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Point-of-Care Testing

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Basics and use of continuous glucose monitoring (CGM) in diabetes therapy

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Abstract

Background: For a long time, self-monitoring of blood glucose (SMBG) was widely viewed as the essential glucose measurement procedure in the therapy of insulin-treated people with diabetes. With increasing accuracy and simplified handling of continuous glucose monitoring (CGM) systems, this evolving technology challenges and at least partly replaces SMBG systems.

Content: Sensors of all currently available CGM systems measure glucose levels in the subcutaneous interstitial fluid for 6–14 days. The only available implantable sensor facilitates a measurement span of up to 6 months. Depending on the used system, glucose levels are either shown in real time (rtCGM systems) or after scanning (iscCGM systems). Functions such as alerts, alarms and trend arrows and data presentation encourage independent self-management of diabetes therapy. The high frequency of glucose data and the multitude of existing functions require an extensive training of people with diabetes and their caregivers.

Summary: CGM systems provide a much more detailed picture of glycemia in people with diabetes. Educated patients can use these data to react adequately to their glucose levels and therefore avoid hypoglycemic and hyperglycemic events. Studies showed that glycated hemoglobin (HbA_{1c}) levels and hypoglycemic events can be significantly reduced by frequent use of CGM systems.

Keywords: blood glucose; continuous glucose monitoring; diabetes; glycemic variability; hypoglycemia; mean absolute relative difference.

Regular measurem

Background

Regular measurement of blood glucose (BG) levels by selfmonitoring of blood glucose (SMBG) is a prerequisite for an adequate therapeutic treatment of patients with diabetes mellitus, especially for those with an intensified insulin therapy, for example patients with type 1 diabetes [1]. SMBG systems are essential tools in intensified insulin therapy of people with diabetes, because they provide the possibility to calculate bolus doses for carbohydrate intake, as well as the detection and subsequent counteraction of hypo- or hyperglycemia [2]. The amount of usually performed measurements per day, however, is too low to allow a statement about the kinetics of BG and therefore only represents a snapshot of the actual glycemic status. Furthermore, SMBG requires a fingerstick to obtain a blood sample, which can be painful and time-consuming, subsequently leading to poor compliance [3]. In addition, dysglycemic events, for example nocturnal or asymptomatic hypoglycemia, may not be recognized and consequently threaten the health of people with diabetes [4]. Severe hypoglycemia can lead to coma or death and has been linked to increased mortality [1, 5]. Fear of hypoglycemia often leads to a rethinking of patients in the direction of an acceptance of higher BG levels, and subsequently increased glycated hemoglobin (HbA₁) values, to avoid the risk of getting into a state of hypoglycemia. However, increased HbA_{1c} levels are related to short- and long-term complications and diseases, and should be consequently reduced to close-to-normal levels.

Since the first continuous glucose monitoring (CGM) system, developed in the early 1990s [6] and marketed in 1999, many developmental steps of CGM systems were performed. Current CGM systems are smaller, have lower weight, are easier to use, have a prolonged wearing time and are more accurate than older ones [7]. All of these systems continuously measure the glucose concentration in the interstitial fluid and transfer the data via a transmitter to a receiver which displays the results. In the past, all CGM systems were intended by their manufacturers for adjunctive use in addition to SMBG measurements, because accuracy was not sufficient for making treatment decisions. Since a few years, some devices (see section

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"Current status of CGM") are claimed for non-adjunctive use due to their improved accuracy [8]. Nevertheless, the point accuracy of CGM systems remains still behind that of SMBG systems.

