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Measurement of glucose concentration in interstitial fluid — an alternative or a supplement to conventional blood glucose monitoring?

ABSTRACT

The paper describes currently available interstitial glucose monitoring systems and discusses their advantages and disadvantages in comparison with conventional blood glucose measurements using glucose meters. Furthermore, it describes clinical trials assessing these systems in terms of their usefulness, safety and influence on therapeutic management in diabetes. (Clin Diabetol 2019; 8, 2: 121–126)

Key words: interstitial glucose levels, diabetes, self-monitoring of glycemia, CGM, FGM

Introduction

Glucose monitoring is an integral part of an effective diabetes treatment. It has been proven that patients who perform regular glucose level measurements achieve better metabolic control of diabetes [1]. The Diabetes Poland recommends adjusting the number of blood glucose measurements during the day to specific groups of patients with diabetes [2]. In the light of these recommendations, those who are treated with diet only can measure blood glucose least often. In this group of patients it is recommended to perform a 4-point blood glucose profile once a month (fasting and 2 hours after the main meals) and weekly blood glucose measurements at different times of the day. Patients on oral antidiabetic agents and/or GLP analogs should perform a 4-point blood glucose profile once a week and daily blood glucose measurements at different times of a day. Patients on insulin therapy are advised to measure blood glucose more often. Patients treated with fixed doses of insulin should perform 1–2 blood glucose measurements daily, and additionally 4-point blood glucose profile once a week and 7-point blood glucose profile once a month. The most frequent measurements are recommended for patients treated with multiple insulin injections. These patients should measure blood glucose at least 4 times daily. It is recommended that these patients should measure blood glucose both before and after meals and additionally at bedtime, before physical activity, when suspecting hypoglycemia, and also when performing activities during which hypoglycemia may be particularly dangerous. In addition, all patients, regardless of the treatment used, should monitor blood glucose levels more frequently in case of feeling unwell or sudden deterioration of their health status.

Regular self-monitoring of blood glucose (SMBG) should help in achieving good glycemic control. A general glycated hemoglobin (HbA_{1c}) target for diabetic patients is ≤ 7%, which translates into an average

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plasma glucose level of 154 mg/dL [3]. In patients with type 1 diabetes, the individualized HbA_{1c} target of ≤ 6.5% is recommended, if this can be achieved without significant decrease in life quality and increased risk of hypoglycemia. Fasting and preprandial glucose levels should be within the range of 80–110 mg/dL, and 2-hour postprandial blood glucose should not exceed 140 mg/dL. The glycated hemoglobin target of ≤ 6.5% is also recommended in patients with type 2 diabetes of short duration, in children and adolescents, regardless of the type of diabetes, and in women with pregestational diabetes who are planning to become pregnant. However, in the second and third trimester of pregnancy more stringent metabolic control is indicated and HbA_{1c} should be targeted at < 6%, providing that this does not lead to frequent hypoglycemic episodes. In elderly patients with macroangiopathic complications and multiple comorbidities HbA_{1c} levels higher than 7.0% but not exceeding 8.0% are acceptable [4].

Blood glucose monitoring

It is recommended that diabetic patients perform SMBG using personal glucose meters. They should be taught how to use glucose meter and interpret SMBG data. The current European standard (EN ISO 15197:2015) includes requirements for blood glucose meters and outlines the following acceptable minimum accuracy criteria: 95% of the results must be within ± 15 mg/dL for blood glucose values < 100 mg/dL or less than 15% for blood glucose values ≥ 100 mg/dL [5]. Currently available blood glucose monitoring devices use the electrochemical or spectrophotometric method. More frequently used is the electrochemical method that involves the measurement of electrons released during the reaction between glucose in a blood sample and the reagent contained in the test strip. The spectrophotometric method consists in measuring the amount of a colored product of the enzymatic reaction of glucose with the appropriate reagents. This method is associated with a larger measurement error resulting from possible contamination of the sample.

Nowadays, there are many types of glucometers available on the market. They differ in weight, size of the device, size of the screen, memory (data storage), the possibility of removing a test strip after measurement without touching it, measurement time, volume of blood sample and the range of blood glucose values evaluated. Some glucose meters, in addition to the measurement of glycemia, allow the determination of ketone and cholesterol in the blood. Newer devices also have the ability to connect to a computer or smartphone and send measurement results wirelessly.

