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RESEARCH ARTICLE

Novel ambulatory glucose-sensing technology improves hypoglycemia detection and patient monitoring adherence in children and adolescents with type 1 diabetes

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Abstract

Purpose Glucose monitoring [GM] is a mainstay of diabetes control and management. Improving glycemic control is essential to prevent microvascular complications. However, adherence to GM can be a challenge in children and adolescents. Detecting hypoglycemia is essential for its prevention and treatment. We aim to study the impact of the flash ambulatory glucose monitoring in detecting hypoglycemia and enhancing adherence in children and adolescents with type 1 diabetes.

Methods The study is prospective involving 3 hospital visits. Children and adolescents with diabetes were enrolled in the study which involved a period on conventional glucose self-monitoring [glucometers] followed by a similar period of monitoring using the flash glucose monitoring device (FreeStyle Libre). Frequency of GM, duration and frequency of hypoglycemia were compared on conventional and the flash monitoring.

Results 75 subjects were studied. Age mean (range) was 11.9 years (2–19). Significant difference was seen in hypoglycemia detection between both testing devices. 68 (94%) and 65 (90%) patients detected nocturnal and diurnal hypoglycemia respectively on Flash monitoring compared to 12 (16.6%) and 30 (41%) on glucometer testing ($p < 0.00$). Mean (range) duration of hypoglycemia was 95 min (15–330). Statistically-significant difference was found between the frequency of GM on glucometer testing compared with Flash monitoring (2.87 and 11.6/day) ($p < 0.001$).

Conclusions Flash monitoring is a useful tool to improve adherence to GM and detecting hypoglycemia [diurnal and nocturnal] in children and adolescents with type 1 diabetes.

Keywords Ambulatory · Libre · Glucose · Monitoring · Flash · Hypoglycemia

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Introduction

Several landmark studies over the years have demonstrated that improved glycemic control reduces the risk of diabetes complications in type 1 diabetes [1]. However, control of diabetes in young people can be challenging. The challenge results from the variable patterns of physical activity, higher frequency of intercurrent illness and hormonal changes. All these factors lead to a higher glycemic variability with fluctuations between hyperglycemia and hypoglycemia [2]. Glucose monitoring (GM) plays an important role in diabetes control and reducing the risk of complications [3]. It allows patients with diabetes to recognize and correct abnormal glucose values and enables them to calculate and adjust insulin dosages and make decisions related to carbohydrate and insulin doses in relation to physical activity [4]. In addition, it allows health care professionals to advise on best insulin dosing both in emergency and routine diabetes care. However, lack of adherence in GM is a well-known problem particularly in the adolescent age group [5].

GM can be done by self-monitoring of blood glucose (SMBG) or continuous glucose monitoring (CGM). In a multicenter analysis including 24,500 patients, it was shown that more frequent blood GM is associated with a better metabolic control in patients with type 1diabetes [6]. CGM is an effective way of monitoring glucose profile. Randomized controlled trials proved its safety and efficacy in children [7].

As with the self-monitoring of glucose, studies have identified multiple barriers leading to underuse of CGM in children. These include pain, difficulty in sensor insertion which is required to be done weekly, skin complications related to adhesive strips, alarm fatigue, concerns about accuracy, loss of sensor connectivity, discrepancies compared to capillary glucose readings and interference with daily activity and exercise. A major downside of sensor use is the need for multiple self-monitoring tests for calibration [8]. The FreeStyle® Libre™ Flash glucose monitoring system (Abbott Diabetes Care, Alameda, CA) is an interstitial ambulatory glucose monitoring system (AGM). Its wired enzyme sensor is calibrated in the factory. The sensor has a life of 14 days during which no calibration is required. Edge et al., have recently confirmed its accuracy, safety and user acceptability in the paediatric population [9].

Hypoglycemia is a common complication of diabetes management. It is estimated that 30–40% of people with type 1 diabetes experience one to three episodes of severe hypoglycemia each year [10]. Nocturnal hypoglycemia, in particular, is a major reason for fear in parents of children with diabetes. It, often, goes undetected as night time monitoring is a major challenge and adversely affects quality of life [11]. Studies using continuous glucose monitoring [CGM] have documented that nocturnal hypoglycemia, is more frequent than has been recognized based on capillary glucose measurement [12]. The flash glucose monitoring device when scanned, produces a glucose result along with historic results with a 15-min frequency for up to 8 h. Its use resulted in reduction of the frequency of hypoglycemia in well controlled adults with type 1 diabetes [13]. In another study on adults with tight diabetes control, use of Flash monitoring device was shown reduce hypoglcymia frequency and time spent in hypoglycemia [14].

