (0.54)	2.57 (0.49)	
MODD	mg/dL	75.39 (28.25)	91.91 (27.22)	0.315
	mmol/L	4.19 (1.57)	5.11 (1.51)	
LBGI		2.51 (1.81)	3.26 (2.55)	0.013*
High: >5.0	%	8.6	23.7	<0.001*
Adherence				
SMBG frequency	/day	3.16 (1.2)	3.14 (1.4)	0.946
Time wearing CGM (isCGM or retrospective CGM)	%	93.1 (12.6)	92.5 (7.7)	0.750
Frequency of isCGM scanning	/day	11.9 (6.8)	N.A.	N.A.

Numbers are mean (standard deviation) or percentage. * <0.05. N.A., not applicable; TIR, time in range; TAR, time above range; ADRR, average daily risk range; MODD, mean of daily differences; LBGI, low blood glucose index; SMBG, self-monitoring of blood glucose; CGM, continuous glucose monitoring; isCGM, intermittent-scanning continuous glucose monitoring.

Table 3
Detailed data of TBR, TIR and TAR in each period.

		Period 1	Period 2	Treatment effect	Period effect	Carry-over effect
TBR						
Sequence Intervention/ Control	h	2.35 (1.70)	2.47 (1.99)	0.012*	0.151	0.0504
	%	9.8 (7.1)	10.3 (8.3)			
Sequence Control/ Intervention		3.74 (2.40)	2.52 (1.66)			
		15.6 (10.0)	10.5 (6.9)			
TIR						
Sequence Intervention/ Control	h	14.40 (2.52)	13.27 (2.45)	0.451	0.289	0.192
	%	60.0 (10.5)	55.3 (10.2)			
Sequence Control/ Intervention		14.23 (2.38)	14.69 (2.81)			
		59.3 (9.9)	61.2 (11.7)			
TAR				0.035*	0.091	0.029*
Sequence Intervention/ Control	h	7.27 (3.05)	8.28 (3.41)			
	%	30.3 (12.7)	34.5 (14.2)			
Sequence Control/ Intervention		6.02 (3.24)	6.82 (3.22)			
		25.1 (13.5)	28.4 (13.4)			

Numbers are mean (standard deviation). * <0.05. TBR, time below range; TIR, time in range; TAR, time above range.

Intervention was 11.9 times a day. One of the most interesting findings among the secondary endpoints were those of the PAID scores and HFS scores; they did not differ between the two arms, suggesting that the use of isCGM device did not relieve such distress in the study participants. Given that the HFS scores were improved in studies using rtCGM [25,26], the present findings might have been due to the lack of the alert functions of the first-generation FreeStyle Libre. The reason why there was no significant difference in the PAID score between the two arms remains unclear, however it is possible that additional improvement in the treatment might be necessary to alleviate the burden of having T1DM.

There are several limitations associated with the present study. This was an open-label study due to the nature of the intervention. Although no carry-over effect was observed in the primary endpoint, it was observed in the TAR, a secondary endpoint. As the participants were successfully allocated to either sequence Intervention/Control or sequence Control/Intervention by the minimization method, analysis of TAR limited to Period 1 was considered to be adequate. One possible background of the carry-over effect observed in TAR might be the short wash-out period of 28 days. Another possibility might be the partially remaining effect of the structured education which could not be washed-out, for example, the improved blood glucose awareness in the participants acquired by the structured education or some change in the lifestyle happened during the Intervention period. As the change in the body weight did not differ between the arms, there might be no difference in the entire energy intake; however, there is possibility that the timing of food intake might have been changed during the Intervention period in order to prevent hypoglycemia. As this study did not investigate the detailed food intake by the participants, this possibility remained hypothetical. This study did not include patients who had had SH within the past year, which might have influenced the observations, although CGM devices with alert functions are considered to be more suitable for such patients. This study did not investigate the education history of the participants, which might have influenced the effect of the intervention. As this study included only adult subjects 20–74 years old, the reproducibility in children and adolescent T1DM patients needs to be investigated in the future. This study included only patients using MDIs and did not include those using CSII; using sensor-augmented pumps (SAPs) with predictive low-glucose suspend function may be more beneficial with less TBR compared to the combination of CSII and isCGM [27]. The change in HbA1c was not evaluated, as this study design was a crossover style with a short wash-out period of 28 days; alternatively, the change in GA was measured. The structured education used in this study did not include the bolus insulin dose adjustment according to the trend arrow [21], and adding this education might have been useful to further reduce TBR. The MARD of FreeStyle Libre was different from that previously reported by the manufacturer [28], and this might be due to the difference of the patient characteristics and the environment in which it was used in this study. The data of anti-GAD antibody were not collected, although individual participant was diagnosed as T1DM according to the criteria by JDS [18]; a sub-population of T1DM is known to be negative for anti-GAD antibody and they need to be classified according to the clinical presentation of the disease, and the inclusion criteria of being treated by multiple daily insulin injections and the exclusion criteria regarding oral hypoglycemic agents warranted the clinical characteristics of the participants particular to T1DM. The data of serum c-peptide levels were not collected; as the participants with the disease duration of ≥5 years were included in this study, their capability to secrete intrinsic insulin was considered to be impaired to certain degree or completely lost. Due to the study design of the

