A pragmatic real-life study of flash glucose monitoring versus self-monitoring of blood glucose

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ABSTRACT

INTRODUCTION: The aim of this study was to investigate if the flash glucose level monitoring system (FGM) is better than traditional self-monitoring of blood glucose level (SMBG) in helping patients in the outpatient clinic control their blood glucose and improve glycaemic control measured by the concentration of glycated haemoglobin (HbA_{1c}).

METHODS: This was an observational real-life study based on data retrieved from a regional diabetes database and conducted in patients with Type 1 diabetes. HbA_{1c} levels at baseline, and at six, nine and 12 months were compared in and between two groups counting 128 patients each. One group included patients who had recently started using the FGM system; the other patients who were using SMBG and otherwise following the routine protocol of the outpatient clinic.

RESULTS: We found no difference between the FGM group and the SMBG group with respect to age, sex, weight, diabetes duration or HbA_{1c} at baseline. After six months, HbA_{1c} had been reduced from 64 to 60 mmol/mol (p = 0.00) in the FGM group, whereas it remained unchanged in the SMBG group (from 63 to 63 mmol/mol, p = 0.66). According to the ANOVA repeated measures test, HbA_{1c} measures showed a significant trend of reduction from 65 to 60 mmol/mol (p = 0.002) over 12 months in the FGM group and no trend of reduction in the SMBG group (from 63 to 64 mmol/mol, p = 0.386)

CONCLUSIONS: Changing the blood glucose measuring method from SMBG to FGM helped patients with Type 1 diabetes in an outpatient clinic reduce their HbA_{1c}.

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Self-monitoring of blood glucose level (SMBG) using a finger-prick blood test has been the standard of care for patients with Type 1 diabetes (T1D) for many decades. In patients with T1D, the importance of keeping good glycaemic control and maintaining the concentration of glycated haemoglobin (HbA_{1c}) as close to normal as safely possible is well known [1-5]. For each percentage increase in HbA_{1c}, the risk of cardiovascular disease increases by 42% [1] and the risk of albuminuria by 16% [6]. In a Swedish study, no participants developed proliferative retinopathy if $HbA_{1c} < 60$ mmol/mol [7].

SMBG is a precise method for measuring blood glucose (BG), using clean fingers, a lancet, test sticks and a measuring device. Even so, it takes a few minutes and leaves a bloody finger and waste. BG is affected by almost everything, why patients with T1D have to do SMBG several times daily to keep their BG within the appropriate range; furthermore, a troublesome measuring method might be one of the reasons why keeping T1D patients' BG in range is so difficult [8].

The flash glucose level monitoring system (FGM) is a novel method to estimate BG from interstitial fluid using a factory-calibrated sensor attached on the upper arm. The method was introduced in Denmark in 2016 [9]. Glucose levels are measured every five minutes and collected by holding a monitor close to the sensor. Glucose levels are stored for eight hours in the sensor. This allows changes in BG for a whole day to be displayed on the monitor if it is used at least four times a day at eight-hour intervals. The monitor also has arrows displaying if BG is increasing, stable or declining. As clinicians in the outpatient clinic, we experience on a daily basis that many patients with T1D wish to use the FGM system instead of the SMBG because it is easy to use and provides all the information needed in a single flash.

To investigate the quality of care of patients with T1D in the outpatient clinic of Odense University Hospital Svendborg, Section of Endocrinology, this study was conducted to study if this novel FGM system is better than the traditional SMBG in helping patients in the outpatient clinic control their BG and improve glycaemic control measured by HbA_{1c}.

METHODS
Study design
This was an observational real-life study based on data retrieved from the regional diabetes database Funen's Diabetes Database (FDDB), which is updated for each patient at every visit to the diabetes clinic. According to guidelines by the Danish Patient Safety Authority, no need for informed consent from the patients was required because all data were retrieved from the patients' medical record since the aim was to investigate the quality of care in the clinic and all personal information

