


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

Eri Wada,¹ Takeshi Onoue ,¹ Tomoko Kobayashi,¹ Tomoko Handa,¹ Ayaka Hayase,¹ Masaaki Ito,¹ Mariko Furukawa,¹ Takayuki Okuji,¹ Norio Okada,¹ Shintaro Iwama,¹ Mariko Sugiyama,¹ Taku Tsunekawa,¹ Hiroshi Takagi,¹ Daisuke Hagiwara,¹ Yoshihiro Ito,^{1,2} Hidetaka Suga,¹ Ryoichi Banno,^{1,3} Yachiyo Kuwatsuka,⁴ Masahiko Ando,⁴ Motomitsu Goto,¹ Hiroshi Arima¹

To cite: Wada E, Onoue T, Kobayashi T, *et al.* Flash glucose monitoring helps achieve better glycemic control than conventional self-monitoring of blood glucose in non-insulin-treated type 2 diabetes: a randomized controlled trial. *BMJ Open Diab Res Care* 2020;**8**:e001115. doi:10.1136/bmjdr-2019-001115

► Additional material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjdr-2019-001115>).

Received 12 December 2019
Revised 5 May 2020
Accepted 13 May 2020



© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Takeshi Onoue;
t-onoue@med.nagoya-u.ac.jp
and Dr Hiroshi Arima;
arima105@med.nagoya-u.ac.jp

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

Significance of this study

What is already known about this subject?

► Flash glucose monitoring (FGM) has been shown to reduce hypoglycemia and glycosylated hemoglobin compared with self-monitoring of blood glucose (SMBG) with conventional finger-pricking method in patients with type 1 and type 2 diabetes treated with insulin.

What are the new findings?

► Compared with SMBG, FGM significantly improved mean glucose levels, glucose variability indices, time in hyperglycemia and treatment satisfaction (as measured by Diabetes Treatment Satisfaction Questionnaire score) in patients with non-insulin-treated type 2 diabetes.
► Intervention with FGM preserved good glycemic control even after the cessation of glucose monitoring.

How might these results change the focus of research or clinical practice?

► It is important to clarify in future whether the intervention with FGM leads to lifestyle improvement in patients with type 2 diabetes during or even after glucose monitoring.

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 diabetes¹ and in those with type 2 diabetes treated with insulin.² On the other hands, the efficacy of SMBG for patients with non-insulin-treated type 2 diabetes has been inconsistent among studies.³ 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.^{3–8} 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)⁹ and to reduce glycated hemoglobin (HbA1c) in observational studies^{10–13} in patients with type 1 diabetes. FGM has also been shown to be superior to SMBG in reducing hypoglycemia¹⁴ and HbA1c level^{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, Saisyukan 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 $\geq 7.5\%$ (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 m²¹⁷), (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/m² or ≤ 25 kg/m²) 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 Association¹⁸ and the ‘Standards of Medical Care in Diabetes’ of the American Diabetes Association.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,²⁰ and the Japanese version of DTSQ²¹ 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),

urinary albumin, DTSQ score, antidiabetic drugs and sensor-derived glucose variability measures. Sensor-derived glucose variability measures comprised time in hypoglycemia (<70 mg/dL (3.9 mmol/L), <55 mg/dL (3.1 mmol/L) and <45 mg/dL (2.5 mmol/L)), time in sensor glucose 70–180 mg/dL (3.9–10.0 mmol/L), time in hyperglycemia >180 mg/dL (10.0 mmol/L) and >240 mg/dL (13.3 mmol/L) and >300 mg/dL (16.7 mmol/L)), mean glucose and glucose variability measures. Glucose variability measures included SD of glucose, glucose coefficient of variation (CV), mean amplitude of glycemic excursions (MAGE), blood glucose risk index (BGRI), continuous overlapping net glycemic action (CONGA) 2 hour and mean of daily difference (MODD).^{22–24}

