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The impact of a structured education and treatment programme (FLASH) for people with diabetes using a flash sensor-based glucose monitoring system: Results of a randomized controlled trial

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ABSTRACT

Aims: Flash sensor-based glucose monitoring (FSGM) provides people with diabetes considerably more information on their glycaemic control. We have developed and evaluated a structured education and treatment programme, termed FLASH, to assist FSGM users to understand and use the available glycaemic information for optimization of their diabetes treatment.

Methods: We report on a multi-centre, randomized, parallel trial with a six-month follow-up involving 216 eligible participants (16–75 years old) on intensive insulin therapy. The primary outcome was HbA1c change from baseline to six months. Secondary outcomes were measures of glucose control as assessed by FSGM, as well as changes in behavioural and psychosocial measures.

Results: At six months, the between-group difference in HbA1c reduction was significant, favouring FLASH education compared to the control group receiving no FLASH education (−0.28%, 95% CI −0.16% to −0.40% vs.−0.11%, 95% CI 0.00% to −0.22%; with a between-group difference of −0.17%, 95% CI −0.01% to −0.33%; p = 0.033). Participation in FLASH education also resulted in significant improvements in time spent in the target glucose range, in diabetes-related distress scores and in satisfaction with the glucose monitoring method. FLASH education also resulted in significant improvements in the use of glycaemic information provided by FSGM and in reduced self-monitoring of blood glucose (SMBG) fingerstick testing.

Abbreviations: FSGM, flash sensor-based glucose monitoring; SMBG, self-monitoring of blood glucose; ISF, interstitial fluid; AGP, the ambulatory glucose profile; CGM, continuous glucose monitoring; MDI, multiple daily insulin-injections; CSII, continuous subcutaneous insulin infusion therapy; PAID, Problem Areas in Diabetes Scale; CES-D, Center for Epidemiologic Studies Depression Scale; CRF, case report forms; ANCOVA, analyses of covariance

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Conclusion: FLASH is an effective programme to improve glycaemic control and lower diabetes-related distress in users of FSGM.

The study was registered in ClinicalTrials: NCT03175315.

1. Introduction

The FreeStyle Libre flash sensor-based glucose monitoring system (FSGM; Abbott Diabetes Care, Witney, Oxon, UK) measures glucose continuously in the interstitial fluid (ISF) [1]. Each time the sensor is scanned glucose data are transferred to a reader or smartphone.

Compared to traditional self-monitoring of blood glucose (SMBG), FSGM provides several benefits for people with diabetes. They can access their current glucose level as often as they want without the need for pricking a finger to obtain a blood sample. Along with the current glucose value, the reader or a smartphone app also displays a glucose trend arrow and a graph of the glucose readings over the preceding 8 h. Glucose values are stored every 15 min for up to 90 days. Stored glucose values can also be uploaded to a cloud-based system (e.g., LibreView™, Abbott Diabetes Care, Witney, Oxon, UK, Tidepool, Palo Alto, California, USA or DIASEND/GLOOKO, Mountain View, California, USA) or downloaded to a personal computer [1,2]. Up- or downloading stored glucose values allows the application of more advanced analytical methods that permit better discovery and analysis of problematic glucose patterns. This includes summary reports such as the ambulatory glucose profile (AGP) that can help FSGM users and their care givers make targeted adjustments to diabetes treatment [3,4]. New FSGM- or continuous glucose monitoring (CGM)-derived parameters such as time in range and time spent in hypoglycaemia, respectively hyperglycaemia or glycaemic variability, allow a more comprehensive overview of glycaemic control than established quality indicators, such as HbA1c. This information can be used for more informed treatment decisions than a single spot SMBG can provide.

However, the abundance of glucose data that are provided by FSGM or CGM systems can also be perceived as challenging, burdensome or overwhelming by individuals with diabetes [5–7]. Given the amount and new quality of glucose data, it seems crucial that people with diabetes know how to interpret and apply the data that they receive from the system [8]. Gonder-Frederick concludes that the adoption and utilization of continuous glucose data requires ample patient education not only on the specific features and functions of the device but also on how to utilize glucose feedback to improve diabetes self-management [5]. In addition, diabetes education should also address emotional aspects of using continuous glucose data. Currently, no structured diabetes education programme for people with diabetes using FSGM exists.

We have developed a structured education and treatment programme for people using FSGM who are on an intensive insulin regimen. This programme, termed FLASH, is designed to provide skills and knowledge to make use of the greater amount of glucose information provided by CGM systems such as FSGM. In addition, the FLASH programme also addresses psychosocial issues that are associated with the use of FSGM technology, such as coping with the amount of glucose information and the sometimes exaggerated expectation it creates about glucose management [5]. FLASH is based on the empowerment/self-management approach and focuses on empowering participants to use the new technology effectively in daily life.

In this randomized controlled trial, we examined the impact of participation in the FLASH structured diabetes education and treatment programme on HbA1c as a primary outcome for FSGM users and on a broad set of glycaemic, psychosocial and behavioural outcomes.

2. Material and methods

2.1. Study design

This investigator-initiated study was designed as an open-label, parallel, randomized, controlled trial with a six-month follow-up. It was conducted in an outpatient setting of 26 secondary-care practices (study centres) throughout Germany. A study centre was defined as a specialized diabetes care practice operated by a diabetologist and employing at least one certified diabetes educator. Ethics approval was obtained from the competent ethics committee (EK-Hermanns-032017).