was omitted. This study was conducted in accordance with the principles of the Declaration of Helsinki.
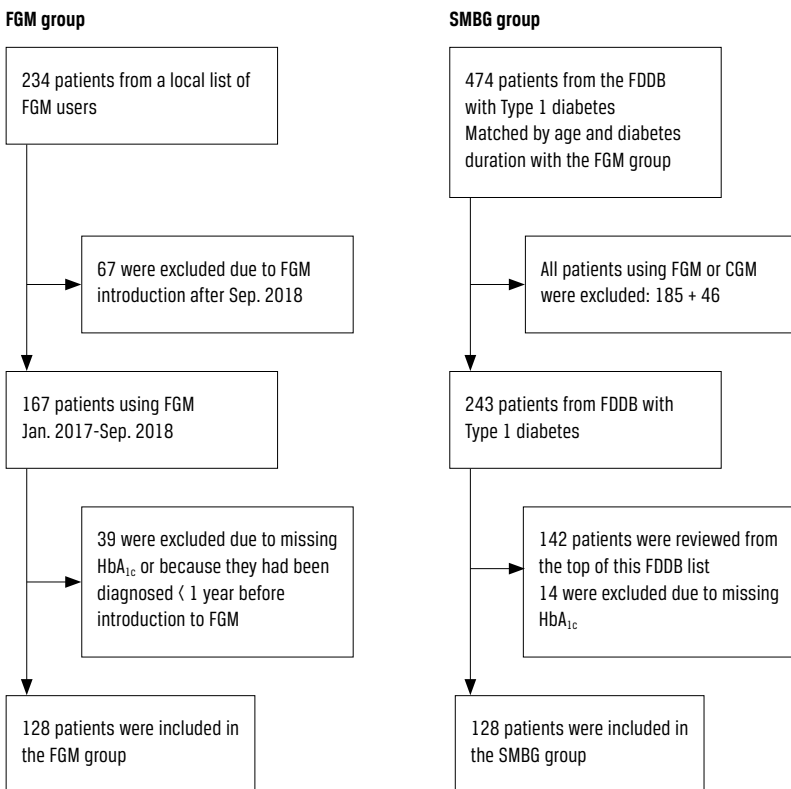
Study population

From January 2017 to September 2018, patients with T1D in the Region of Southern Denmark could be assigned a FGM device provided one of the following criteria was met: 1) Need to reduce BG or keep BG at a specific level; 2) Need to reduce periods of hypoglycaemia; 3) Risk of losing a job due to diabetes; 4) Problems using SMBG due to a handicap or other disease; or 5) Pregnancy or planned pregnancy. Whether a criterium was met was determined during the usual doctors' appointments held in the outpatient clinic every 3-6 months.

Patients in the FGM group were retrieved from the local list of 234 patients in the clinic who had been assigned an FGM device. The list did not state which (one or more) criterion was met for each individual. To secure a minimum six-month follow-up and include as many patients as possible in the FGM group, 67 patients starting FGM after September 2018 were excluded. A total of 39 patients were excluded from the FGM group due to missing data on HbA$_{1c}$ or because

their diabetes diagnosis was made less than one year before starting FGM, leaving 128 patients with T1D measuring BG using an FGM system in this group (**Figure 1**). Patients in the SMBG group were retrieved from the regional diabetes database FDDB, a database updated at every clinical visit and containing data on blood and urine samples, information of episodes of severe hypoglycaemia and diabetic ketoacidosis, and information about any diabetic complications and anti-diabetics. This database was searched for patients with T1D attending the outpatient clinic in Odense University Hospital Svendborg, Department of Endocrinology, and whose age and duration with diabetes matched those of the FGM group. This produced a list of 474 patients visualised alphabetically. In all, 231 patients using FGM or continuous glucose level monitoring (CGM) were excluded from this group. Patients were included in the SMBG group consecutively from the top of this list; and after screening 142 patients, excluding 14 due to missing data on HbA$_{1c}$, 128 patients were included in the SMBG group (Figure 1).

We sought to avoid regression towards the mean by analysing a subgroup of participants with a baseline HbA$_{1c}$ below 100 mmol/mol and by excluding extremely dysregulated patients. One of the inclusion criteria for the FGM group was "need to reduce BG", why the limit for this subgroup was not set lower.

Data collection

All data on age, sex, weight, diabetes duration and HbA$_{1c}$ at baseline, at six, nine and 12 months were collected from the FDDB. For the FGM group, HbA$_{1c}$ at baseline was defined as HbA$_{1c}$ on the day FGM was applied or the last HbA$_{1c}$ value up to three months before this date. The time limit was set to three months because HbA$_{1c}$ is a result of BG over the past three months [10]. For the SMBG group, baseline HbA$_{1c}$ was defined as the HbA$_{1c}$ one year before the latest HbA$_{1c}$ registered in the FDDB. This was an observational study based on existing data and, using the past year of HbA$_{1c}$ results made it possible to keep the study period within the time span covered by the FGM group.

Statistical analysis

Data were analysed using IBM SPSS software (IBM SPSS Statistics for Windows, Version 24). Categorical variables were described as percentages, and continuous variables were described as means ± standard deviations. Differences between groups were analysed using the independent t-test and differences within groups were analysed using the paired t-test. To investigate trends in repeated measures, ANOVA repeated measures and the Wilks' lambda test were used.

A two-tailed p value of < 0.05 was considered significant.

FIGURE 1 / Flow chart of the inclusion process.

CGM = continuous glucose level monitoring; FDDB = Funen's Diabetes Database; FGM = flash glucose level monitoring; HbA$_{1c}$ = concentration of glycated haemoglobin; SMBG = self-monitoring of blood glucose level.