Measurements of interstitial glucose

Continuous glucose monitoring (CGM) and flash glucose monitoring (FGM) systems are becoming more and more popular. They enable glucose measurements to be made with an electrode immersed in interstitial fluid. This may cause a slight delay in relation to the conventional method of glucose measurement, because the concentration of glucose first changes in the blood, and subsequently in the interstitial fluid. This should be taken into account during rapid blood glucose fluctuations and additional verification of the results obtained using the conventional method of measuring blood glucose should be made. Table 1 presents key differences between the two methods of blood glucose monitoring.

Currently, the most popular CGM systems in Poland are Medtronic Enlite, Dexcom G4 Platinum from Willcare and the recently available Eversense system from Roche. There is also an FGM system — Libre from Abbott. CGM systems measure interstitial glucose every 5 minutes. In the Libre system, the measurement is made while the reader is placed over the sensor, which results in the inability to trigger alarms in the event of hypo- or hyperglycemia. On the other hand, it should be noted

Table 1. Comparison of two methods of glucose monitoring

Feature compared	Conventional blood glucose monitoring	Interstitial glucose monitoring
Costs	Low	High
Availability	Available at every pharmacy	Not readily available — few pharmacies, online orders
Pain associated with measurement	During finger pricking	Painless or minimal pain during implantation
Traumatization	Fingertip injury	Possible allergic reaction in the sensor application site
Number of available devices	Many types	Several types
Measurement result	Individual glycemic values	Individual values with trends

that the Libre system has precalibrated sensors, while the other CGM systems require additional calibration.

Characteristics of currently available systems for measuring interstitial glucose

Enlite

This system uses a glucose sensor that can be worn for up to 6 days. It works in conjunction with the Guardian 2 Link transmitter, which has a range of less than 2 meters. The user can connect the device wirelessly with Medtronic pumps to take full advantage of their functions. Medtronic Veo pump automatically suspends insulin delivery when glucose level is low. Another insulin pump from Medtronic, MiniMed 640G, thanks to the SmartGuard function, can predict hypoglycemia and suspend insulin infusion until blood glucose normalization. It is worth noting that patients treated with multiple insulin injections also can use the Enlite sensors with Guardian Real-Time — a stand-alone CGM system [6, 7].

Dexcom G4 Platinum

The system consists of a sensor, a transmitter and a receiver. It differs from the Enlite device by a much larger range — the maximum distance between the transmitter and the receiver is 6–7 meters. The sensor remains on the skin for 7 days. This system can be used both by patients treated with personal insulin pumps and those on multiple insulin injections [8].

Eversense

This is a new CGM system, available in Poland since October 2017. It consists of a sensor, a transmitter and an Eversense CGM application. The sensor (size: 3.5 mm × × 18.3 mm) is implanted subcutaneously, and the transmitter that connects wirelessly to the smartphone is fixed to the skin with an adhesive right above the sensor. Two types of sensors differing in terms of time of use have been designed: a 90-day sensor and a 180-day sensor. However, currently only 180-day sensors are available on the market. After this time, the sensor should be removed [9].

Libre

This is the only flash system. The result is obtained when the sensor is scanned. The system differs from previously described systems by the lack of alarms and the fact that it is precalibrated. The system consists of a reader and a 14-day sensor attached to the skin with an adhesive. The site recommended by the manufacturer for placing the sensor is the back of the arm. Additionally, Libre reader can be used to measure glucose and ketone bodies in the blood. During the congress of the European Association for the Study on Diabetes, which was held in Berlin in October 2018, Abbott presented a new version of the device — the FreeStyle Libre 2 system. It enables wireless Bluetooth communication between the sensor and the reader, so that it will be possible to receive notifications when the glucose value is outside the normal range [10]. It is worth noting that FreeStyle Libre, which is not designed as a CGM system, can also be used as such system with a special supplementary device. Currently, there are two available devices: MiaoMiao and Blucon from Ambrosia. These small transmitters read the FreeStyle Libre sensor and pass data to smartphone via Bluetooth every 5 minutes [11, 12]. However, it should be borne in mind that these devices have not been evaluated in clinical trials.

Table 2 present basic parameters of interstitial glucose monitoring systems and differences between these systems.