2.2. Participants

Eligible subjects were people with diabetes currently on intensive treatment with multiple daily insulin - injections (MDI) or on continuous subcutaneous insulin infusion therapy (CSII). In addition, only participants already using or intending to use a FSGM system, the FreeStyle Libre system from Abbott Diabetes Care, Witney, Oxon, UK, were included. Further inclusion criteria were as follows: 16–75 years of age; prior participation in a structured diabetes education programme on intensive insulin therapy (to guarantee that all participants had the proper knowledge and basic skills to treat their diabetes with insulin); HbA1c at screening 7.5%–14% (58–130 mmol/mol); ability to understand, speak and write the German language; and informed consent (if necessary, informed consent of the parents). The exclusion criteria were diabetes duration < 1 year; type 2 diabetes not treated by MDI, severe organic disease preventing regular participation in the education courses; pregnancy; severe cognitive impairment; current treatment for a psychiatric disorder; or renal disease requiring dialysis.

Eligible people with diabetes were recruited at each study centre. Prior to inclusion, participants were fully informed both orally and in writing about the study and gave written informed consent. Participants received no monetary compensation for participation in this study.

2.3. Randomization and masking

After completion of the baseline phase, participants were randomly assigned to one of two study groups: (1) participation in the FLASH education and treatment programme (FLASH group) or (2) treatment-as-usual without FLASH education (control group). Thus, both groups were using FSGM but differed only in their participation in the FLASH education and treatment programme. Randomization was performed centrally at the study coordinating centre, whose staff were not involved with recruitment or treatment of study participants. A computer-generated algorithm (using SYSTAT 12.0; Systat Software Inc., Chicago, IL) with the study centre as a stratification factor and using a 1:1 allocation was used to randomize subjects. Once a study centre had recruited 6 to 16 participants and completed the baseline assessment for all recruited participants, they contacted the study coordinating centre, and block randomization was used, with the block size depending on the participant pool for each study centre (n = 6–16). The results of the randomization were sent to the study centre, and participants were informed about their group allocation. Due to the nature of the intervention, blinding of participants as well as diabetes educators who provided the intervention was not possible.

2.4. Procedures

After participants provided informed consent, a blood sample was drawn for HbA1c measurement in a central laboratory. Participants also completed a series of questionnaires to evaluate their psychosocial experiences of living with diabetes. All participants in the study were provided with a FreeStyle Libre FSGM system, including a reader and sensors. During the baseline phase, lasting 14 days, all participants were instructed to upload glucose values into the DIASEND/Glooko System (Glooko Inc., 303 Bryant St., Mountain View, CA 94041, USA). After this baseline assessment, randomization of the participants either to the FLASH programme or the control group took place. Participants allocated to the FLASH group received the respective programme; participants of the control group received treatment as usual without education. At the end of the FLASH programme, all participants in the control group and the FLASH group provided a blood sample for HbA1c measurement. At week 24 following FLASH intervention, glucose data were collected for 2 weeks for the follow-up phase. At week 26 after the end of the FLASH intervention, a blood sample was drawn for HbA1c measurement in central laboratory and all other follow-up measurements were taken, assessing the same variables as at baseline. Participants in both groups were assessed at the same time point. More details on the conduct of the study are described in Schipfer et al. [9].

FLASH takes place over 6 weeks. It consists of four education sessions, lasting 90 min each. There is a 1-week interval between sessions 1 and 2 and 2-week intervals between sessions 2 and 3 and sessions 3 and 4. These intervals give patients time to practise the newly learned techniques in their daily lives. An overview of the FLASH content is provided in Supplementary Table S1. FLASH is conducted as a group programme (3–8 participants per group). Participants are provided with written material and worksheets and encouraged to test the contents of each lesson on their own and to then discuss their experiences in the group setting. FLASH is based on the self-management/empowerment approach and focuses on helping participants effectively use information about the course of their previous glucose levels, their current glucose values and the displayed glucose trend arrow information to make informed decisions about their diabetes treatment. Participants are also introduced to computer-based data analysis software and familiarized with graphical displays of their recent AGP data, and they are trained to recognize problematic patterns in their glucose profiles. Another key topic of FLASH is the psychosocial impact of FSGM. Throughout the course, emotional and motivational obstacles as well as negative attitudes towards use of FSGM are addressed. The programme is also aimed at individualized goal-setting for diabetes treatment and shared decision-making [10]. Participants discuss their individual goals to achieve within the course, reflect upon the status of their goal attainment and assess their handling of barriers to achievement. Between lessons, participants are instructed to use various materials (e.g., complete worksheets for individual goal-setting and attainment, use ambulatory glucose profiles to display their glycaemic control, complete glucose logs) [3]. In the study centres, the FLASH programme was conducted by a single certified diabetes educator in person on the study centre premises. Each diabetes educator received 8 h of training to ensure standardized delivery of the FLASH content. This pre-study training was conducted by a diabetologist and a psychologist to deliver the medical and psychological components of FLASH. In addition, each diabetes educator received a written curriculum. Before the start of the study, each study centre received an initiation visit. All major changes in the diabetes regimen were supervised by the diabetologist.

