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Flash Glucose Monitoring in the Netherlands: Increased monitoring frequency is associated with improvement of glycemic parameters

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ABSTRACT

Aims: To evaluate the association between Flash Glucose Monitoring (FLASH) frequency and glycemic parameters during real-life circumstances in the Netherlands.

Methods: Obtained glucose readings were de-identified and uploaded to a dedicated database when FLASH reading devices were connected to internet. Data between September 2014 and March 2020, comprising 16,331 analyzable readers (163,762 sensors) were analyzed. Scan rate per reader was determined and each reader was sorted into 20 equally sized rank ordered groups (n = 817 each).

Results: Users performed a median of 11.5 [IQR 7.7–16.7] scans per day. Those in the lowest and highest ventiles scanned on average 3.7 and 40.0 times per day and had an eHbA1c of 8.6% (71 mmol/mol) and 6.9% (52 mmol/mol), respectively. Increasing scan rates were associated with more time in target range (3.9–10 mmol/L), less time in hyperglycemia (>10 mmol/L), and a lower standard deviation of glucose. An eHbA1c of 7.0% (53 mmol/mol) translated in approximately 65% time in target range, 30% time in hyperglycemia and 5% time in hypoglycemia (<3.9 mmol/L).

Conclusions: These outcomes among Dutch FLASH users suggest that with higher scan rate glycemic control improves.

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1.   Introduction

Adequate and timely glucose level assessment is indispensable for patients with diabetes mellitus (DM) treated with multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) when aiming for adequate glycemic control. Glucose measurements enable patients and caregivers to make insulin dose adjustments and to aim for changes in lifestyle and dietary habits, which will help to improve metabolic control. Ultimately, with optimized glycemic control micro- and macrovascular complications can be delayed or prevented [1–3].

The opportunity to quickly assess capillary glucose concentrations with finger pricks has been a major breakthrough since the 1980's. Nevertheless, finger prick testing has several limitations. Since they are point measurements, information on glucose trends is limited. Many patients feel reluctant to perform finger pricks many times daily, since it can be disruptive to daily activities and painful. Continuous Glucose Monitoring (CGM), either by real time Continuous Glucose Monitoring (rt-CGM) or by Flash Glucose Monitoring (FLASH), allows a more frequent assessment of glucose concentrations in the interstitial fluid and also provides information on glucose trends. CGM is changing diabetes management and often contributes to increased quality of life, treatment satisfaction, better and more stable glycemic control and improved short term outcomes [4–11].

In 2014, the first version of the FreeStyle Libre® Flash Glucose Monitoring System (Abbott Diabetes Care, Witney, UK) system was introduced in the Netherlands and from December 2019 the FLASH is reimbursed for patients with DM using MDI or CSII. The FLASH performs on partially different principles than earlier CGMs. The user must proactively obtain the results by using a reader instead of data being relayed automatically to a receiver. Furthermore, the FLASH is already factory calibrated with no need for daily calibration by the patient during the 14-day sensor wear, and is meant to be inserted in the upper arm only. Several studies demonstrated better glycemic control, improved quality of life and lower disease burden among persons with DM using FLASH [4–7,12–15].

With increasing possibilities to use FLASH, there is a clear need for information on the effects of its use under real life circumstances by larger groups of patients with DM. The aim of the present study was to evaluate the use of FLASH under real-life circumstances in the Netherlands and to assess the effects on glycemic parameters.

2.   Patients and methods

2.1.   Study design and aims

This is a nationwide study with a cross-sectional design. The aim was to investigate the magnitude of FLASH reader use in the Netherlands during the period September 2014 to March 2020 and to examine associations between FLASH scan frequency and glycemic parameters under real life circumstances.

2.2.   Data collection

The FLASH monitors glucose levels in interstitial fluid for up to 14 days. A dedicated reader or a smartphone app is used to scan the FLASH sensor to collect the current glucose, the last 8 h history and glucose trend. Up to 8 h of glucose readings are automatically stored every 15 min on the sensor. This study only included data collected via the specific reading devices, but not with the smartphone app. When a reader was connected to personal computer-based software with an internet connection, the reader's 90-day memory was de-identified and uploaded to a database. The report software, available for free download, includes an agreement that de-identified data will be collected at each internet-connected use of the software [16].

