Effect of Flash Glucose Monitoring Technology on Glycemic Control and Treatment Satisfaction in Patients With Type 2 Diabetes

Marianna Yaron,[1,2] Eytan Roitman,[1] Genya Aharon-Hananel,[1] Zohar Landau,[1,2,3] Tali Ganz,[3] Ilan Yanuv,[4] Aliza Rozenberg,[4] Moshe Karp,[1] Maya Ish-Shalom,[1,2] Joelle Singer,[1,2] Julio Wainstein,[1,2,3] and Itamar Raz[1,4]

Diabetes Care 2019;42:1178–1184 | https://doi.org/10.2337/dc18-0166

OBJECTIVE

To assess treatment satisfaction and the effectiveness of a flash glucose monitoring (FGM) system in patients with type 2 diabetes using insulin.

RESEARCH DESIGN AND METHODS

A total of 101 patients with type 2 diabetes on multiple daily insulin injections (MDI) for at least 1 year were assigned randomly to the FGM intervention (n = 53) or the standard care (control) group (n = 48) and followed for 10 weeks. Both groups were instructed to adjust their insulin doses in face-to-face and telephone visits. Satisfaction with treatment, quality of life, comfort using FGM, HbA_{1c}, and frequency of hypoglycemic events were evaluated.

RESULTS

The intervention group found treatment significantly more flexible (P = 0.019) and would recommend it to their counterparts (P = 0.023). Satisfaction using the FGM system was high. The changes in HbA_{1c} were –0.82% (9 mmol/mol) vs. –0.33% (3.6 mmol/mol) in the intervention and control group, respectively (P = 0.005); in nonprespecified post hoc analysis, 68.6% of the patients in the intervention group had their HbA_{1c} reduced by ≥0.5% (5.5 mmol/mol) compared with 30.2% in the control group (P < 0.001), and 39.2% had their HbA_{1c} reduced by ≥1.0% (10.9 mmol/mol) vs. 18.6% in the control group (P = 0.0023) without an increased frequency of hypoglycemia.

CONCLUSIONS

FGM tends to improve treatment satisfaction and may lead to amelioration of glycemic control in patients with type 2 diabetes on MDI without increasing the frequency of hypoglycemia.

Self-monitoring of blood glucose (SMBG) is the standard of care for patients with type 2 diabetes treated with multiple daily insulin injections (MDI) (1). For these patients, four or more daily blood glucose (BG) tests are recommended to safely and effectively adjust insulin doses (2). The drawbacks of SMBG are well-known and include pain, inconvenience, sleep disturbance for nighttime tests, and embarrassment. Continuous glucose monitoring (CGM) overcomes some of the limitations of SMBG and provides a continuum of glucose data.

Recently, a flash glucose monitoring (FGM) system (FreeStyle Libre; Abbott Diabetes Care, Alameda, CA) for interstitial glucose fluid measurement was

[1]Diabetes Medical Center, Tel Aviv, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Diabetes Unit, E. Wolfson Medical Center, Holon, Israel
[4]Hebrew University, Jerusalem, Israel

Corresponding author: Itamar Raz, ntv502@netvision.net.il

Received 23 January 2018 and accepted 1 April 2019

Clinical trial reg. no. NCT02809365, clinicaltrials.gov

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-0166/-/DC1.

This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

M.Y. and E.R. contributed equally to this work.

© 2019 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at http://www.diabetesjournals.org/content/license.

Downloaded from http://diabetesjournals.org/care/article-pdf/42/7/1178/530321/dc180166.pdf by guest on 02 October 2022

introduced. The FGM system is composed of a small, single-use, factory-calibrated sensor that continuously measures interstitial glucose levels. The sensor is placed on the back of the upper arm for up to 14 days and automatically stores glucose data every 15 min. The sensor is scanned by a separate reader, and real-time glucose levels can be obtained every minute. Data including the glucose trend; i.e., an arrow and a curve of glucose values for the previous 8-h period are also displayed (3).

This study was designed to assess the impact of this FGM system on treatment satisfaction and diabetes control in patients with type 2 diabetes on MDI.

RESEARCH DESIGN AND METHODS

The trial was conducted in two medical institutions (E. Wolfson Medical Center and the Diabetes Medical Center) in Israel. Study inclusion criteria were as follows: age 30–80 years, diagnosis of type 2 diabetes for at least 1 year, treatment by two or more insulin injections daily (with at least one prandial insulin injection) for at least 6 months, and glycated hemoglobin (HbA_{1c}) of 7.5–10.0% (58–86 mmol/mol). Patients were eligible for the study if they were willing to complete daily BG tests, seven times a day, at least 1 day a week. The exclusion criteria included type 1 diabetes, a cardiovascular event within the last 6 months, steroid therapy >7 days in the last 6 months prior to enrollment, a history of proliferative diabetic retinopathy, a creatinine level ≥2 mg/dL, and pregnancy or planned pregnancy within the upcoming 6 months. All participants provided written consent. The local ethics committee approved the protocol, consent forms, and patient information sheets. The study was registered in an approved ICMJE (International Community of Medical Journal Editors) clinical trial registry.

