RESEARCH ARTICLE

Diabetes Management

Experience of short-term continuous glucose monitoring in people with Type 1 diabetes with persistent poor glycemic control

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Practice points

- Continuous glucose monitoring (CGM) through the use of the FreeStyle Navigator (FSN) could aid treatment in improving HbA1c without increasing the risk of hypoglycemia.
- A 6-month, multicenter, single-arm, pilot, intervention trial in the UK was conducted in 32 subjects who had previously completed a structured education program, and who maintained regular glucose testing.
- CGM results from the FSN were used to support glucose management and any regimen changes, and glucose data were reviewed by the healthcare professional (HCP) at days 90 and 180.
- At 6 months, mean change in HbA1c from baseline was -0.3%.
- Significant reductions were also seen at days 21 and 95.
- At 6 months, 44% of participants had a ≥0.5% HbA1c reduction from baseline.
- At days 21 and 95, 38 and 25% of participants achieved this reduction.
- There was no difference in number of blood glucose excursions per day or time spent in hypoglycemia.
- There was no improvement in the time spent in glucose levels >10.0 mmol/l.
- An improvement was observed in time spent in very high glucose levels >14.4 mmol/l.
- No difference in mean glucose concentration was observed from baseline to 6 months.
- Mean scores for Hypoglycemic Fear Survey behavior and Hypoglycemic Fear Survey worry components did not change significantly from baseline to study day 180.
- No significant difference in present quality of life scores in the Audit of Diabetes-Dependent Quality of Life from study day 1–180 was observed.
- Mean scores on 'impact of diabetes on quality of life' significantly improved.
- Twenty five percent of HCPs responded that they learned about patients' lifestyle and activity, 19% learned about patients' compliance to advice, 16% about patients' dietary habits and 16% learned about the duration and action of insulin.
- HCPs were asked about which features of the FSN they found most useful: 34% quoted the logbook, 28% the diary list, 25% the pie charts and 25% the overnight data.
- Short or intermittent use of CGM with real-time glucose results displayed on the device resulted in significant improvements in HbA1c.
- HCPs gained insight into insulin action and duration, overnight glucose trends and the effects of daily activities on glucose patterns.

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Future Medicine part of fsg

Aim: This study assessed the effect of short/intermittent use of continuous glucose monitoring in poorly controlled Type 1 diabetes. **Methods:** A 6-month, multicenter, single-arm, pilot study, enrolling 32 people on multiple daily injections who had completed a structured education program. The primary end point was to evaluate HbA1c change from baseline to 6 months. **Results:** Median HbA1c change from baseline was -0.4% at day 21, -0.3% at day 95 and -0.3% at 6 months. At 6 months, 44% of participants had a ≥0.5% HbA1c reduction from baseline. Hypoglycemia frequency and time spent in hypoglycemia did not change. **Conclusion:** Short/intermittent use of continuous glucose monitoring with real-time glucose values, in conjunction with a healthcare professional diabetes management review, resulted in significant HbA1c improvements.

KEYWORDS
• continuous glucose monitoring • FreeStyle Navigator • HbA1c • insulin • Type 1 diabetes

The Diabetes Control and Complications Trial (DCCT) showed that tight glucose control in people with Type 1 diabetes (T1D) reduced the risk of development or progression of long-term diabetes complications [1]. However, despite intensive treatment and educational activities such as carbohydrate counting, many people with T1D do not reach a goal of HbA1c <7%. Factors associated with poor glycemic control include variability, hypoglycemia, nonconcordance with treatment regimens, dietary choices, injection technique and social and psychological issues.

Studies have demonstrated that the use of continuous glucose monitoring (CGM) may aid treatment in improving HbA1c, without an increased risk of hypoglycemia [2–4]. Additional research has shown that the information obtained allows the patient and healthcare team to adjust the timing and dosage of insulin, and the nutrition plan, to improve glycemic control [5].