2.5. Outcomes

The primary outcome was change in HbA1c from baseline to the six-month follow up. HbA1c was measured in a central laboratory using the high-performance liquid chromatography method (Tosoh Automated Glycohemoglobin Analyzer HLC-723G11; normal range 21–43 mmol/mol; 4.1–6.1%). Laboratory personnel were blinded to the randomized treatment allocation of the study participants.

Secondary glycaemic outcomes were as follows: percentage of glucose values that were in the hypoglycaemic range (<70 mg/dL), in the hyperglycaemic range (>180 mg/dL) and in the normal target glucose range (70–180 mg/dL). In addition, glucose variability was expressed as the coefficient of variation (CV), and the daily number of scans was determined. Glucose values and frequency of scans at baseline and at 6-month follow-up were aggregated per patient. Secondary outcomes referring to participants' psychological

and behavioural variables were measured by diabetes-, programme- and device-related questionnaires as detailed.

- **Diabetes distress:** The Diabetes Distress Scale (DDS) assesses psychosocial adaptation to the burden of living with and treating diabetes [11]. The mean scale scores range from 0 to 5, with higher values indicating higher distress.
- **Satisfaction with glucose monitoring** was assessed using the Glucose Monitoring Satisfaction Survey [12]. This scale provides a total score ranging from 1 to 5 and 4 subscales (flexibility of glucose monitoring, emotional barriers of glucose monitoring, behavioural barriers of glucose monitoring and trust) with the respective scale range.
- **Depressive symptoms** were assessed with the German version of the Center for Epidemiologic Studies Depression Scale (CES-D) [13]. The scale ranges from 0 to 60, with higher values indicating more depressive symptoms.
- **Diabetes empowerment** was assessed by the German short version of the Diabetes Empowerment Scale. The scale ranges from 0 to 33, with higher values indicating higher diabetes empowerment [14].
- **Self-efficacy** was assessed by a diabetes-specific self-efficacy scale. The scale ranges from 0 to 33, with higher values indicating higher diabetes-related psychosocial self-efficacy and higher diabetes empowerment [15].
- **Treatment satisfaction**: Satisfaction with the current treatment was assessed via a 10-item questionnaire [16]. The scale ranges from 10 to 60, with lower scores indicating higher satisfaction.
- **Hypoglycaemia worry** was assessed using the worry scale of the hypoglycaemia fear survey. The scale ranges from 0 to 54, with higher values indicating greater worries about hypoglycaemia [17].
- **Hypoglycaemia awareness:** The German version of the hypoglycaemia awareness questionnaire [18] provides a score indicating the severity of hypoglycaemia unawareness. The scale ranges from 0 (maximum hypoglycaemia awareness) to 7 (minimum hypoglycaemia awareness); a score of 4 or higher suggests reduced hypoglycaemia awareness.
- **Use of glucose monitoring features** (trend arrows, course of glucose, analysis of glucose course by using the reader, analysis of glucose course by using analysis software, e.g., AGP and frequency of blood glucose testing) were assessed via self-report on a scale of 0–4 (0: not at all; 1: 1–3 times per month; 2: at least once a week; 3: several times a week; 4: daily).

Key demographics (age, sex, education, body-mass index) as well as medical information (diabetes type, diabetes duration, duration of CSII-therapy, late complications [retinopathy, nephropathy, neuropathy, diabetic foot syndrome, coronary heart disease]) were retrieved from patient files and documented via case report forms (CRF) completed by the study personnel.

2.6. Statistical analysis

Based on the assumption of an expected HbA1c difference between the two groups of 0.3% and a standard deviation of 0.7% for each group (effect size $d = 0.43$), power analysis revealed that 86 participants per group and a total sample of 172 participants were needed to achieve a power of $1-\beta = 0.80$ with a two-sided alpha-error of $\alpha = 0.05$. Assuming a non-evaluable rate of 20% (e.g., not suitable for per-protocol analysis), a total of 216 participants were needed. Primary and secondary outcomes were analysed by analyses of covariance (ANCOVA), with the primary and secondary outcomes at follow-up as dependent variables, treatment groups and study centres as independent factors and the respective baseline values as covariates. Because the frequency of the use of glucose monitoring features could not be assessed at baseline in participants who did not use the FreeStyle Libre FSGM system already and the frequencies were not an interval scale, we calculated a two-factor analysis of variance with group allocation and study centre as independent variables and frequency of use of glucose monitoring features at follow-up as the dependent variable using ranks transformed to van der Waerden scores.

The alpha level was set to 0.05 (two-sided). The per protocol sample included participants with complete data for the primary outcome. For the primary outcome, intention to treat analysis was performed, including all participants who completed baseline measurement. For the intention to treat analysis, missing values were replaced using multiple imputation. Missing data at the follow-up phase were imputed using a Markov Chain Monte Carlo multivariate imputation algorithm (missing data module in SPSS 25) with 10 estimations per missing value using the following variables as estimators: age, diabetes duration, treatment allocation, previous use of FSGM and CSII use. Exploratory secondary analyses were conducted to identify baseline factors as possible moderators of change in HbA1c. Analyses of covariance were performed for each baseline factor with HbA1c at follow-up as the dependent variable controlling for baseline HbA1c and study centre effects. The main effect of the moderator variable and group as well as the interaction term between group and moderator variables were included to test for moderation. The following moderator variables were tested: CSII use, previous FSGM use prior to study entry, gender and diabetes type. Besides people with type 1 and type 2 diabetes, two persons with pancreatic diabetes were included. For the moderator analysis, they were added to the group of type 1 diabetes, since this subgroup was too small to be included in the moderator analysis. The trial was registered at ClinicalTrials.gov (trial identifier: NCT03175315).