Trial Design and Outcomes

This open-label randomized (1:1) controlled trial was designed to evaluate whether the use of an FGM impacts treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire [DTSQ]) in patients with type 2 diabetes treated with MDI over a short time period. The prespecified secondary end points included assessment of the changes (improvement) in HbA_{1c}, changes in quality of life (QoL) score, percentage of patients achieving physician-recommended personal target of HbA_{1c}, and changes in total hypoglycemic events (defined as BG <70 mg/dL and BG <54 mg/dL). On the first visit, HbA_{1c} blood tests were obtained. After a 2-week run-in period and insulin dose stabilization, patients eligible for randomization filled out the DTSQ, status version (DTSQs), and the Audit of Diabetes Dependent Quality of Life 19 (ADDQoL) questionnaires. During this visit, eligible patients were randomly assigned to the intervention or standard care groups as a function of age (<65 vs. ≥65 years) and HbA_{1c} values (<8.5% vs. ≥8.5%). Seventeen patients presenting with borderline baseline HbA_{1c} values were also included into the study. In total, 101 patients were randomized: 53 to the intervention and 48 to the standard care (control) groups. Participants in the intervention group used the FGM system for a period of 10 weeks and were instructed to scan at least every 8 h. The data from the FGM system were downloaded by Abbott Libre software (https://www.freestylelibre.co.uk) every 2–4 weeks as required by the study protocol. All patients were given the same amount of counseling (~30 min) and diabetes management instructions including a detailed carbohydrate counting consultation from trained diabetes nurses and a dietitian, and both groups were instructed on how or whether to adjust their insulin dose in frequent face-to-face visits and telephone calls (Supplementary Table 1 and Supplementary Fig. 1). Total contact time (face-to-face and phone visits) with health care professionals was the same in both groups.

Participants in the standard care group were instructed to maintain their routine SMBG using FreeStyle Optium Neo glucometers at least four times a day. Participants in both groups were instructed to use FreeStyle Optium Neo glucometers if they experienced symptoms of hypoglycemia. In addition, both groups were asked to assess BG seven times a day 1 day each week, preferably on the day prior to the visit, to evaluate asymptomatic hypoglycemic events. All patients were given an unlimited number of strips. All symptomatic hypoglycemic events were recorded in a personal diary by both groups. We do not report asymptomatic hypoglycemic events obtained from the FGM system and only report asymptomatic hypoglycemic events that were measured by the glucometer during the once-a-week collection in both groups.

During the inpatient visits, health care providers discussed the data (either FGM or SMBG) with the participants. The duration of the sessions was identical for both groups, and recommendations were recorded and reviewed during the next session. After randomization, only insulin dose adjustment and carbohydrate counseling were permitted; neither pharmacological intervention was authorized.

The safety variable was comprised of *1*) severe hypoglycemic episodes, defined as events requiring third-party assistance; *2*) hypoglycemic episodes <70 mg/dL; and *3*) hypoglycemic episodes <54 mg/dL. Hypoglycemia was documented as either symptomatic or asymptomatic.

Data Collection

During intake on visit 1, clinical information was collected via case report forms. Baseline information included sociodemographic characteristics (age, sex, and highest educational level achieved) and clinical characteristics (duration of diabetes, type of insulin therapy and dosage of insulin, presence of severe complications, comorbidities, and concomitant treatment). Blood pressure, body weight, complete physical examination, fasting plasma glucose, HbA_{1c}, complete blood count, chemistry profile, and renal and liver functions were assessed at baseline at 6 and at 10 weeks after randomization (Supplementary Table 1). Some of the blood tests were taken for the safety follow-up. The scanning frequency for each sensor was calculated by counting the number of scans per day in the 14 days prior to each visit.