The availability of CGM technology has also generated clinical practice protocols for short-term professional use of CGM, generally for 3–7 days, for studying trends of glycemic control and to help tailor disease management for individuals with diabetes. During short-term use of CGM, the patient is often unaware of the results of monitoring until the data are downloaded and reviewed (blinded or masked wear) [6,7]. A tool that aids patients with diabetes to improve glycemic control with reduced risk of severe hypoglycemia could have psychological benefits such as enhanced feelings of security and reduced fears about hypoglycemia [8].

While CGM technology has developed and been evaluated over the last decade, there has been limited assessment of the benefits of short-term CGM by healthcare professionals (HCPs) in clinical management of people with poor glycemic control, and there is currently no consensus on the use of short-term professional CGM.

The aim of the study was to assess the effect of short or intermittent use of CGM in people with T1D with persistently poor glycemic control, despite participation in educational activities.

Methods

• Study cohort

This was a UK, five-center, single-arm, pilot, interventional trial conducted over 6 months. Adult patients aged ≥18–65 years, with T1D treated with multiple daily injections of insulin (MDI) for >1 year, with HbA1c ≥8.0% for the previous two HbA1c tests (the last HbA1c result being obtained within 3 months prior to study entry), frequency of SMBG testing ≥4-times per day and who had completed a structured education program 6–24 months were enrolled. Patients currently using an insulin pump or another CGM device or who had previously used real-time CGM were excluded.

During this study, the FreeStyle Navigator (FSN) Continuous Glucose Monitoring System (Abbott Diabetes Care, Maidenhead, UK) was used in accordance with the product labeling. Interstitial glucose data were used to support diabetes management (except when glucose levels were rapidly changing), to confirm hypoglycemia, or if the participant's symptoms did not match their CGM reading. In masked mode, continuous glucose data are collected but levels are not displayed on the CGM receiver. During the masked phases of CGM, patients used traditional self-monitored blood glucose (SMBG) test results from the functionality built into the FSN.

The target enrollment was 50 participants, with the aim of completing the study with 40 participants for statistical analysis. The planned recruitment phase was 12 weeks, but, following a review of the recruitment rate, this was extended and finally ceased in September 2011, resulting in 32 enrolled subjects.

• Study design

Following consent and enrollment, subjects completed a 5-day baseline phase of masked CGM

to collect continuous glucose data. In addition to SMBG, subjects logged their insulin, food intake and state of health during the baseline phase. At the next clinic visit, the masked data were downloaded and the FSN was changed to unmasked mode.

For the first 2 weeks of the intervention phase of the study, participants managed their glucose levels using results from the unmasked FSN, then returned to the clinic to have their data uploaded and reviewed with their HCP. In accordance with the study protocol, HCPs were not directed on how to review downloaded glucose data or how to use the data to support their review of the study participant's diabetes management. Following the review of their unmasked CGM data (day 21), the participants then continued with SMBG only, to support any diabetes management or regimen changes agreed with the HCP at this review. At day 90, study participants wore the unmasked FSN for a further 5 days, after which the HCP again reviewed the glucose data and made further adjustments to the participant's diabetes management as required. Participants then continued as before, with SMBG only, to support any glucose management or regimen changes. From study day 180, there was a final masked CGM data collection phase for 5 days **(Figure 1)**.

• Outcome measures

The primary end point was to evaluate change in HbA1c from baseline to 6 months. The secondary effectiveness end points included: proportion of participants with HbA1c reduction ≥0.5%; glucose mean; number of hypoglycemic (defined as <3.9 mmol/l or <3.1 mmol/l) and hyperglycemic (>10.0 mmol/l) excursions per day; proportion of time in euglycemia (3.9–10.0 mmol/l); Hypoglycemic Fear Survey (HFS); Audit of Diabetes-Dependent Quality of Life (ADDQoL) questionnaire; adjustments to insulin.

Safety end points included adverse events, and signs and symptoms.

• Questionnaires

All participants completed the HFS [9] and ADDQoL [10] questionnaires at baseline and study day 180. The HFS is composed of two subscales: behavior (measures behavior to avoid hypoglycemia and its negative consequences) and worry (measures worries about hypoglycemia and its negative effects). The ADDQoL questionnaire is a diabetes-specific instrument that assesses the impact of diabetes on 19 life domains. The study investigators also completed an HCP questionnaire at study day 180. The questionnaire given to the HCPs focused on use of CGM device features for review of individual participants and what the study participants had learned about their diabetes.

