Flash glucose monitoring helps achieve better glycemnic control than conventional self-monitoring of blood glucose in non-insulin-treated type 2 diabetes: a randomized controlled trial

Eri Wada, Takeshi Onoue, Tomoko Kobayashi, Tomoko Handa, Ayaka Hayase, Masaaki Ito, Mariko Furukawa, Takayuki Okuji, Norio Okada, Shintaro Iwama, Mariko Sugiyama, Taku Tsunekawa, Hiroshi Takagi, Daisuke Hagiwara, Yoshihiro Ito, Hidetaka Suga, Ryoichi Banno, Motomitsu Goto, Hiroshi Arima

ABSTRACT

Introduction The present study aimed to evaluate the effects of flash glucose monitoring (FGM) and conventional self-monitoring of blood glucose (SMBG) on glycemic control in patients with non-insulin-treated type 2 diabetes.

Research design and methods In this 24-week, multicenter, open-label, randomized (1:1), parallel-group study, patients with non-insulin-treated type 2 diabetes at five hospitals in Japan were randomly assigned to the FGM (n=49) or SMBG (n=51) groups and were provided each device for 12 weeks. The primary outcome was change in glycated hemoglobin (HbA1c) level, and was compared using analysis of covariance model that included baseline values and group as covariates.

Results Forty-eight participants in the FGM group and 45 in the SMBG group completed the study. The mean HbA1c levels were 7.83% (62.1 mmol/mol) in the FGM group and 7.84% (62.2 mmol/mol) in the SMBG group at baseline, and the values were reduced in both FGM (−0.43% (−4.7 mmol/mol), p<0.001) and SMBG groups (−0.30% (−3.3 mmol/mol), p=0.001) at 12 weeks. On the other hand, HbA1c was significantly decreased from baseline values in the FGM group, but not in the SMBG group at 24 weeks (FGM: −0.46% (−5.0 mmol/mol), p<0.001; SMBG: −0.17% (−1.8 mmol/mol), p=0.124); a significant between-group difference was also observed (difference −0.29% (−3.2 mmol/mol), p=0.022). Diabetes Treatment Satisfaction Questionnaire score was significantly improved, and the mean glucose levels, SD of glucose, mean amplitude of glycemic excursions and time in hyperglycemia were significantly decreased in the FGM group compared with the SMBG group.

Conclusions Glycemic control was better with FGM than with SMBG after cessation of glucose monitoring in patients with non-insulin-treated type 2 diabetes.

Trial registration number UMIN000026452, jRCTs041180082.

INTRODUCTION

Self-monitoring of blood glucose (SMBG) helps achieve better glycemic control in patients with diabetes on insulin therapy by facilitating appropriate titration of insulin doses based on the blood glucose levels. Such improvements in glycemic control by SMBG have been shown in patients with type 1 diabetes and in those with type 2 diabetes treated with insulin. On the other hands, the efficacy of SMBG for patients with non-insulin-treated type 2 diabetes has been inconsistent among studies. This discrepancy may be attributed to differences in study...
designs; some studies showed that SMBG improved glycemic control, when combined with training to learn how to adjust diet and lifestyle, in patients with non-insulin-treated type 2 diabetes under poor metabolic control.\textsuperscript{3,4} The recently developed flash glucose monitoring (FGM)—also referred to as intermittently scanned continuous glucose monitoring—technology allows for continuous monitoring of interstitial glucose levels using a sensor worn on the back of the upper arm. Compared with SMBG with conventional finger-pricking method, FGM has been shown to reduce the time and frequency of hypoglycemia in a randomized controlled trial (RCT)\textsuperscript{9} and to reduce glycated hemoglobin (HbA1c) in observational studies\textsuperscript{10–13} in patients with type 1 diabetes. FGM has also been shown to be superior to SMBG in reducing hypoglycemia\textsuperscript{14} and HbA1c level\textsuperscript{15,16} in patients with type 2 diabetes treated with insulin.

In this study, we conducted an RCT to compare the effects of glucose monitoring with FGM and SMBG on glycemic control of patients with non-insulin-treated type 2 diabetes to clarify whether the reported superiority of FGM over SMBG is due only to adjustments in insulin dosage.