Health-Related Quality of Life Measures

Changes from baseline in satisfaction from diabetes treatment and health-related QoL were evaluated using the Hebrew version of the DTSQs and DTSQ, change version (DTSQc) (4), and ADDQoL-19. DTSQ evaluates satisfaction with the diabetes treatment regimen over past weeks and is composed of eight items, six of which are summed into a single score on a 7-point scale,

Downloaded from http://diabetesjournals.org/care/article-pdf/42/7/1178/530321/dc180166.pdf by guest on 02 October 2022

ranging from very satisfied to very dissatisfied. DTSQ measures overall satisfaction, convenience, flexibility, understanding of diabetes, willingness to recommend current treatment to others, and willingness to continue the current treatment. The remaining two items are treated individually and explore the perceived frequency of hyperglycemic and hypoglycemic episodes. For these two items, low scores represent good BG control. The DTSQc compares the experience of the current treatment with the experience of the treatment before initiation of the study. Scores range from +3 ("much more satisfied now") to −3 ("much less satisfied now"), with 0 (midpoint) representing no change. Higher scores on the DTSQ total score indicate higher treatment satisfaction, and lower scores indicate lower treatment satisfaction.

The ADDQoL was originally presented in reference no. 5 and was later modified in reference no. 6 and consists of 19 questions on QoL with diabetes. Overall comfort using the FGM system was evaluated by Libre user evaluation questionnaires that included items assessing ease of use, comfort, pain, design, and system operation. DTSQs and ADDQoL were administered on the randomization visit and at the end of the study. The DTSQc and Libre user evaluation questionnaires were administered at the end of the study.

Statistical Methods

The summary statistics for the continuous variables were *N*, the mean and the SD, and percentages for the categorical variables. For the continuous variables, the treatment groups were compared using *t* tests or the rank-sum Wilcoxon test as appropriate. For the categorical variables, Wald or Fisher exact test was used as appropriate.

The summary of the scanning data is presented by summary metrics (the mean and the median and interquartile range) and the cumulative frequency distribution. The association between the number of scans and the reduction in HbA_{1c} was tested using Pearson correlation coefficients and *t* tests for dichotomous reduction.

The medical data, and specifically HbA_{1c}, were analyzed based on the predefined observed intent-to-treat (ITT) analysis; for sensitivity analysis, missing data at the end of the follow-up were imputed using the last observation carried forward method. A multivariate linear regression was performed to test the effect of the treatment groups on changes in HbA_{1c}, adjusted for baseline values of HbA_{1c}. An additional multivariate model was performed with addition of an adjustment for sex, age, and disease duration as well as baseline values of HbA_{1c}. A nonprespecified post hoc analysis was performed to analyze the probability of significant reduction in HbA_{1c} (defined as achieving a difference in HbA_{1c} of at least 0.5% [5.5 mmol/mol] or at least 1% [10.9 mmol/L]), using a logistic regression with adjustment for the same variables as in the linear regression mentioned above. The sample size was calculated under the assumption that the difference in the mean change in total satisfaction (DTSQs) between treatment groups would be 0.5 with an SD of 0.8; in this case, a sample size of 41 in each group was required for a power of 80%. The assumption for the difference in the mean change in HbA_{1c} was similar, with a power of 80% for a significant difference of 0.5% (5.5 mmol/mol) in HbA_{1c} with an SD of 0.8. We aimed to recruit 100 patients assuming that 15% would either withdraw consent, drop out of the study, not fully complete the questionnaire, and/or have technical or side effects related to the use of Libre. All statistical analyses were performed using R 3.1.1 software. *P* values <0.05 were considered statistically significant.

RESULTS

From 15 November 2016 to 31 August 2017, a total of 101 patients with type 2 diabetes who were treated with MDI were recruited and randomized to the intervention group ($n = 53$) or the control group ($n = 48$) (Supplementary Fig. 2). Fewer patients than those randomized completed the baseline questionnaire (96 of 101) and end of study questionnaires (82 of 101) due to unwillingness.

Patient characteristics as a function of group are shown in Table 1. The two groups did not differ on any of the sociodemographic or clinical characteristics, with the exception of a higher baseline level of HbA_{1c} and statin treatment in the intervention group.

QoL and Patient Satisfaction

Patient-reported treatment satisfaction using the FGM system was assessed in 82 patients (46 in the intervention and 36 patients in the control group). After 10 weeks, patient satisfaction with their diabetes treatment as evaluated by the DTSQc was high in both study groups; in the intervention group, the mean (SD) score per subject for each question was 2.47 (0.77) vs. 2.18 (0.83) in the control group ($P = 0.053$) (Table 2). Furthermore, patients in the intervention group found treatment by FGM significantly more flexible (2.28 [1.28] vs. 1.61 [1.59] in the control group, $P = 0.019$), and would recommend it more to their counterparts (2.61 [0.86] vs. 2.19 [1.04] in the control group, $P = 0.023$). Diabetes treatment satisfaction as evaluated by the DTSQs (Supplementary Tables 2 and 3) yielded similar results. The perceived frequency of hypoglycemia improved significantly for the intervention group (0.88 [1.88]) compared with the control group (0.20 [1.60]; $P = 0.013$) (Supplementary Table 3).

