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)

Shota SUZUKI[*1,*2], Atsuhito TONE[*3], Takashi MURATA[*4], Kunihiro NISHIMURA[*5], Yoshihiro MIYAMOTO[*6], Naoki SAKANE[*7], Noriko SATOH-ASAHARA[*8], Masao TOYODA[*9], Yushi HIROTA[*10], Munehide MATSUHISA[*11], Akio KURODA[*11], Ken KATO[*12], Ryuji KOUYAMA[*13], Junnosuke MIURA[*14], Akiko SUGANUMA[*7], Tsutomu TOMITA[*15], Michio NOGUCHI[*15], Cheol SON[*15], Masato KASAHARA[*1], Yukie ITO[*16], Shu KASAMA[*1] and Kiminori HOSODA[*15]

[*1]*Institute for Clinical and Translational Science, Nara Medical University Hospital*
[*2]*Department of Health Informatics, School of Public Health, Kyoto University*
[*3]*Department of Internal Medicine, Okayama Saiseikai General Hospital*
[*4]*Diabetes Center, National Hospital Organization Kyoto Medical Center*
[*5]*Department of Preventive Medicine, National Cerebral and Cardiovascular Center*
[*6]*Open Innovation Center, National Cerebral and Cardiovascular Center*
[*7]*Division of Preventive Medicine, Clinical Research Institute, National Hospital Organization Kyoto Medical Center*
[*8]*Department of Endocrinology, Metabolism, and Hypertension Research, Clinical Research Institute, National Hospital Organization Kyoto Medical Center*
[*9]*Division of Nephrology, Endocrinology and Metabolism, Department of Internal Medicine, Tokai University School of Medicine*
[*10]*Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine*
[*11]*Diabetes Therapeutics and Research Center, Institute of Advanced Medical Sciences, Tokushima University*
[*12]*Diabetes Center, National Hospital Organization Osaka National Hospital*
[*13]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Tsuchiura Kyodo General Hospital*
[*14]*Diabetes Center, Tokyo Women's Medical University School of Medicine*
[*15]*Division of Diabetes and Lipid Metabolism, National Cerebral and Cardiovascular Center*
[*16]*Bioethics Supervisory Office, Nara Medical University Hospital*

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Objective: Intermittent-scanning continuous glucose monitoring (isCGM) is widely used in type 1 diabetes (T1D) patients; however, the education required to prevent hypoglycemia by using isCGM is not established. This study examines the combined effect of isCGM device usage and the education to reduce the time in hypoglycemia in comparison to conventional self-monitoring of blood glucose (SMBG).

Methods: The 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), a randomized, crossover trial, enrolls 104 T1D patients (age, 20−74 years) with T1D. Participants are randomized to use isCGM combined with structured education (Intervention period) or SMBG (Control period) for 84 days, followed by the other for a further 84 days. During the Intervention period, participants have access to the sensor glucose levels and trend arrow of the device. During the Control period, participants conduct SMBG at least three times a day, and retrospective CGM is used to record the blinded sensor glucose levels. The primary endpoint is the decrease of time in hypoglycemia (< 70 mg/dL) per day (hour/day) during the Intervention period compared with the Control period. The secondary endpoints include other indices of glycemic control, glycoalbumin, accuracy of isCGM, diabetes-related quality of life (QOL), adherence, and cost-effectiveness. The study protocol has received Certified Review Board (CRB) approval from National Hospital Organization Osaka National Hospital (N2018002, February 14, 2019). This study is carried out in accordance with the Declaration of Helsinki and the Clinical Trials Act. The findings will be published in peer-reviewed journals.

Conclusion: The ISCHIA study will contribute to the standardization of patient education regarding the prevention of hypoglycemia by using isCGM.

Key words: continuous glucose monitoring, hypoglycemia, type 1 diabetes, educational program, trend arrow

Takashi MURATA, Diabetes Center, National Hospital Organization Kyoto Medical Center, 1-1 Fukakusamukaihata-cho, Fushimi-ku, Kyoto, Kyoto 612-8555, Japan Tel: +81-75-641-9161 Fax: +81-75-643-4325 E-mail: drmurata@nifty.com

INTRODUCTION

Hypoglycemia is a significant adverse effect that may occur in patients undergoing insulin therapy for type 1 diabetes (T1D). This problem became a greater concern since the results of the Diabetes Control and Complications Trial (DCCT) were published, as the incidence of severe hypoglycemia in patients undergoing intensive therapy for T1D was found to be approximately three-times higher than that in conventional therapy [1]. Severe hypoglycemia is a potentially fatal condition that may cause traffic accidents, and which worsens the quality of life (QOL) [2–6]. Thus, the early detection and prevention of hypoglycemia are essential in insulin therapy for T1D.

Self-monitoring of blood glucose (SMBG) by sampling a small amount of capillary blood from the fingertip has been the standard modality for monitoring blood glucose levels. In contrast, continuous glucose monitoring (CGM) devices measure the glucose concentration of the interstitial tissue. There are mainly two categories of CGM. One is real-time CGM (RT-CGM); the other is retrospective CGM [7]. RT-CGM shows the real-time glucose level estimated according to the glucose concentration of subcutaneous tissue by transmitting sensor data almost continuously to the receiver. Some RT-CGM devices are approved for non-adjunctive usage to SMBG, and others are not [7, 8]. On the other hand, retrospective CGM is only used for the retrospective analysis of the glucose levels, and lacks the ability to display the glucose level in real time.