**PATIENTS AND METHODS**

**Study design**

This was a 24-week, multicenter, open-label, randomized (1:1), parallel-group study. Patients with type 2 diabetes were recruited at five participating hospitals in Japan (Nagoya University Hospital, Chunichi Hospital, Saiyukan Hospital, Konan Kosei Hospital and Japanese Red Cross Nagoya Daini Hospital). This clinical trial is registered in the Japanese University Hospital Medical Information Network Clinical Trials Registry (URL: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000030387) and the Japan Registry of Clinical Trials. Written informed consent was obtained from all participants after detailed counseling about the purpose of the study as well as the potential risks and benefits.

**Patients**

Patients were eligible for inclusion if they (1) had type 2 diabetes, (2) had HbA1c ≥7.5% (59 mmol/mol) and <8.5% (69 mmol/mol) and (3) were aged ≥20 years and <70 years. Patients were excluded if they (1) were treated with insulin, (2) had been using SMBG or FGM, (3) were on dialysis, (4) had severe renal failure (estimated glomerular filtration rate <30 mL/min/1.73 m\textsuperscript{2})\textsuperscript{17}, (5) had preproliferative diabetic retinopathy or proliferative diabetic retinopathy, (6) could not properly operate the devices or (7) were judged by their physicians to be unsuitable for participation in the study.

**Randomisation and masking**

The enrollment, randomization and follow-up schedule are outlined in online supplementary figure S1. Participants who qualified according to the above criteria and who visited one of the five participating hospitals between July 4, 2017 and November 19, 2018 were eligible for recruitment. After obtaining the consent of the participants, the researcher entered the information required for enrollment in a web-based registration system developed by the Department of Advanced Medicine at the Nagoya University Hospital. The system automatically determined the eligibility of each participant and randomly assigned him/her in a 1:1 ratio to the FGM or SMBG group with a dynamic allocation strategy using a minimization method. Stratification criteria included the hospital that the patient visited, sex, age (>60 or ≤60 years), body mass index (BMI >25 kg/m\textsuperscript{2} or ≤25 kg/m\textsuperscript{2}) and the use or non-use of oral hypoglycemic agents. The participants, investigators and study staff were not masked to group allocation.

**Interventions**

All participants wore a sensor (Free Style Libre Pro; Abbott Diabetes Care, Alameda, California, USA) for a baseline period of >7 days; the sensor glucose measurements obtained during this period were blinded (not visible) to the participants and investigators.

Subsequently, participants in the FGM group were provided an FGM device (Free Style Libre; Abbott Diabetes Care) and participants in the SMBG group were provided an SMBG device (Free Style Precision Neo; Abbott Diabetes Care). The participants in each group were instructed on how to use each device and how to adjust their diet and lifestyle based on the blood glucose levels. The target fasting and postprandial blood glucose levels were set at <130 mg/dL (7.2 mmol/L) and <180 mg/dL (10.0 mmol/L), respectively, based on the ‘Japanese Clinical Practice Guideline for Diabetes’ of the Japan Diabetes Association\textsuperscript{18} and the ‘Standards of Medical Care in Diabetes’ of the American Diabetes Association.\textsuperscript{19} The devices were provided for 12 weeks. Participants in the SMBG group wore a blinded sensor (Free Style Libre Pro) again for the last 2 weeks of the 12-week period.

In both groups, laboratory data in fasting condition, weight, blood pressure and changes in diabetes medication were collected at enrollment, 12 weeks and 24 weeks. The Diabetes Treatment Satisfaction Questionnaire (DTSQ) is used to assess patient satisfaction with the diabetes treatment,\textsuperscript{20} and the Japanese version of DTSQ\textsuperscript{21} was answered anonymously at enrollment and at 12 weeks. Higher scores on the DTSQ total score indicate greater treatment satisfaction, and lower scores indicate lesser treatment satisfaction.

**Outcomes**

The primary outcome was change in HbA1c level. Secondary outcomes included changes in BMI, blood pressure (BP), fasting plasma glucose (FPG), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, uric acid (UA),
Sample size
Based on the results of previous clinical trials that evaluated the effects of educational intervention on patients with type 2 diabetes,25 26 the geometric SD of change in HbA1c at the last observation period was assumed to be 0.7% (7.7 mmol/mol). We estimated that at least 48 participants were required in each treatment group to confer a statistical power of 80% to detect a significant difference of 0.4% (4.4 mmol/mol) change from baseline in the two groups at the end of the intervention. We thus planned to recruit 50 participants per group (100 in total) in consideration of potential discontinuation or dropout of enrolled participants during the study period.