Content

Current status of CGM

CGM systems typically consist of the following three components: (a) a glucose oxidase (GOD)-based glucose sensor which is inserted into the subcutaneous fatty tissue and continuously measures glucose concentration in the interstitial fluid, (b) a transmitter which is attached to the sensor and transfers the data to (c) a receiver/smartphone which displays the results (Figure 1). Glucose concentration is estimated based on the production of hydrogen peroxide by GOD and the associated release of electric current, which is directly proportional to the concentration of glucose in the interstitial fluid. In detail, GOD and its cofactor, which works as the initial electron acceptor, catalyze the oxidation of glucose to hydrogen peroxide (H₂O₂) and gluconic acid, whereas the cofactor is reduced: $Glucose + GOD - cofactor_{(oxidized)} \rightarrow$ $Gluconic \quad acid + GOD - cofactor_{(reduced)}. \quad The \quad cofactor \quad is$ regenerated in a reaction with oxygen (O₂), which leads to the formation of H_2O_2 : $GOD-cofactor_{(reduced)} + O_2 \rightarrow GOD$ $cofactor_{(oxidized)} + H_2O_2$. H_2O_2 is oxidized at a catalytic electrode where the amount of transferred electrons is detected: $H_2O_2 \rightarrow 2H^+ + O_2 + 2e^-$. This electron flow is proportional to the glucose concentration in the interstitial fluid. Currently, two different types of CGM systems are available on the market: real-time continuous glucose monitoring (rtCGM) systems and intermittently scanned continuous glucose monitoring (iscCGM, flash glucose monitoring [FGM]) systems. rtCGM systems measure the

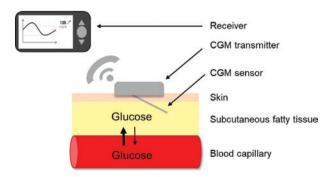


Figure 1: Components of a CGM system (scheme).

glucose values and automatically display, e.g. every 5 min, a recent value. In contrast, the sensor of iscCGM systems measures glucose levels every minute and stores one value every 15 min. iscCGM systems need to be actively scanned to obtain glucose information and to show it on the device display. The scans have to be performed at least every 8 h to retain the whole daily glycemic data [7]. Scanned glucose values of iscCGM systems can be either downloaded to a personal computer or uploaded to a cloud-based system [9].

Typical sensor application sites for rtCGM systems, such as Dexcom $G6^{\circ}$, are abdomen and upper arm for iscCGM systems, such as FreeStyle Libre 2. However, in order to allow a correct determination of the glucose values, sensors may only be used at the approved application sites.

The sensor wear time of non-implantable sensors is limited to up to 10 days for rtCGM systems and to 14 days for iscCGM systems. In contrast, the sensor wear time of implantable, fluorescence-based sensors, like in the case of the rtCGM system Eversense®/Eversense® XL, is 90 up to 180 days (Table 1) [10]. All rtCGM systems, except for Dexcoms' current G6® system, have to be manually calibrated to BG levels approximately 2 times per day (see also section "Sensor calibration"). The iscCGM systems provide factory calibration and therefore do not need SMBG measurements for calibration. Also, the Dexcom G6® provides a factory calibration with the option of additional fingerstick calibration. The CGM devices Dexcom G5[®] and G6[®], as well as FreeStyle® Libre and FreeStyle® Libre 2, are claimed by their manufacturers as a replacement of fingerstick testing for diabetes treatment decisions [8].

Unlike current iscCGM systems, most rtCGM systems can be linked to insulin pumps, representing so-called (hybrid) closed-loop systems. A sensor-augmented pump system displays CGM data on the screen of the insulin pump and enables patients to manually adapt insulin doses based on the current glucose value. Some of these pump systems already use a low glycemic suspend to stop basal rate for up to 2 h if glucose is low [11]. Recently, the first sensor-integrated pump systems that automatically adapt basal insulin delivery by the pump based on CGM data became available. This helps to achieve a consistent glucose profile and might reduce the incidence of hypoglycemic events, especially during night [12].