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,

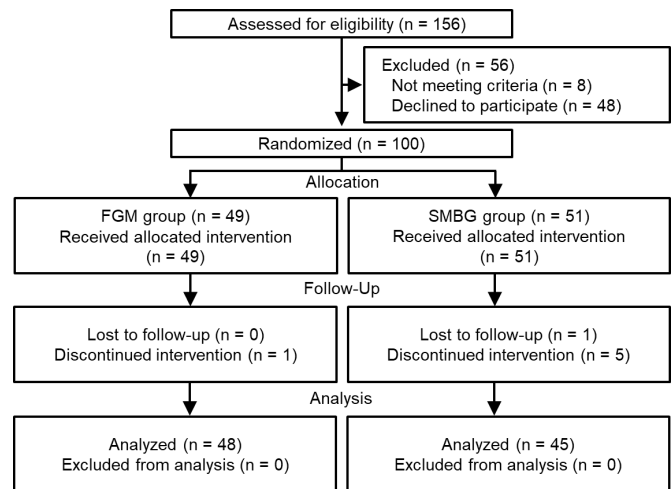


Figure 1 Schematic illustration of the study design. One-hundred participants were randomly assigned to the flash glucose monitoring (FGM) (n=49) or self-monitoring of blood glucose (SMBG) (n=51) group. Forty-eight participants in the FGM group and 45 participants in the SMBG group completed the study.

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 analyses.

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%

Table 1 Baseline characteristics

	FGM group (n=49)	SMBG group (n=51)	P value
Age (years)	58.1 (9.8)	58.7 (10.0)	0.76
Sex			
Female	15 (31%)	17 (33%)	0.48
Male	34 (69%)	34 (67%)	
Body weight (kg)	74.8 (22.1)	71.3 (14.0)	0.34
Body mass index (kg/m ²)	27.5 (6.5)	26.1 (4.1)	0.22
Blood pressure (mm Hg)			
Systolic blood pressure	134 (19)	132 (13)	0.64
Diastolic blood pressure	79 (12)	80 (10)	0.68
HbA1c (%)	7.83 (0.25)	7.84 (0.27)	0.75
HbA1c (mmol/mol)	62.1 (2.7)	62.2 (2.9)	0.75
FPG (mg/dL)	161 (40)	159 (42)	0.87
Total cholesterol (mg/dL)	191 (32)	192 (42)	0.95
Triglyceride (mg/dL)	155 (92)	173 (146)	0.47
HDL cholesterol (mg/dL)	54 (13)	52 (13)	0.49
LDL cholesterol (mg/dL)	110 (26)	111 (36)	0.93
UA (mg/dL)	5.3 (1.4)	5.0 (1.1)	0.39
Cr (mg/dL)	0.77 (0.20)	0.75 (0.18)	0.54
Urinary albumin (mg/gCr)	37 (56)	103 (334)	0.17
AST (IU/L)	26 (15)	23 (9)	0.18
ALT (IU/L)	34 (26)	29 (19)	0.29
Use of antidiabetic drugs	48 (98%)	49 (97%)	0.58
Use of antihypertensive drugs	23 (47%)	24 (47%)	0.99
Use of lipid-lowering drugs	31 (63%)	29 (57%)	0.51

Data are expressed as mean (SD) or n (%).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; FGM, flash glucose monitoring; FPG, fast plasma glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SMBG, self-monitoring of blood glucose; UA, uric acid.