Trial registration: not relevant.

RESULTS

Characteristics of the population

There was no difference between the SMBG group and the FGM group with respect to: age (57 ± 13 years vs 56 ± 15 years, p = 0.53), weight (82 ± 17 kgs vs 80 ± 17 kgs, p = 0.56), diabetes duration (26 ± 13 years vs 27 ± 17 years, p = 0.44) or sex (35% women vs 38% women, p = 0.61) (**Table 1**).

Glycaemic control

There was no significant difference in HbA_{1c} between the two groups at baseline (62 mmol/mol in the SMBG group vs 64 mmol/mol in the FGM group, p = 0.20). At six months of follow-up, HbA_{1c} was reduced by 4 mmol/mol in the FGM group, which was close to being significantly lower than in the SMBG group (Table 1). During the 12-month follow-up, mean HbA_{1c} increased by 2 mmol/mol in the SMBG group and declined by 4 mmol/mol in the FGM group. The difference between the groups was not significant (p = 0.10) (Table 1).

No difference was observed in mean HbA_{1c} in the SMBG group between baseline and the six-month follow-up (p = 0.66), baseline and the nine-month follow-up (p = 0.14) or baseline and the 12-month follow-up (p = 0.20) analysed with paired t-test. In the FGM group, we recorded a significant reduction of HbA_{1c} between baseline and the six-month follow-up, baseline and the nine-month follow-up, and baseline and the 12-month follow-up (p = 0.00, p = 0.04 and p = 0.01, respectively). HbA_{1c} was reduced from 64 mmol/mol to 60 mmol/mol after 12 months using FGM, and this reduction was evident already after six months (**Table 2**).

To investigate the impact of glycaemic control over time, an ANOVA repeated measures analysis was performed in which only patients who had HbA_{1c} measured at baseline, six months and 12 months were included. In the SMBG group, there was no sign of increasing or decreasing HbA_{1c} values according to the Wilks' lambda test (p = 0.386), but in the FGM group a significant reduction was recorded in HbA_{1c} over these repeated measures of HbA_{1c} (HbA_{1c} 65, 58 and 60 mmol/mol, p = 0.002) (**Table 3**).

The HbA_{1c} at baseline was not significantly different between the two groups, but the mean was slightly lower in the SMBG group than in the FGM group (62 vs 64 mmol/mol, p = 0.20) (Table 1). To reduce the risk of regression towards the mean, data were re-analysed after having excluded persons with an $HbA_{1c} > 100$ mmol/mol, assuming that there are other factors than the measuring device that impact such an elevated BG. This excluded five persons from the FGM group and none from the SMBG group. This exclusion of very

poorly controlled patients produced a baseline mean of 62 mmol/mol in both groups (p = 0.97). Using the paired t-test, HbA_{1c} fell from 63 to 59 mmol/mol from baseline to the six-month follow-up (p = 0.00) and from 61 to 58 mmol/mol between baseline and the 12-month follow-up (p = 0.02). In the repeated ANOVA using the Wilks' lambda test, the reduction in HbA_{1c} at repeated measurements at baseline, six months and 12 months still showed significant reduction (HbA_{1c} 61, 56 and 58 mmol/mol, p = 0.004).

TABLE 1 / Characteristics of the study population.

	SMBG (n = 128)	FGM (n = 128)	p-value
Age, mean (± SD), yrs	57 (± 13)	56 (± 15)	0.53
Sex, % women	35	38	0.61
Weight, mean (± SD), kg	82 (± 17)	80 (± 17)	0.44
T1D duration, mean (± SD), yrs	26 (± 13)	27 (± 17)	0.56
HbA_{1c}, mean (± SD), mmol/mol			
Baseline	62 (± 11)	64 (± 16)	0.20
6 mo.s	63 (± 11)	60 (± 13)	0.07
9 mo.s	61 (± 9)	63 (± 15)	0.21
12 mo.s	64 (± 11)	60 (± 14)	0.10

T1D = Type 1 diabetes; FGM = flash glucose level monitoring; HbA_{1c} = concentration of glycated haemoglobin; SD = standard deviation; SMBG = self-monitoring of blood glucose level.

TABLE 2 / Changes in the concentration of glycated haemoglobin (HbA_{1c}) at six, nine and 12 months compared with baseline within the self-monitoring of blood glucose level (SMBG)- and the flash glucose level monitoring (FMG) group.

Group	n	HbA_{1c}, mean, mmol/mol				p-value
		baseline	6 mo.s	9 mo.s	12 mo.s	
SMBG	123	63	63	-	-	0.66
	104	62	-	61	-	0.14
	105	63	-	-	64	0.20
FGM	122	64	60	-	-	0.00
	62	65	-	63	-	0.04
	39	64	-	-	60	0.01

TABLE 3 / Repeated measures of the concentration of glycated haemoglobin at baseline, six months and 12 months of follow-up.