• Statistical analysis

A total of 40 subjects were required to detect an absolute change in HbA1c of 0.4% with 5% statistical significance and 80% power, based on a standard deviation (SD) of 0.9% for change in HbA1c in subjects with a baseline HbA1c above 8.0%. After an enrollment review, recruitment ceased on 02 September 2011 with only 32/50 subjects recruited. The screening/recruitment phase had been 12 weeks but was significantly extended. Only 7/32 subjects had completed 6-month HbA1c measurements when recruitment ceased. Although only 32 subjects were enrolled in the study, the primary end point results show that this was sufficient to detect a change of 0.4%.

Only FSN continuous glucose readings were used to assess glycemic variability. Missing data were not estimated in the statistical analysis. Measures of glycemic variability and control were considered comparing the final masked CGM phase (study days 180–185) to the baseline masked CGM phase (study days 1–6) by paired *t*-test.

An excursion event is defined as all consecutive recordings outside the predefined acceptable glucose value boundaries and at least 10 min in duration.

HbA1c at 6 months was compared with baseline HbA1c. In the intent-to-treat analysis, when an HbA1c value at 6 months was not available, baseline HbA1c was carried forward, as study days 21 and 95 occur after unmasked CGM wear periods and are therefore considered nonconservative (last eligible observation carried forward). A per-protocol analysis was also performed including only subjects who completed the study protocol.

All statistical tests and associated p-values are two-sided. When the normality assumption required to perform a two-sided *t*-test was violated, Wilcoxon's rank test was employed as a nonparametric alternative. The 95% CI for the mean difference was calculated using a two-sided *t*-test while the 95% CI for the median is distribution free. The CI for the proportion was an exact binomial interval.

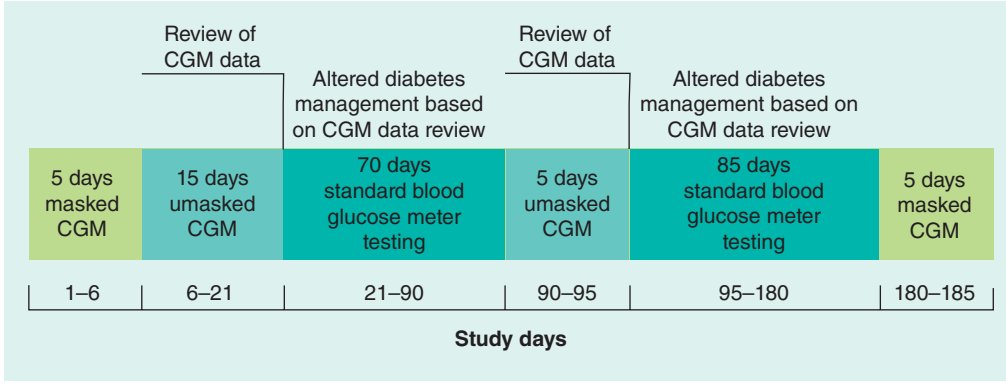

Figure 1. Periods of continuous glucose monitoring use and self-management with blood glucose meter during study.
CGM: Continuous glucose monitoring.

Results

• Study population

A total of 32 people were included in the study. Two participants withdrew before study completion and one was lost to follow-up, resulting in 29 subjects completing the 3-month study. There were 23/32 (71.9%) females and 9/32 (28.1%) males recruited into the study. Severe hypoglycemia was experienced by 15.6% (5/32) of patients in the 6 months before study entry. At baseline, mean age was 42.5 years (range: 18–63 years), mean HbA1c was 9.3% (range: 8.0–13.2%), mean diabetes duration was 17.6 years (range: 0.7–48.0 years), mean number of insulin (U100) injections per day was 4.1 (range: 3–6) and mean number of self-reported blood glucose tests per day was 4.5 (range: 4–10) **(Table 1)**.