(-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

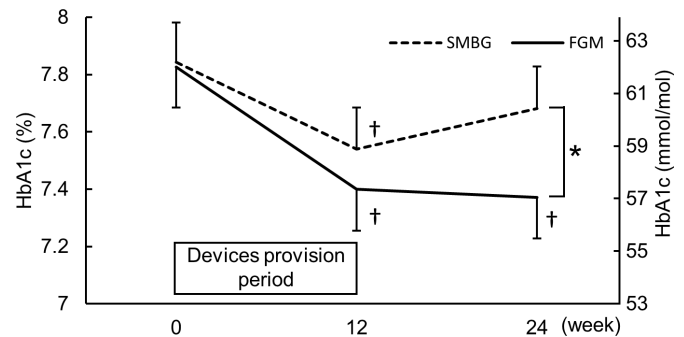


Figure 2 Change in glycated hemoglobin (HbA1c). HbA1c was reduced from baseline level in both groups at 12 weeks (flash glucose monitoring (FGM): -0.43% (-4.7 mmol/mol), 95% CI -0.57 to -0.28, $p<0.001$; self-monitoring of blood glucose (SMBG): -0.30% (-3.3 mmol/mol), 95% CI -0.48 to -0.13 $p=0.001$); there were no significant between-group differences in this respect in the analysis of covariance (ANCOVA) model (difference -0.13% (-1.4 mmol/mol), 95% CI -0.35 to 0.09; $p=0.241$). HbA1c was significantly decreased 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; $p=0.022$). 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.

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 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 hyperglycemia 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 hypoglycemia.

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 hyperglycemia', '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

Table 2 Changes in BMI, BP, laboratory data

	At 12 weeks		At 24 weeks		
	Difference in adjusted means in FGM vs SMBG (SE)	Adjusted P value*	Difference in adjusted means in FGM vs SMBG (SE)	Adjusted P value*	P value†
BMI (kg/m ²)	-0.3 (0.2)	0.396	-0.2 (0.2)	0.497	0.162
BP (mm Hg)					
Systolic BP	-0.3 (2.8)	1.000	0.4 (2.9)	0.999	0.877
Diastolic BP	1.2 (1.9)	0.925	1.5 (2.0)	0.865	0.440
FPG (mg/dL)	6.6 (7.4)	0.811	4.4 (7.4)	0.934	0.555
Triglyceride (mg/dL)	-17.9 (29.3)	0.928	-51.7 (29.4)	0.301	0.082
HDL cholesterol (mg/dL)	2.9 (1.7)	0.327	5.4 (1.7)	0.011	0.002
LDL cholesterol (mg/dL)	2.2 (3.7)	0.939	3.0 (3.7)	0.851	0.422
UA (mg/dL)	0.1 (0.2)	0.943	-0.2 (0.2)	0.699	0.280
Urinary albumin (mg/gCr)	-16.8 (15.6)	0.706	-4.6 (15.4)	0.990	0.764

P values <0.05 are shown in bold.

*The amount of change between groups at each evaluation time-point was compared after correcting for multiplicity using the Tukey-Kramer method.

†A linear mixed model was used to compare the change through 24 weeks between groups.

BMI, body mass index; BP, blood pressure; Cr, creatinine; FGM, flash glucose monitoring; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SMBG, self-monitoring of blood glucose; UA, uric acid.

drugs were 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 S3).

Adverse events are shown in online supplementary table S4. One participant in the FGM group was hospitalized because of prostate cancer. One participant in the SMBG group was hospitalized because of ophthalmic surgery. 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.

DISCUSSION

In this randomized controlled study, we showed that providing an opportunity to measure glucose levels with FGM significantly reduced HbA1c levels in patients with non-insulin-treated type 2 diabetes. Furthermore, while HbA1c levels were reduced at 12 weeks in both FGM and SMBG groups, the improved glycemic control was sustained only in the FGM group until 24 weeks, suggesting that the use of FGM enabled patients to preserve good glycemic control even after glucose measurement was discontinued.

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.²⁷ 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,^{9 14} 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.²⁸ 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 hypoglycemia in the FGM group was lower than that in the SMBG group.^{9 14} In our study, the time in hyperglycemia was significantly decreased while that of hypoglycemia