3. Results

3.1. Study recruitment and baseline data

Participants were recruited between March 27, 2017, and April 1, 2017. Follow-up measurements were completed in February 2018. Each study centre contributed one patient pool (median

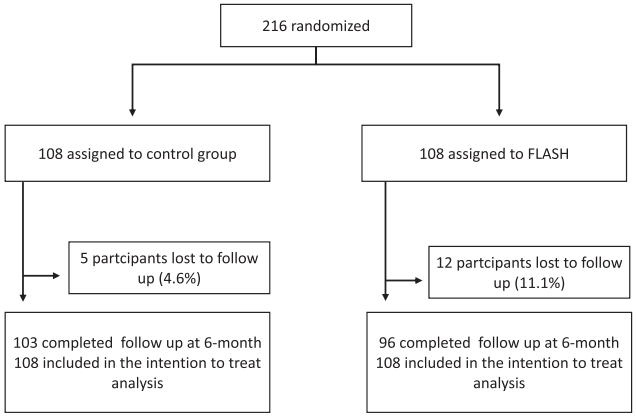

Fig. 1 – Consort statement.

pool size = 9; interquartile range: 8–9). As planned, 216 participants were randomized to either the FLASH group or the control group, and a total of 199 participants were analysed for the per-protocol population. See consort statement in Fig. 1. The non-evaluable rate was 11.1% in the FLASH-group and 4.6% in the control group (p = 0.112). As shown in Table 1, most participants had type 1 diabetes and had a long diabetes duration (mean 20.0 ± 10.6 years). All participants were on MDI treatment with insulin. Despite a long duration of diabetes and participation in several education programmes, glycaemic control, as measured by HbA1c, was unsatisfactory (mean 8.4% ± 1.0) according to the German guidelines for diabetes treatment [19,20]. The proportion of diabetes-related complications was low (Table 1). Ninety percent of the study subjects did not report an episode of severe hypoglycaemia during the past 12 months, which indicates a low prevalence of hypoglycaemia problems. More than 60% of the subjects were already using the FSGM system prior to the baseline examination.

The baseline scores of the participants indicated a rather high level of psychological well-being, satisfaction with the glucose monitoring method, empowerment and self-efficacy. Additionally, rather low levels of depression, diabetes distress, dissatisfaction with insulin treatment, hypoglycaemia worry and hypoglycaemia unawareness were reported at baseline (see Table 2).

3.2. *Primary outcome*

The courses of the baseline- and study-centre-adjusted HbA1c values from baseline, post-intervention and 6-month follow-up are shown in Fig. 2. During the intervention phase, HbA1c was reduced by 0.33 percentage points in the FLASH group and by 0.14 percentage points in the control group. During the follow-up, a slight increase of the HbA1c values was observed in both groups. At 6-month follow-up glycaemic outcomes as measured by HbA1c improved in both the FLASH group (-0.28%, 95% CI −0.16 to −0.40%) and in the control group (−0.11%, 95% CI 0.00 to −0.22%). The between-group difference of this change in HbA1c was significant in favour of FLASH (−0.17%; 95% CI −0.01 to −0.33%; p = 0.033; see Table 2). These results were corroborated by analysing the intention to treat population (−0.16%; 95% CI −0.02 to −0.32%; p = 0.026). There was also a significant study centre effect (p = 0.02) but no significant interaction between study group and study centre. The cumulative distribution of HbA1c values at baseline and follow-up in the control and FLASH group showed a regression to the mean in the control group and a modest improvement of HbA1c values over the whole range in the FLASH group (Fig. 3). In a sensitivity analysis we additionally adjusted the analysis for the demographic variables age, gender and diabetes duration. The results showed nearly identical results as in the main analysis (data not shown). In a moderator analysis we also tested the interaction between baseline variables and baseline

Table 1 – Sample description at baseline.

	FLASH (n = 108)	Control (n = 108)	p
Mean age (yrs) ± SD	44.8 ± 13,9	47,0 ± 13,6	0.244
Number female gender (%)	54 – (50%)	58 (53.7%)	0.586
Mean BMI (kg/m^2) ± SD	27.7 ± 5.6	28.3 ± 4.7	0.437
Mean years of education (yrs) ± SD	12.0 ± 3.6	12.2 ± 3.6	0.731
Number type 1 diabetes (%)	93 (86.1%)	90 (83.3%)	0.353
Number type 2 diabetes (%)	15 (13.9%)	16 (14.8%)	
Number other types (%)	0 (0.0%)	2 (1.9%)	
Mean diabetes duration (yrs) ± SD	20.0 ± 10.9	20.2 ± 10.5	0.898
Number of previous structured diabetes education classes (±SD)	3.1 ± 2.5	3.5 ± 3.1	0.336
Number with CSII therapy (%)	40 (37.0%)	43 (39.8%)	0.675
Mean HbA1c in % ± SD	8.4 ± 0.9	8.4 ± 0.9	0.862
Mean HbA1c in mmol/mol ± SD	68.1 ± 10.2	68.3 ± 10.4	
Mean number of complications ± SD	0.58 ± 0.91	0.53 ± 0.89	0.675
Number with complications[1] (%)	38 (35.6%)	36 (33.3%)	0.736
Number with FSGM use before study (%)	70 (64.8%)	63 (58.3%)	0.327
Number with severe hypoglycemia[2] in past 12 months (%)	10 (9.3%)	12 (11.1%)	0.653
Rate of severe hypoglycaemia per year ± SD	0.22 ± 0.84	0.27 ± 1.06	0.696