2.3.   Analyses

Within this database, completely anonymized information on the use of scanning devices and connected sensors was accumulated. The available data also contained information of the country in which the scanning device was registered. In addition to data from Dutch users, data from users from other countries were retrieved from the database for comparisons. The duration of FLASH monitoring, the number of readers and sensors and the scanning frequency per sensor and individual scanning device could be determined. The scanning frequency for each sensor was calculated by the number of scans divided by the duration of sensor use according to recorded start and end times. Scanning frequency per reader was assessed by calculating the mean scan rate of all its sensors, followed by determining the cumulative frequency distribution and summary metrics (mean, median and interquartile range (IQR)). To investigate patterns of scanning, frequency of scanning per day and per hour was collected.

Furthermore, analyses of glycemia were performed based on all the data that were uploaded. To be included in these analyses it was required for each sensor to have at least 120 operational hours to ensure reliable glucose control measures. Data from all sensors belonging to the same reader were combined and calculated as the mean of all sensor measures. The cumulative frequency of scan rates, as well as the mean eHbA1c, was calculated for each five percent of available readers to stratify the readers into 20 equally sized groups (bins), and descriptive statistics were calculated. The frequency distribution of scans by hour of the day was assessed for scanning patterns across the day. Several measures of glycemia were used including mean glucose, time in target range (defined as glucose between 3.9 and 10 mmol/L), time in hyperglycemia (>10 mmol/L and >13.9 mmol/L) and time in hypoglycemia (<3.9 mmol/L and <3.0 mmol/L) [17].

The available information on glucose per scanner was converted into eHbA1c using an algorithm (eHbA1c (%) = (mean glucose in mmol/L + 2.59)/1.59) [18]. eHbA1c is presented in IFCC (mmol/mol) and DCCT/NGSP units (%).

2.4. Outcomes

Primary outcome was the association between FLASH (scan) frequency and glycemic parameters (estimated HbA1c (eHbA1c), time in target range, time in hyper- and hypoglycemia, and standard deviation of glucose). As secondary outcome, scan frequency during time in target range and time in hypo- and hyperglycemia was assessed for persons with lower and higher eHbA1c values. In addition, the number of obtained glucose readings in the Netherlands, their pattern across the day and comparisons with worldwide data were assessed.

2.5. Statistical analysis

The span of glycemic measures and relative changes were reported from the lowest to highest scan rate groups. The database was analyzed by structured query language routines, and further summarized by KNIME (www.knime.org), the Python programming language (www.python.org), and the R statistical package (www.r-project.org).

3. Results

Up to March 2020, there were 16,331 analyzable readers (163,762 sensors) from the Netherlands, out of a total of 932,793 (10,348,827 sensors) across all countries (Supplementary Table S1). There were 27.9 million glucose scans performed by the users in the Netherlands, and the sensors provided 48.7 million hours of glucose monitoring data. The median [IQR] number of daily scans in the Netherlands was 11.5 [7.7, 16.7] (Fig. 1, panel A). During day hours (6 AM to 10 PM) this number was 8.9 [5.9, 13.2] and during night hours (10 PM to 6 AM) 2.4 [1.6, 3.6]. There were no significant differences in scan frequency between the different days of the week (data not shown).

The 20 bins stratified by mean daily scan rate were analyzed for the associated glycemic metrics (Table 1). The lowest 5% of readers (n = 817) had a mean scan rate of 3.7 scans per day, with a mean eHbA1c of 8.6% (71 mmol/mol), while the 5% of readers with the highest scan frequency had a mean scan rate of 40.0 scans per day and a mean eHbA1c of 6.9% (52 mmol/mol). Indices of glycemia are also presented in Supplementary Figure S1 (panel B to G).

Associations of scan rate with eHbA1c, time in range, time in hyper- and hypoglycemia, and coefficient of variation are presented in Fig. 1. Overall, per bin with increasing scan frequency an association with lower eHbA1c levels, less time in hyperglycemia and improved glucose variability (expressed as a lower standard deviation) was observed. Within the bin that represents persons who scanned more than 40 times per day an eHbA1c below 7.0% (53 mmol/mol) has been achieved. The association of scanning frequency with time in hypoglycemia was less pronounced (Fig. 1, panel D).