QoL, as evaluated on the ADDQoL questionnaires and by comparison of the weighted impact scores, was similar between the groups at baseline. After 10 weeks, the changes in QoL between the intervention and control groups were not significant (Supplementary Fig. 3).

Overall, satisfaction with the FGM system was high: 87.5% of the intervention group felt generally very satisfied using this technology; 12.5% felt moderately satisfied, and no participants felt moderately unsatisfied or unsatisfied.

Glycemic Control

At baseline, the mean (SD) HbA_{1c} was 8.68% (0.87), (71 [9.5] mmol/mol) in the intervention group and 8.34% (0.74) (68 [8.1] mmol/mol) in the control group.

The patient-reported outcome of glycemic control was assessed in 101 patients ($n = 53$ in the intervention group and $n = 48$ in the control subjects). On visit 6, HbA_{1c} data were missing for seven patients ($n = 2$ for intervention and $n = 5$ for control).

In the ITT analysis, after 10 weeks, the mean (SD) change in HbA_{1c} showed a reduction of −0.82% (0.84) (9 mmol/mol) in the intervention group and −0.33% (0.78) (3.6 mmol/mol) in the control group ($P = 0.005$).

HbA_{1c} reduction, with adjustment for HbA_{1c} values at baseline, was −0.85% (0.45) (9.3 mmol/mol) in the intervention group and −0.32% (0.39) (3.5 mmol/mol) in the control group ($P < 0.0001$) (Fig. 1),

Downloaded from http://diabetesjournals.org/care/article-pdf/42/7/1178/530321/dc180166.pdf by guest on 02 October 2022

Table 1—Baseline demographic and clinical characteristics of participants with type 2 diabetes assigned randomly to the intervention or control group

	Control group	Intervention group
N	48	53
Sex, male/female (%)	58.3/41.7	69.8/30.2
Age (years)	65.94 (8.42)	67.55 (6.69)
Diabetes duration (years)	21.53 (8.29)	22.1 (7.00)
BMI (kg/m^2)	30.31 (5.0)	29.65 (4.5)
HbA_{1c} (%), percent in range	8.34 (0.74)	8.68 (0.87)
7–7.5	14.6	7.5
7.5–8.5	43.8	41.5
8.5–10	39.6	41.5
>10	2.08	9.43
Fasting BG (mg/dL)	157.8 (51.17)	167.5 (72.34)
Total insulin (units/day)	70.6 (38.4)	74.2 (47.1)
Short-acting insulin (units/day)	31.1 (21.2)	36.1 (31.4)
Number of meal injections per day (%)		
1	4	3
2	6	9
3	34	36
4	1	2
MIX insulin	3	3
Number of MIX injections per day	BID 1, TID 2	BID 2, TID 1
Metformin (%)	72.9	71.7
DPP4 inhibitors (%)	14.6	7.5
SGLT2 inhibitors (%)	27.7	24.5
GLP 1-RA (%)	31.3	35.8
Sulphonylurea (%)	4.2	0.0
Aspirin (%)	62.5	62.3
β-Blockers (%)	29.2	43.4
ACEi/ARBs (%)	81.3	79.2
CCB (%)	33.3	28.3
Statin treatment (%)	66.7	84.9
Diabetic retinopathy (%)	29.2	24.5
Diabetic nephropathy (%)	39.6	34.0

Data are means (SD) unless stated otherwise. ACEi, ACE inhibitor; ARB, angiotensin II receptor blocker; BID, twice a day; CCB, calcium channel blocker; DPP4, dipeptidyl-peptidase 4; GLP 1-RA, glucagon-like peptide 1 receptor agonist; MIX, mixed insulin with NPH insulin and short analogue insulin lispo in 50:50 and/or 75:25 ratio; SGLT2, sodium–glucose cotransporter 2; TID, 3 times a day.

yielding results similar to the unadjusted values. Subsequently, multivariate models were applied after adjustment for other demographic and medical variables of interest (sex, age, and duration of diabetes), as well as baseline HbA_{1c}, and yielded similar results.

A nonprespecified post hoc analysis was performed on the ITT population, comparing the proportion of subjects with a significant decrease in HbA_{1c} between treatment groups. Significant decrease was defined as achieving a difference in HbA_{1c} of at least 0.5% (5.5 mmol/mol) and was observed in 68.6% of the participants in the intervention group and 30.2% in the control group ($P < 0.001$).