Table 2. Characteristics of currently available interstitial glucose monitoring system

Feature compared	Enlite Medtronic	Dexcom G4 Platinum	FreeStyle Libre	Eversense
Time of use	6 days	7 days	14 days	90 or 180 days
Insertion site	Skin — abdomen, alternatively upper buttocks	Adults: skin — abdomen Children: skin — abdomen or upper buttocks	Skin — back of the arm	Subcutaneously — back of the arm
Users approved	Adults and children	From 2 years of age	From 4 years of age	From 18 years of age
Calibration	Yes	Yes	No	Yes
Alarms	Yes	Yes	No	Yes
Connection between a sensor and a reader	Wireless, radio waves, range: 1.8 meters	Wireless, range: 6 meters	Wireless, NFC, a few centimeters	Wireless, the reader should be placed right above the implantation site
MARD	9.1%	Adults 9% Children 10%	9.4%	8.5%

MARD — mean absolute relative difference

Among the above-described CGM systems, only Medtronic and Willcare devices are subject to reimbursement by the National Health Fund. However, they are available only to a small group of patients. The reimbursement is limited to type 1 diabetes patients under 26 years of age with impaired hypoglycemia awareness, who are treated with insulin pumps. Patients are entitled to purchase 12 Enlite sensors or 9 Dexcom sensors once every 3 months and 1 transmitter every 8 months after paying 30% of the device retail price [13].

CGM systems and conventional blood glucose measurements

The first difference noticed by patients during the use of CGM systems is the fact that they do not need to perform multiple punctures of the fingertips in order to measure blood glucose, which increases the patient's comfort. This is evidenced by the results of a multicenter randomized study. The study showed an increase in treatment satisfaction among patients using the FreeStyle Libre system, which, however, did not translate into an improvement of the quality of life [14].

The usefulness of continuous glucose monitoring systems in the treatment of diabetes was confirmed in the GOLD study [15]. It was a randomized clinical trial lasting 26 weeks. The study included a group of 161 patients with type 1 diabetes treated with multiple insulin injections. There was a greater reduction in HbA_{1c} in patients using CGM (Dexcom G4 Platinum) compared with the conventional method. Additionally, the use of CGM system was associated with a shorter time spent in hypoglycemia and a lower number of severe hypoglycemic episodes compared with conventional glycemic monitoring.

Similar conclusions were reached by the authors of the systematic review and meta-analysis of 14 studies including a total of 1,268 patients with type 1 diabetes [16]. Included in the analysis were trials lasting at least 12 weeks, in which CGM systems were compared with the conventional method of glucose measurement using glucose meters. Reduction in HbA_{1c} by 0.25% in children and adolescents and 0.33% in adults using CGM systems has been demonstrated. In addition, in the group of CGM system users, significantly more patients achieved target HbA_{1c} values and a smaller number of hypoglycemic episodes were observed.

The analysis of data of 17,731 patients with type 1 diabetes showed better metabolic control among patients using CGM systems as compared with conventional glycemic measurements [17]. In the analyzed group, 35% of patients used multiple insulin injections, 50% used insulin pumps, 13% — personal insulin pumps paired with the CGM system, and 2% — multiple insulin injections together with the CGM system. Regardless of the type of insulin therapy, patients using the CGM system achieved better metabolic control of diabetes. In subjects using insulin pumps paired with the CGM system, HbA_{1c} was 7.7%, whereas in users of the CGM system treated with multiple insulin injections HbA_{1c} was 7.6%. It is worth noting that among patients who did not use the CGM system, those treated with personal insulin pumps had HbA_{1c} value of 8.3%, whereas in patients treated with multiple insulin injections, the HbA_{1c} value was 8.8%.

In the COMISAIR study, lasting 12 months and including 65 patients with type 1 diabetes, a greater reduction in HbA_{1c} was observed in the group using the CGM system compared with the group using conventional methods of blood glucose measurement [18]. Improvement in metabolic control in the group using the CGM system was greater both in patients treated with multiple injections of insulin and in those using personal insulin pumps.

Another study evaluated the usefulness of CGM systems (Dexcom G4 Platinum) in patients aged 65 years or older [19]. The 6-month study included 296 patients with diabetes. The control group consisted of patients using the conventional method of blood glucose measurements. It has been shown that CGM use was associated with a reduction in hypoglycemic episodes, frequency of visits related to hypoglycemia, and severe hypoglycemia (requiring the assistance of another person). Furthermore, patients using CGM systems declared less fear of hypoglycemia and less diabetes-related distress.

Similar results were obtained in the IN CONTROL study, which was conducted among patients with impaired awareness of hypoglycemia, treated with personal insulin pumps connected to the CGM system (Medtronic MiniMed Paradigm® Veo™ system) [20]. There was a 2-fold reduction in the time spent in hypoglycemia and a 3-fold reduction in the number of hypoglycemic episodes in the CGM group compared with those using the conventional method of SMBG.