• Change in HbA1c

At 6 months, in the intent-to-treat population, median HbA1c change from baseline was –0.3% (p = 0.014). HbA1c was also significantly reduced from baseline to study day 21 (95% CI: -0.5 to -0.1; p < 0.01) and day 95 (95% CI: -0.4–0.0; p = 0.006) **(Figure 2)**. At 6 months, 44% (95% CI: 26–62) of participants had a ≥0.5% HbA1c reduction from baseline. At days 21 and 95, 38% (95% CI: 21–56) and 25% (95% CI: 11–43) of participants had a ≥0.5% HbA1c reduction from baseline, respectively.

In the per protocol analysis (n = 29), median HbA1c change from baseline at 6 months was -0.4% (p = 0.014). At 6 months, 48% (95% CI: 29–67) of participants had a ≥0.5% HbA1c reduction from baseline. At days 21 and 95, 40% (95% CI: 23–59) and 28% (95% CI: 13–47) of participants had a ≥0.5% HbA1c reduction from baseline, respectively.

• Glycemic measures

There was no statistically significant difference from the baseline masked sensor wear phase to 6 months masked sensor wear phase in the frequency of hypoglycemia, defined as mean number of blood glucose excursions per day <3.9 mmol/l and <3.1 mmol/l (-0.01 [95% CI: -0.26–0.24]; p = 0.94 and 0.07 [95% CI: -0.11–0.25]; p = 0.45, respectively) or the time spent in hypoglycemia (<3.9 mmol/l: 0.13 h/day [95% CI: -0.29–0.55]; p = 0.53 and <3.1 mmol/l: 0.12 h/day [95% CI: -0.0–0.27]; p = 0.12).

There was no statistically significant difference in time spent in glucose levels >10.0 mmol/l (-0.1 h/day [95% CI: -1.6–1.4]; p = 0.91), but there was an indication of an improvement in time in glucose levels >14.4 mmol/l (-0.9 h/day [95% CI: -1.8–0.0]; p = 0.06). There was no difference from baseline to 6 months with regard to mean glucose (-0.4 mmol/l [95% CI: -1.0–0.2]; p = 0.23) **(Table 2)**.

• Patient-reported outcome measures: questionnaires

The (mean [SD]) score for HFS behavior components did not change significantly from baseline (18.5 [5.4]) to study day 180 (19.4 [4.9]; p = 0.246). The (mean [SD]) score for HFS worry components did not change significantly from baseline (20.4 [9.2]) to study day 180 (19.3 [9.1]; p = 0.352) either.

There was no significant difference in (mean [SD]) 'present QoL' scores in the ADDQoL

from study day 1–180 (1.24 [0.91] to 1.17 [0.93]; p = 0.677); however, mean (SD) scores on 'impact of diabetes on QoL' significantly improved from -1.66 (0.97) to -1.14 (1.09); p = 0.011.

• HCP questionnaire

When HCPs were asked what they learned about their patients' diabetes from reviewing the CGM data, 25% responded that they learned about patients' lifestyle/activity effects, 19% about compliance to advice, 16% about diet and 16% about the duration/action of insulin; 16% said that they learned nothing from the CGM data.

When HCPs were asked what features of the FSN they found most useful to review with an individual participant and what data they used to manage their patients' diabetes, 34% quoted the logbook, 28% the diary list, 25% the pie charts and 25% the overnight data.

HCPs reported that they and their study participants in general felt that the time using CGM had been sufficient, although some participants had indicated they would have preferred more time or to use CGM permanently.

• Review of glucose data & adjustments to diabetes management

In a *post hoc* analysis of the case report forms filled out by the HCPs, three categories were identified as the main focus for the clinical review of glucose data from the CGM device: 1) nocturnal glucose data were used for 61% (19/31) of participants to either titrate insulin, split basal insulin or advise on prebedtime snacking; 2) for 42% (13/31) of participants, glucose variability was identified or confirmed with lifestyle as the probable causes of poor glycemic control. A recurring theme in the clinical notes was a need for participants to prioritize their diabetes management and apply previously discussed management guidance; 3) for 16% (5/31) of participants, the glucose data confirmed their engagement with their diabetes management and therapy or identified issues, such as the dawn phenomenon, as the cause of their suboptimal glycemic control. In addition, HCPs highlighted that the overnight data were particularly helpful in detecting hypoglycemic or glycemic patterns in general, and for detecting needs to change overnight basal therapy.