The proportion of patients with a decrease in HbA_{1c} of at least 1% (10.9 mmol/mol) was 39.2% in the intervention group and 18.6% in the control group ($P = 0.023$) (Fig. 2). For a sensitivity analysis, all the HbA_{1c} analyses were repeated using last observation carried forward imputation and yielded similar results.

The frequency of hypoglycemic episodes retrieved from 7-point BG levels and documented symptomatic hypoglycemic episodes reported by patients did not significantly differ between groups at the end of study (Tables 3 and 4). No severe hypoglycemia or serious adverse events occurred during the study. Adherence to 7-point BG levels in the intervention group was 98.04% and 86% in the control group ($P = 0.044$).

The average (SD) number of scans per day using the FGM in the intervention group was 11.44 (7.76) (median 9.75 [interquartile range 6.25–12.75]). There was no correlation between the frequency of glucose scans and reduction in HbA_{1c} ($r = -0.094$, $P = 0.52$). A comparison of the scanning frequency in participants who had their HbA_{1c} reduced by >0.5% (5.5 mmol/mol) and participants whose HbA_{1c} dropped <0.5% (5.5 mmol/mol) showed that the frequency of glucose scanning was similar; namely, the average (SD) was 10.22 (7.11) scans/day vs. 11.91 (8.17) scans/day ($P = 0.50$). Similar results were observed in comparison of participants

Table 2—Scores on the DTSQc questionnaire at the end of the study

Question	Control group (n = 36)	Intervention group (n = 46)	P
Satisfied with current treatment	2.50 (0.85)	2.28 (1.11)	0.458
Convenience of treatment	1.92 (1.18)	2.33 (1.14)	0.052
Flexibility of treatment	1.61 (1.59)	2.28 (1.28)	0.019
Willingness to recommend treatment to someone else	2.19 (1.04)	2.61 (0.86)	0.023
Satisfied to continue present form of treatment	2.17 (1.32)	2.50 (1.05)	0.084
Average score for each question (per patient)	2.18 (0.83)	2.47 (0.77)	0.053
Perceived frequency of hyperglycemia	0.64 (1.69)	0.87 (1.73)	0.490
Perceived frequency of hypoglycemia	0.75 (1.57)	1.41 (1.29)	0.066

Data are means (SD). P values were calculated using the Wilcoxon rank sum test.

Downloaded from http://diabetesjournals.org/care/article-pdf/42/7/1178/530321/dc180166.pdf by guest on 02 October 2022

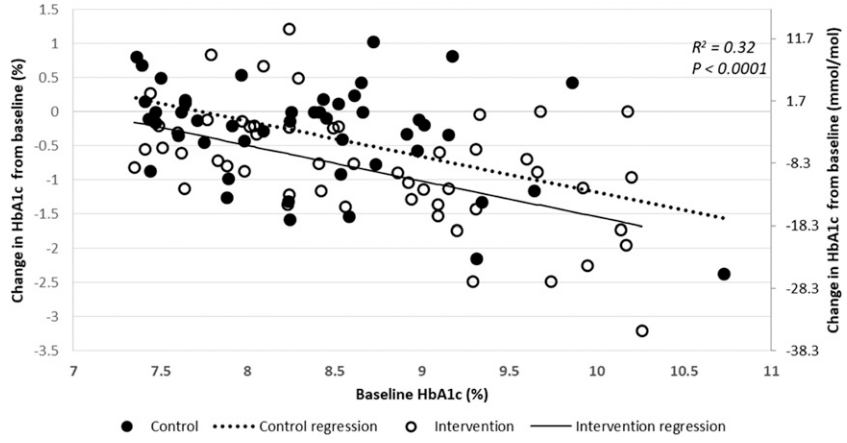

Figure 1—Relationship between the baseline HbA_{1c} and change in HbA_{1c}, by treatment group. The circles represent individual crude value, while the lines represent the estimation derived from the linear regression of these individual observations (adjusted $R^2 = 0.32$). The open circles and solid line represent the intervention group, and the closed circles and dotted line represent the control group. There is a statistically significant difference in the mean change in HbA_{1c} between treatment groups in favor of the intervention ($P < 0.0001$).

whose HbA_{1c} dropped ≥1% (10.9 mmol/mol) with patients whose HbA_{1c} dropped <1% (10.9 mmol/mol): the scanning frequency was almost identical, with 10.39 (6.21) scans/day vs. 12.99 (9.81) scans/day *(P = 0.26)*.

CONCLUSIONS

In this randomized controlled study, there was an overall higher tendency toward diabetes treatment satisfaction with the FGM technology as expressed by the mean DTSQc satisfaction score as compared with the group under standard care. In terms of specific responses, the participants found the treatment to be significantly more flexible and would recommend it more to their counterparts. Subjects using the FGM system reported significant improvement in recognizing hypoglycemia compared with those in the control group.