Table 3 Glycemic outcomes and DTSQ scores

Glycemic outcomes	Baseline mean (SD)		Intervention end mean (SD)		Difference in adjusted means in FGM vs SMBG (95% CI)	P value
	FGM (n=41)	SMBG (n=35)	FGM (n=41)	SMBG (n=35)		
Mean glucose (mg/dL)	170 (29)	158 (32)	146 (19)	156 (31)	-15 (-22 to -8)	<0.001
SD of glucose (mg/dL)	46 (11)	44 (11)	38 (9)	43 (13)	-5 (-8 to -2)	<0.001
Glucose CV (%)	26.9 (5.0)	28.4 (5.9)	26.6 (6.8)	27.4 (5.1)	0.2 (-1.2 to 1.7)	0.762
MAGE (mg/dL)	110 (27)	111 (30)	91 (22)	108 (33)	-17 (-24 to -9)	<0.001
BGRI	9.8 (3.8)	9.1 (4.2)	6.9 (3.4)	8.4 (4.1)	-1.7 (-2.8 to -0.5)	0.005
CONGA 2 hour (mg/dL)	136 (25)	125 (27)	117 (18)	124 (26)	-12 (-18 to -6)	<0.001
MODD (mg/dL)	41 (14)	38 (10)	33 (11)	37 (12)	-5 (-8 to -1)	0.006
Glucose 70–180 mg/dL (3.9–10.0 mmol/L) within 24 hours period						
Duration (hours)	14.36 (4.79)	15.62 (4.27)	18.71 (3.15)	16.65 (4.35)	2.36 (1.21 to 3.51)	<0.001
Glucose <70 mg/dL (3.9 mmol/L) within 24 hours period						
Duration (hours)	0.10 (0.42)	0.78 (3.11)	0.38 (1.10)	0.41 (1.12)	0.13 (-0.19 to 0.45)	0.423
AUC (hour×mg/dL)	0.80 (3.17)	13.84 (66.42)	5.51 (19.49)	3.03 (8.36)	3.46 (-1.37 to 8.29)	0.163
Glucose <55 mg/dL (3.1 mmol/L) within 24 hours period						
Duration (hours)	0.01 (0.05)	0.41 (2.16)	0.16 (0.64)	0.03 (0.11)	0.13 (-0.03 to 0.28)	0.103
AUC (hour×mg/dL)	0.09 (0.38)	5.02 (27.91)	1.64 (7.04)	0.14 (0.53)	1.51 (-0.15 to 3.17)	0.077
Glucose <45 mg/dL (2.5 mmol/L) within 24 hours period						
Duration (hours)	0.00 (0.02)	0.30 (1.73)	0.10 (0.43)	0.00 (0.01)	0.10 (-0.00 to 0.20)	0.064
AUC (hour×mg/dL)	0.05 (0.23)	4.42 (25.46)	1.38 (6.12)	0.02 (0.11)	1.37 (-0.07 to 2.81)	0.065
Time in hyperglycemia glucose level within 24 hours period						
>180 mg/dL (10.0 mmol/L) (hours)	9.53 (4.91)	7.60 (4.48)	4.94 (3.25)	6.94 (4.72)	-2.66 (-3.85 to -1.48)	<0.001
>240 mg/dL (13.3 mmol/L) (hours)	2.60 (2.49)	2.16 (2.36)	0.75 (0.83)	1.86 (2.30)	-1.23 (-1.73 to -0.73)	<0.001
>300 mg/dL (16.7 mmol/L) (hours)	0.47 (0.92)	0.33 (0.67)	0.04 (0.11)	0.39 (0.88)	-0.39 (-0.57 to -0.20)	<0.001
DTSQ score						
	FGM (n=45)	SMBG (n=45)	FGM (n=45)	SMBG (n=45)		
Total score	31.3 (6.2)	31.0 (6.7)	34.9 (5.2)	31.4 (6.6)	3.4 (1.9 to 5.0)	<0.001
Q1 current treatment	4.8 (1.0)	4.6 (1.4)	5.1 (1.0)	4.8 (1.0)	0.3 (-0.0 to 0.5)	0.070
Q2 frequency of hyperglycemia	3.6 (1.9)	3.5 (1.7)	3.6 (1.6)	3.2 (1.6)	0.4 (0.0 to 0.9)	0.047
Q3 frequency of hypoglycemia	1.2 (1.5)	0.8 (1.1)	1.4 (1.6)	1.4 (1.4)	-0.0 (-0.4 to 0.5)	0.938
Q4 convenience	4.3 (1.2)	4.5 (1.3)	5.1 (1.0)	4.2 (1.4)	0.9 (0.6 to 1.3)	<0.001
Q5 flexibility	4.3 (1.2)	4.4 (1.2)	4.8 (1.1)	4.2 (1.4)	0.6 (0.3 to 1.0)	<0.001
Q6 understanding	4.0 (1.3)	4.2 (1.2)	4.6 (1.2)	4.4 (1.0)	0.2 (-0.1 to 0.5)	0.120
Q7 recommend	4.5 (1.2)	4.4 (1.3)	5.4 (1.0)	4.6 (1.4)	0.7 (0.4 to 1.1)	<0.001
Q8 continue	4.6 (1.2)	4.5 (1.4)	5.0 (1.1)	4.6 (1.1)	0.3 (0.0 to 0.6)	0.040