In a randomized clinical trial conducted on a group of 129 patients with good glycemic control, i.e. with HbA_{1c} values < 7.0%, the use of the CGM system was found to reduce the time spent in hypoglycemia compared to the conventional method [21]. In the group using the CGM system, the mean time in glycemia ≤ 70 mg/dL was 54 minutes/day, while in the group using the conventional method it was longer and amounted to 91 minutes/day. The time spent in glycemia ≤ 60 mg/dL in the CGM group was almost two time shorter than in the conventional SMBG group (18 minutes/day *vs*. 35 minutes/day).

When CGM was paired with an insulin pump with a predictive suspend feature (Medtronic MiniMed 640), the hypoglycemic episodes were of shorter duration and less troublesome for patients compared with the group using CGM with a pump without this option. The duration of hyperglycemia was also reduced [22].

The authors of the GLADIS study [31] point out that the use of CGM system is associated with longer time spent in blood glucose range of 70–180 mg/dL. It was a 100-day, randomized, controlled study in which 160 patients with type 1 or type 2 diabetes participated. The subjects were divided into 3 groups: patients using the CGM system with alarms, patients using the CGM system without alarms and patients using the conventional method of blood glucose monitoring. Time spend outside the normal blood glucose range was 9.7 h/day in the group using the CGM system with alarms, 9.9 h/day in the group using the CGM system without alarms and 10.6 h/day in the group not using the CGM system.

Future perspectives

Continuous development of CGM systems leads to the increased accuracy of measurements, which is expressed by the mean absolute relative difference (MARD). The smaller the value of this parameter, the greater the reliability of the results. Of the systems described, Eversense from Roche is a clear leader. According to the manufacturer of this system, the MARD value is 8.5% [24]. The PRECISE II study showed that the MARD value when using a 90-day sensor was 8.8% [25]. In the PRECISE I study, which assessed a 180-day sensor, the MARD value was 11.1% [26]. The MARD value of another CGM system, Dexcom G4 Platinum with the new 505 software, is 9% in adults and 10% in children [27, 28]. It is worth noting that in previous studies this value was shown at 13%. Medtronic declares that the MARD value for MiniMed systems is 9.1% [29], whereas the MARD value for FreeStyle Libre system, according to Abbott, is 9.4% [10].

Which of the CGM systems is the best?

Most of the trials performed to date compared CGM systems with conventional blood glucose measurements. However, there are only few trials comparing specific CGM systems. The I HART study (performed in August 2018) compared the FreeStyle Libre system with the Dexcom system [30]. After 2 weeks of using blinded CGM, participants were randomly assigned to flash (Libre) or real-time continuous glucose monitoring (RT-CGM) (Dexcom) for 8 weeks. Then, all participants were offered to continue the study with RT-CGM. In the group switched from flash to RT-CGM, the percentage time in hypoglycemia decreased from 5% to 0.8% and the percentage time in normoglycemia increased from 60% to 67.4%.

In a study comparing three CGM systems: Dexcom G4 Platinum, Enlite and FreeStyle Navigator (not available on the Polish market), it was found that the Dexcom system is the most accurate [31]. However, one should bear in mind that this study was performed in 2014, and currently used devices allow for obtaining better results.

Summary

The continuous development of technologies enabling monitoring glucose levels in blood and interstitial fluid has a positive effect on both metabolic control and the quality of life of patients with diabetes. Numerous clinical trials have demonstrated the beneficial effect of CGM systems on the reduction of glycated hemoglobin, longer time in normoglycemia, and decrease in the duration and the number of hypoglycemic episodes. Newer versions of glucose monitoring systems are characterized by greater accuracy of measurements. More advanced systems for monitoring glucose levels in interstitial fluid are emerging on the market. They are becoming more and more popular because they offer convenient and less invasive measurements. A greater selection of devices can be found among CGM than FGM systems, but the advantage of the latter is a significantly lower cost of use. Currently Eversense is the most accurate CGM system. Besides accuracy of measurements, an additional advantage of this device is that the sensor is implanted subcutaneously, which prevents its accidental removal. The implantation and removal procedure, however, requires the incision of the skin. The advantage of Medtronic CGM systems is compatibility with Medtronic insulin pumps.

It is worth noting that the choice of a specific device should be made according to patient's individual needs, bearing in mind the type of insulin therapy used, obligatory calibration, the way the sensor is implanted, and the financial capability of the patient. The introduction of interstitial glucose monitoring systems in patients with diabetes gives hope for more effective control of this disease, but at the moment we cannot conclude that the interstitial glucose monitoring is an alternative to conventional methods of measuring blood glucose. However, it seems that it can be a valuable supplement to it.

Conflict of interest

None declared.

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