Aim

We aim to study the impact of use of the flash glucose monitoring system on improving patients' adherence to GM and to evaluate its benefit on capturing hypoglycemia compared to self-monitoring blood glucose and assess the duration of hypoglycemia by using the device.

Study specified outcomes

The study outcomes are related to adherence to glucose monitoring and rate of capturing hypoglycemia by using the ambulatory glucose monitoring.

Materials & method

The study is prospective involving children and adolescents with *type I diabetes*. Patients following up for diabetes management at the Paediatric Endocrinology Department in Mafraq hospital are approached to enroll in the study. Freestyle Libre device was introduced to patients and those who elected to use it are approached to enroll in the study. We planned to collect a minimum of 1 month data on using the device and compare it with data from a similar period of time data obtained with conventional glucose capillary self-monitoring by glucometers. The hypoglycemia definition used was blood glucose level less than 3.9 mmol/L (70 mg/dL).

The study was powered to detect, with a 0.05 significance level and 80% power, an effect size of 1/3, i.e. a difference of 1/3 of the standard deviation of each parameter. The study was approved by the Research and Ethics committee of Mafraq hospital, Abu Dhabi, UAE. Approval number is MAFREC-094.

The study included 3 visits to the hospital:

- Visit 1

Written consent was obtained from the participating children parents/guardians.

– Patients are explained the aim and methods of the study
– Demographic information including age, duration of diabetes, method of insulin delivery are recorded

– Capillary HbA1c is recorded

• Visit 2

– Glucometers were downloaded and data of up to 6 weeks prior to the visit is stored.
– Of the glucometer data stored, frequency and timing of hypoglycemia detected are captured and daily number of glucose checking is recorded.
– Patients are trained on the use of the Flash monitoring device and had the first sensor inserted by one of a team of diabetes educators.

• Visit 3

– Patients are seen 2–4 weeks after the first visit. During this period, they would have worn 1–2 sensors.
– Data is downloaded from the device reader and saved in the study records.
– Number of daily scans by patients, number of diurnal and nocturnal hypoglycemia detected by patients on scanning and average duration of hypoglycemia episode were retrieved from the downloaded data and recorded.

Data analysis

Duration of data monitoring obtained from the download of glucometers and Flash monitoring device was equivalent for individual patient. The parameters of number of diurnal and nocturnal hypoglycemia are compared during the glucometer and the Flash monitoring device use. Average daily checks by the glucometer is compared with the number of scans [flashing] patients did to check their blood glucose. Average duration of hypoglycemia [time spent in hypoglycemia] is recorded from the Flash monitoring device download.

Statistical methods

Non-parametric tests (Wilcoxon signed rank test for paired observations) were used to examine the difference between the parameters. p values below 0.05 were considered significant. Box plots were used to display distributions. Medians and Inter Quartile Ranges (IQR) were used as measures of location and dispersion. For the mean duration of hypoclycemia, the mean and 95% CI was used for these measures.

Results

75 subjects (47 females) were enrolled in the study. Age mean (range) was 11.9 years (2–19). All patients had type 1 diabetes with a mean (range) duration of diabetes of 4 years (0.6–12). Mean (range) HbA1c was 8.2 g% (5.9–10.2), 66.1 mmol/mol (41.0–88.0). 15 were on insulin pump therapy and 60 on multiple daily injection of insulin.

3 patients had data for less than 14 days as they lost the sensor before the life time of 14 days and did not replace it. Their data was not included in the analysis. Out of the remaining 72 patients, 61 wore 2 sensors during the study periods providing 28 days of complete data while 11 had complete data for 14 days (1 sensor duration). Overall, we had 1862 complete days of data.

Glucose monitoring frequency by glucometer and the flash device

The median (IQR) of the average daily frequency of GM using the glucometers was 2.87 (1–6) compared with 11 (3–44) scans per day on using the flash device. The difference was statistically significant ($p < 0.001$). The difference was similar across all age groups (Table 1).

Diurnal hypoglycemia detected by glucometer and flash monitoring

30 patients (41%) had diurnal hypoglycemia detected on glucometer compared to 65 patients (90%) who had diurnal hypoglycemia detected with the Flash monitoring. Wilcoxon's signed ranks test showed a significant difference between the number of diurnal hypoglycemia episodes detected by Flash monitoring compared with the glucometer (median of 4.0 vs 0.0, $p < 0.01$).

Nocturnal hypoglycemia frequency comparison

68 (94%) of patients had detected nocturnal hypoglycemia on Flash monitoring as opposed to 12 (16.6%) on glucometer testing. The difference between the number of hypoglycemia episodes detected by Flash monitoring and the glucometers was statistically significant (median 3.0 vs 0.0, $p < 0.01$) by Wilcoxon signed ranks test.