Another type of CGM called intermittent-scanning continuous glucose monitoring (isCGM) displays the real-time glucose level only when the sensor is scanned by a reader. There is limited evidence regarding the direct comparison of RT-CGM and isCGM [9].

The first-generation isCGM device, FreeStyle Libre (Abbott Diabetes Care, Alameda, CA, UA), has been covered by health insurance in Japan since September 2017; however, it is not approved for non-adjunctive usage to SMBG, unlike the situation in the European Union and the United States [10].

One of the advantages of isCGM is that it is inexpensive in comparison to other RT-CGM devices. The sensor is factory calibrated [11]; thus, users do not need to calibrate it by SMBG; however, users must conduct SMBG to confirm hypoglycemia. They must also conduct SMBG when the sensor glucose levels are rapidly changing and when users find that the sensor glucose levels do not match their symptoms. Unlike SMBG, an isCGM device displays not only the current glucose levels but also a trend arrow [12]. It is noteworthy that education on utilization of the information from the trend arrow, the types of proactive measures that are needed to prevent hypoglycemia, and how frequently the user should scan the sensor has not been well examined [12, 13]. Regarding the accuracy of FreeStyle Libre, a study conducted by its manufacturer revealed that the mean absolute relative difference (MARD), one of the standard benchmarks of CGM devices, was 11.4% [14]. This value slightly exceeded the MARD threshold for safe insulin dosing in the non-adjunctive usage of CGM to SMBG (threshold: 10%), as estimated by an *in silico* study [15].

Evidence that supports the benefits of using RT-CGM is accumulating [16–18]. In contrast, although the number of publications on the topic is increasing, evidence on isCGM is relatively sparse, especially evidence obtained from randomized controlled trials. In a manufacturer-funded randomized controlled trail that recruited T1D patients with HbA1c levels of ≤ 7.5% (IMPACT study), the use of isCGM was associated with a 37% reduction in time in hypoglycemia (< 70 mg/dL) in comparison to SMBG [19]. However, the observations in that study may not be generalized to the entire T1D population, as its participants were limited to those with relatively low HbA1c levels. In addition, what kind of education accompanying the use of isCGM is required for the prevention of hypoglycemia is unclear from this study. Another randomized controlled trial conducted in a summer camp setting for children with T1D found that the non-adjunctive usage of isCGM significantly reduced the time spent in hyperglycemia (> 180 mg/dL) and improved the time in range (TIR) (70–180 mg/dL) in comparison to SMBG in a sub-population with suboptimal metabolic control (HbA1c > 7%) [20]. The observations in this study may not be generalized to the entire T1D population, as the children (age, 6–15 years old) who participated in this study may have simultaneously received extra supervision for insulin dosing from the summer camp personnel, considering their limited self-management capability at their age. In an RCT, the HbA1c levels of isCGM users were reported to have improved after educational intervention; however, the time in hypoglycemia was not significantly different [13]. Therefore, whether or not structured education concerning isCGM is beneficial for hypoglycemia prevention is unclear from this study. An observational study conducted by the manufacturer suggested an association between more frequent scanning of the isCGM sensor and a shorter time in hypoglycemia [21]. However, due to the nature of observational studies, whether or not hypoglycemia prevention is possible by frequently scanning the isCGM sensor remains unclear from this study.

As described above, further investigation is required to clarify the safety and the effectiveness of the usage of isCGM. In addition, establishing the adequate educational method regarding the usage of isCGM to improve the clinical outcomes is critically important [22]. Thus, a clinical trial should be performed to investigate the effects of isCGM accompanied by education on the trend arrow and the impact of the scanning frequency on the prevention of hypoglycemia.

PATIENTS AND METHODS

Study design

The Effect of Intermittent-Scanning Continuous Glucose Monitoring to Glycemic Control Including Hypoglycemia and Quality of Life of Patients with T1D Study (ISCHIA Study) is a multicenter, prospective, open-label, randomized crossover trial to compare the usage of isCGM and structured education on isCGM with SMBG in adult patients with T1D. The study is conducted at 17 institutes in Japan. The locations and investigators of each site are stated in the **LIST OF INVESTIGATORS**. These institutes include university hospitals, general hospitals and a diabetes-specialized clinic. This trial is conducted in an outpatient