Table 4
Secondary outcomes (continued).

Variables		Intervention (isCGM with structured education)			Control (SMBG)			*P* value
		Baseline	Follow-up	Difference	Baseline	Follow-up	Difference	
Secondary outcomes (continued)								
GA	%	21.8 (3.4)	22.1 (3.3)	0.3 (2.3)	21.9 (3.3)	22.0 (3.5)	0.1 (2.3)	0.498
BW	kg	60.4 (9.9)	60.5 (9.9)	0.1 (1.1)	60.4 (9.9)	60.6 (10.1)	0.2 (1.2)	0.472
Psychological distress								
PAID	points	31.9 (18.3)	32.9 (18.4)	1.0 (9.2)	33.4 (19.2)	33.8 (17.4)	0.4 (9.8)	0.206
HFS (Total)	points	30.5 (13.8)	30.1 (13.5)	−0.4 (8.1)	29.0 (12.9)	28.5 (12.2)	−0.5 (6.6)	0.600
HFS-B	points	16.8 (6.4)	17.5 (6.0)	0.7 (3.9)	16.0 (5.6)	16.5 (6.0)	0.5 (3.6)	0.534
HFS-W	points	13.7 (9.6)	12.6 (9.4)	−1.2 (6.9)	13.0 (10.1)	12.0 (8.1)	−1.0 (6.0)	0.799

Numbers are mean (standard deviation). GA, glycated albumin; BW, body weight; PAID, Problem Areas in Diabetes; HFS-II, Hypoglycemia Fear Survey-Second Version (HFS-II-B for behavior, HFS-II-W for worry); isCGM, intermittent-scanning continuous glucose monitoring; SMBG, self-monitoring of blood glucose.

combined intervention of the isCGM use and structured education, the effect of structured education could not be separately evaluated from the effect of the isCGM use; the use of a medical device always needs some education, and the current study would contribute to the standardization of the education regarding the hypoglycemia prevention by CGM. In some countries, isCGM has been superseded by rtCGM due to the introduction of FreeStyle Libre 3(Abbott Diabetes Care); however, FreeStyle Libre 3 is not available in other countries including Japan, and there are many patients still using isCGM.

The strength of this study was the high retention rate, and the inclusion of patients with HbA1c levels <8.5 % (69 mmol/mol) which represents the general T1DM population. Furthermore, to our knowledge, this is the first report to attempt to prevent hypoglycemia by means of structured education regarding the use of isCGM device. The content of the structured education used in this study is publicly available [21], which will help patients with T1DM using isCGM device through its simple message to keep tracking the trend arrow, so that they can ingest sugar before hypoglycemia actually occurs, and to scan the sensor frequently (≥10 times a day).

5. Conclusions

The use of isCGM device combined with structured education reduced the TBR in patients with T1DM. Deteriorations in the TIR, TAR or GA were not observed. The use of isCGM device significantly reduced the LBGI, with much fewer patients included in the high-risk categories.