Duration of hypoglycemia

The median (IQR) number of episodes (day and night combined) of hypoglycemia captured by Flash monitoring is 9 (4–14) per patient during the study period. Mean (range) duration of hypoglycemia was 96 min (95%CI 81–111).

Out of 44,688 h monitored by Flash monitoring for all the study group. 1185.6 h were spent in hypoglycemia (2.7%).

Table 1 Comparison of various parameters between glucometer and flash monitoring

Parameter	Glucometer	Flash monitoring device
Number of patients detected diurnal hypoglycemia	30 (41%)	65 (90%)
Number of patients detected nocturnal hypoglycemia	12 (16.6%)	68 (94%)
Average frequency of monitoring/day	2.87 (1–6)	11.6 (3–44)

Discussion

GM is a major requirement of diabetes management. O'Connell et al., demonstrated that HbA1c decreased by 0.2% for each additional blood glucose check per day [15]. It is recommended that glucose checks to be done with meals, exercise before bed time and in other situations where abnormal glucose level is suspected [16]. Overall, compliance with these recommendations results in a typical frequency of monitoring of 4–10 checks per day [16]. In children and adolescents with type 1 diabetes, studies show a suboptimal rates of glucose self- monitoring with adherence rate ranging from 31 to 69% [15]. There is a multitude of reasons to poor adherence in monitoring which is considered a major burden in diabetes management. These barriers can be related to psychological issues of frustration, distress, financial issues and social issues in the form of peer relations and workplace barriers. In children, pain, inconvenience, disturbance of night sleep and embarrassment are common barriers reported [17]. Self-monitoring of blood glucose [SMBG] provides single intermittent readings and does not detect period of glucose fluctuations and variability [18]. Studies have shown that even multiple and structured blood glucose monitoring cannot, at times, prevent hypoglycemia or hyperglycemia [19]. Use of the flash glucose monitoring device in our study has markedly encouraged patients to comply with GM. We found a statistically-significant difference between the frequency of scans done by patients when using the flash glucose monitoring device compared with the number on SMBG [$p = 0.000$]. The increased frequency of monitoring was seen across all age groups. Similarly, in a study by Bolinder et al., using the flash glucose monitoring device, the sensor utilization was over 90% and scanning was 3 times more self-monitoring. The study outcome showed marked improvement in those who used the device [13].

Regular use of GM device/method is not always feasible. It is shown that less than half of the children use CGMS at a frequency of 6 days/week [20]. It is well known that the effectiveness of CGM depends on sufficient sensor utilization and the improvement of glucose profile is reversed following stopping usage of the monitoring [21]. The Juvenile Diabetes Research Foundation [JDRF] randomized clinical trial showed that improvement in glycemic control is directly related to the frequency of CGM use [22]. Cost of CGM has been reported to be a barrier to the consistency of CGM use [23]. However, decline of CGM use has also been observed in centers where expenses related to CGM accessories is covered by national insurance programs [24]. CGM devices rely on patient calibration by a capillary blood sample. SMBG tests for calibration can be a major downside of regular CGM use [8]. Factory calibration is a unique feature of the flash glucose monitoring system compared to other sensors which require multiple capillary measurements for calibration [25]. The lack of user calibration adds major benefit to the system as it eliminates potential variations introduced by inappropriate glucose values used for calibrations. In addition, this function prevents the use of sensor rather than capillary glucose for calibration and eliminates missing calibration errors and warnings [26]. As reducing barriers increases the utility of GM devices in the young age group [27], the distinctive feature of the flash monitoring device of being factory-calibrated makes it an attractive feature for GM in the younger population. Another special feature of the flash monitoring device is its relatively long duration of the sensor life of 14 days. Sensor short life led to limiting the widespread use of CGM [27]. In children, researchers found a decline in use of CGM, with only 41% of children using CGM at least 6 days/week after about 6 months of continuous use [28]. Results from the JDRF-CGM showed a greater decline in CGM use in adolescents [6.3 to 3.3 days/week] and children [6.8 to 3.7 days/ week] [8]. Another drawback of some CGM systems is the excessive alarms leading to "alarm fatigue". The flash glucose monitoring system displays trends and alerts on the Reader but does not have real-time alarms. While this feature can be considered a deficiency of the system, it might provide a good option for individuals who complain of alarm fatigue [29]. A major factor in recommending a form of GM by health care professional to patients is ease of data analysis to identify problems and conclude recommendations. The FreeStyle system is found to provide an easy analysis of continuous glucose levels and identifying disease patterns [30]. In our study, majority of patients expressed the ease of use of the device and the clarity of interpreting the result as major reasons of sticking to its use. Accuracy is another major criterion for accepting the GM device. The flash glucose monitoring system is found to be accurate compared with capillary BG reference values in adult patients with *type 1* and *type 2 diabetes* patients. In this study, the accuracy remained stable over 14 days of wear and unaffected by patient characteristics [31]. Similarly, Edge et al.

confirmed accuracy, safety and user acceptability of the flash monitoring system in the paediatric population. Investigators showed the system accuracy was unrelated to specific characteristics of patients [age, gender, body weight, method of insulin delivery] which enables its use for a wide range of young people [9]. In addition, patients' satisfaction with the flash glucose monitoring system was high and 96.3% of participants stated that they would recommend the use of the system to somebody else [9].