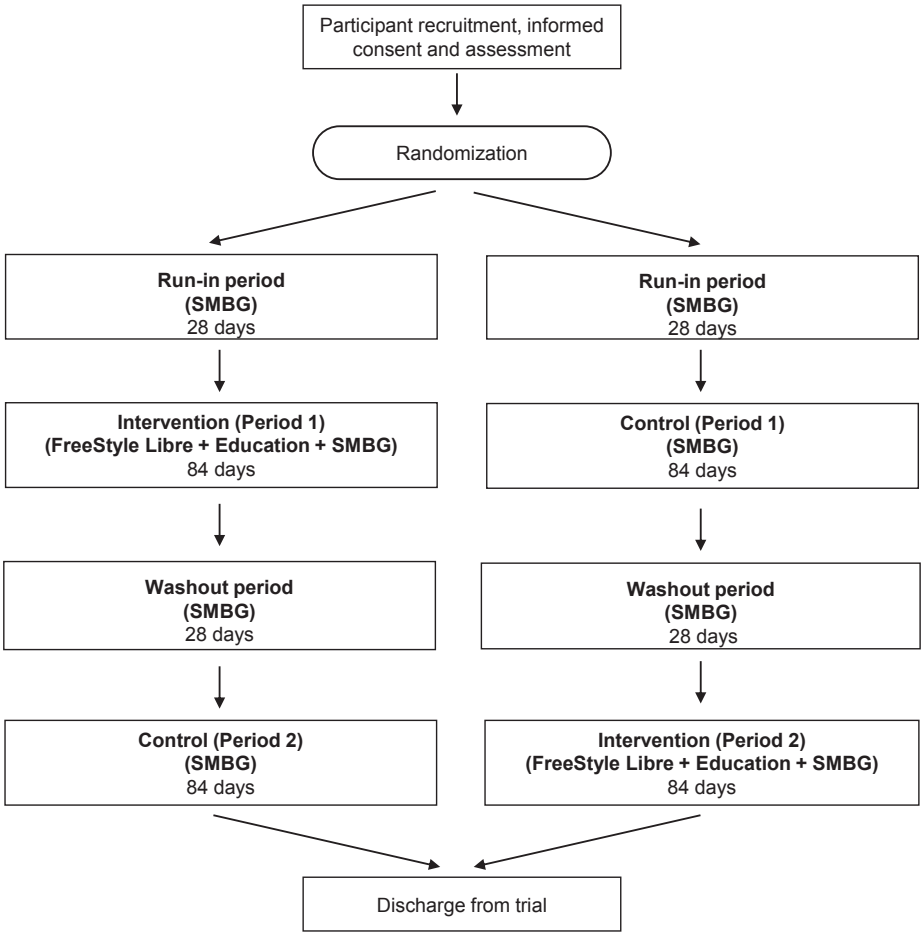

Figure The study design and visit plan
Participants are randomized at Visit 1 to either Intervention/Control or Control/Intervention. After the Run-in period of 28 (± 14) days, participants start Period 1 for 84 (± 14) days. Then, after the Washout period of 28 (± 14) days, participants start Period 2 for 84 (± 14) days.

setting.

We chose a crossover design for this study because T1D is a relatively rare disease in comparison to type 2 diabetes in Japan [23–25]. In addition, patient preferences regarding the use of isCGM or conventional SMBG can be a potential barrier to participant recruitment, because FreeStyle Libre had already received health insurance coverage in Japan prior to the initiation of the study. As the benefit of isCGM is expected to be lost when participants do not have access to isCGM based on the previous observation in a crossover trial using RT-CGM (SWITCH study) [18], any carryover effect is expected to be minimal, although this is assessed by a statistical analysis. The total study duration for the participants is 225 days (total 10 visits) and is separated into the following periods: 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) (Table 1, Figure). The reporting of this protocol is in accordance with the SPIRIT guidelines [26].

Trial objectives

This trial aims to prove that combined intervention consisting of the use of isCGM and structured education on isCGM is associated with reduced time in hypoglycemia in patients with T1D. The structured education focuses on the frequent scanning of the sensor and the trend arrow. This study also aims to evaluate the following secondary endpoints: other indices of glycemic control, device accuracy, glycoalbumin, diabetes-related QOL, adherence, and cost-effectiveness.

Study participants

The inclusion and exclusion criteria are listed in Table 2. Severe hypoglycemia is defined as an episode of hypoglycemia requiring assistance [27]. Participants continue flexible insulin regimens as the standard treatment for T1D during the trial. T1D patients using flexible insulin regimens adjust their insulin dosage according to their glucose levels, food intake and exercise [1].

Participants are provided an incentive equivalent to JPY 1,000, which is paid four times, in order to promote cooperation in completing a self-reported questionnaire to evaluate the diabetes-related QOL. Devices and consumables for isCGM and SMBG are purchased by the research budget and provided to the participants during Run-in period, Period 1, Washout period and Period 2.

Randomization and blinding

Participants are randomized to use isCGM combined with structured education to prevent hypoglyce-

Table 1 Study summary

		Screening	Run-in	Period 1			Washout	Period 2			Evaluation
Visit number		1	2	3	4	5	6	7	8	9	10
Day (Margin)		-84–1	1	29 (± 14)	57 (± 14)	85 (± 14)	113 (± 14)	141 (± 14)	169 (± 14)	197 (± 14)	225 (± 14)
Inclusion/Exclusion criteria, informed consent, randomization		X									
Patient characteristics†		X		X							
Height		X									
Weight		X		X			X	X			X
Vital Sign‡		X	X	X	X	X	X	X	X	X	X
Clinical laboratory test§		X		X			X	X			X
SMBG		◄	———	———	———	———	———	———	———	———	►
FreeStyle Libre and FreeStyle Libre Pro; details below											
Pharmacotherapy		X		X							X
Questionnaires				X			X	X			X
Adverse event		◄	———	———	———	———	———	———	———	———	►
Analysis											X
FreeStyle Libre and FreeStyle Libre Pro											
Intervention/ Control	Wearing FreeStyle Libre			◄	———	———	►				
	Download FreeStyle Libre				X	X	X				
	Wearing Libre Pro / Record the serial number							X	X	X	
	Download FreeStyle Precision Neo			X				X	X	X	X
Control/ Intervention	Wearing FreeStyle Libre							◄	———	———	►
	Download FreeStyle Libre								X	X	X
	Wearing Libre Pro / Record the serial number			X	X	X					
	Download FreeStyle Precision Neo			X	X	X	X	X			