Statistical analysis
Continuous variables are expressed as mean (SD) and nominal variables are expressed as frequency (%), unless stated otherwise. Between-group differences with respect to baseline values of continuous variables were assessed using the unpaired two-sample t-test; those with respect to nominal variables were assessed using the Fisher’s exact test.

The primary outcome, change in HbA1c, was compared using analysis of covariance (ANCOVA) model that included baseline values and group as covariates. In case of significant between-group difference at 24 weeks, the changes in HbA1c at 12 weeks are compared in the same way. In addition, a linear mixed model, which included baseline values, time, group and interactions between time and group as fixed effects, was used to compare the change in HbA1c from baseline at 12 and 24 weeks between groups. Student’s paired t-test was used to compare changes in HbA1c between baseline and 12 or 24 weeks in each group.

A linear mixed model, which included baseline values, time, group and interactions between time and group as fixed effects, was used to compare the change in BMI, BP, FPG, TG, HDL cholesterol, LDL cholesterol, UA and urinary albumin from baseline at 12 and 24 weeks between groups. The amount of changes in both groups at each evaluation time-point was compared after correcting multiplicity using the Tukey-Kramer method. Changes in antidiabetic drugs were classified as increased medicine, no change or decreased medicine, and were analyzed using the Mantel-extension test stratified by sex, age (>60 or ≤60 years), BMI at entry (>25 or ≤25 kg/m²) and the use or non-use of oral hypoglycemic agents. Changes in questionnaire responses were compared using ANCOVA model including baseline values and group as covariates. For the sensor data-derived secondary outcomes, the 120 hours after excluding the first 24 hours of the available recorded results were used. Sensor results of the FGM group were available from the final sensor wear. Sensor-derived glucose variability measures were compared between groups using ANCOVA model including baseline values and group as covariates. Analyses were conducted using two-sided tests at a significance level of 0.05. SAS V.9.4 software (SAS Institute, Cary, North Carolina, USA) was used for all statistical analyzes.

RESULTS
A schematic illustration of the study design is shown in figure 1. A total of 100 participants (49 in the FGM group and 51 in the SMBG group) were enrolled in the study. Forty-eight participants in the FGM group and 45 in the SMBG group completed the study. The baseline characteristics are shown in table 1. There were no significant between-group differences with respect to baseline characteristics including HbA1c levels (FGM: 7.83% (SD 0.25) (62.1 mmol/mol); SMBG: 7.84% (SD 0.27) (62.2 mmol/mol)).

The primary outcome, change in HbA1c level, is shown in figure 2. HbA1c was significantly reduced from baseline values in both groups at 12 weeks (FGM: –0.43% (–4.7 mmol/mol), 95% CI –0.57 to –0.28, p<0.001; SMBG: –0.30% (–3.3 mmol/mol), 95% CI –0.48 to –0.13, p=0.001), and there were no significant between-group differences in the ANCOVA model (difference –0.13%
Changes in BMI, BP and laboratory data between baseline and 24 weeks are shown in table 1. HbA1c was significantly higher at 24 weeks in the FGM group compared with the SMBG group at 24 weeks in the ANCOVA model (FGM: −0.46% (−5.0 mmol/mol), 95% CI −0.59 to −0.32, p<0.001; SMBG: −0.17% (−1.8 mmol/mol), 95% CI −0.05 to 0.11, p=0.124; difference −0.29% (−3.2 mmol/mol), 95% CI −0.54 to −0.05; p=0.022). HbA1c was significantly decreased in the FGM group compared with the SMBG group at 24 weeks in the ANCOVA model (−0.46% (−5.0 mmol/mol), 95% CI −0.59 to −0.32, p<0.001; SMBG: −0.17% (−1.8 mmol/mol), 95% CI −0.05 to 0.11, p=0.124; difference −0.29% (−3.2 mmol/mol), 95% CI −0.54 to −0.05; p=0.022). Change in HbA1c throughout the 24 weeks analyzed using a linear mixed model showed significant improvement in the FGM group compared with the SMBG group (−0.29% (−3.2 mmol/mol), 95% CI −0.53 to −0.06; p=0.014). Data are expressed as mean (95% CI). *Significant difference between groups, p<0.05. †p<0.05 vs baseline.