At study days 21 and 96, following the unmasked CGM sensor wear phases, the HCPs reviewed the participants' data and recommended changes to glucose management when needed. A total of 24 participants (80%) were recommended to make changes to their diabetes management at study day 21. Out of these, 20 had maintained the changes at study day 90.

At study day 95, 12 of those who had made changes at day 21 were recommended to make further changes, and three participants with no prior management changes during the study were also recommended to make changes.

• Insulin management

Recommended changes to insulin management are summarized in **Table 3**. Changes were recommended for 21 patients at day 21. A total of 17 patients were recommended to change their insulin doses, six to change the timing, four to change both doses and timing, and two to change another aspect of their insulin management, for example, injection site, length of needles. In total (day 21 and day 95), there were 18 changes to patients' bolus insulin dose: 14 increases and four decreases.

Table 1. Baseline characteristics.

Characteristic	Mean (SD)	Range
Female/male (%)	71.9/28.1	–
Age (years)	42.5 (10.8)	18–63
BMI (kg/m^2)	26.3 (3.9)	19.6–37.0
Duration of diabetes (years)	17.6 (13.4)	0.7–48.0
Number of blood glucose measurements per day	4.5 (1.2)	4–10
Number of insulin injections per day	4.1 (0.5)	3–6
Total daily insulin dose – basal, units	24.9 (14.1)	0–62
Total daily insulin dose – bolus, units	28.0 (14.8)	10–60
HbA1c (%)	9.3 (1.3)	8.0–13.2
HbA1c (mmol/mol)	78 (14)	64–121
Experienced severe hypoglycemia in last 6 months, % (n)	15.6 (5.0)	–

n = 32.
SD: Standard deviation.

