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

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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 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 design. FGM may provide advantages over SMBG for patients with non-insulin-treated type 2 diabetes because it is more convenient than SMBG and facilitates appropriate titration of insulin doses based on glycemic excursions.
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. 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) and to reduce glycated hemoglobin (HbA1c) in observational studies in patients with type 1 diabetes. FGM has also been shown to be superior to SMBG in reducing hypoglycemia and HbA1c level 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, Saiseikukan 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 m²), (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 Association and the ‘Standards of Medical Care in Diabetes’ of the American Diabetes Association. 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, and the Japanese version of DTSQ 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), mean of daily difference (MODD), 22–24 excursion (MAGE), blood glucose risk index (BGRI), continuous overlapping net glycemic action (CONGA) 2,22–24,25,26 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.

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 V9.4 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 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 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 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 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.

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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 drugs were used, the results were shown in supplementary table S1.
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. 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. 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.

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## Table 3 Glycemic outcomes and DTSQ scores

<table>
<thead>
<tr>
<th>Glycemic outcomes</th>
<th>Baseline mean (SD)</th>
<th>Intervention end mean (SD)</th>
<th>Difference in adjusted means in FGM vs SMBG (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FGM (n=41)</td>
<td>SMBG (n=35)</td>
<td>FGM (n=41)</td>
<td>SMBG (n=35)</td>
</tr>
<tr>
<td>Mean glucose (mg/dL)</td>
<td>170 (29)</td>
<td>158 (32)</td>
<td>146 (19)</td>
<td>156 (31)</td>
</tr>
<tr>
<td>SD of glucose (mg/dL)</td>
<td>46 (11)</td>
<td>44 (11)</td>
<td>38 (9)</td>
<td>43 (13)</td>
</tr>
<tr>
<td>Glucose CV (%)</td>
<td>26.9 (5.0)</td>
<td>28.4 (5.9)</td>
<td>26.6 (6.8)</td>
<td>27.4 (5.1)</td>
</tr>
<tr>
<td>MAGE (mg/dL)</td>
<td>110 (27)</td>
<td>111 (30)</td>
<td>91 (22)</td>
<td>108 (33)</td>
</tr>
<tr>
<td>BGRI</td>
<td>9.8 (3.8)</td>
<td>9.1 (4.2)</td>
<td>6.9 (3.4)</td>
<td>8.4 (4.1)</td>
</tr>
<tr>
<td>CONGA 2 hour (mg/dL)</td>
<td>136 (25)</td>
<td>125 (27)</td>
<td>117 (18)</td>
<td>124 (26)</td>
</tr>
<tr>
<td>MODD (mg/dL)</td>
<td>41 (14)</td>
<td>38 (10)</td>
<td>33 (11)</td>
<td>37 (12)</td>
</tr>
</tbody>
</table>

- **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 |
- **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 |

<table>
<thead>
<tr>
<th>DTSQ score</th>
<th>Baseline mean (SD)</th>
<th>Intervention end mean (SD)</th>
<th>Difference in adjusted means in FGM vs SMBG (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FGM (n=45)</td>
<td>SMBG (n=45)</td>
<td>FGM (n=45)</td>
<td>SMBG (n=45)</td>
</tr>
<tr>
<td>Total score</td>
<td>31.3 (6.2)</td>
<td>31.0 (6.7)</td>
<td>34.9 (5.2)</td>
<td>31.4 (6.6)</td>
</tr>
<tr>
<td>Q1 current treatment</td>
<td>4.8 (1.0)</td>
<td>4.6 (1.4)</td>
<td>5.1 (1.0)</td>
<td>4.8 (1.0)</td>
</tr>
<tr>
<td>Q2 frequency of hyperglycemia</td>
<td>3.6 (1.9)</td>
<td>3.5 (1.7)</td>
<td>3.6 (1.6)</td>
<td>3.2 (1.6)</td>
</tr>
<tr>
<td>Q3 frequency of hypoglycemia</td>
<td>1.2 (1.5)</td>
<td>0.8 (1.1)</td>
<td>1.4 (1.6)</td>
<td>1.4 (1.4)</td>
</tr>
<tr>
<td>Q4 convenience</td>
<td>4.3 (1.2)</td>
<td>4.5 (1.3)</td>
<td>5.1 (1.0)</td>
<td>4.2 (1.4)</td>
</tr>
<tr>
<td>Q5 flexibility</td>
<td>4.3 (1.2)</td>
<td>4.4 (1.2)</td>
<td>4.8 (1.1)</td>
<td>4.2 (1.4)</td>
</tr>
<tr>
<td>Q6 understanding</td>
<td>4.0 (1.3)</td>
<td>4.2 (1.2)</td>
<td>4.6 (1.2)</td>
<td>4.4 (1.0)</td>
</tr>
<tr>
<td>Q7 recommend</td>
<td>4.5 (1.2)</td>
<td>4.4 (1.3)</td>
<td>5.4 (1.0)</td>
<td>4.6 (1.4)</td>
</tr>
<tr>
<td>Q8 continue</td>
<td>4.6 (1.2)</td>
<td>4.5 (1.4)</td>
<td>5.0 (1.1)</td>
<td>4.6 (1.1)</td>
</tr>
</tbody>
</table>

P values <0.05 are shown in bold.

AUC, area under the curve; BGRI, blood glucose risk index; CONGA, continuous overlapping net glycemic action; CV, coefficient of variation; DTSQ, Diabetes Treatment Satisfaction Questionnaire; FGM, flash glucose monitoring; MAGE, mean amplitude of glycemic 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 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.

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**Contributors** TOn, TK, MG and HA designed the study. EW, TK, TH, AH, MI, MF, TöKE, 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.

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