Additionally, the number of readers in each bin with zero time in hypo- and hyperglycemia was evaluated (Fig. 2). At hypoglycemia with a glucose level <3.0 mmol/L (54 mg/dl) (Fig. 2, panel B), there was a decrease followed by an increase

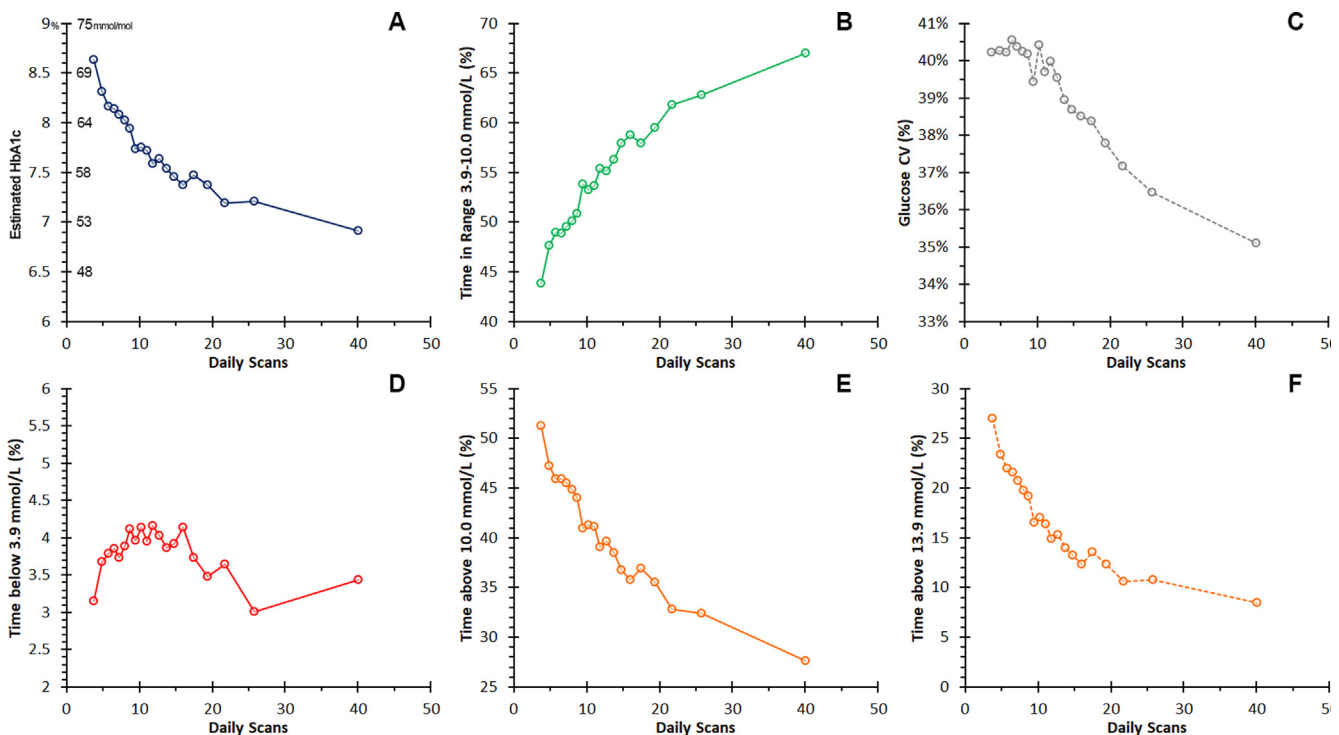Fig. 1 – Daily scan rate with the FLASH and associations with glycemia per bin of scan frequency. Daily scans (20 equally sized groups, n = 817 each) versus A. Mean estimated HbA1c; B. Mean time in target range (glucose 3.9–10.0 mmol/L); C. Mean coefficient of variation; D. Median time in hypoglycemia (<3.9 mmol/L); E. Mean time in level 1 hyperglycemia (>10.0 mmol/L); F. Mean time in level 2 hyperglycemia (>13.9 mmol/L).

Table 1 – Twenty bins ordered by scan rate, comprising 817 readers each, with associated indices of glycemia.