Clinical benefits of CGM

Various studies demonstrated the benefits of CGM systems in diabetes therapy [9, 13, 14], whereby the

Table 1: Comparison of current subcutaneous continuous glucose monitoring (CGM) systems available on the market (November 2019)

	System					
	Dexcom G5®	Dexcom G6®	Eversense®/Eversense® XL	Freestyle® Libre	Freestyle® Libre 2	Guardian TM connect (elite sensor)
CGM group Sensor life	rtCGM 7 days	rtCGM 10 days	rtCGM 90 days/180 days	iscCGM (FGM) 14 days	iscCGM (FGM) 14 days	rtCGM 6 days
Sensor application Calibration	Abdomen 2 h after warm-up,	Abdomen Factory-calibrated. Optional	Upper arm (implanted) Four calibrations every 2–12 h	Back of upper arm Factory-calibrated	Back of upper arm Factory-calibrated	Abdomen 2 h and 5 h after warm-
	then every 12 h	manual calibration possible	after warm-up, then every 10–14 h			up, then every 12 h
Frequency of readings	5 min	5 min	5 min	Per scanning/stored every 15 min	Per scanning/stored every 15 min	5 min
Sensing technology Manufacturer	Enzyme electrode Dexcom	Enzyme electrode Dexcom	Optical fluorescence Senseonics	Enzyme electrode Abbott	Enzyme electrode Abbott	Enzyme electrode Medtronic

scCGM, intermittently scanned CGM; rtCGM, real-time CGM

number of hypoglycemic events could be decreased and glycemic control could be improved. In addition, a significant reduction in HbA_{1c} (1.0% reduction from baseline versus 0.4%; p<0.001) and a decreased time spent out of the desired target glucose range (37 min/day less time spent <70 mg/dL; p = 0.002) were shown [13]. Further studies have evaluated the effectiveness of CGM systems in helping patients with a history of severe hypoglycemia events or impaired hypoglycemia awareness [15]. For example, in a 6-month, multicenter study with type 1 diabetes patients and a history of impaired hypoglycemia awareness or severe hypoglycemia, performed in 12 diabetes practices in Germany, the so-called HypoDE study, a significantly reduced incidence of hypoglycemia events by 72% (p<0.0001) was observed for the use of CGM compared to SMBG [15]. In addition, clinical trials have shown that use of CGM systems may also attenuate the fear of hypoglycemia events and diabetes-related stress and therefore improve quality of life [16]. Not only rtCGM systems, but also iscCGM systems showed a reduction in HbA_{1c} levels, both in patients with type 1 diabetes and type 2 diabetes, compared to SMBG systems. Furthermore, iscCGM was positively correlated with the time spent in euglycemia and inversely associated with the time spent in hypo- or hyperglycemia [17].

Even though the use of CGM systems shows several benefits, you still have to take into account that the results of CGM studies are dependent on various factors, such as study design, study patient population and the CGM system used (see also section "Sensor metrics and accuracy"). For example, time below the range (<70 mg/dL) differs for people with diabetes between different studies, whereas HbA_{1c} and the number of patients was similar [17]. One explanation for these varying results could be the differences in the patient population between these studies, e.g. different inclusion or exclusion criteria, or the differences between the accuracy of the used rtCGM and iscCGM systems.

Alerts, alarms and trend arrows

One feature of rtCGM systems is the availability of programmable alerts and alarms, which warn of impending or occurring hypo- or hyperglycemia events (Table 1). As a result, rapidly increasing or decreasing glucose levels can be noticed and subsequently counteracted. With the launch of Abbotts' Freestyle® Libre 2, an alarm function has been added to this iscCGM system; however, a scan after the alarm to provide the glucose value is still necessary. Through the early perception of changing glucose

levels, the probability of nocturnal hypoglycemic events [18], as well as missed bolus insulin injections for meals, can be reduced. Nonetheless, excessive occurrence of alarms can also lead to reduced compliance in patients ("alarm fatigue") [19].

Not only alerts and alarms, but also trend arrows in CGM systems serve as an early warning for impending hypoglycemia and hyperglycemia events. Downward trend arrows appear when glucose level is falling, whereas upward arrows appear when it is rising. Consequently, the trend arrows may indicate the need to ingest carbohydrates or for correcting insulin dose. However, trend arrows do not always match future glucose change, especially in the first hours after carbohydrate intake or insulin delivery [20]; therefore, this has to be considered in the correct interpretation of trend arrows and subsequent therapy decisions. Furthermore, trend arrows are not standardized among CGM systems from different manufacturers and can therefore not be compared. For example, two upward arrows in the Guardian™ Connect system indicate a glucose rising of about 2–3 mg/dL/min, whereas the Dexcom G6[®] system displays only one arrow for that case. In addition, rapidly rising or falling glucose levels (>3 mg/dL/min) are not indicated with certain trend arrows by the Eversense® and FreeStyle® Libre systems. That is one important reason why patients and their caregivers should be trained in detail with their specific CGM system.