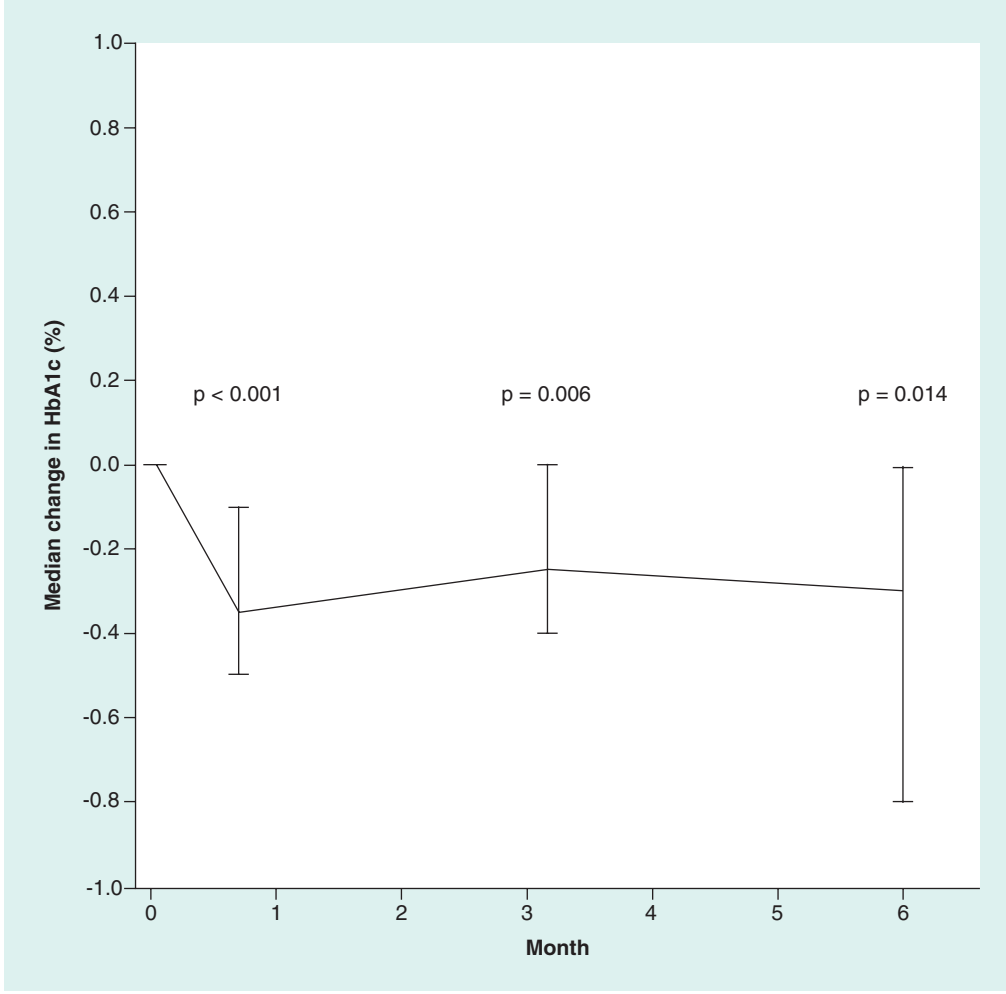

Figure 2. Median change in HbA1c from baseline. Bars show 95% CIs.

• Safety analysis

Out of the 32 participants with sensors, five (16%) reported six adverse events in total, three of which were reported as serious events; none of the adverse events were deemed to be related to the study device. Six participants (19%) reported a total of 15 anticipated sensor insertion symptoms. The most commonly reported insertion-site symptoms were erythema (9% of participants), itching (9%) and rash (6%).

Discussion

In this study, periods of short-term FSN use over 6 months resulted in a statistically significant improvement in HbA1c, and almost half of the participants had an HbA1c reduction of ≥0.5%. However, no significant changes were seen in overall frequency or duration of hypoglycemia, or participant-reported worry about hypoglycemia.

In our study, HbA1c reduction was evident at 3 months and maintained at 6 months. In a similar study, participants completed 72–120-h professional CGM, based on which physicians recommended changes to insulin dose and/or timing in 96% of participants. In this study, HbA1c level decreased 3–6 months after the monitoring period (0.18%; $p = 0.04$), with the largest drop being in a subgroup of patients considered hyperglycemic (0.4%; $p < 0.02$) [7]. Other small studies have reported that there were no benefits to HbA1c levels with short-term professional use, especially compared with long-term use [6,11].

Disappointingly, there was no reduction in the number of hypoglycemic excursions in our study. In the study by Leinung and colleagues [7] in a subgroup of people with frequent hypoglycemia, while HbA1c did not change, 70% of participants reported a drop in self-reported

Table 2. Measures of glycemic variability for the masked sensor wear phases at baseline (study days 1–6) and 6 months (study days 180–185).

Glycemic measure	Baseline, mean (SD)	6 months, mean (SD)	Difference, mean (SD)	Difference (95% CI)	p-value
Time spent in <3.9 mmol/l (h/day)	0.93 (0.84)	1.06 (1.02)	0.13 (1.08)	-0.29–0.55	0.5304
Time spent in <3.1 mmol/l (h/day)	0.23 (0.30)	0.35 (0.44)	0.12 (0.40)	-0.03–0.27	0.1229
Number of excursions per day <3.9 mmol/l	0.87 (0.59)	0.86 (0.83)	-0.01 (0.65)	-0.26–0.24	0.9386
Number of excursions per day <3.1 mmol/l	0.29 (0.32)	0.36 (0.46)	0.07 (0.46)	-0.11–0.25	0.4475
Time spent in >10.0 mmol/l (h/day)	11.4 (4.4)	11.4 (4.1)	-0.1 (3.9)	-1.57–1.41	0.9106
Time spent in >14.1 mmol/l (h/day)	4.05 (3.03)	3.19 (2.55)	-0.86 (2.30)	-1.75–0.03	0.0577
Number of excursions per day >10.0 mmol/l	2.58 (0.83)	2.72 (0.66)	0.14 (0.92)	-0.22–0.49	0.4423
Number of excursions per day >14.1 mmol/l	1.58 (0.99)	1.47 (0.79)	-0.10 (0.89)	-0.45–0.24	0.5432
Time spent in 3.9–10.0 mmol/l (h/day)	11.6 (3.9)	11.6 (3.5)	-0.0 (3.2)	-1.30–1.21	0.9391
Time spent in 3.1–14.4 mmol/l (h/day)	19.7 (2.9)	20.5 (2.4)	0.7 (2.1)	-0.08–1.56	0.0757
Mean glucose (mmol/l)	10.3 (1.9)	9.9 (1.7)	-0.4 (1.6)	-0.96–0.24	0.2286