P values <0.05 are shown in bold.

AUC, area under the curve; BGRI, blood glucose risk index; CONGA, continuous overlapping net glycaemic action; CV, coefficient of variation; DTSQ, Diabetes Treatment Satisfaction Questionnaire; FGM, flash glucose monitoring; MAGE, mean amplitude of glycaemic excursions; MODD, mean of daily difference; SMBG, self-monitoring of blood glucose.

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 glycaemic 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

¹Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, Nagoya, Japan

²Department of CKD Initiatives Internal Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan

³Research Center of Health, Physical Fitness and Sports, Nagoya University, Nagoya, Japan

⁴Department 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 Department of Advanced Medicine, Nagoya University Hospital.

Contributors TOn, TK, MG and HA designed the study. EW, TK, TH, AH, MI, MF, TOK, NO, TK, SI, MS, TT, HT, DH, YI, HS and RB acquired data. YK and MA analyzed data. EW, TOn, MG and HA interpreted data. EW and TOn 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. TOn 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

Takeshi Onoue <http://orcid.org/0000-0002-8589-9937>

REFERENCES

- 1 Miller KM, Beck RW, Bergenstal RM, *et al*. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. *Diabetes Care* 2013;36:2009–14.
- 2 Karter AJ, Ackerson LM, Darbinian JA, *et al*. Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente diabetes registry. *Am J Med* 2001;111:1–9.
- 3 Gagliardino J, Bergenstal R, Colagiuri S. *IDF guideline on self-monitoring of blood glucose in non-insulin treated type 2 diabetes*. Brussels: International Diabetes Federation, 2008.
- 4 Towfigh A, Romanova M, Weinreb JE, *et al*. Self-monitoring of blood glucose levels in patients with type 2 diabetes mellitus not taking insulin: a meta-analysis. *Am J Manag Care* 2008;14:468–75.
- 5 McIntosh B, Yu C, Lal A, *et al*. Efficacy of self-monitoring of blood glucose in patients with type 2 diabetes mellitus managed without insulin: a systematic review and meta-analysis. *Open Med* 2010;4:e102–13.
- 6 Schütt M, Kern W, Krause U, *et al*. Is the frequency of self-monitoring of blood glucose related to long-term metabolic control? Multicenter analysis including 24,500 patients from 191 centers in Germany and Austria. *Exp Clin Endocrinol Diabetes* 2006;114:384–8.
- 7 Davidson MB, Castellanos M, Kain D, *et al*. The effect of self monitoring of blood glucose concentrations on glycosylated hemoglobin levels in diabetic patients not taking insulin: a blinded, randomized trial. *Am J Med* 2005;118:422–5.
- 8 Guerci B, Drouin P, Grangé V, *et al*. Self-monitoring of blood glucose significantly improves metabolic control in patients with type 2 diabetes mellitus: the Auto-Surveillance intervention active (ASIA) study. *Diabetes Metab* 2003;29:587–94.
- 9 Bolinder J, Antuna R, Geelhoed-Duijvestijn P, *et al*. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet* 2016;388:2254–63.
- 10 Dover AR, Stimson RH, Zammit NN, *et al*. Flash glucose monitoring improves outcomes in a type 1 diabetes clinic. *J Diabetes Sci Technol* 2017;11:442–3.
- 11 Kramer G, Michalak L, Müller UA, *et al*. Association between flash glucose monitoring and metabolic control as well as treatment satisfaction in outpatients with diabetes type 1. *Exp Clin Endocrinol Diabetes* 2019. doi:10.1055/a-0875-3988. [Epub ahead of print: 11 Jun 2019].
- 12 Tyndall V, Stimson RH, Zammit NN, *et al*. Marked improvement in HbA1c following commencement of flash glucose monitoring in people with type 1 diabetes. *Diabetologia* 2019;62:1349–56.
- 13 Paris I, Henry C, Pirard F, *et al*. The new FreeStyle libre flash glucose monitoring system improves the glycaemic control in a cohort of people with type 1 diabetes followed in real-life conditions over a period of one year. *Endocrinol Diabetes Metab* 2018;1:e00023.
- 14 Haak T, Hanaire H, Ajjan R, *et al*. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. *Diabetes Ther* 2017;8:55–73.
- 15 Yaron M, Roitman E, Aharon-Hananel G, *et al*. Effect of flash glucose monitoring technology on glycemic control and treatment satisfaction in patients with type 2 diabetes. *Diabetes Care* 2019;42:1178–84.
- 16 Ajjan RA, Jackson N, Thomson SA. Reduction in HbA1c using professional flash glucose monitoring in insulin-treated type 2 diabetes patients managed in primary and secondary care settings: a pilot, multicentre, randomised controlled trial. *Diab Vasc Dis Res* 2019;16:385–95.
- 17 Matsuo S, Imai E, Horio M, *et al*. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53:982–92.