[1] Retinopathy, nephropathy, neuropathy, coronary heart, disease, diabetic foot syndrome, amputation.
[2] Third party assistance for recovery.

Table 2 – Glycaemic and psychosocial outcomes.

	Baseline		Follow up		Adjusted between group difference (95% CI)	p
	FLASH (n = 96)	Control (n = 103)	FLASH (n = 96)	Control (n = 103)		
Primary outcome HbA1c						
Mean HbA1c % ±SD	8.31 ± 0.80	8.35 ± 0.87	8.04 ± 0.75	8.23 ± 0.92	−0.17 (−0.01 to −0.33)	0.033
Mean HbA1c mmol/mol ± SD	67.35 ± 8.74	67.72 ± 9.56	64.42 ± 8.15	66.43 ± 10.06	−1.89 (−0.16 to −3.63)	
Secondary outcomes: FSGM characteristics						
Mean glucose mg/dl ± SD1	183.7 ± 29.5	185.2 ± 38.7	183.2 ± 33.1	190.7 ± 37.4	−5.2 (−12.7 to 2.6)	0.217
Mean % 70–180 mg/dl ± SD	47.3 ± 11.7	47.5 ± 14.2	49.1 ± 13.6	45.3 ± 15.0	−3.8 (−7.0 to −0.5)	0.027
Mean % <70 mg/dl ± SD	6.1 ± 4.2	5.6 ± 4.0	4.7 ± 4.4	4.4 ± 3.8	−0.2 (−1.3 to 1.0)	0.878
Mean % >180 mg/dl ± SD	46.7 ± 13.1	46.8 ± 16.0	46.1 ± 15.3	50.3 ± 16.2	−3.8 (−7.6 to 0.0)	0.062
Coefficient of variation % ±SD	42.9 ± 6.8	41.4 ± 6.9	39.2 ± 6.9	38.2 ± 7.2	0.3 (−1.5 to 2.1)	0.920
Mean number of scans per day ± SD	13.9 ± 9.7	11.6 ± 9.0	10.1 ± 6.8	9.4 ± 7.2	0.1 (−1.5 to 1.8)	0.933
Secondary Outcome: Patient reported outcomes						
Diabetes Distress Score ±SD	1.5 ±0.8	1.2 ±0.69	1.1±0.7	1.1 ±0.7	−0.2 (−0.3 to −0.1)	0.029
Glucose Monitoring Satisfaction Score ±SD	3.7 ± 0.6	3.9 ±0.6	4.2 ±0.5	4.1 ±0.5	−0.1 (−0.3 to 0.0)	0.050
WHO 5 Score	14.6± 4.6	14.8 ± 4.7	15.4 ±5.1	15.1 ±5.0	0.4 (−0.7 to 1.6)	0.456
Depression Score (CESD) ± SD	14.4 ±9.8	13.7 ±8.5	13.2 ±10.2	13.6 ±9.6	−0.9 (−3.0 to 1.1)	0.371
Empowerment Score ±SD	25.8 ±4.7	27.0 ±4.3	27.1 ±3.7	27.2 ±3.6	−0.3 (−0.5 to 1.2)	0.447
Self Efficacy Score ±SD	22.7 ±4.5	23.4 ±3.9	23.9 ±4.1	23.6 ±4.5	0.8 (−0.2 to 1.7)	0.113
Satisfaction Score with Insulin therapy ±SD	27.5 ±6.5	27.6 ±6.7	25.2 ±6.6	26.4 ±6.4	−1.2 (−2.8 to 0.3)	0.118
Hypoglycaemia Worry Score ±SD	21.3 ±14.9	17.5 ±12.8	16.2 ±13.4	15.8 ±12.9	−1.9 (−4.6 to 0.7)	0.150
Hypoglycaemia Unawareness Score	1.1 ±1.4	1.0 ±1.4	1.0 ±1.4	0.9 ±1.4	0.0 (−0.3 to 0.3)	0.932