† Age, sex, duration of type 1 diabetes mellitus, history of severe hypoglycemia within 1 year, history of insulin pump use, history of FreeStyle Libre use, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, pregnancy, planning pregnancy, life style (drinking habit, smoking habit), and social influence (employment situation).

‡ Blood pressure and pulse rate.

§ Biomedical examination: HbA1c (Visit 1), glycoalbumin (Visits 3, 6, 7, and 10), urinalysis; Qualitative (Visit 1), albumin/creatinine ratio (Visit 1)

Table 2 Inclusion criteria and exclusion criteria

Inclusion criteria.
・Adults aged between 20 and 74 years
・Have been diagnosed with T1D based on the criteria of Japan Diabetes Society (JDS) for 5 years or longer [28]
・Have a baseline HbA1c value of 8.5% or lower. HbA1c was measured at each institute following the standardized method determined by JDS [29]
・Have been managing their T1D with at least three daily insulin injections and performing SMBG at least three times per day within 30 days prior to providing their informed consent
・Provide written informed consent before enrolment. Participants may withdraw the informed consent at any time
Exclusion criteria.
・Pregnancy or planning pregnancy within 1 year after providing their informed consent
・End-stage renal failure (under hemodialysis or after kidney transplantation)
・Blindness
・Using an embedded medical device (cardiac pacemaker device, etc.)
・Using insulin pump therapy
・Using premixed insulin
・Any episode of severe hypoglycemia episodes within the previous 1 year prior to the provision of informed consent
・Using oral hypoglycemic agents to manage their T1D within the previous 1 year prior to the provision of informed consent
・Unable to participate due to other factors, based on the opinion of the treating clinician at trial entry

mia (Intervention period) or SMBG (Control period) for 84 days, followed by the other for a further 84 days, using a central web randomization system CliSSS Randoman (Medical Edge, Tokyo, Japan) in a 1:1 ratio. Randomization is performed by the minimization method. Participants are stratified before allocation according to the history of previous isCGM usage. The minimization factors are age, sex, and HbA1c.

As the participants have to manipulate isCGM and receive education, the intervention cannot be blinded. However, both the participants and the study investigators are blinded to data obtained by retrospective CGM in the Control period in order to avoid interference from the usage of retrospective CGM data.

Run-in period

All participants use the FreeStyle Precision Neo (Abbott Diabetes Care, Alameda, CA, USA) as SMBG device (Visit 2). All participants are educated on how to conduct SMBG accurately by washing their hands prior to blood sampling. Study participants continue to conduct SMBG at least three times a day.

Interventions

(1) Intervention period

The FreeStyle Libre Reader and FreeStyle Libre Sensor are used as the isCGM device for the Intervention period (Period 1 or Period 2). It is used as a tool to reduce time in hypoglycemia, and structured education regarding the trend arrow and the frequency of scanning is provided to the participants when they start to use the device (Visit 3 or Visit 7). The summary of the structured education to prevent hypoglycemia is presented in Table 3, and the details are described elsewhere [30]. The study participants use FreeStyle Libre throughout the Intervention period. As each FreeStyle Libre Sensor functions for maximum of 14 days, participants replace it with a new one by themselves according to the instructions provided at the beginning of the Intervention period as a part of the structured education. Participants continue to conduct SMBG at least three times a day to observe the intended usage of FreeStyle Libre (as approved in Japan) [10]. The non-adjunctive usage of FreeStyle Libre to SMBG by the participants in this study is not allowed, in order to comply with the Clinical Trials Act (Act No. 16 of April 14, 2017), Japan [31].

FreeStyle Libre Sensor glucose data are transmitted to FreeStyle Libre Reader every time the participants scan the Sensor. Data that accumulate in FreeStyle Libre Reader as log files are downloaded by the study investigators periodically (Visit 4, 5, and 6 or Visit 8, 9, and 10). The log files contain both the sensor glucose levels and SMBG results, accompanied by the time stamp information. The sensor glucose levels are recorded only at the timing of scanning, and are also automatically recorded every 15 minutes. The participants receive feedback on the downloaded data from the study investigators at Visit 4, 5, and 6 or Visit 8, 9, and 10. Data downloaded as log files at Visit 6 or Visit 10 are used for the statistical analyses; however, in the event that FreeStyle Libre Reader is lost or broken during the Intervention period, data downloaded at Visit 4, 5, 8, and 9 are also used for the statistical analyses.

(2) Control period

FreeStyle Precision Neo is used as SMBG device in the Control period. The study participants continue to conduct SMBG at least three times a day.