- 18 Haneda M, Noda M, Origasa H, *et al.* Japanese clinical practice guideline for diabetes 2016. *Diabetol Int* 2018;9:1–45.
- 19 American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 2019;42:S61–70.
- 20 Bradley C, Gamsu DS. Guidelines for encouraging psychological well-being: report of a working group of the world Health organization regional office for Europe and international diabetes Federation European region St Vincent Declaration action programme for diabetes. *Diabet Med* 1994;11:510–6.
- 21 Ishii H. The Japanese Version of the Diabetes Treatment Satisfaction Questionnaire (DTSQ) : translation and clinical evaluation. *J Clin Exp Med* 2000;192:809–14.
- 22 Kovatchev BP, Clarke WL, Breton M, *et al.* Quantifying temporal glucose variability in diabetes via continuous glucose monitoring: mathematical methods and clinical application. *Diabetes Technol Ther* 2005;7:849–62.
- 23 McDonnell CM, Donath SM, Vidmar SI, *et al.* A novel approach to continuous glucose analysis utilizing glycemic variation. *Diabetes Technol Ther* 2005;7:253–63.
- 24 Clarke W, Kovatchev B. Statistical tools to analyze continuous glucose monitor data. *Diabetes Technol Ther* 2009;11(Suppl 1):S-45–54.
- 25 Arambepola C, Ricci-Cabello I, Manikavasagam P, *et al.* The impact of automated brief messages promoting lifestyle changes delivered via mobile devices to people with type 2 diabetes: a systematic literature review and meta-analysis of controlled trials. *J Med Internet Res* 2016;18:e86.
- 26 Orsama A-L, Lähteenmäki J, Harno K, *et al.* Active assistance technology reduces glycosylated hemoglobin and weight in individuals with type 2 diabetes: results of a theory-based randomized trial. *Diabetes Technol Ther* 2013;15:662–9.
- 27 Al Hayek AA, Robert AA, Al Dawish MA. Differences of FreeStyle Libre flash glucose monitoring system and finger pricks on clinical characteristics and glucose monitoring Satisfaction in type 1 diabetes using insulin pump. *Clin Med Insights Endocrinol Diabetes* 2019;12:117955141986110.
- 28 Saisho Y. Use of diabetes treatment satisfaction questionnaire in diabetes care: importance of patient-reported outcomes. *Int J Environ Res Public Health* 2018;15. doi:10.3390/ijerph15050947. [Epub ahead of print: 09 May 2018].