It is important to highlight that the overall satisfaction with diabetes treatment was high in both groups at the end of the study, in particular when compared with similar studies (7). The intensive follow-up in our study may have led to greater overall satisfaction in the control group. In the Haak et al. (7) trial, which successfully showed significant improvement in treatment satisfaction with the FGM technology, the participants only visited the clinic twice in 6 months of follow-up. These results strengthen the hypothesis that the frequent inpatient visits in our study were responsible for the improved treatment satisfaction in both groups, thus masking the satisfaction in the intervention group. Another important factor is that the satisfaction level was already high in both groups prior to the trial, which may have resulted in a smaller increase in the satisfaction level at the end of the study.

At the same time, our study shows that offering the FGM technology to patients with type 2 diabetes on MDI leads to a significant HbA_{1c} improvement over the course of 10 weeks as compared with the control group that was limited to SMBG alone. Patients using this FGM technology reduced their mean HbA_{1c} considerably, by 0.82% (9 mmol/mol), without an increase in the frequency of hypoglycemia; the magnitude in the drop in HbA_{1c} is even more impressive given the short intervention time (10 weeks); this was observed also after adjustment for baseline HbA_{1c}. Moreover, counseling was restricted to insulin dose adjustment and carbohydrate counseling, without additional pharmacological interventions. This significant reduction in HbA_{1c} was present for the entire group of participants in the FGM group regardless of age, sex, or disease duration.

In addition, when using FGM, more than two-thirds of patients had their HbA_{1c} brought down at least 0.5% (5.5 mmol/mol) and nearly 40% had their HbA_{1c} reduced by at least 1% (10.9 mmol/mol), which is more than twice as many when compared with the control group. We assume, corresponding with the recently published review by Edelman et al. (8), that the features of FGM in people with type 2 diabetes who are required to perform SMBG for clinical decision-making may have helped participants in the intervention group to improve their glycemia.

The absence of a relationship between the number of daily glucose scans and a reduction in HbA_{1c}, however, suggests that the main reason for HbA_{1c} reduction in the intervention group was related to the physician and dietitian's instructions regarding diet and adjustment of insulin doses.

There is a paucity of evidence on the effectiveness of CGM in patients with

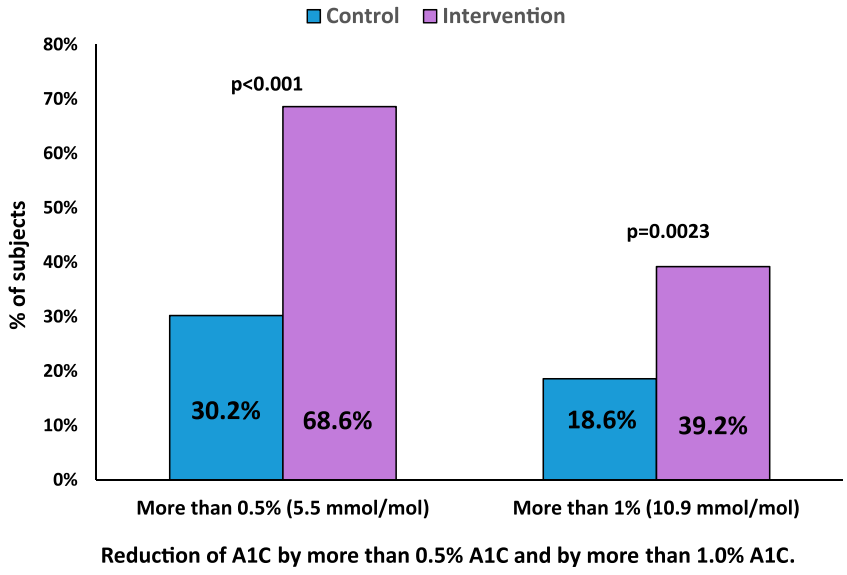

Figure 2—Percentage of patients in each group whose HbA_{1c} was reduced by ≥0.5% (5.5 mmol/mol) and ≥1% (10.9 mmol/mol) at the end of the study.