CGM measurement compartment

Glucose results of SMBG systems are accomplished by multiple daily capillary BG measurements. Each measurement procedure requires fingersticks to get capillary blood. In contrast to that, CGM measures in the subcutaneous interstitial fluid. The CGM device displays a measurement result that is calculated by an algorithm based on tissue glucose and BG values (capillary glucose values) used for calibration. The diffusion of glucose from the intravascular to the subcutaneous interstitial fluid compartment leads to a physiologic delay (Figure 1), whereas the processing of the gained data results in a technological delay, whereby a time lag between the measurement and display of the result occurs [21]. The physiological time lag amounts to around 7-8 min [22] and the technological time lag amounts to around 4–6 min [23, 24]. The algorithms of currently used CGM systems intend not only to correctly calculate a tissue glucose value approximated to the capillary BG value, but also to reduce the time lag to a minimum.

Sensor calibration

Sensor calibration of CGM systems is necessary to convert the signal of the electric current into the corresponding glucose concentration. This calibration is performed either during the manufacturing process, for example in the case of Dexcom G6® and FreeStyle® Libre/Libre 2, or implemented by users themselves, or both. In factorycalibrated CGM systems, the sensitivity of the sensor is determined by a sensor code which is preprogrammed into its electronic. Most of the current rtCGM systems require user calibration against a capillary BG measurement result every 12 h, which has to be entered by the user (Table 1). Therefore, the accuracy of a CGM system is directly dependent and determined by the accuracy of the used SMBG system. In addition, accuracy can be also affected by choosing an inadequate point of time for calibration, for example during rapidly changing glucose levels [25], or by user mistakes. Calibration errors will have an impact at least until the next calibration occurs. In factory-calibrated CGM systems, this calibration step is not required, whereby potential handling and transcription errors are excluded. However, because these systems do not offer the possibility of correction, a sensor has to be replaced by a new one if it turns out to be biased [26]. The combination of a factory-calibrated sensor, which can be manually re-calibrated if necessary, such as that implemented in the Dexcom G6® system, could furthermore increase the accuracy of the sensor by re-calibration [27].

Sensor metrics and accuracy

In contrast to SMBG systems, there is neither a generally accepted metric available, nor requirements to determine and compare the accuracy of CGM systems reproducibly. Often the number of CGM values within 20 mg/dL or 20% of reference values [28], corresponding to the accuracy criteria of SMBG systems (for example ± 15 mg/dL or ± 15 %, respectively ± 10 mg/dL or ± 10 %), or the mean absolute relative difference (MARD), are used for accuracy reporting.

MARD is calculated by averaging the absolute values of relative differences between CGM system measurement results and corresponding comparison method results, mainly obtained from SMBG systems. Each individual relative difference value, irrespective of whether the calculated difference with respect to the comparison result is positive or negative, is considered as a positive value. A MARD of 10% or less for a CGM system is under discussion as being accurate enough for making insulin dosing decisions based

on the determined readings [29]. Accuracy of early sensors of CGM systems showed a MARD of nearly 20% [30], which has been significantly improved over the last two decades. Current CGM (rtCGM and iscCGM) systems reach MARD values in the range of approximately 9%-14%. A limiting factor of MARD is the fact that it may vary through the glucose ranges, for example in the hypoglycemic and the hyperglycemic range, and that information about the direction of the error is not provided. The higher the rates of change are, positive or negative, the higher the MARD will be. Also, other factors regarding the study design, e.g. included patients (people with type 1 or type 2 diabetes), influence the MARD. In addition, the MARD also depends on the reference measurements, which are used in different studies, and its calculation is not standardized [31]. For these reasons, the study design should be standardized. If different CGM systems are worn in parallel and compared in the same subject in so-called head-to-head studies, the MARD values between these devices are comparable. A head-to-head study from 2014, for example, showed a greater accuracy for one of the two tested devices [32], whereas a current head-to-head study from 2019 showed similar overall accuracy for all tested CGM systems (MARD: 10.1%-11.9%) and that the performance of these systems was improved after the first day of use [33].