There were no significant between-group differences with respect to the changes in glucose CV and the time in hypoglycaemia. Changes in DTSQ score are shown in table 3. The DTSQ scores were collected from 45 participants in the FGM group and from 35 participants in the SMBG group. Mean glucose levels, SD of glucose, BGRI, CONGA 2 hour, MAGE, MODD, time in sensor glucose 70–180 mg/dL (3.9–10.0 mmol/L) and time in hyperglycaemia were significantly improved after intervention in the FGM group compared with the SMBG group. There were no significant between-group differences with respect to the levels of BMI, BP, FPG, TG, LDL, UA and urinary albumin.

The sensor data-derived glycemic outcomes are shown in table 3. Patients with sensor data recorded for <5 days were excluded, and data were collected from 41 participants in the FGM group and from 35 participants in the SMBG group. Mean glucose levels, SD of glucose, BGRI, CONGA 2 hour, MAGE, MODD, time in sensor glucose 70–180 mg/dL (3.9–10.0 mmol/L) and time in hyperglycaemia were significantly improved after intervention in the FGM group compared with the SMBG group. There were no significant between-group differences with respect to the changes in glucose CV and the time in hypoglycaemia.

Changes in DTSQ score are shown in table 3. The DTSQ scores were collected from 45 participants in the FGM group and from 45 participants in the SMBG group. The total score and scores for ‘Q2: frequency of hyperglycaemia’, ‘Q4; convenience’, ‘Q5: flexibility’, ‘Q7: recommend’ and ‘Q8; continue’ were significantly improved after intervention in the FGM group compared with the SMBG group.

Changes in antidiabetic drugs are shown in online supplementary table S2. No significant between-group differences were observed in this respect at 12 and 24 weeks. In the analysis of subgroups in which antidiabetic (-1.4 mmol/mol), 95% CI −0.35 to 0.09; p=0.241). On the other hand, HbA1c was significantly decreased from baseline values in the FGM group, but not in the SMBG group, at 24 weeks (FGM: −0.46% (−5.0 mmol/mol), 95% CI −0.59 to −0.32, p<0.001; SMBG: −0.17% (−1.8 mmol/mol), 95% CI −0.05 to 0.11, p=0.124); a significant between-group difference in this respect was observed in the ANCOVA model (difference −0.29% (−3.2 mmol/mol), 95% CI −0.54 to −0.05; p=0.022). Analyses with a linear mixed model also revealed that HbA1c was significantly decreased in the FGM group compared with the SMBG group throughout the study (−0.29% (−3.2 mmol/mol), 95% CI −0.53 to −0.06; p=0.014) (online supplementary table S1).

Changes in BMI, BP and laboratory data between baseline and 24 weeks are shown in table 2. HDL cholesterol level was significantly higher at 24 weeks in the FGM group compared with the SMBG group. There were no significant between-group differences with respect to the change in the levels of BMI, BP, FPG, TG, LDL, UA and urinary albumin.
The use of FGM also improved the glucose variability indices, mainly due to the reduction in the time in hyperglycemia, accompanied by a significant increase in HDL cholesterol levels. A previous study demonstrated that glucose measurement with FGM improved glycemic control and decreased the daily intake of carbohydrates in patients with type 1 diabetes. The authors of the study interpreted the data that the use of FGM might help patients in estimating their blood glucose levels in response to alterations made in their lifestyle; however, further analysis is necessary to prove this.

Consistent with previous studies, the improvement in DTSQ score in the FGM group was significantly greater than that in the SMBG group, which indicates that patient satisfaction with the diabetes treatment was higher in the FGM group. This may be due to the visual presentation of the glucose profile with FGM. Moreover, measurement of glucose with FGM is convenient and painless, which may have contributed to better patient satisfaction. Improvement in treatment satisfaction has been shown to enhance the self-efficacy of patients, improve their treatment compliance and promote lifestyle modifications. All these could have contributed to the result of this study.