FreeStyle Libre Pro Sensor (Abbott Diabetes Care, Alameda, CA, USA) is used as retrospective CGM. The accuracy of this device is reported to be similar to that of the FreeStyle Libre [32]. FreeStyle Libre Pro Sensors are attached to the body of the participants and are activated by the healthcare providers (Visit 3, 4, and 5 or Visit 7, 8, and 9). After 14 days of usage, the participants directly send all FreeStyle Libre Pro Sensors back to the data center by postal mail for the data analysis. After sending the sensor back to the data

Table 3 Summary of the structured education to prevent hypoglycemia

To measure blood glucose level accurately by yourself.
・Wash your hands before the measurement.
Effective use of FreeStyle Libre.
・You are encouraged to frequently scan the sensor 10 times a day or more.
・In addition to watching the sensor glucose level, the direction of trend arrow should be carefully watched.
・The direction of the trend arrow indicates whether the glucose level is increasing, stable, or decreasing (five grades).
How to prevent low blood sugar.
・The downward vertical trend arrow indicates that the glucose level is decreasing at a rate of 2 mg/dl per minute (= 120 mg/dl per hour) or more.
・Determine whether hypoglycemia is impending by reflecting on the past insulin dosage, timing, physical activity, food intake, and glucose trend pattern even if you have no symptoms of hypoglycemia.
・If you find impending hypoglycemia, check the blood glucose level by finger prick glucose test if needed, and ingest a sufficient amount of sugar like glucose to stop the rapid decrease in glucose level.
・Discuss with your doctor and diabetes team beforehand about what and how much to ingest, as the required amount differs among individuals and situations.
・If you ingest too much sugar, you may experience rebound high. Follow actions after ingesting glucose to prevent hypoglycemia. Note that the change in the sensor glucose value is 5 to 10 minutes behind the finger prick glucose test, and you need to confirm your blood glucose levels by finger prick glucose test when the sensor glucose value does not change much after ingesting sugar.

center the participants do not wear FreeStyle Libre Pro Sensor, until their next visit (Visit 4 and 5 or Visit 8 and 9) or the end of the Control period (Visit 6 or Visit 10). The sensor glucose levels are automatically recorded every 15 minutes by FreeStyle Libre Pro sensor, and are downloaded as log files at the data center. Neither the participants nor the investigators receive any feedback from the FreeStyle Libre Pro data to avoid the interference from retrospective CGM.

Washout period

During this 28-day period, participants use the FreeStyle Precision Neo as SMBG device. Study participants continue to conduct SMBG at least three times a day.

Outcomes

The primary and secondary endpoints are listed in Table 4.

The primary endpoint is the decrease of time in hypoglycemia (< 70 mg/dL) per day (hour/day) during the Intervention period in comparison to the Control period. It is calculated from the downloaded log files of FreeStyle Libre (isCGM) used in the Intervention period and FreeStyle Libre Pro (retrospective CGM) used in the Control period. These log files contain sensor glucose levels that are recorded automatically every 15 minutes, and the time in hypoglycemia (hour/day) is calculated based on the number of instances in which the recorded sensor glucose level is < 70 mg/dL and the number of the overall recorded sensor glucose levels in the log files.

The TIR is calculated from the number of the sensor glucose levels of 70–180 mg/dl and the overall sensor glucose levels in the log files. Time Above Range (TAR) is calculated from the number of instances in which the sensor glucose level is >180 mg/dl and the overall sensor glucose levels in the log files.

The calculation of other indices of glycemic control such as ADRR, MODD, and LBGI is described elsewhere [33, 34].

Glycated albumin (GA) is measured using a Lucica® GA-L (Asahi Kasei Pharma Corporation, Tokyo, Japan) kit.

The accuracy of FreeStyle Libre is calculated from log files downloaded from FreeStyle Libre Readers. The log file contains both FreeStyle Libre Sensor glucose levels recorded at the time of scanning and the SMBG results, together with the time stamp of each measured value. The calculation of MARD and the mean absolute difference (MAD) is described elsewhere [32].

The diabetes-related QOL of the participants during the Intervention and Control periods is assessed at the beginning and at the end of both Period 1 and Period 2 (Visit 3, 6, 7, 10). PAID (Japanese version) is used to measure the psychological burden of diabetes and HFS (Japanese version) is used to measure the fear for hypoglycemia [35–37]. The incremental cost-effectiveness ratio (ICER) is calculated by dividing the difference in mean cost by the difference in the mean health outcome (e.g., hypoglycemia), using disutility associated with hypoglycemia in reference to a previous study [38]. The cost of isCGM and SMBG is calculated from the price list of the health insurance system in Japan.

Data collection, management and monitoring

The Case Report Form (CRF), Treatment Form and Adverse Events Form are first completed on paper copies and then double-entered into the Electronic Data Capture (EDC) system. The second level of data integrity includes data monitoring and validation, which are conducted on a regular basis throughout the study.

The safety of the study is monitored by a Data and Safety Monitoring Board (DSMB), which consists of independent clinical experts with access to unblinded data. DSMB provide advice to the principal investigator. The DSMB is independent from the funder.

Safety is assessed continuously in each institution. Any adverse events (AEs) are recorded and reported to the principal investigator, in accordance with the regulations stipulated in the Clinical Trials Act [31].