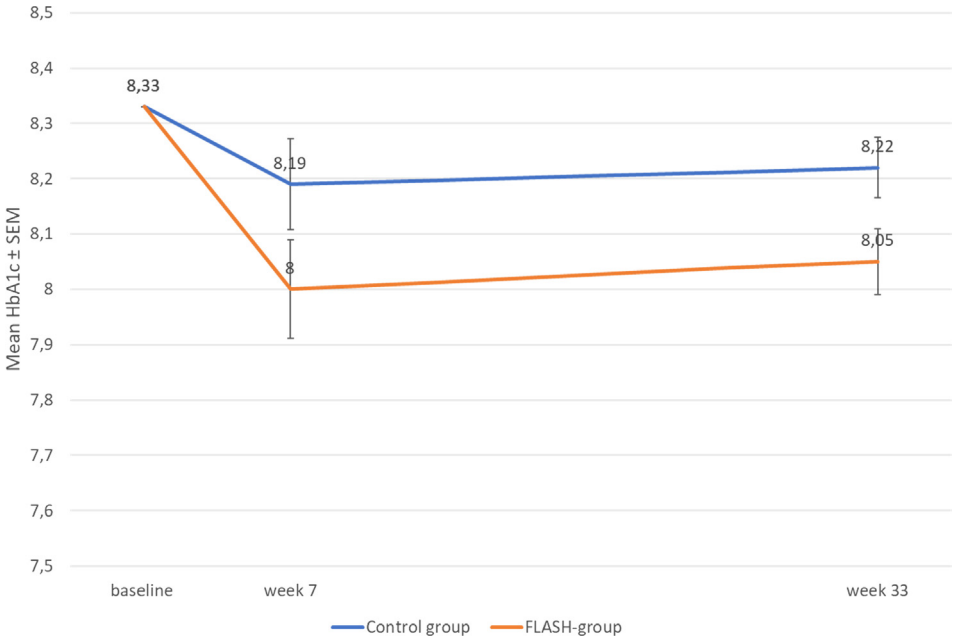

Fig. 2 – Course of adjusted HbA1c values from baseline, end of intervention and follow up.

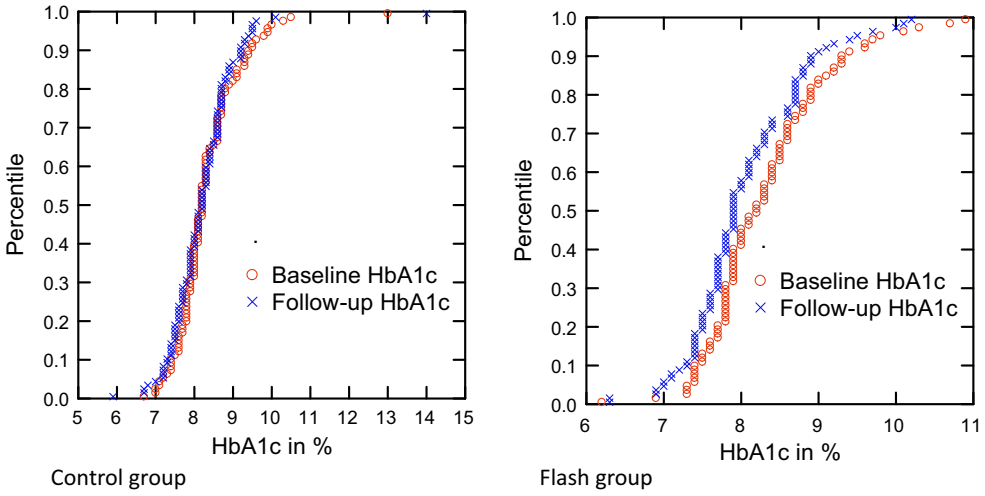

Fig. 3 – Cummulative distribution of the HbA1c in the control group (A) and FLASH Group (B) at baseline and follow-up (For any given HbA1c measurement (x-axis) the percentage of cases with HbA1c values at that level or lower in baseline and follow-up phase (y-axis) can be determined from the figure).

characteristics of the sample like CSII use, previous FSGM-use, diabetes type and gender (see Supplementary Table 2). There were no significant interaction effects between the FLASH education programme and these baseline characteristics indicating that these variables did not moderate the effect of FLASH education on HbA1c outcomes.

3.3. *Secondary outcomes*

The mean glucose level differed by 5.2 mg/dl (95% CI −12.7 mg/dL to 2.6 mg/dL, p = 0.217). Analysis of the FSGM data revealed that the proportion of glucose values in the target glucose range (70–180 mg/dL) was significantly increased by 3.8 pecentage points (95% CI −7.0 to −0.5, p = 0.027) in the FLASH group compared to the control group. The percentage of values in hyperglycaemia (>180 mg/dL) was reduced by 3.8 percentage points (95% CI −7.6 to 0.0), but this was not significant (p = 0.062). The percentage of hypoglycaemic glucose values lower than 70 mg/dl was 0.2 percentage points (95% CI −1.3 to 1.0, p = 0.878) lower in the FLASH group than in the control group. Severe hypoglycaemia (third party assistance for recovery) was not significantly affected by FLASH. The rate of severe hypoglycaemia events per patient and per 6 months was 0.18 ± 0.85 in FLASH compared to 0.28 ± 1.10 in the control group (p = 0.470).

Glucose variability was reduced in both groups, and the adjusted between-group difference was 0.3% (95% CI −1.5% to 2.1%, p = 0.920). The number of daily scans was reduced

Table 3 – Behavioral outcomes: use of flash sensor-based glucose monitoring features.