Scan rate per day	Estimated HbA1c (%)	Estimated HbA1c (mmol/mol)	Glucose < 2.5 mmol/L (min/day)	Glucose < 3.0 mmol/L (min/day)	Glucose < 3.9 mmol/L (min/day)	Glucose 3.9–10.0 mmol/L (hours/day)	Glucose > 10.0 mmol/L (hours/day)	Glucose > 13.9 mmol/L (hours/day)
3.7	8.6	71	4.1	12.0	45.4	10.5	12.3	6.5
4.9	8.3	67	5.2	14.3	53.0	11.4	11.3	5.6
5.7	8.2	66	5.3	14.3	54.5	11.7	11.0	5.3
6.5	8.1	65	5.5	15.9	55.5	11.7	11.0	5.2
7.3	8.1	65	5.1	13.8	53.8	11.9	10.9	5.0
8.0	8.0	64	5.0	14.1	55.9	12.0	10.8	4.7
8.7	7.9	63	5.2	13.9	59.4	12.2	10.6	4.6
9.4	7.7	61	4.9	14.2	57.1	12.9	9.8	4.0
10.2	7.8	61	5.4	14.6	59.6	12.8	9.9	4.1
11.0	7.7	61	5.0	13.9	57.0	12.9	9.9	3.9
11.9	7.6	59	5.6	15.8	60.0	13.3	9.4	3.6
12.7	7.6	60	4.6	13.0	58.1	13.2	9.5	3.7
13.7	7.5	59	4.7	13.1	55.7	13.5	9.2	3.4
14.8	7.5	58	5.3	14.1	56.5	13.9	8.8	3.2
16.0	7.4	57	5.0	14.2	59.6	14.1	8.6	3.0
17.5	7.5	58	4.2	12.1	53.8	13.9	8.9	3.3
19.3	7.4	57	4.1	11.2	50.1	14.3	8.5	3.0
21.8	7.2	55	4.0	11.8	52.5	14.8	7.9	2.6
25.8	7.2	55	3.1	9.1	43.3	15.1	7.8	2.6
40.0	6.9	52	2.9	8.7	49.5	16.1	6.6	2.0

Data are presented as means, except for time below 2.5, 3.0 and 3.9 mmol/L; these are medians.
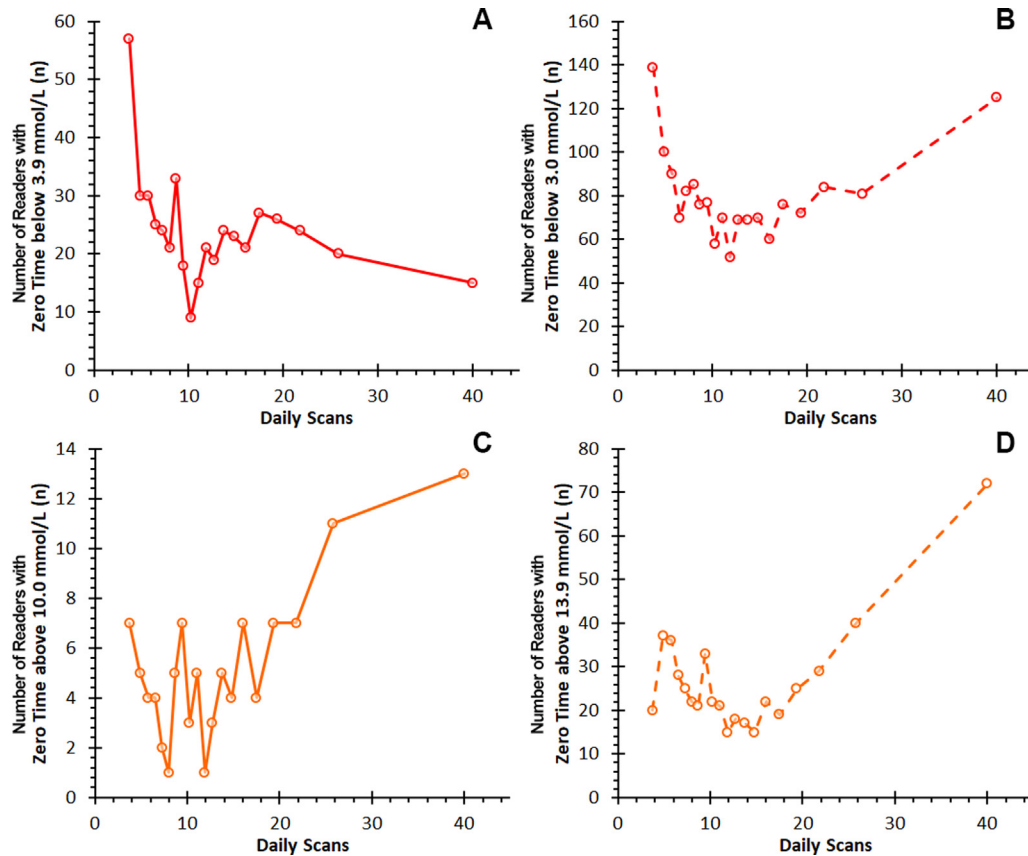
Fig. 2 – Daily scan rate with the FLASH and associations with zero time in hypo- and hyperglycemia. Daily scan rate versus number of readers with A. Zero time a glucose below 3.9 mmol/L. B. Zero time a glucose below 3.0 mmol/L. C. Zero time a glucose above 10.0 mmol/L. D. Zero time a glucose above 13.9 mmol/L.