Table 4 Endpoints and measurement or assessment method

1. Endpoint	2. Measurement or assessment method
Primary	
Time spent in hypoglycemia per day (hours/day)	Assessed by the isCGM, FreeStyle Libre, (Intervention period), and by the retrospective CGM, FreeStyle Libre Pro, (Control period) to collect the sensor glucose data. Sensor glucose levels are recorded every 15 minutes in the log file of the device. Time spent in hypoglycemia (hours/day) is calculated by analyzing the log file.
Secondary	
Body weight	(Visit 1, 3, 6, 7 and 10)
Type of prescribed insulin	(Visit 1 and 10)
Total daily dose of prescribed insulin	(Visit 1 and 10)
Total daily dose of prescribed basal insulin	(Visit 1 and 10)
Frequency of injection of prescribed insulin	(Visit 1 and 10)
Glycoalubumin	(Visit 3, 6, 7 and 10)
Mean sensor glucose levels	Assessed by analyzing the log file of FreeStyle Libre and FreeStyle Libre pro.
Frequency of severe hypoglycemia	Self-reported (Visit 3, 6, 7 and 10).
Indexes for glucose fluctuation [average daily risk range (ADRR), mean of daily difference of blood glucose (MODD), low blood glucose index (LBGI), time in range 70–180 mg/dl (TIR), time above range >180 mg/dl (TAR)]	Assessed by analyzing the log file of FreeStyle Libre and FreeStyle Libre pro.
Emotional burden of diabetes [problem areas in diabetes (PAID)]	Assessed by a specifically designed self-reported questionnaire (Visit 3, 6, 7 and 10).
Fear of hypoglycemia [hypoglycemia fear survey (HFS)]	
Frequency of SMBG (measured)	Assessed by analyzing the log file of FreeStyle Presicion Neo and FreeStyle Libre.
Usage of isCGM	Assessed by analyzing the log file of FreeStyle Libre.
Mean absolute relative difference (MARD) , mean absolute difference (MAD)	Assessed by analyzing the log file of FreeStyle Libre.
Frequency of hypoglycemia per month	Self-reported (Visit 3, 6, 7 and 10).
Hypoglycemia unawareness	
Index for medical economics [cost effectiveness ratio (CER), incremental cost effectiveness ratio (ICER), quality-adjusted life years (QALY)]	Assessed by analyzing the log file of FreeStyle Libre and FreeStyle Libre pro.
Severe adverse event (SAE)	(At any time)
Adverse event (AE)	

Ethics and dissemination

This study is registered in the Japan Registry of Clinical Trials (jRCT1052180075). The study protocol received Certified Review Board (CRB) approval from National Hospital Organization Osaka National Hospital (N2018002, originally approved on February 14, 2019, Version 0.7; the latest revision was approved on May 26, 2020, Version 1.6).

This study is carried out in accordance with the principles of the Declaration of Helsinki and the Clinical Trials Act [31]. All participants receive a thorough explanation from the investigators before the study. Only those participants that provide their written informed consent are included (the details of the informed consent form, including the details on the secondary usage of the data, are described elsewhere) [39]. The personal data collected in the study are managed anonymously to protect personal information. National Hospital Organization Kyoto Medical Center has insurance to cover for non-negligent harm associated with the study.

The results of this study will be disseminated through peer-reviewed journals. Authorship eligibility will follow the recommendation by International Committee of Medical Journal Editors [40]. There is no plan for the intended use of professional writers. Individual deidentified participant data will be shared upon reasonable request to the Contact for Scientific Queries. This policy will be applied to all study data. Related documents, such as the study protocol will also be shared upon reasonable request; but only in Japanese. The data will become available in April 2024; however, the timing can be changed. Data will be available until March 2027.

Sample size estimation and statistical analysis

The sample size of the 104 participants is calculated assuming a matched-pairs *t*-test and a type I error of 5%, using the PASS 15 (NCSS, LLC, Kaysville, Utah, USA) software. With this sample size, the study has 80% power to detect a mean group difference of 1.24 in time in hypoglycemia per day (hour/day) based

on the observation of IMPACT study [19], and the assumed standard deviation (SD) is 3.70. In order to include a 10% allowance for size of prevention effects (assumed from the difference of the upper limit of HbA1c of 8.5% [in IMPACT study it was 7.5%]) and 20% allowance for withdrawals, the sample size is increased to 104. There is possibility that recruiting isCGM-naïve participants is difficult; the recruitment of a minimum of 42 and a maximum 62 participants with past experience of using isCGM is planned.

The last observation carried forward method is used to impute missing values. The carry-over effect is judged by Mainland-Gart test. If it exists, it is adjusted by a repeated measure ANOVA and mixed models using time and group interaction terms. Data from participants who withdraw from the study before randomization are deleted. When device malfunction occurs, data are handled according to the content of the deviation reports.

DISCUSSION

The ISCHIA study is the first randomized controlled trial to assess the effect of combined intervention involving the usage of and structured education on isCGM to decrease time in hypoglycemia in comparison to conventional SMBG. This is the first RCT of isCGM in Japan and is the first RCT for patients with T1D in Japan. This study receives no financial support from the manufacturer of the isCGM or SMBG devices.