Group	n	HbA_{1c}, mean, mmol/mol			p-value
		baseline	6 mo.s	9 mo.s	
SMBG	101	63	63	64	0.386
FGM	35	65	58	60	0.002

FGM = flash glucose level monitoring; HbA_{1c} = concentration of glycated haemoglobin; SMBG = self-monitoring of blood glucose level.

DISCUSSION

This real-life observational study indicated that the FGM is better than the SMBG for monitoring BG and helping some T1D patients in an outpatient clinic reduce their HbA_{1c}. Recent studies, featuring a 3-12-month follow-up, have reported similar results; i.e. improved HbA_{1c} while using FGM [11-15]. Furthermore, a recent study showed how FGM decreases time in hypoglycaemia while maintaining HbA_{1c} levels [16].

The present study was conducted to examine the quality of care in the outpatient clinic, and only data from patient journals were available. The study could therefore not be set up as a random clinical trial. The positive aspect of this type of real-life study is that patients in both groups maintained their previous appointment frequency in the clinic, seeing doctors and nurses as always. Patients did not know they were in a study, why no group measured BG more frequently because they were being observed. Thus, there is no risk of a placebo effect in any of the groups. This study provides true insight into the glycaemic changes in a population with T1D.

Data on HbA_{1c} were retrieved from the FDDB. No information about type of glucose-monitoring device is recorded in the FDDB. Therefore, it was not possible to exclude patients who changed back to SMBG after starting FGM. Some patients dislike having a device taped onto their body; others get rashes from the tape; and some just do not use the FGM due to compromised compliance. Consequently, the difference between FGM and SMBG recorded in this study might be falsely small.

The criteria indicating the use of an FGM were very broad during the study period. To take an example, no specific limit for BG or HbA_{1c} was applied in criterion 1. This left room for an individual evaluation in cases where an FGM device was considered beneficial for the patient. This may be one reason why the glycaemic control results recorded in the study were so good.

A disadvantage of the setup of this study was the lack of a full 12-month follow-up period for all patients. The inclusion criteria were defined to include as many patients as possible with at least six months of follow-up. A total of 39 patients in the FGM group had HbA_{1c} measured at baseline and at 12 months (Table 2). Similarly, 35 patients in the FGM group had HbA_{1c} measured at baseline and at six and 12 months of follow-up (Table 3), which was considered a sufficient number of participants.

This study has no data on "time in range", i.e., the time BG is between 3.9 mmol/l and 10 mmol/l, which is another measurement of glycaemic control. Furthermore, it was impossible to establish if FGM affected the patients' time in hypoglycaemia, which the use of FGM has been reported to reduce in other studies [17].

The reduction in HbA_{1c} reported in this study is significant but small for a 12-month period. It may therefore be discussed if a so limited reduction is clinically relevant. Several studies have shown the importance of reducing HbA_{1c} as soon as possible and demonstrated that injuries in microvasculature are not reversible and that even small changes in HbA_{1c} do reduce the risk of diabetic complications [1-5].

It was not possible to investigate how the change from SMBG to FGM affected quality of life among patients in this study because only data from medical journals are allowed in this type of quality-of-care studies. Other studies in this field have found a significant positive effect on quality of life from the use of the FGM system [14, 18]; and that may be an even more important reason than improved glycaemic control to shift patients from SMBG to FGM.

Unlike a CGM system, the FGM system does not communicate with insulin pumps and cannot trigger an alarm if BG is declining or increasing. In Denmark, SMBG devices are classified as an assisting device, whereas a CGM is a treatment device. Therefore, the costs for the two devices are defrayed from different pools of tax funding. This has caused a fervent discussion about which of the pools should cover the costs generated by the new FGM device, because – using different arguments – it may be classified as either an assisting or a treatment device. These classification difficulties should not impede T1D patients' access to the best possible treatment of their chronic disease.

A study from the United Kingdom [19] and another from Sweden [20] have compared the cost-effectiveness of FGM to that of SMBG in T1D patients, concluding that the reduction of hypoglycaemia and the improved health owing to FGM may be considered cost effective. There are no studies on the cost-effectiveness of FGM in Denmark.

FGM offers patients with T1D an easy method to monitor their BG during daily life to ensure that they keep BG in range and hence avoid diabetic complications for as long as possible. This study shows that FGM could help some patients with T1D improve glycaemic control as measured by HbA_{1c} slightly better than by SMBG after six and 12 months. To establish the exact effect of FGM on glycaemic control, diabetic complications and quality of life, more studies are warranted, including randomised trials.

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