Downloaded from http://diabetesjournals.org/care/article-pdf/42/7/1178/530321/dc180166.pdf by guest on 02 October 2022

Table 3—Documented symptomatic hypoglycemia and/or self-reported hypoglycemia

Population	Control	Intervention	*P*
Entire sample			
Hypo <54	9% (4/44)	11% (6/52)	0.75
Number of events, mean (SD)	0.2 (0.82)	0.38 (1.29)	0.43
Hypo <70	36% (16/44)	28% (15/52)	0.51
Number of events, mean (SD)	0.86 (1.97)	0.69 (1.5)	0.63
Inclusion criteria HbA_{1c} 7.5≤ and ≤10% (58≤ and ≤86 mmol/mol)			
Hypo <54	8% (3/37)	13% (6/43)	0.40
Hypo <70	37% (14/37)	32% (14/43)	0.62
HbA_{1c} at baseline of 7.5–8.5% (58–69 mmol/mol)			
Hypo <54	5% (1/18)	9% (2/22)	0.67
Hypo <70	38% (7/18)	36% (8/22)	0.87
HbA_{1c} at baseline of 8.5–10% (69–86 mmol/mol)			
Hypo <54	11% (2/8)	18% (4/22)	0.52
Hypo < 70	38% (7/18)	27% (6/22)	0.44

Data are % of patients (number of patients with at least one hypoglycemic event/total evaluated patients) unless otherwise indicated. *P* values were calculated using the Wald or Wilson test for proportions. Hypo, hypoglycemia (mg/dL).

type 2 diabetes treated with MDI. Vigersky et al. (9) showed that even intermittent use of real-time CGM in patients with type 2 diabetes who are not on prandial insulin significantly decreased their HbA_{1c} at the end of a 3-month active intervention, which was sustained over the 40 weeks of the follow-up period. The same author, in his recently published review, summarizes that among other advantages, CGM enables health care providers to discover previously unknown hyper- and hypoglycemic events, directly visualizes the patients' glycemic control and variability, analyzes the effectiveness of new therapeutic interventions, and modifies behavior patterns in some patients with diabetes (10). The recently published DIAMOND (Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes) study (11) evaluated comparable cohorts of patients with type 2 diabetes on MDI and showed that mean HbA_{1c} levels in the CGM group decreased significantly by 1.0% (10.9 mmol/mol) (from 8.5% [SD 0.6] [69 mmol/mol] to 7.5% [SD 0.7] [58 mmol/mol]) compared with the control group where HbA_{1c} decreased by 0.6% (6.6 mmol/mol) (from 8.5% [SD 0.7] [69 mmol/mol] to 7.9% [SD 0.8] [63 mmol/mol]) in a 12- week intervention period. Similar to results in our study, the DIAMOND study participants did not show improvement on any of QoL parameters.

Contrary to our results and those reported in other randomized controlled trials (9,11), REPLACE (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) (7) used an identical FGM technology on a comparable population with type 2 diabetes on MDI but did not report a reduction in HbA_{1c}. The drop in HbA_{1c} was only more pronounced for participants below the age of 65 years. Interestingly, our population was older than in REPLACE (mean [SD] 66.7 [7.5] vs. 59.3 [10.4] years old in REPLACE), had a lower BMI (29.9 [4.7] vs. 33.2 [5.8] kg/m^2), and had longer disease durations (21.7 [7.7] vs. 17.5 [8] years). This may hint that more frequent contact and consultations with patients using FGM may affect and improve patient motivation and lead to behavioral changes.

Table 4—Documented symptomatic hypoglycemia and/or self-reported hypoglycemia

	Control (*n* = 44)		Intervention (*n* = 52)		
	n	%	*n*	%	*P*
Number of episodes of hypo 55–70					
0	28	63.6	37	71.2	0.34
1	10	22.7	6	11.5	
2+	6	13.6	9	17.3	
Number of episodes of hypo <54					
0	40	90.9	46	88.5	0.89
1	2	4.5	2	3.8	
2+	2	4.5	4	7.7	

P values were calculated using Fisher exact test. Hypo, hypoglycemia (mg/dL).

There is only one RCT comparing patients with diabetes with and without the FreeStyle Libre system, which, however, failed to show HbA_{1c} improvement (7). An extension of this trial to 12 months yielded similar results. In addition, several accuracy FGM trials (some even including comparison with CGM) have been conducted but mostly with subjects with type 1 diabetes. Several studies with larger sample sizes have tested the FreeStyle Pro system (12), which differs from the FreeStyle Libre in that the patients are blind to the BG data that can only be collected, seen, and analyzed by clinicians. The recent announcement of the FreeStyle Libre 2 system with increased accuracy and hypoglycemia/hyperglycemia alerts has the possibility of further improving glycemic control and needs to be evaluated in clinical trials (abbott.mediaroom.com).