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Ethics approval and consent to participate

The study protocol was approved by the Certified Review Board (National Hospital Organization Osaka National Hospital: N2018002). Clinical Research Service, Co. (Osaka, Japan), supported the preparation for the ethical review. All participants provided their written informed consent before enrolment. This study was conducted in accordance with the principles of the Declaration of Helsinki as revised in 2008 and the Clinical Trials Act [22]. Clinical trial registration: jRCT1052180075 (approval date of registry; 26 February 2019).

Availability of data and materials

The individual deidentified participant data will be shared upon reasonable request to the corresponding author. This policy will be applied to all the study data. Related documents such as study protocol will be shared upon reasonable request too, but only in Japanese. The data will become available in April 2024, however the timing can be changed. They will be available until March 2027. The data will be shared with non-profit investigators for meta-analyses purpose by electronic records.

Contributors

All authors contributed equally. The roles of individual investigators in the ISCHIA study group were described in the **Acknowledgments**. All authors have approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The potential conflicts of interest concerning all individual investigators were reviewed by the Certified Review Board in accordance with the Clinical Trials Act [22].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.110147.

References

[1] Przezak A, Bielka W, Molęda P. Fear of hypoglycemia-an underestimated problem. Brain Behav 2022;12:e2633.

[2] Cox DJ, Gonder-Frederick LA, Singh H, Ingersoll KS, Banton T, Grabman JH, et al. Predicting and reducing driving mishaps among drivers with type 1 diabetes. Diabetes Care 2017;40(6):742–50.

[3] Urakami T. Severe hypoglycemia: is it still a threat for children and adolescents with type 1 diabetes? Front Endocrinol (Lausanne) 2020;11:609. https://doi.org/10.3389/fendo.2020.00609.

[4] Amiel SA, Aschner P, Childs B, Cryer PE, de Galan BE, Frier BM, et al. Hypoglycaemia, cardiovascular disease, and mortality in diabetes: epidemiology, pathogenesis, and management. Lancet Diabetes Endocrinol 2019;7(5):385–96.

[5] Choudhary P, Amiel SA. Hypoglycaemia in type 1 diabetes: technological treatments, their limitations and the place of psychology. Diabetologia 2018;61:761–9. https://doi.org/10.1007/s00125-018-4566-6.

[6] Kudva YC, Ahmann AJ, Bergenstal RM, Gavin, Kruger DF, Midyett LK, et al. Approach to Using Trend Arrows in the FreeStyle Libre Flash Glucose Monitoring Systems in Adults. J Endocr Soc 2018;2:1320–37. https://doi.org/10.1210/js.2018-00294.

[7] Dunn TC, Xu Y, Hayter G, Ajjan RA. Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: a European analysis of over 60 million glucose tests. Diabetes Res Clin Pract 2018;137:37–46. https://doi.org/10.1016/j.diabres.2017.12.015.

[8] Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet 2016;388:2254–63. https://doi.org/10.1016/s0140-6736(16)31535-5.

[9] Hermanns N, Ehrmann D, Schipfer M, Kröger J, Haak T, Kulzer B. The impact of a structured education and treatment programme (FLASH) for people with diabetes using a flash sensor-based glucose monitoring system: results of a randomized controlled trial. Diabetes Res Clin Pract 2019;150:111–21.

[10] Murata T, Sakane N, Kato K, Tone A, Toyoda M. The current intermittent-scanning CGM device situation in japan: only adjunctive use to SMBG is approved and the latest health insurance coverage details. J Diabetes Sci Technol 2018;12:729–30. https://doi.org/10.1177/1932296817749860.

[11] Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464–76. https://doi.org/10.1056/nejmoa0805017.

[12] Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycemia awareness or severe hypoglycemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet 2018;391:1367–77. https://doi.org/10.1016/s0140-6736(18)30297-6.

[13] Battelino T, Conget I, Olsen B, Schütz-Fuhrmann I, Hommel E, Hoogma R, et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia 2012;55(12):3155–62.