n = 32.
SD: Standard deviation.

hypoglycemia ($p < 0.01$). In our study, the patients were selected due to poor glycemic control, rather than recurrent hypoglycemia. No differences were seen in worry about hypoglycemia after short periods of CGM use; however, in one survey study, CGM use demonstrated significant improvement in QoL, level of stress associated with having and managing diabetes and reduction of severe hypoglycemia [12].

Despite some studies showing no immediate results with regards to glycemic control, short-term CGM use in clinical practice may still be of interest from a pedagogic perspective, or for physicians to gain detailed information on glucose patterns to aid treatment changes [11]. In our study, when asking the treating physician how they used the data downloaded from the CGM device, all HCPs noted a benefit from the short-term use of the FSN. The technology was especially useful for supporting diabetes management changes based on more detailed insight into insulin action and duration, overnight glucose trends and the effects of daily activities on glucose variability. In some cases, CGM has potential for adverse psychological effects: if the patient's focus of attention on their diabetes increases, the perceived burden of the disease may increase and create a constant concern about glucose excursions. In such cases, there may be greater value in wearing a masked sensor, where data are used only by the treating physician as a tool for better understanding each patient's day-to-day glucose control [8].

In this study, among the 24 participants who were recommended to make changes to their diabetes management at study day 21, 20 had

Table 3. Changes to insulin management.

Day	Insulin management	Insulin dose	Timing of insulin
Day 21 (n):			
– Maintained change	17	14	4
– Did not maintain change	4	3	2
Day 95 (n):			
– Maintained change	12	8	1
– Did not maintain change	2	2	0

maintained the changes at day 90. All participants included in this study had undergone structured diabetes education within the previous 2 years, but still had poor glycemic control. Real-time feedback from CGM may be used as a motivational tool to implement lifestyle changes [13], and learning how to interpret CGM data can empower patients to make appropriate changes to their insulin regimens, as well as possibly enabling them to see the direct effects of changes to their regimen.

A limitation of this study is the absence of a control group and the relatively small sample size, which did not allow extensive characterization of subgroups. It should also be noted that, despite all patients having received similar structured diabetes education and training on masked and unmasked use of the CGM device, the level of suitability and interest in the therapy in this study may be heterogeneous and affects how well changes in diabetes management are received.

In conclusion, short or intermittent use of CGM with real-time glucose results displayed on the device, in conjunction with a diabetes management review with an HCP, resulted in significant improvements in HbA1c. All HCPs involved in the study noted a benefit from using short-term CGM, especially to gain insight into insulin action and duration, overnight glucose trends and to better understand the effects of daily activities on glucose patterns.

Future perspective

As important as it is to achieve a statistically significant reduction in HbA1c levels, it could well be that the main improvement brought about through use of CGM is in the enhanced information profile for each particular patient. In time it may be shown that CGM also has a subsequent positive therapeutic effect with respect to hypoglycemia outcomes, but for now the main benefit appears to be in the tools for clinical management now granted to the HCP.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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•• **Questionnaires were used to measure a range of qualitative factors concerning the impact of CGM on quality of life. The authors determined one clear effect of CGM to be a reduction in patient fear of hypoglycemia and severe hypoglycemia. Significant patient empowerment through use of CGM was achieved.**

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