	Follow-up		p
	FLASH (n = 96)	Control (n = 103)	
Median frequency of using trend arrows (IQR)	4.0 (3.0, 4.0)	4.0 (3.0, 4.0)	0.003
Median frequency of using glucose course for treatment adjustments (IQR)	4.0 (3.0, 4.0)	3.0 (3.0, 4.0)	0.138
Median frequency of evaluating glucose control by reader (IQR)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	0.520
Median frequency of evaluating glucose control by downloads to cloud or computer (IQR)	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.030
Median frequency of blood glucose tests (IQR)	2.5 (1.0, 4.0)	4.0 (1.0, 4.0)	0.030

at follow-up compared to baseline, but the between-group difference was not significant (0.1, 95% CI −1.5 to 1.8, p = 0.933) (see Table 2).

Although the participants in the FLASH group reported significant lower diabetes-related distress scores (-0.2, 95% CI −0.3 to −0.1; p = 0.029) and higher satisfaction with the glucose monitoring method (-0.1, 95% CI −0.3 to 0.0, p = 0.050) at follow-up than the control group, no significant effects of FLASH were observed regarding psychological well-being, depression score, empowerment, self-efficacy, satisfaction with insulin therapy, hypoglycaemia worry score or hypoglycaemia unawareness score (see Table 2).

In terms of the utilization of the features of the FSGM system, there was a demonstrable impact of FLASH education on the behaviour of study participants (Table 3). Participants in the FLASH group reported significantly more frequent use of trend arrows for daily treatment adjustments compared to the control group (69.6% vs 54.6%, p = 0.003) and reported much more frequent evaluation of their glucose data following downloading to a computer or from the cloud for analysis (71.0% vs 38.5%, p = 0.030). The FLASH group also had less frequent SMBG tests for verifying the FSGM glucose readings (54.2% at least once daily SMBG vs. 70.4% at least once daily SMBG; p = 0.030) (see Table 3).

4. Discussion

This is the first randomized controlled study to demonstrate the efficacy of a structured education programme specifically designed for people with diabetes using FSGM technology. Engagement with the FLASH programme led to a significantly greater improvement in overall glycaemic control as measured by HbA1c, and the results provide clear evidence as to the efficacy of structured diabetes education on the use of FSGM technology.

The observed reduction of HbA1c associated with participation in FLASH has to be evaluated in the context of two randomized controlled trials, the REPLACE study [2] and the IMPACT study [1]. Both studies evaluated the impact of FSGM technology without education on glycaemic control. The REPLACE study in adults with type 2 diabetes observed a reduction of HbA1c from 8.65% to 8.37% in the FSGM group, whereas the control group reduced HbA1c from 8.75% to 8.37%, resulting in a between-group difference of 0.03% ± 0.11%, p = 0.822. Additionally, in the IMPACT study on adults with type 1 diabetes, there was no difference in the mean HbA1c between the FSGM and SMBG arms at 6 months (between group difference 0.0 ± 0.06, p = 0.956). Notably, the IMPACT study group was adults with well-controlled type 1 diabetes, with a baseline HbA1c of 6.78% (FSGM arm) and 6.79% (SMBG arm), such that a change in HbA1c was not a primary endpoint. Only in the non-randomized and uncontrolled SELFY study [21] overall glycaemic control as measured by HbA1c was improved significantly after switching from SMBG to FSGM. In 76 children and teenagers with type 1 diabetes, FSGM users had a mean reduction in HbA1c of −0.4% (7.9% − 7.5%, p < 0.0001) after 8 weeks compared to previous standard care with SMBG. However, the magnitude of this effect was similar to the improvement observed in the control group of the REPLACE study. Thus, the current evidence from methodologically sound studies suggests that education regarding FSGM use can lead to an additional significant benefit regarding the reduction of HbA1c compared to the use of FSGM technology alone.

The observed increase in time in the range and the marginally significant reduction in the percentage of hyperglycaemic glucose values correspond with the observed HbA1c reduction.

In contrast to the REPLACE and IMPACT [1] studies, we did not observe a beneficial impact of FLASH on exposure to hypoglycaemic values. However, this sample differs from the IMPACT sample regarding baseline exposure to biochemical hypoglycaemia. Due to the HbA1c inclusion criterion, hypoglycaemia problems in this sample were rather uncommon (more than 90% did not experience severe hypoglycaemia during the past year), and baseline exposure to biochemical hypoglycaemia was also rather low. Approximately 6% of all glucose values in this sample were lower than 70 mg/dl, whereas in the IMPACT study, exposure was much higher (>14%), which might be due to the rather low baseline HbA1c. In summary, an additional effect of diabetes education on exposure to biochemical hypoglycaemia was not observed in this sample. This could be due to the sample composition of this study. There was a high proportion of people with type 1 diabetes without any significant hypoglycaemia problems. Notably, in the SELFY study with children and young people with type 1 diabetes [21], biochemical hypoglycaemia was also not significantly reduced in this population with type 1 diabetes.

FSGM use alone showed a positive impact on improved diabetes treatment satisfaction scores and diminished worries for children or adults with type 1 or type 2 diabetes [1,2,21]. In this study, FLASH participants reported significantly less diabetes distress and higher satisfaction with the glucose monitoring method than the control group. This indicates that education can reduce diabetes distress and

enhance satisfaction with glucose monitoring beyond the effect that FSGM has per se. However, it has to be kept in mind that the observed between group improvements were rather small with a reduction of distress of 17% from baseline values and an improvement of satisfaction with glucose monitoring of 7% from baseline values.