The bias is defined as the systematic difference between measurement results from the CGM system under investigation and the comparison method. The difference between bias and MARD is that the bias calculation incorporates the directionality of the difference, whether positive or negative, compared to the value of the comparison method. Bland and Altman suggested plotting individual differences between results of the investigated systems and the comparison method against their mean value, in response to limitations posed by the use of correlation methodologies in comparing two quantitative measurement systems [34].

Evaluation and visualization of CGM data

CGM provides a much larger number of glucose readings than occasional SMBG, whereby a comprehensive picture of daily glucose course is obtained. Up to 288 glucose measurement results every day (within a 5-min interval) make the use of easy understandable and standardized data readouts and graphical presentations necessary. Retrospective CGM data enable patients to enhance their glycemic management by adjustment of their therapy and behavior with the help of their clinicians under consideration of supplementary disclosures,

such as insulin dosing and carbohydrate intake. These data, for example, can enable insights into the patterns of hypo- and hyperglycemia events that occur over time and lead to a change in their therapy to avoid such events in the future [35].

The ambulatory glucose profile (AGP) is generated via a combination of all data from several days or weeks and translating them into one period with a length of 24 h (Figure 2). Key elements of the AGP are a plotted median curve (50th percentile), two curves above and below the median which represent the interquartile range (IQR), and the 10th and 90th percentile curves on the sides of the IQR. The IQR describes glucose variability by showing the glucose range in which 50% of all data points are located. The 50th percentile depicts glucose stability, and the 10th and 90th percentile curves allow the backtracking of extreme glucose excursions. Therefore, the AGP report can serve as a fast and easy-to-assess entry point for data analysis of CGM data by physicians and caregivers [35].

The current international consensus report on use of CGM systems provides a comprehensive list of descriptions and recommendations of key metrics that should be assessed in the analysis of retrospective data and be utilized to assess glycemic control (Table 2) [36]. Data sufficiency, for example, indicates the time period (at least 10 of the 14 days of CGM use) which is necessary to receive representative data, as well as for adequate decision-making, and the coefficient of variation (%CV) indicates the level of glycemic variability (GV) over the reported CGM time period (target ≤36%). Further parameters such as glucose management indicator (GMI) and time in ranges (TiRs) have, in addition, the potential to monitor diabetes control. HbA_{1c} is currently used and recommended as the key laboratory parameter for monitoring diabetes [37]. HbA_{1c} can not only be determined directly, but also be estimated based on calculation rules and average BG levels measured by SMBG ($\triangleq eA_{10}$). The so-called GMI, however, calculates the estimated A₁₀ based on CGM-derived glucose values [38]. TiR describes the time that people with diabetes spend within the desired target glucose range (usually 70-180 mg/dL). Because glucose fluctuations are captured continuously with CGM systems, this parameter is more sensitive than HbA_{1c} and is recommended by an international group of experts as the new key metric of glycemic control [36]. However, as TiR alone is not sufficient to describe the overall glycemic control, it is also necessary to indicate and quantitate the time below target range (TbR) and time above target range (TaR) [39]. These times in ranges enable the possibility to provide a more detailed view of GV (Figure 2). Increased HbA_{1c} levels are related

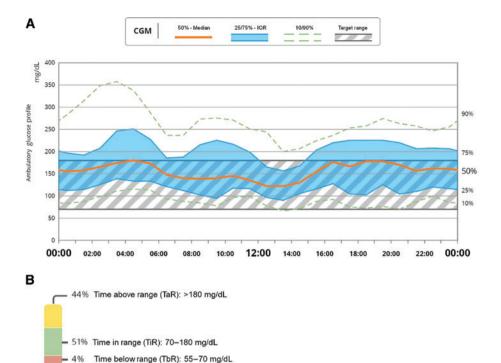


Figure 2: Dexcom CLARITY® software.