To the best of our knowledge, this study is the first RCT showing an HbA_{1c} reduction in patients with type 2 diabetes using FGM technology. The findings point to the impact of FGM in the glycemic control of patients with type 2 diabetes treated with insulin. The role of FGM is more clear-cut in type 1 diabetes (3) and

Downloaded from http://diabetesjournals.org/care/article-pdf/42/7/1178/530321/dc180166.pdf by guest on 02 October 2022

the considerable health fund reimbursements in several countries currently only apply to FGM for type 1 diabetes. Our study is thus important in stressing the efficacy of FGM for type 2 diabetes, which brings it significant advantage over SMBG, as stated also synchronously in a recent review by Edelman et al. (8).

This study has some limitations that deserve consideration. Because a number of participants were unwilling to complete the questionnaires, the power of the primary outcome may have been undermined. In addition, given recruitment issues, the short time frame, and the fact that HbA_{1c} was a secondary end point, we expanded the inclusion criteria for HbA_{1c} to 7.4–10.2% (57–88 mmol/mol) from the original 7.5–10% (58–86 mmol/mol). This led to the lower mean HbA_{1c} in the control group at baseline. Nevertheless, the multivariate models assessing change in HbA_{1c} still showed a significant reduction in HbA_{1c} in the intervention group.

Conclusion

This 10-week randomized controlled trial indicates that using FGM technology for BG monitoring and care in patients with type 2 diabetes on MDI may lead to improvement in treatment satisfaction and a significant reduction in HbA_{1c} without increased risk of hypoglycemia.

Acknowledgments. The authors acknowledge Rebecca Sprung (Hadassah Medical Center, Jerusalem, Israel) for linguistic support and for valuable remarks that contributed to the writing of this manuscript.

Funding. The authors acknowledge funding support from Abbott Laboratories USA.

The funding did not affect the collection, analysis, or presentation of the data.

Duality of Interest. M.Y., E.R., G.A.-H., Z.L., M.K., M.I.-S., J.S., J.W., and I.R. give regular consultations to the patients treated at the Diabetes Medical Center, which is partially owned by the licensed FreeStyle Libre distributor in Israel (Geffen Medical Ltd.). No other potential conflicts of interest relevant to this article were reported.

Author Contributions. M.Y. had full access to all of the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and wrote the manuscript. E.R., G.A.-H., Z.L., and T.G. contributed to the writing of the protocol, researched data, and contributed to the writing of the manuscript. I.Y. and A.R. prepared the statistical basis for analyzing the protocol and performed statistical analysis, including tables and graphs. M.K., M.I.-S., and J.S. were the trial investigators, researched the data, and contributed to the discussion. J.W. prepared the concept and protocol of the study and contributed to the methods and critical revision of the manuscript. I.R. prepared the concept and design of the study and reviewed the manuscript. M.Y. and I.R. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, 22–26 June 2018.

References

1. Parkin CG, Davidson JA. Value of self-monitoring blood glucose pattern analysis in improving diabetes outcomes. J Diabetes Sci Technol 2009;3:500–508

2. American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes–2017*. Diabetes Care 2017;40(Suppl. 1):S48–S56

3. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet 2016;388:2254–2263

4. Bradley C. The Diabetes Treatment Satisfaction Questionnaire: DTSQ. A guide to psychological measurement in diabetes research and practice. In *Handbook of Psychology and Diabetes*. Chur BC, Ed. Chur, Switzerland, Harwood Academic Publishers, 1994, p. 111–132

5. Bradley C, Todd C, Gorton T, Symonds E, Martin A, Plowright R. The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. Qual Life Res 1999;8:79–91

6. Bradley C, Speight J. Patient perceptions of diabetes and diabetes therapy: assessing quality of life. Diabetes Metab Res Rev 2002;18(Suppl. 3):S64–S69

7. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. 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

8. Edelman SV, Argento NB, Pettus J, Hirsch I. Clinical implications of real-time and intermittently scanned continuous glucose monitoring. Diabetes Care 2018;41:2265–2274

9. Vigersky RA, Fonda SJ, Chellappa M, Walker MS, Ehrhardt NM. Short- and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes. Diabetes Care 2012;35:32–38

10. Vigersky R, Shrivastav M. Role of continuous glucose monitoring for type 2 in diabetes management and research. J Diabetes Complications 2017;31:280–287

11. Beck RW, Riddlesworth TD, Ruedy K, et al.; DIAMOND Study Group. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. Ann Intern Med 2017;167:365–374

12. Kesavadev J, Shankar A, Ashok AD, et al. Our first 825 T2DM patients on 14-day factory-calibrated glucose monitoring system: clinical utility and challenges. J Diabetes Sci Technol 2018;12:230–231

Downloaded from http://diabetesjournals.org/care/article-pdf/42/7/1178/530321/dc180166.pdf by guest on 02 October 2022