Patient-reported outcomes regarding empowerment, self-efficacy, hypoglycaemia worries, psychological well-being and satisfaction with insulin therapy did not show a benefit from participating in the FLASH programme. However, it must be kept in mind that baseline values for these indicators were at a favourable level, such that improvements because of structured diabetes education might have been difficult to achieve.

There was also a significant impact of FLASH education on a behavioural level. Compared to the control group, the FLASH study group exhibited more frequent use of trend arrow information and engaged significantly more with a structured analysis of their glucose data using dedicated software on a personal computer or on a cloud-based system. In addition, there was a significant reduction in blood glucose self-monitoring for verifying FSGM glucose readings. The latter might be a direct effect from providing information about the difference between blood glucose measurements and glucose measurements in the interstitial tissue. These behavioural changes achieved by participation in FLASH might explain the observed improved glycaemic control as measured by HbA1c and time in range.

This is the first randomized controlled study of the efficacy of structured diabetes education on the use of FSGM technology. A strength of the study is that the impact of the structured diabetes education programme can be separated from the effects of FSGM use because all participants were either provided with the FreeStyle Libre FSGM system at the start of the study or were already using this device at study inclusion. A further strength is the conduct of the study in multiple specialized diabetes care centres throughout Germany; thus, the conduct of the study was representative of the reality of diabetes care. However, a clear limitation of the study are the post hoc large differences observed between study centres regarding the primary outcome measure. These centre differences might be due to different pre-study skills regarding the use of FSGM or other CGM technologies and the interpretation of their results. These centre differences were evident despite the standardized training for diabetes educators in the delivery of the FLASH intervention programme. The centre differences might have limited the effect of the FLASH group on study outcomes. These centre differences also indicate the need for further education of health care professionals in the interpretation of CGM-derived data. Another limitation might be related to the sample selection. Due to the inclusion criteria of elevated HbA1c values, the studied sample consisted of people with type 1 and type 2 diabetes who were not able to achieve satisfactory glycaemic control despite a long disease duration and participation in several structured education programmes. This negative selection might have also contributed to the observed modest effect in glycaemic control.

Although statistically not significant, there was a rather large difference regarding the dropout rates between the groups (11.1% vs. 4.6%). Dropout occurred rather early during the group intervention, due to time restrictions. The need to participate in group sessions at a specific time and place is a clear limitation of group education compared to individual education or internet-based education.

Unlike the REPLACE [2], the IMPACT [1] and the SELFY [21] study, people with type 1 as well as type 2 diabetes were included in this study. The key inclusion criterion was that they were on an intensive insulin regimen. This mirrors our experience of the clinical practice in many countries. The moderator analysis did not show a diabetes type specific moderator effect. However, these results only apply for people with type 2 diabetes on an intensified insulin regimen and cannot be generalized to people with type 2 diabetes and other treatment regimens (e.g. oral treatments, combination of oral agents and basal insulin or biphasic insulin therapy).

5. Conclusion

In summary, this randomized controlled trial has shown that structured diabetes education about the use of FSGM can lead to a significant improvement in glycaemic control for people with diabetes on intensive insulin therapy. The addition of diabetes education to the use of FSGM has the potential to improve the outcomes of this innovative glucose monitoring method beyond the improvements observed by FSGM use per se.

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Authors' contributions

NH, DE and BK designed the study, collected and analysed data and wrote the manuscript. TH, MS, JK interpreted the data and revised the manuscript.

Declaration of interest

NH is an advisory board member of Novo Nordisk, Abbott, Lilly, Roche Diabetes Care, and Ypsomed. He received speakers' honoraria from Novo Nordisk, Abbott, Berlin Chemie, Lilly, and Ypsomed. He has received grants in support of investigator trials from Dexcom, Berlin Chemie, Ypsomed, Abbott, and Roche Diabetes Care. DE received speakers' honoraria from Berlin Chemie, Sanofi, and Roche Diabetes Care. MS received speakers' honoraria from Medtronic and Lilly. BLG is an advisory board member of Abbott and Novo Nordisk. He received speakers' honoraria from Abbott, Berlin Chemie, and Lilly. JK serves on advisory boards for Abbott Diabetes Care, Astra Zeneca, Merck Sharp & Dome, MSD, Novo-Nordisk and Lilly. He received lecture honoraria from Abbott Diabetes Care, Astra Zeneca, Bayer vital, Boehringer Ingelheim, Boehringer Mannheim, Glaxo SmithKline, Medtronic, Merck Sharp and Dohme, Novo Nordisk, Lilly, Roche and Sanofi Aventis. TH is an advisory board member of MSD, AstraZeneca, Roche Diabetes Care, and Abbott. He received speakers' honoraria from Novo Nordisk, Lilly, AstraZeneca, Abbott, and Berlin Chemie. He has received grants in support of investigator trials from Abbott, Boehringer Ingelheim, and AstraZeneca. BK is an advisory board member of Berlin Chemie, Roche Diabetes Care, Novo Nordisk, Medtronic, and Ascensia Diabetes Care. He received speakers' honoraria from Berlin Chemie, Novo Nordisk, Roche Diabetes Care, Abbott, Lilly, and Ascensia Diabetes Care. He has received grants in support of investigator trials from Berlin Chemie, Abbott, and Roche Diabetes Care.

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Availability of data

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.03.003.

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