(A) Ambulatory glucose profile (AGP) generated and modified from Dexcom CLARITY® software; (B) graph represents an exemplary overview of the percentage of time spent in specific ranges (generated and modified from Dexcom CLARITY® software).

Table 2: Key metrics for CGM data analysis and reporting [36].

#	Key metrics	
1	Mean glucose, mg/dL	
2	Number of days CGM is worn (recommendation: 14 days)	
3	Percentage of time CGM is active (recommendation: at least 10 from 1	4 days = 70%)
4	Glucose management indicator (GMI)	
5	Glycemic variability (<36% = stable, >36% = unstable)	
6	Time above range (TaR): % of readings and time >250 mg/dL	Level 2
7	Time above range (TaR): % of readings and time 181–250 mg/dL	Level 1
8	Time in range (TiR): % of readings and time 70–180 mg/dL	In range
9	Time below range (TbR): % of readings and time 54-69 mg/dL	Level 1
10	Time below range (TbR): $\%$ of readings and time $<$ 54 mg/dL	Level 2

to short- and long-term microvascular complications and long-term macrovascular diseases [40]. Even though there is some correlation between TbR and HbA_{1c} , such a relation to clinical outcomes still remains to be established for TiR [41]. To efficiently gain control of diabetes therapy management, TiRs should be considered in addition to HbA_{1c} in decision-making. Although GV has also been linked to micro- and macrovascular complications and to increased mortality in people with diabetes [39, 42], no studies have been published so far which show

a direct effect of a reduction of GV on improved clinical outcomes.

Education and training

The effective and safe use of CGM systems and the correct interpretation of provided data require that patients and caregivers are trained in using their CGM system and in interpreting the displayed data. Besides education materials and comprehensive training, which is offered by the manufacturers, for example FLASH (for iscCGM systems), independent training programs, for example Spectrum (for rtCGM systems), are also available [43, 44].

The training program Spectrum is offered either for parents of children with diabetes, adolescents or adults. Its aim is to mediate basic information to users of rtCGM systems and to accompany the start of the usage. During this training program, the participants are trained on the readout, analysis and course of glucose data, as well as on the setup and usage of alarms, respectively [43]. In the evaluations study of the iscCGM training program FLASH, it could be shown that clinical parameters, such as HbA, and TiR (see also section "Evaluation and visualization of CGM data"), were significantly improved by participating in this training program and moreover, that the communication between patients and their caregivers was also improved [45].

Summary

Current CGM systems have the advantage that glucose levels can be monitored continuously in the course of a day. Therefore, they provide a detailed picture of patients' glucose metabolic state and enable patients to quickly react to their glucose levels and to avoid hypoglycemia and hyperglycemia events. The level of HbA₁₀, the key laboratory parameter for monitoring diabetes, can be significantly reduced through the use of CGM, and the risk of short- and long-term complications, and diseases, is decreased. In addition, severe glycemic events, such as nocturnal or asymptomatic hypoglycemia, and severe hypoglycemia, can be counteracted or significantly reduced, which leads to an improvement in the quality of life of people with diabetes.

For the proper use of CGM systems, to become familiar with the functions and the correct interpretation of the CGM data, as well as to perform beneficial therapeutic decisions, patients and their caregivers should read the detailed instructions provided by the manufacturers and should additionally be trained either with one of the available trainee programs or certain chapters of it.

Impact statement

1. This review presents a broad overview of the basics of continuous glucose monitoring (CGM).

- It will improve the understanding about the use of CGM in the therapy of people with diabetes, especially of those with an intensified insulin therapy, and the resulting benefits.
- As CGM provides lots of additional information, a replacement of HbA_{1c} and blood glucose values is discussed.

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