The present study trial is associated with some limitations. It is an open-label study due to the nature of the intervention, and there is a possibility of carry-over effect due to the crossover design. The 10% allowance for the size of prevention effects related to the change of the HbA1c threshold used in the sample size estimation may not be accurate, as there are no available data from previous studies regarding this point.

This study will contribute to the standardization of patient education on isCGM to prevent hypoglycemia, with a particular focus on the importance of frequent scanning of the sensor and the utilization of the trend arrow. This study will provide additional information regarding the accuracy and cost-effectiveness of isCGM, as well as diabetes-specific QOL in patients using isCGM devices.

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LIST OF INVESTIGATORS

Steering Committee: Kiminori Hosoda, Division of Diabetes and Lipid Metabolism, National Cerebral and Cardiovascular Center, Osaka, Japan; Kunihiro Nishimura, Department of Preventive Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan; Yoshihiro Miyamoto, Open Innovation Center, National Cerebral and Cardiovascular Center, Osaka, Japan; Takashi Murata, Diabetes Center, NHO Kyoto Medical Center, Kyoto, Japan; Naoki Sakane, Division of Preventive Medicine, Clinical Research Institute, NHO Kyoto Medical Center, Kyoto, Japan; Noriko Satoh-Asahara, Department of Endocrinology, Metabolism, and Hypertension Research, Clinical Research Institute, NHO Kyoto Medical Center, Kyoto, Japan; Masao Toyoda, Division of Nephrology, Endocrinology and Metabolism, Department of Internal Medicine, Tokai University School of Medicine, Kanagawa, Japan; Yushi Hirota, Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Hospital, Hyogo, Japan; Munehide Matsuhisa and Akio Kuroda, Diabetes Therapeutics and Research Center, Institute of Advanced Medical Sciences, Tokushima University, Tokushima, Japan; Ken Kato, Diabetes Center, NHO Osaka National Hospital, Osaka, Japan; Ryuji Kouyama, Division of Endocrinology and Metabolism, Department of Internal Medicine, Tsuchiura Kyodo General Hospital, Ibaraki, Japan; Junnosuke Miura, Diabetes Center, Tokyo Women's Medical University School of Medicine, Tokyo, Japan; Atsuhito Tone, Department of Internal Medicine, Okayama Saiseikai General Hospital, Okayama, Japan; Masato Kasahara, Shu Kasama and Shota Suzuki, Institute for Clinical and Translational Science, Nara Medical University Hospital, Nara, Japan; Yukie Ito, Bioethics Supervisory Office, Nara Medical University Hospital, Nara, Japan.
Data and safety monitoring committee: Cheol Son, Tsutomu Tomita and Michio Noguchi, National Cerebral and Cardiovascular Center, Osaka, Japan.
ISCHIA study Group: The study group consists of the Steering Committee and the following members; Tomokazu Watanabe and Akiko Suganuma, NHO Kyoto Medical Center, Kyoto, Japan; Zhuo Shen, Hiroko Kobayashi, Satoshi Takagi, Sari Hoshina, Kanako Shimura and Yukiko Tsuchida, Tokyo Women's Medical University School of Medicine, Tokyo, Japan; Moritsugu Kimura and Nobumichi Saito, Division of Nephrology, Endocrinology and Metabolism, Department of Internal Medicine, Tokai University School of Medicine, Kanagawa, Japan; Akira Shimada, Yoichi Oikawa, Atsushi Satomura and Akifumi Haisa, Saitama Medical University, Saitama, Japan; Satoshi Kawashima, Kanda Naika Clinic, Osaka, Japan; Shu Meguro, Hiroshi Itoh, Yoshifumi Saisho, Junichiro Irie, Masami Tanaka, Masanori Mitsuishi, Yuya Nakajima, Jun Inaishi, Kenichiro Kinouchi, Shintaro Yamaguchi, Arata Itoh, Kazutoshi Sugiyama, Kazuma Yagi, Tami Tsuchiya and Noriko Kodani, Keio University School of Medicine, Tokyo, Japan; Ikki Shimizu and Tetsuya Fukuda, Sakakibara

Heart Institute of Okayama, Okayama, Japan; Yoshiki Kusunoki and Tomoyuki Katsuno, Hyogo College of Medicine, Hyogo, Japan; Yuka Matoba, Yumi Hitaka, Kentaro Abe, Natsuko Tanaka, Ryoko Taniguchi and Toshihiko Nagao, NHO Kokura Medical Center, Fukuoka, Japan; Kazuyuki Hida, Izumi Iseda, Masaya Takeda, Yuichi Matsushita and Masafumi Tenta, NHO Okayama Medical Center, Okayama, Japan; Tsuyoshi Tanaka, NHO Mie Chuo Medical Center, Mie, Japan; Kunichi Kouyama and Michiru Fukunaga, NHO Hyogo-Chuo National Hospital, Hyogo, Japan.