The IMPACT (NCT02232698) and REPLACE (NCT02082184) studies were large-scale RCTs that compared the effects of FGM and SMBG on glycemic control in type 1 and type 2 diabetes treated with insulin. Both studies found no significant differences in HbA1c levels between groups; however, the incidence of hyperglycemia in the FGM group was lower than that in the SMBG group. In our study, the time in hyperglycemia was significantly decreased while that of hypoglycemia was not changed, HbA1c at 24 weeks was significantly decreased in the FGM group (−0.46% (−5.0 mmol/mol), 95% CI −0.60 to −0.31) compared with the SMBG group (−0.18% (−2.0 mmol/mol), 95% CI −0.41 to 0.05) in the ANCOVA model that included baseline value and group as covariates (p=0.044) (online supplementary table S4).

Adverse events are shown in online supplementary table S4. One participant in the FGM group was hospitalized because of prostate cancer. Three hypoglycemia adverse events were experienced by three participants (two in the FGM group and one in the SMBG group). None of the hypoglycemia adverse events was related to the device or study procedure. Eight participants reported eight device-related adverse events (seven in the FGM group and one on the SMBG group). All device-related adverse events involved skin problems related to physical contact with the sensor and none of these was serious adverse events. All were resolved at study exit.
was not changed in the FGM group compared with the SMBG group. The differences between studies may be attributable to the fact that the participants in our study were not treated with insulin, and therefore were at a relatively low risk of hypoglycemia. This may also explain why HbA1c levels were decreased in the FGM group in our study but not in previous studies.9 14

It is not clear from this study why the improved glycemic control was sustained even after the cessation of glucose monitoring in the FGM group. The first limitation of this study is that we did not evaluate lifestyle changes in patients enrolled, and it should be clarified in future whether or not the intervention with FGM leads to lifestyle improvement during and even after glucose monitoring.
Second limitation is that the antidiabetic drugs were not fixed during the 24-week long study period. However, there were no significant between-group differences with respect to change in antidiabetic drugs; in the analysis of subgroups with no changes in antidiabetic drugs, HbA1c at 24 weeks was significantly decreased in the FGM group compared with the SMBG group. Third, because FGM sensors were not worn at 24 weeks, the details about glucose variability at this point were not clear. Fourth, the research period was only 24 weeks, and it is unclear whether the improvement in glycemic control with the FGM would last longer.

In conclusion, while both FGM and SMBG had a comparable effect in improving glycemic control in patients with non-insulin-treated type 2 diabetes during 12-week glucose monitoring, glycemic control was better with FGM than with SMBG at additional 12 weeks after the cessation of glucose monitoring. Our results indicate that providing an opportunity to use FGM in patients with non-insulin-treated type 2 diabetes has the potential to provide a sustained improvement in glycemic control that persists after discontinuation of use.

Author affiliations
Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, Nagoya, Japan
1Department of CKD Initiatives Internal Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan
2Research Center of Health, Physical Fitness and Sports, Nagoya University, Nagoya, Japan
3Department of Advanced Medicine, Nagoya University Hospital, Nagoya, Japan

Acknowledgements The authors would like to thank the patients who participated in this study. The authors would like to thank Kaori Hosokawa (Chunichi Hospital), Koichi Mori (Saisyukan Hospital), Yoh Ariyoshi (Konan Kosei Hospital) and Akemi Inagaki (Japanese Red Cross Nagoya Daini Hospital) for their assistance in participant enrollment at their respective institutions. The authors would like to acknowledge support by the Clinical Research Coordinators at the Clinical Development.

Contributors TÖn, TK, MG and HA designed the study. EW, TK, TH, AH, MI, MF, TÖk, NO, TK, SI, MS, TT, HT, DH, YI, HS and RB acquired data. YK and MA analyzed data. EW, TÖn, MG and HA interpreted data. EW and TÖn wrote the first draft of the manuscript and together with all the coauthors worked collaboratively to write, discuss and review this manuscript which was revised and edited by HA. All authors have read and approved the final manuscript. TÖn 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.

Funding This study was supported by the Nagoya University Hospital Funding for Clinical Development.

Disclaimer The funder of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

Competing interests HA reports grants and speaker honoraria from Abbott Japan outside the submitted work.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the Ethical Committee of the Nagoya University Graduate School of Medicine (No. 2017–0091). This study was performed in accordance with the ethical principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC-BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD
Takeishi Onoue http://orcid.org/0000-0002-8589-9937

REFERENCES