in the number of readers with zero exposure to this level of hypoglycemia across the scan groups. For zero exposure to hyperglycemia, the association was clearer; persons with higher scan rates were more likely to have zero time in hyperglycemia. Concerning hyperglycemia above 13.9 mmol/L (250 mg/dl), at the highest scan group of 40 scans per day, 72 of 817 (8.8%) readers had no exposure to this level of hyperglycemia.

When grouping the readers into 20 equal bins defined by eHbA1c, the highest eHbA1c bin performed just under 10 scans per day, while the lowest bin had a daily scan rate of 18 per day (Fig. 3). The association with the other glucose metrics was also evident; those with the lowest eHbA1c had the highest time in range and in hypoglycemia, and the lowest time in hyperglycemia. For glucose variability, there is an increasing relationship between eHbA1c and standard deviation of glucose levels. Of notice, an eHbA1c of 7.0% (53 mmol/-mol) corresponded with a scan frequency of 15 scans per day and translated in approximately 65% time in target range, 30% time in hyperglycemia (>10 mmol/L) and 5% time in hypoglycemia (below 3.9 mmol/L) (see Fig. 4, panel B to D).

To evaluate the scan behavior between eHbA1c groups in more detail, the scan rates (scaled to units of scans per day) during each glucose range was determined for each bin (Fig. 4). During glucose levels within the target range or in hyperglycemia persons with lower average estimated HbA1c values tend to scan more frequently as compared to those with higher estimated HbA1c values, whereas the scan frequency in hypoglycemia tends to stay relative stable over the different average eHbA1c levels.

Comparison of data from the Netherlands with the worldwide data is presented in Supplementary Table S1 and Figure S2. Overall, there was a – virtually – similar daily scan rate (mean 13.4 vs. 13.2) and parameters of glycemia demonstrate a slightly higher HbA1c 7.7 (1.4)% (61 (15.3) mmol/mol) vs. 7.5 (1.5)% (58 (16.4) mmol/mol) and less time in target range (13.1 (4.5) vs. 13.9 (4.9) hours per day) in the Dutch population.

4. Discussion

This study describes the impact of FLASH use in the Netherlands up to March 2020. Although one should be careful to not draw too firm conclusions from cross-sectional data as analyzed in the present study, the findings definitely allow some tentative clinically meaningful interpretations.