AUTHORS' CONTRIBUTIONS

Takashi Murata, Naoki Sakane, Masao Toyoda, Kiminori Hosoda conceived the design of the study. Naoki Sakane and Kunihiro Nishimura planned the statistical analyses. Shota Suzuki, Yukie Ito, Shu Kasama, Masato Kasahara, Akiko Suganuma planned the monitoring procedure. Tsutomu Tomita, Michio Noguchi and Cheol Son planned the assessment of the efficacy and safety of the study. Takashi Murata, Yoshihiro Miyamoto, Naoki Sakane, Shota Suzuki, Atsuhito Tone, Noriko Satoh-Asahara, Masao Toyoda, Yushi Hirota, Munehide Matsuhisa, Akio Kuroda, Ken Kato, Ryuji Kouyama, Junnosuke Miura wrote the protocol. Takashi Murata chaired the study and the protocol writing. Kiminori Hosoda supervised the project.

COFLICT OF INTEREST

The author(s) declare the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Atsuhito Tone discloses the following relationships: personal fees from Sanofi, Medtronic, Eli Lilly, Takeda, Tanabe-Mitsubishi, Novo Nordisk, Sanwa Kagaku, MSD, Sumitomo Dainippon, Astellas, Novartis, Taisho, Kyowa Kirin, Ono, Abbott, Boehringer Ingelheim, and AstraZeneca. Takashi Murata discloses the following relationships: personal fees from Sanofi, Kowa, Novo Nordisk, and Takeda; grants from Sanofi and Kowa. Naoki Sakane discloses the following relationships: grants, personal fees, and non-financial support from MSD, Sanofi, Eli Lilly, Novartis, Takeda, Astellas, Daiichi Sankyo, Tanabe-Mitsubishi, and AstraZeneca. Noriko Satoh-Asahara discloses the following relationships: grants from Takeda, Eli Lilly, Novartis, Novo Nordisk, MSD, Daiichi Sankyo, Tanabe-Mitsubishi, Teijin Pharma, and Mochida. Masao Toyoda discloses the following relationships: personal fees from Medtronic, Terumo, Abbott, MSD, Eli Lilly, Novartis, Takeda, Sumitomo Dainippon, Sanofi, Novo Nordisk, Daiichi Sankyo, Tanabe-Mitsubishi, Ono, Boehringer Ingelheim, AstraZeneca, and Astellas; grants from MSD, Eli Lilly, Takeda, Sanofi, Novo Nordisk, Daiichi Sankyo, Life Scan, and Tanabe-Mitsubishi. Yushi Hirota discloses the following relationships: personal fees from Novartis, Novo Nordisk, Taisho Pharma, AstraZeneca, Eli Lilly, Sanofi, MSD, Abbott, Astellas, Daiichi Sankyo, Sanwa Kagaku, Takeda, Ono, Sumitomo Dainippon, Terumo, Medtronic, Boehringer Ingelheim, Kowa, and Alcon Pharma. Munehide Matsuhisa discloses the following relationships: personal fees from Tanabe-Mitsubishi, Novartis, Novo Nordisk, Takeda, Sanofi, Astellas, MSD, and Eli Lilly; grants from Tanabe-Mitsubishi, Novartis, Boehringer Ingelheim, Ono, Sysmex, and Nissui. Akio Kuroda discloses the following relationships: personal fees from Novo Nordisk, Eli Lilly, Sanofi, Medtronic, and Life Scan. Ken Kato discloses the following relationships: personal fees from Medtronic, Sanofi, Novo Nordisk, Eli Lilly, Ono, Kowa, Arkray, Sanwa Kagaku, Takeda, Astellas, Tanabe-Mitsubishi, Terumo, and Boehringer Ingelheim. Ryuji Kouyama discloses the following relationships: personal fees from Sanofi, Eli Lilly, Novo Nordisk, MSD, Novartis, Takeda, Sumitomo Dainippon, Taisho Pharma, Ono, Astellas, Mitsubishi Tanabe, Boehringer Ingelheim, and AstraZeneca. Junnosuke Miura discloses the following relationships: personal fees from Taisho, Novo Nordisk, Novartis, Eli Lilly, Sanofi, Johnson & Johnson, Abbott, Terumo, Boehringer Ingelheim, Kyowa Kirin, Kanro, Takeda, Tanabe-Mitsubishi, MSD, Mylan, Kowa, AstraZeneca, and Astellas. Michio Noguchi discloses the following relationships: grants from Takeda, Novartis, Eli Lilly, Sanofi, and MSD. Tsutomu Tomita discloses the following relationships: grants from Takeda, Eli Lilly, Sanofi and MSD. Cheol Son discloses the following relationships: personal fees from MSD, Takeda, Ono, Sumitomo Dainippon, and Taisho Pharma; grants from MSD, Sanofi, Eli Lilly, Novartis, and Takeda. Masato Kasahara discloses the following relationships: personal fees from Reason Why; grants from Daiichi Sankyo. Kiminori Hosoda discloses the following relationships: grants, personal fees, and non-financial support from Mitsubishi Tanabe; personal fees from MSD, Sanofi, Eli Lilly, Novartis, Takeda, Astellas, Daiichi Sankyo, Amgen, Novo Nordisk, Kyowa Hakko Kirin, Ono, Sumitomo Dainippon, AstraZeneca, Taisho Pharma, Boehringer Ingelheim, and Omron Healthcare; grants from MSD, Sanofi, Eli Lilly, and Takeda. Other author declares no conflict of interest.

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