Use of CGM has improved glucose control and reduced frequency of hypoglycemia [32]. In addition, CGM use enhances patients' treatment satisfaction and improves perception of diabetes control and hypoglycemia safety [33]. Hypoglycemia might be undetected on conventional SMBG. In our study, we have captured a mean number of 10.4 episodes of hypoglycemia with a range of 1 to 40 per patient during the study period. Diurnal hypoglycemia was detected in 65 patients (90%) on the Flash monitoring system while it was seen on only 30 (41%) when they were using SMBG for GM.

Nocturnal hypoglycemia accounts for approximately half the episodes of hypoglycemia experienced [34]. A further challenging factor is that bed time glucose has been shown to be a poor predictor to nocturnal hypoglycemia [35]. We found a statistically significant difference between the median number of nocturnal hypoglycemia detected by Flash monitoring device compared with the SMBG ($p \leq 0.001$). 68 (94%) of patients had detected nocturnal hypoglycemia on Flash monitoring as opposed to 12 (16.6%) on SMBG testing.

Data showed that use of Freestyle AGM resulted in reduction of the frequency of hypoglycemia in well controlled adults with type 1 diabetes [13]. In a group of 241 participants with an average HbA1c of 6.7%, a decrease of 74 min per day in hypoglycemia was noted in the group randomized to the flash monitoring use compared to those using finger stick glucose checks [13]. The "Impact" study on the flash monitoring device is shown to reduce hypoglycemia in people with tight diabetes control [14].

In addition to hypoglycemia frequency, time spent in hypoglycemia is a critical issue in diabetes management. In a study using blinded CGM, prolonged nocturnal hypoglycemia of more than 2 h was detected in a quarter of patients [36]. Another study utilizing CGM in a group of very young children revealed periods of nocturnal hypoglycaemia with an average of an hour duration varying from 10 to 480 min [37]. In our study, we had 44,688 h monitored by Flash monitoring for all the study group participants. Out of that period, 1185.6 h were spent in hypoglycemia [2.7%]. The mean duration of hypoglycemia was 95 min averaging between 15 and 330 min.

CGM use is shown to reduce hypoglycemia and reduce hypoglycemia time without increasing HbA1c [38]. Bolinder et al. showed that use of the FreeStyle system resulted in a decrease of nocturnal hypoglycemia by 33 min per day [13]. In this study, reduction of time spent in hypoglycemia by 38% was seen in patients using the Flash monitoring system [13].

Study limitation

In our study, patients were recruited from a single centre. Designing a multi-centric study will improve the power of the study. In addition, the relatively shorter duration of the study made conclusion about impact on glycemic control not feasible. Use of the devise for 8–12 weeks will enable comparing the HbA1c before and after the study period and drawing a conclusion about the effect of the flash glucose monitoring use on glycemic control. Longer study duration will also enable demonstration of the hypoglycemia reduction after the ongoing use of the device. Randomization patients for flash monitoring or SMBG and switching patients from one device to other might confirm the results' consistency.

Conclusions

Our study shows that use of flash glucose monitoring for AGM enhances patients' compliance of GM. It improves detection of hypoglycemia and its duration. Lack of calibration requirement and the longer wear period of the sensor help improving clinical outcome of diabetes in children and young people.

To the best of our knowledge, this is the first study undertaken in children and adolescents to examine the impact of flash AGM use on glucose profile, GM compliance and hypoglycemia detection.

Author contributions Asma Deeb designed the study, coordinated work between co-authors, finalized data collection, wrote and submitted the manuscript. Hana Yousef, Shaker Suliman, Layla Abdulrahman and Mary Tomy trained the study subjects the technical part on the use of the Flash monitoring device. They downloaded the patients' glucometers and the Flash monitoring device in a shared folder for data saving. Nabras Al Qahtani created the "case record form". She, also recruited patients for the study. Hana Al Suwaidi and Salima Attia recruited patients under their care for the study. Ifrah Artan participated in data collection and helped with literature search. Nico Nagelkerke performed the statistical analysis and revised the manuscript.

Compliance with ethical standards

Conflict of interest Authors have no conflict of interest to declare.

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