First and foremost, there is an association between increasing scan frequency with better glycemic control. In general, a scanning frequency of >20 times per day is associated with an eHbA1c level close to 7.0% (53 mmol/mol), in line with previous results presented by Dunn et al. [19]. The other way around: the lower the daily scan frequency, the higher
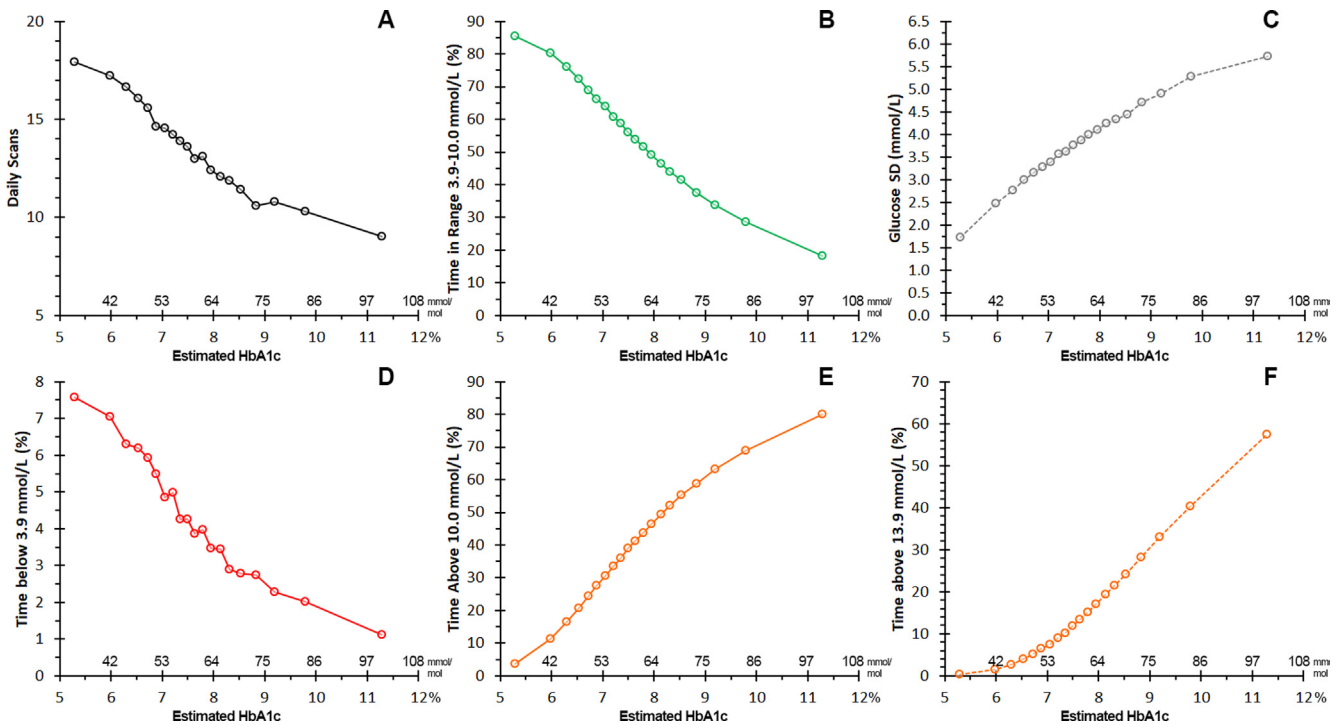
Fig. 3 – Daily scan rate with the FLASH and indices of glycemia per bin of eHbA1c. Estimated HbA1c (20 equally sized groups, n = 817 each) versus A. Daily Scans; B. Mean time in target range (glucose 3.9–10.0 mmol/L). C. Mean standard deviation of glucose; D. Median time in hypoglycemia (<3.9 mmol/L); E. Mean time in level 1 hyperglycemia (>10.0 mmol/L); F. Mean time in level 2 hyperglycemia (>13.9 mmol/L).
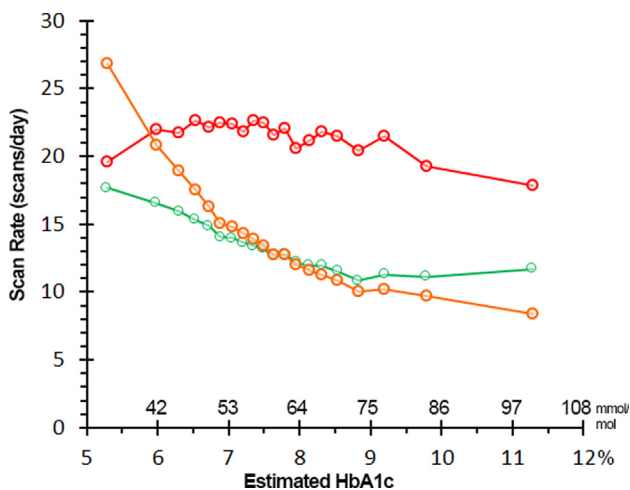