[14] Suzuki S, Tone A, Murata T, Nishimura K, Miyamoto Y, Sakane N, et al. Protocol for a randomized, crossover trial to decrease time in hypoglycemia by combined intervention of the usage of intermittent-scanning continuous glucose monitoring device and the structured education regarding its usage: effect of intermittent-scanning continuous glucose monitoring to glycemic control including hypoglycemia and quality of life of patients with type 1 diabetes mellitus study (ISCHIA Study). Tokai J Exp Clin Med 2021;46:59–68.

[15] Kawasaki E. Type 1 diabetes and autoimmunity. Clin Pediatr Endocrinol 2014;23:99–105. https://doi.org/10.1297/cpe.23.99.

[16] Onda Y, Sugihara S, Ogata T, Yokoya S, Yokoyama T, Tajima N. Incidence and prevalence of childhood-onset Type 1 diabetes in Japan: the T1D study. Diabet Med 2017;34(7):909–15.

[17] Ogawa Y, Uchigata Y, Otani T, Iwamoto Y. Proportion of diabetes type in early-onset diabetes in Japan. Diabetes Care 2007;30:e30.

[18] Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus, Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, et al. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig 2010;1:212–28. https://doi.org/10.1111/j.2040-1124.2010.00074.x.

[19] Haneda M, Utsunomiya K, Koya D, Babazono T, Moriya T, Makino H, et al. A new classification of diabetic nephropathy 2014: a report from joint committee on diabetic nephropathy. J Diabetes Investig 2015;6(2):242–6.

[20] Araki E, Goto A, Kondo T, Noda M, Noto H, Origasa H, et al. Japanese clinical practice guideline for diabetes 2019. Diabetol Int 2020;11(3):165–223.

[21] The ISCHIA study group: Instructions for proper usage of the FreeStyle Libre. https://researchmap.jp/tmurata/others/31268710 [accessed 7 July 2022].

[22] Ministry of Health, Labour and Welfare, Japan: Clinical Trials Act (Act No. 16 of April 14, 2017). https://www.mhlw.go.jp/file/06-Seisakujouhou-10800000-Iseikyoku/0000213334.pdf [accessed 7 July 2022].

[23] Murata T, Nirengi S, Kawaguchi Y, Sukino S, Watanabe T, Sakane N. Accuracy of a novel "Factory-Calibrated" continuous glucose monitoring device in normal glucose levels: a pilot study. Biomed Sci 2017;3:109–13. https://doi.org/10.11648/j.bs.20170306.11.

[24] Kovatchev BP, Cox DJ, Gonder-Frederick LA, Young-Hyman D, Schlundt D, Clarke W. Assessment of risk for severe hypoglycemia among adults with IDDM:

validation of the low blood glucose index. Diabetes Care 1998;21:1870–5. https://doi.org/10.2337/diacare.21.11.1870.

[25] Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Beck RW, Lawrence JM, Laffel L, Wysocki T, Xing D, et al. Quality-of-life measures in children and adults with type 1 diabetes: juvenile diabetes research foundation continuous glucose monitoring randomized trial. Diabetes Care 2010; 33:2175–7. https://doi.org/10.2337/dc10-0331.

[26] Murata T, Kuroda A, Matsuhisa M, Toyoda M, Kimura M, Hirota Y, et al. Predictive factors of the adherence to real-time continuous glucose monitoring sensors: a prospective observational study (PARCS STUDY). J Diabetes Sci Technol 2021;15 (5):1084–92.

[27] Massa GG, Gys I, Bevilacqua E, Wijnands A, Zeevaert R. Comparison of flash glucose monitoring with real time continuous glucose monitoring in children and adolescents with type 1 diabetes treated with continuous subcutaneous insulin infusion. Diabetes Res Clin Pract 2019;152:111–8. https://doi.org/10.1016/j.diabres.2019.05.015.

[28] Hoss U, Budiman ES. Factory-calibrated continuous glucose sensors: the science behind the technology. Diabetes Technol Ther 2017;19(S2):S44–50. https://doi.org/10.1089/dia.2017.0025.