Fig. 4 – Scan frequency during time in range, hypo- and hyperglycemia according to average estimated HbA1c. The red line represents the scan rate during hypoglycemia (<3.9 mmol/L), the green line the scan rate during target range (3.9–10.0 mmol/L) and the orange line the scan rate during hyperglycemia (>10.0 mmol/L). Dots correspond to the 20 bins of eHbA1c. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the associated eHbA1c. Therefore, we hypothesize that advising users who scan with a low frequency to scan more often may result in better glycemic control. Furthermore, persons

who scan with low frequency tend to concentrate scanning in the hypoglycemic range and tend to disregard scanning in the hyperglycemic range. This suggests that users with a low scan rate potentially do not reap the benefits of FLASH compared to users who scan more frequently.

Of notice, a scanning frequency to reach an eHbA1c level of <7.0% (53 mmol/mol) – currently the most often used target for HbA1c levels – corresponds with a time in target range (glucose 3.9–10.0 mmol/L) of 65% in our analysis. This percentage of time is less than current guidelines advice as ideal time in range (<70%) for most people with type 1 and type 2 diabetes [17]. This finding emphasizes the difference between eHbA1c (more stable) and time in range as (more dynamic) outcome parameter. When educating healthcare professionals and FLASH users, these findings can be incorporated, aiming for a more satisfactory use of FLASH. In contrast to more recent CGM devices, the FLASH we analyzed has no alarm function for (predicted) hypo- or hyperglycemia. The upcoming use of (FLASH) CGM devices with alarm function will possibly have an additional positive effect on the ability to reach glycemic targets [20].

Data as acquired from Dutch users are mostly in line with the worldwide data. On average, users scan about 13 times daily. The eHbA1c in the Netherlands tends to be somewhat higher as well as the amount of time spent in hyperglycemia. It should be mentioned that comparisons are hampered by the lack of information concerning the population, including indication for FLASH use. Until December 2019, the use of FLASH in the Netherlands was mainly restricted to persons who failed to reach adequate glycemic control. This selection,

in contrast to the more heterogeneous worldwide population with regards to diabetes management, could well account for the current findings. The considerable number of scans (>30) needed to achieve the internationally defined target glycemic variability of ≤36% is presumably also related to the expected high amount of FLASH users with inadequate glycemic control in this study, related to the reimbursement criteria in The Netherlands until December 2019.

Limitations of this study should be acknowledged. As mentioned before, the cross-sectional design of this study precludes conclusions concerning causality. As a consequence of the anonymous nature of the database used for this study, detailed information concerning characteristics of FLASH users was unavailable. Ideally, users' characteristics and longitudinal analyses should be included in future analyses. In addition, the lack of information concerning carbohydrate intake and exercise patterns during FLASH should also be taken into account. As there is a heterogeneous population with various indications for FLASH use, we were unable to define specific subgroups who might benefit the most from FLASH. As parameter of glycemic variability, the coefficient of variation of glucose concentrations was used. It should be noted that outcomes for the standard deviation of glucose levels (data presented in Supplementary Figure S3) were in line with the coefficient of variation (the ratio of the standard deviation divided by the mean, Fig. 1C). Lastly, it should be noted that eHbA1c does not always closely approximates a laboratory measured HbA1c [21]. After this study ended, the term eHbA1c has been changed to Glucose Management Indicator (GMI) in the Netherlands.

5.   Conclusions

The observed outcomes suggest that with increasing FLASH scan rate glycemic parameters improve, including eHbA1c, time in range, time in hyperglycemia and standard deviation of glucose. Although causality between scan rate and described outcomes is not proven, both users and health care professionals have to be aware of this probable relationship.

Declaration of Competing Interest

Initial study design was by TCD, HJGB, PRD, and MJF. Data collection and statistical analysis was performed by employees of Abbott Diabetes Care (TCD, KK, YX). Further detailing after the original study design was possible in cooperation of the above named and AL, MAE, ROBG, and NL. All authors contributed to the interpretation of the results and in writing the manuscript. This work was partly funded by the University Medical Center Groningen (Department of Internal Medicine) and partly by Abbott Diabetes Care (the last part being in the form of an unconditional research grant).

Appendix A.   Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2021.108897.

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